

NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

Final appraisal determination

Eribulin for the treatment of locally advanced or metastatic breast cancer

This guidance was developed using the single technology appraisal (STA) process

1 Guidance

- 1.1 Eribulin is not recommended, within its licensed indication, for the treatment of locally advanced or metastatic breast cancer that has progressed after at least two chemotherapy regimens for advanced disease.
- 1.2 People currently receiving eribulin within its licensed indication for the treatment of locally advanced or metastatic breast cancer that has progressed after at least two chemotherapy regimens should have the option to continue therapy until they and their clinicians consider it appropriate to stop.

2 The technology

- 2.1 Eribulin (Halaven, Eisai) has a UK marketing authorisation as a monotherapy 'for the treatment of patients with locally advanced or metastatic breast cancer who have progressed after at least two chemotherapeutic regimens for advanced disease'. Prior therapy should have included an anthracycline and a taxane unless these were unsuitable for the patient. The recommended dose of eribulin as the ready to use solution is 1.23 mg/m² (equivalent to 1.4 mg/m² eribulin mesilate), which is administered intravenously over 2-5 minutes on days 1 and 8 of every 21-day cycle.

- 2.2 The most common adverse effects of eribulin are fatigue, alopecia, peripheral neuropathy, nausea, neutropenia, leukopenia and anaemia. For full details of side effects and contraindications, see the summary of product characteristics.
- 2.3 The cost of eribulin mesilate is £313 per 2 ml vial (0.44 micrograms/ml eribulin; excluding VAT; 'British National Formulary' [BNF] edition 62). The manufacturer has agreed a patient access scheme with the Department of Health, which makes eribulin available at a discounted price. The size of the discount is commercial-in-confidence. Costs may vary in different settings because of negotiated procurement discounts. 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 (appendix A) considered evidence submitted by the manufacturer of eribulin and a review of these submissions by the Evidence Review Group (ERG; appendix B).

- 3.1 The manufacturer's submission presented data on clinical effectiveness from one randomised controlled trial. EMBRACE ('Eisai metastatic breast cancer study assessing physician's choice versus Eribulin') was a multi-centre, phase III, open-label, randomised parallel two-arm study that compared the efficacy and safety of eribulin with treatment of physician's choice (TPC; see 3.2). The study included 762 women (508 randomised to the eribulin arm, 254 randomised to the TPC arm) and was conducted at 135 centres in 19 countries, with 51 women entered across 10 UK centres. The patients in the trial had locally advanced or metastatic breast cancer and had previously been treated with between two and five chemotherapy regimens, including a taxane

and an anthracycline; at least two regimens had to have been given for locally advanced or metastatic breast cancer. The median age of patients was 55 years, 75.9% patients were post-menopausal and 92.3% were white. Approximately 92% of patients in the trial had an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1. Eribulin was administered as an intravenous infusion of 1.4 mg/m² over 2–5 minutes on days 1 and 8 of a 21-day cycle. The primary outcome measured by the trial was overall survival. Secondary outcome measures included progression-free survival, objective response rate (the number of patients with a confirmed complete response or confirmed partial response divided by the number of patients with assessable disease parameters), clinical benefit rate (the number of patients with a confirmed complete response, a confirmed partial response, or stable disease for at least 6 months, divided by the number of patients with assessable disease parameters) and duration of response (time from first documented complete response or partial response until disease progression or death from any cause).

- 3.2 Patients in the EMBRACE trial were pre-stratified according to geographical region (region 1 – North America, Western Europe and Australia; region 2 – Eastern Europe, Russia and Turkey; and region 3 – Latin America and South Africa), human epidermal growth factor receptor 2 (HER2) status and prior treatment with capecitabine, and then randomised in a 2:1 ratio to receive either eribulin or TPC. Pre-planned subgroup analyses explored the effect of these strata, as well as other characteristics commonly assessed in cancer studies. Overall survival results for patients from region 1 (approximately 64% of the total population in both treatment arms) were presented separately, alongside results for the overall intention-to-treat (ITT) population. Additional post-hoc subgroup analyses were conducted to investigate eribulin compared with the

individual treatments within the TPC group that were defined as comparators in the NICE scope (that is, capecitabine, vinorelbine and gemcitabine). The manufacturer stated that, because the investigator had to pre-specify the individual TPC that patients would have received had they been randomised to the TPC group, it was possible to make comparisons between patients given eribulin who would have received that TPC and those who did receive that TPC, hence maintaining randomisation for these individual comparisons. The TPC group contained 254 patients. The treatments they were given included vinorelbine (61 patients, 24.0% of those in the TPC group), gemcitabine (46 patients, 18.1%), capecitabine (44 patients, 17.3%), taxanes (38 patients, 15.0%), anthracyclines (24 patients, 9.4%), other chemotherapy (25 patients, 9.8%) and hormone therapy (9 patients, 3.5%). The choice of TPC was governed by previous treatment, tolerability and patient preference. A taxane had previously been given to 99.0% of patients in the overall ITT population, 98.7% had received an anthracycline and 73.4% had received capecitabine.

- 3.3 The primary analysis was conducted when 55% of the patients had died. An updated analysis was conducted, at the request of the regulatory authorities, when 77% of the patients had died. The manufacturer reported that median overall survival in the primary analysis for the overall ITT population was statistically significantly longer with eribulin (13.1 months) versus TPC (10.6 months) with a hazard ratio of 0.809 (95% confidence interval [CI] 0.660 to 0.991, $p = 0.041$). This indicated that eribulin reduced the hazard or risk of death by 19% compared with TPC. Sensitivity analysis, adjusting for the number of prior chemotherapy regimens and oestrogen receptor status, produced results that were consistent with the primary analyses, with the hazard ratio favouring treatment with eribulin compared with TPC. In the updated analysis, the median

overall survival remained statistically significantly longer with eribulin (13.2 months) versus TPC (10.5 months) with a hazard ratio of 0.805 (95% CI 0.667 to 0.958, $p = 0.014$).

- 3.4 The results of all secondary endpoints were reported from the time of the primary analysis. Median progression-free survival was statistically significantly longer with eribulin (3.6 months) than with TPC (2.2 months), when assessed by investigator review ($p = 0.002$). However, the difference was not statistically significant when assessed by independent review (3.7 months with eribulin and 2.2 months with TPC; $p = 0.137$). The manufacturer stated that this difference arose because almost twice as many patients were censored in the independent review than in the investigator review. Sensitivity analyses, whereby different censoring rules were applied, reported similar results to the primary analysis. The objective response rate was statistically significantly higher for eribulin compared with TPC for the independent assessment (12.2% [95% CI 9.4 to 15.5] versus 4.7% [95% CI 2.3 to 8.4], $p = 0.002$) as well as for the investigator-based assessments (13.2% [95% CI 10.3 to 16.7] versus 7.5% [95% CI 4.3 to 11.9], $p = 0.028$). The difference in the clinical benefit rate for eribulin compared with TPC was not statistically significant (22.6% [95% CI 18.9 to 26.7] versus 16.8% [95% CI 12.1 to 22.5]), although the manufacturer noted that this reflected the similar proportions of patients with stable disease in the eribulin and TPC arms. An independent assessment of the duration of response indicated that the difference in median duration of response with eribulin compared with TPC was not statistically significant (4.2 months/128 days [95% CI 116.0 to 152.0] versus 6.7 months/205 days [95% CI 205.0 to 212.0]; $p = 0.159$). The manufacturer stated that given the small numbers of patients whose disease responded in the TPC group ($n = 10$), comparing

duration of response between the two groups was not meaningful. Similar trends were observed for the investigator assessment of duration of response.

- 3.5 Overall survival was analysed according to geographical region, in both the primary and updated analyses. In both analyses, a statistically significant median overall survival gain of 3.1 months was observed for patients from region 1 who were randomised to eribulin compared with patients who received TPC (13.1 months versus 10 months in the primary analysis and 13.2 months versus 10.1 months in the updated analysis). Secondary outcome data for patients in region 1 were not presented in the manufacturer's submission. The manufacturer also presented confidential results of post-hoc subgroup analyses that were conducted to investigate the comparison of eribulin with individual treatments of the TPC group (capecitabine, vinorelbine and gemcitabine), for the overall ITT population as well as the region 1 population.
- 3.6 No health-related quality of life data were collected during the EMBRACE trial. The manufacturer presented health-related quality of life evidence from two phase II, multi-centre, single-arm, open-label trials (described in the manufacturer's submission as Study 201 and Study 211). Study 201 used the FACT-B tumour-specific quality of life questionnaire and the manufacturer noted that the mean change from baseline in the Trial Outcomes Index was similar for patients whose disease responded and those whose disease did not respond to eribulin therapy. However, 57% of patients whose disease responded to eribulin showed an increased quality of life compared with 45% of those whose disease did not respond. None of the patients whose disease responded to eribulin reported deterioration in quality of life, although 11% of the overall study population did report deterioration. Based on the responses to the FACT-B questionnaire, the manufacturer concluded that

quality of life may be improved in patients whose tumour responds to eribulin treatment. The manufacturer was unable to interpret data for the assessment of tumour-related symptoms because of the level of non-response. Study 211 used the EORTC Quality of Life QLQ-C30 with the breast cancer-specific module. The manufacturer reported that the quality of life data were difficult to interpret because of the level of non-response, but that exploratory analyses indicated no symptomatic change among patients with tumour response, whereas symptomatic deterioration was experienced by patients whose disease had progressed by the end of treatment cycle two. The manufacturer did not use data from Studies 201 and 211 in any further analyses of health-related quality of life.

- 3.7 In the EMBRACE study, most adverse events experienced were mild or moderate (Common Terminology Criteria for Adverse Events [CTCAE] grade 1 or 2) and treatment discontinuations overall as a result of adverse events were lower in the eribulin arm of the trial compared with the TPC arm (13.3% versus 15.4%). Haematological toxicity (for example, neutropenia) with eribulin was common, and neutropenia (CTCAE grade 3 or 4) occurred in 21.1% and 24.1% of patients receiving eribulin, respectively. Neutropenia led to discontinuation in 0.6% of these patients. Febrile neutropenia occurred in 4.6% of patients receiving eribulin. Common non-haematological adverse events experienced during eribulin treatment in the EMBRACE study included asthenia/fatigue (270 patients, 53.7% of the 503 patients in this arm), alopecia (224 patients, 44.5%), nausea (174 patients, 34.6%) and peripheral neuropathy (174 patients, 34.6%). Grade 3 and 4 non-haematological adverse events were observed in more than 5% of patients: asthenia/fatigue (around 9%) and peripheral neuropathy (around 8%).

- 3.8 The manufacturer developed a semi-Markov state transition model that compared eribulin monotherapy with TPC as well as individual chemotherapy agents (capecitabine, gemcitabine and vinorelbine). Data from patients in region 1 of the EMBRACE trial were used in the manufacturer's base-case analyses because the manufacturer considered this population to be most relevant to clinical practice in England and Wales. The manufacturer conducted a sensitivity analysis using data from the overall ITT population. The Department of Health has approved a patient access scheme for eribulin and these discounted costs were incorporated in the manufacturer's analysis.
- 3.9 The model had three main health states: treated, progressive and dead. All patients in the model were initially assigned to the 'treated' health state, which comprised both stable and responsive patients, therefore assuming that treatment response was not a significant predictor for disease progression or death. Patients in the 'treated' health state incurred the costs of drug acquisition and administration, as well as grade 3 and grade 4 treatment-related adverse events. Different utility values for stable and responsive disease were used and weighted by the proportion of patients responding. The 'progressive' health state captured the clinical outcomes and resource use for patients whose disease progressed following previous treatment. Cycles continued until all patients were in the 'dead' state and for the purposes of resource use and quality of life estimations, patients were assumed to enter a 'terminal' state for one cycle before entering the 'dead' state. The probabilities of disease progression and death were derived from survival functions based on time-to-event patient-level data from the EMBRACE trial. A trial duration time horizon was used in the model. This meant that no extrapolation of trial outcomes was carried out by the manufacturer, and when the trial ended (after

2.89 years) all patients who were alive moved into a 'terminal' state. The manufacturer stated that this was a conservative assumption because no further potential additive benefits of eribulin on survival were taken into consideration.

3.10 The economic evaluation adopted an NHS and Personal Social Services perspective. Costs and benefits were discounted at 3.5% per annum. The emergence of grade 3 and grade 4 treatment-related toxicities in EMBRACE was modelled to estimate the associated costs and utility decrements. Because EQ-5D data were not collected during the EMBRACE trial, quality-adjusted life years (QALYs) were estimated using utility values from published literature. The manufacturer identified five studies of interest and focused on the study by Lloyd et al. (2006); this study assessed UK-based societal preferences for different stages of metastatic breast cancer and toxicities. The manufacturer's model assumed that patient health-related quality of life is a function of current disease state and the presence of grade 3 or grade 4 treatment-related toxicities (those affecting 10% or more patients were included in the model). To estimate QALYs, time spent in each health state was multiplied by a corresponding utility value composed of the underlying health state utility value and the mean toxicity-related decrement. The manufacturer used utility values from the Lloyd et al. (2006) study for the treated health state (0.715 for patients with stable disease and 0.790 for patients with responsive disease) and the progressive health state (0.443). The value used for the terminal health state (0.160) was derived from the economic study by Hutton et al. (1996), using values obtained from oncology nurses using standard gamble methodology, because this was not reported in the Lloyd et al. (2006) study.

3.11 The manufacturer included drug-related costs, including administration costs, health-state costs and costs related to

adverse events. Categories and components of resource use were defined for each of the three states based on a literature review and clinical opinion. Unit drugs costs (including co-medications) were based on the prices listed in the BNF 60. Drug administration costs were based on the NHS Reference Cost Schedule 08/09. It was assumed that any drug left over from a treatment was wasted. For vinorelbine, the base case included the costs for oral capsules, but the sensitivity analysis included costs for the intravenous infusion. The costs of the individual TPCs were assumed to be for the full dose specified in each individual summary of product characteristics. The manufacturer used the median of the listed prices (if branded and generic formulations were available). Resources used in all three health states included chemotherapy support medication, scans and laboratory tests, admissions to hospital and outpatient visits. In the stable health state, additional resources were also included when considered as 'follow-up' care and included chemotherapy support medication, scans and laboratory tests. An average body surface area of 1.74 m² was assumed, based on the mean value reported in a study of UK women with breast cancer receiving chemotherapy.

- 3.12 The manufacturer presented four scenarios as the base-case analysis based on region 1 data. These were eribulin versus TPC as reported in the EMBRACE trial, and eribulin versus the three individual drugs outlined in the NICE scope: capecitabine, vinorelbine and gemcitabine. The base-case results for each of the comparisons indicated incremental costs for eribulin of £5586, £5177, £4041 and £12,779 compared with TPC, gemcitabine, vinorelbine and capecitabine respectively and incremental QALYs of 0.1213, 0.1904, 0.1136 and 0.2683 respectively. This resulted in incremental cost-effectiveness ratios (ICERs) for eribulin of £46,050 per QALY gained versus TPC, £27,183 versus

gemcitabine, £35,602 versus vinorelbine and £47,631 versus capecitabine.

- 3.13 The manufacturer carried out one-way deterministic sensitivity analysis on all model parameters except overall survival and progression-free survival (for which one-way deterministic sensitivity analysis was not considered appropriate). The results were most sensitive to the cost and dose of eribulin, mean body surface area and utility values for the progressive stable and responsive states. A probabilistic analysis was carried out for each of the four base-case analyses and, with a maximum variation of £141 per QALY gained from the base-case results, it demonstrated a low level of uncertainty around the base-case results.
- 3.14 Several scenario analyses were carried out to demonstrate the cost effectiveness of eribulin in alternative settings. Firstly, sensitivity analysis was carried out to determine the cost effectiveness of eribulin when drug costs were calculated using per-milligram rather than per vial pricing and therefore assuming no wastage. This reduced the ICER to £42,672 per QALY gained for eribulin compared with TPC and to £26,330, £22,473 and £45,085 per QALY gained for eribulin when compared with gemcitabine, vinorelbine and capecitabine respectively.
- 3.15 Secondly, the manufacturer stated that the cost of vinorelbine was uncertain in the model because some centres use the intravenous formulation and others use the oral formulation. These formulations have substantially different prices so an analysis was carried out using the intravenous cost of vinorelbine. Results indicated that this increased the ICER for eribulin to £52,407 per QALY gained compared with TPC and to £54,817 per QALY gained compared with vinorelbine.

- 3.16 Thirdly, a scenario analysis was carried out to examine the cost effectiveness of eribulin versus TPC when using data for all regions in the clinical trial (the overall ITT population). This resulted in ICERs of £50,059, £26,242, £41,276 and £92,084 per QALY gained for eribulin compared with TPC, gemcitabine, vinorelbine and capecitabine respectively.
- 3.17 Lastly, the manufacturer carried out a structural sensitivity analysis by using hazard ratios calculated from the clinical trial to estimate the survival of patients in each of the treatment arms instead of using Kaplan-Meier curves. This resulted in ICERs of £48,110, £37,292, £22,996 and £35,493 per QALY gained for eribulin compared with TPC, gemcitabine, vinorelbine and capecitabine respectively.

ERG comments on the manufacturer's submission

- 3.18 The ERG commented that the manufacturer's search strategy was appropriate and that all relevant studies were presented in the manufacturer's submission. The ERG noted that the EMBRACE trial formed most of the clinical-effectiveness evidence in the manufacturer's submission. The ERG commented that the design of the EMBRACE trial was robust and that the baseline characteristics were well balanced across treatment arms and across regions. In addition, the post-progression treatments appeared to be similar in number and type across both arms of the trial, thereby minimising the likelihood of affecting the overall survival results.
- 3.19 The ERG commented that the findings from the EMBRACE trial were generalisable to UK clinical practice because there were enough patients in the trial from European Union countries with care pathways similar to those in the UK. The ERG noted that the patients in the overall EMBRACE trial and in the region 1 subgroup

were younger (median age of 55 years and 56.5 years respectively) than patients typically seen in UK clinical practice, who are likely to have a median age of between 60 and 65 years. The ERG was satisfied that TPC treatments given in the EMBRACE trial reflected UK clinical practice.

3.20 The ERG commented that the statistical approach used in the EMBRACE trial was generally appropriate, but raised concerns about post-hoc analyses conducted by the manufacturer that split the TPC treatment arm into seven groups (capecitabine, vinorelbine, gemcitabine, taxanes, anthracyclines, hormonal therapy and other drugs) without appropriate adjustment for multiple testing, thus increasing the risk of chance findings. The ERG highlighted that the results from these post-hoc analyses should be interpreted with caution. It also noted that the definition for patient censoring differed between the primary and updated analyses (when 55% and 77% of patients respectively had died). In the updated analysis, those lost to follow-up were censored at the data cut-off date, whereas in the primary analysis they were censored at the last known visit date.

3.21 The ERG noted that the relative improvement in median overall survival for eribulin compared with TPC in the region 1 population was 3.1 months in both the primary and updated analyses, whereas in the overall ITT population the relative improvement was 2.5 months (primary analysis) and 2.7 months (updated analysis). To explore whether or not differences in prognosis existed between patients from region 1 and the remaining trial population (that is, patients from region 2 [Eastern Europe] and region 3 [Latin America/South Africa]), the ERG compared the mean overall survival for region 1 with the mean overall survival for regions 2 and 3 combined. No significant differences were noted, which suggested that patients in region 1 did not differ in terms of

prognosis from the patients in the remainder of the trial population. Therefore, the ERG did not consider the results of the subgroup analyses of patients in region 1 to be more appropriate than those of the overall ITT population. The ERG also highlighted that the European marketing authorisation for eribulin was based on the results of the overall EMBRACE population. It also noted that the evidence on health-related quality of life was weak because it was based on data from a small number of patients and was derived from phase II trials in which there was no comparator arm.

- 3.22 The ERG commented that the manufacturer's economic model was generally well constructed and in line with the scope issued by NICE. The ERG made some minor corrections to the manufacturer's model that reduced the base-case ICER for eribulin compared with TPC for the overall ITT population from £50,059 to £48,536 per QALY gained. The ERG also highlighted several issues around the identification, measurement and valuation of costs and consequences. The ERG noted that all patients in the EMBRACE trial received chemotherapy treatments based on the body surface area of the individual patient. However, the model used a fixed average value for all patients (1.74 m²) sourced from a UK survey of chemotherapy patients, rather than taking account of body surface area differences between patients. The ERG re-estimated the costs of chemotherapy drugs per cycle by using body surface area values from the Sacco et al. (2010) study using the population of breast cancer patients receiving palliative chemotherapy. The ERG's estimated costs, including wastage, were lower by £13.28 for eribulin, £299.22 for gemcitabine, £224.05 for capecitabine, £273.98 for the first cycle and £45.19 for subsequent cycles of oral vinorelbine, than those used in the manufacturer's model.

- 3.23 The ERG also noted that the cost of administration of chemotherapy estimated in the manufacturer's submission may not be accurate for several reasons: unit costs of administration relating to the NHS Reference Cost Schedule 08/09 were used, rather than the most recent figures from the NHS Reference Cost Schedule 09/10; all chemotherapy administration was allocated to an outpatient department, but clinical advice to the ERG indicated that such therapy would normally be administered in a designated chemotherapy day-case unit; the manufacturer had not incorporated the different healthcare resource group costs appropriate to the first administration of a course of therapy (using the 'subsequent cycles' costs instead). Adjusting for these discrepancies resulted in higher costs of administration in nearly all cycles of both arms of the model. Incorporating the ERG's revisions described here and in section 3.22 increased the ICER for eribulin compared with TPC from £48,536 to £85,323 per QALY gained for the overall ITT population.
- 3.24 The ERG also expressed concerns about the cost of supportive care estimated in the manufacturer's submission. The ERG noted that in the progression-free survival health state, costs for a quarterly bone scan, together with a set of pathology tests twice per treatment cycle, were included in the manufacturer's model. However, the ERG noted that regular bone scans for monitoring disease response were specifically not recommended in 'Advanced breast cancer: diagnosis and treatment' (NICE clinical guideline 81), and for costing purposes the ERG commented that routine pre-infusion pathology testing is included in the health resource group costs for chemotherapy delivery. In addition, the ERG highlighted that the manufacturer's model did not provide for the cost of primary and community-based services received before disease progression. The ERG estimated the annual cost per

patient of monitoring and supportive care in the progression-free survival state to be £2915.34 using the NHS Reference Cost Schedule 09/10 and Personal Social Services Research Unit (PSSRU) 'Unit Costs of Health and Social Care 2010', in contrast to £2836.24 in the manufacturer's base case.

- 3.25 In the post-progression survival state, the ERG commented that the most appropriate basis for cost estimation was that used in NICE clinical guideline 81, based on a package of care from community nurses (including specialist nurses), therapists and GP home visits. Using the latest PSSRU unit costs, this package resulted in an annual cost of £5720.79 per patient. By contrast, the manufacturer's model appeared to be based on a more hospital-centred pattern of care with outpatient visits to a specialist oncologist every 3 weeks, and to an oncology nurse every 6 weeks. A set of pathology tests was included every 3 weeks, along with regular bone scans and computed tomography (CT) scans. In addition, approximately 10% of patients received radiotherapy in each 3-week model period. The total estimated annual cost per patient in the manufacturer's base case was £4059.82.
- 3.26 The ERG noted that the cost per patient in the terminal state in the manufacturer's model was large (£19,711.85) and dominated by hospice care. Moreover, in the absence of available cost information for hospice services, hospital critical care daily costs were used instead. The ERG commented that a more appropriate approach to estimating the cost of terminal care in the UK setting would be to use the method described in NICE clinical guideline 81, based on a Marie Curie report (which assumed 40% of patients died in hospital, 10% in a hospice and 50% at home), updating the cost estimates to current prices. This yielded a lower estimate of £4,003.05 per patient. Incorporating these revisions to state-based costs (described here and in sections 3.24 and 3.25) increased the

base-case ICER for eribulin compared with TPC for the overall ITT population from £48,536 to £52,446 per QALY gained.

3.27 The ERG raised several concerns about the manufacturer's approach to utility estimation. The ERG noted that the manufacturer used the Lloyd et al. (2006) mixed model analysis results to generate utility values for the economic model. However, the ERG noted these utility values were based on the age of the participants in the study by Lloyd et al. (2006), taken from a sample of the general UK population, and not on the age of breast cancer patients. The ERG proposed that, to ensure consistency with standard UK EQ-5D tariff scores, the mean age should be set to 47 years (the mean age of the original UK York study sample used) and recalculated the expected utility values for patients in the stable, responder and progression states (without adverse events) on this basis. The revised utility estimates were consistently higher than those in the submitted model (0.756 instead of 0.715 for stable; 0.823 instead of 0.790 for responder; 0.496 instead of 0.443 for progression). Incorporating these revisions to utility values reduced the base-case ICER for eribulin compared with TPC for the overall ITT population from £48,536 to £44,076 per QALY gained.

3.28 The ERG also noted that the utility model by Lloyd et al. (2006) included only six specific adverse events. The manufacturer's model had extended the range of adverse events in the analysis by calculating an average disutility for four of the six adverse events estimated by Lloyd et al. (2006) and then applying this average value to all other adverse events. The ERG highlighted that this method was prone to distortion because some of the adverse events in the EMBRACE trial have been found in other studies to have larger disutility values than the average used in the manufacturer's model (-0.124). In addition, the ERG highlighted

that the manufacturer's base-case model limits consideration only to those grade 3 or 4 adverse events that feature in 10% or more of patients, with an option to use a 5% threshold instead. The ERG commented that these restrictions were arbitrary and risked excluding small events of great importance in terms of disutility and cost because they had too few events recorded, even though the difference between trial arms may be significant. The ERG cited the example of grade 3/4 febrile neutropenia, which occurred in 4.6% of eribulin patients but in only 1.6% of TPC patients and was therefore excluded from the model, despite being one of the most serious and potentially life-threatening consequences of chemotherapy. Incorporating the costs and disutility of febrile neutropenia increased the base-case ICER for eribulin compared with TPC for the overall ITT population from £48,536 to £49,081 per QALY gained.

- 3.29 The ERG noted that in the manufacturer's submission investigators assessed disease progression through scans and patient examinations, whereas the independent reviewers assessed disease progression via imaging data only. The investigator records were complete for all patients, whereas those from the independent assessors were only available when sufficient scan results were available for the patient. The ERG was aware that although the manufacturer had cited several limitations associated with the independent review, the economic model was populated with results from the independent review, supplemented as necessary by investigator data to supply missing values, stating that these should be considered more objective. The ERG commented that, because the independent assessors were only able to verify a reduced number of patient outcomes, the investigator results should have been used in the economic evaluation, noting that this would also have been more reflective of clinical practice.

Incorporating only investigator progression-free survival data increased the base-case ICER for eribulin compared with TPC for the overall ITT population from £48,536 to £50,074 per QALY gained.

3.30 The ERG noted that the manufacturer calculated the Kaplan-Meier product-limit estimates of progression-free survival and overall survival from the patient records for the selected population and comparators up to the time of death or censoring. Instead of projecting expected life-time experience of those patients still alive at the time of data cut-off, it was assumed that all such patients died at the time of censoring. The ERG highlighted that although this method of dealing with censored individual records seems straightforward, there is potential for bias to be introduced, which can have a significant impact on the incremental survival (survival gain). The ERG also commented that the NICE reference case requires decision analysis to take account of costs and outcomes that are likely to be affected by the choice of treatment at any subsequent time, and in the case of advanced or metastatic cancers this is generally interpreted as the whole of the remaining lifetime of patients.

3.31 The ERG highlighted that a Kaplan-Meier plot can become unstable and erratic when only small numbers of cases remain alive and uncensored, because a single event can give rise to very large changes in the survival estimate towards the tail of the distribution. This long tail could contribute disproportionately to the estimated mean survival that is equivalent to the total area under the Kaplan-Meier plotted curve (AUC), and because it may occur in either arm of a trial it could, in some cases, completely reverse a small but consistent treatment benefit seen in most of the trial population. The ERG noted that the manufacturer's model did not make any adjustments to lessen this risk, and therefore it was likely

that in some model scenarios overall survival may be either over- or under-estimated by using the Kaplan-Meier analyses without amendment. The ERG carried out an exploratory survival analysis to compare with unadjusted survival estimates. This involved truncating the accumulation of survival time (AUC) at a common time in both trial arms, to eliminate the effect of residual 'tails' of different sizes and durations. To preserve as much of the original data as possible, this time was set as the time of the last recorded trial event (that is, death in the case of overall survival) in the two trial arms, and truncating the analysis at the earlier of these times. The ERG highlighted that, in both eribulin- and TPC-treated populations, the estimated mean gain in overall survival from use of eribulin was reduced by 10–14 days (14–15%), which alone may increase the size of the estimated ICER by approximately 18–19%.

- 3.32 In addition, the ERG explored the potential impact on the cost-effectiveness results of projecting survival trends to the end of life. The ERG examined the cumulative mortality hazard plots for the EMBRACE trial arms, which revealed consistent long-term linear trends for both eribulin and TPC beyond the first 3–4 months of the trial. This indicated that exponential survival functions would be appropriate for projecting overall survival beyond the available data. Maximum likelihood estimates of the exponential parameter were calculated from the post-100 days' trial evidence. The lifetime estimated overall survival was then obtained as the sum of the observed survival time (AUC) up to 750 days from randomisation, and the exponential projected survival time from 750 days until the death of all patients. The overall survival gain with eribulin compared with TPC was estimated to be 2.69 months for the overall ITT population and 3.25 months for the region 1 population. It was not possible for the ERG to amend the submitted model directly to incorporate the effects of using projected overall survival

estimates. However, an approximation was made by increasing the aggregated post-progression survival, and adjusting post-progression costs and post-progression utility values in parallel.

- 3.33 The ERG's exploratory analyses using the manufacturer's model (including projected overall survival, amended drug and administration costs, amended state-based costs, amended utility values, investigator rather than independent progression-free survival data, including febrile neutropenia as an adverse event, vinorelbine as a intravenous rather than an oral drug and correcting for minor errors found in the manufacturer's model) resulted in an incremental cost of £8269 and an incremental QALY of 0.1229 for eribulin compared with TPC. This resulted in an incremental cost per QALY gained of £68,590 in the overall ITT population. For the region 1 population, these revisions resulted in an incremental cost of £8454, an incremental QALY of 0.1548 and an incremental cost per QALY gained of £55,905 for eribulin compared with TPC.

Manufacturer's additional submission

- 3.34 In response to consultation, the manufacturer presented additional evidence for the use of eribulin in patients who had previously received treatment with capecitabine. The manufacturer presented data on clinical effectiveness for this subgroup from the EMBRACE trial, stating that prior treatment with capecitabine was a pre-planned stratification factor in the trial and 73.4% of patients in the trial had received prior capecitabine. The manufacturer reported that median overall survival for the prior capecitabine-treated subgroup in the overall ITT population was statistically significantly longer with eribulin (13.1 months) versus TPC (10.2 months) with a hazard ratio of 0.787 (95% confidence interval [CI] 0.645 to 0.961, $p = 0.018$), a difference of 2.9 months. These results indicated that

eribulin reduced the hazard or risk of death by 21% compared with TPC.

- 3.35 The manufacturer outlined NICE clinical guideline 81, which recommends sequential systemic chemotherapy after anthracyclines in the following order: docetaxel; vinorelbine or capecitabine; followed by capecitabine or vinorelbine (whichever has not been used previously). The manufacturer proposed that for the prior capecitabine-treated subgroup, the most relevant comparator would be vinorelbine. The manufacturer acknowledged that because no one drug made up the majority of the comparator (TPC) arm the power of the study to detect incremental benefit compared with individual drugs would be reduced. The manufacturer compared the improvement in overall survival of eribulin compared with vinorelbine in the EMBRACE trial (4.2 months) with the results from a meta-analysis (4.33 months) and concluded that these results provided confidence in the estimated mean differences generated from the modelling of the EMBRACE trial for the cost-effectiveness analysis of eribulin versus vinorelbine.
- 3.36 The manufacturer presented 24 different overall survival modelling scenarios based on different populations, comparators and survival projection methods. The manufacturer first presented the survival results using the method adopted by the ERG in their original report, which estimated overall survival beyond the available data using an exponential distribution. These results showed an increase in overall survival of 2.06–3.84 months for eribulin compared with TPC and 3.10–5.21 months for eribulin compared with vinorelbine depending on whether patients from the ITT population, region 1 or the prior capecitabine-treated subgroup were considered and the degree of parameterisation in the modelling. The manufacturer also submitted its preferred analysis

using proportional hazards methods to model survival. These results showed an increase in overall survival of 3.86–5.55 months for eribulin compared with TPC depending on whether patients from the overall ITT population, region 1 or the prior capecitabine-treated subgroup were considered and the form of the comparator survival curve. No overall survival results were presented for the comparison of eribulin with vinorelbine using the proportional hazards method .

- 3.37 The manufacturer presented 21 different cost-effectiveness modelling scenarios stating that the base-case analyses consisted of the comparison of eribulin with vinorelbine in the region 1 population using several proportional hazards methods. The manufacturer stated that the analysis for the prior capecitabine-treated subgroup was not available in time for the submission, but indicated that region 1 represented a good proxy for the prior capecitabine-treated subgroup because 95% of patients in region 1 who were randomised to vinorelbine had received prior capecitabine. The base-case ICERs ranged from £23,790 to £26,475 per QALY gained depending on the form of the survival distribution incorporated (log logistic, exponential or log normal).
- 3.38 In response to consultation, the manufacturer emphasised that eribulin was associated with a predictable and well-characterised safety profile and could offer efficiency savings to the NHS because of its ready-to-use formulation; it requires no routine pre-medication and can be given as a quick 2–5 minute infusion. The manufacturer also submitted evidence to indicate that patients rated longer survival as the most important attribute of a treatment for advanced breast cancer and that approximately 40% of patients with advanced breast cancer found hair loss distressing.

ERG comments on the manufacturer's additional submission

- 3.39 The ERG stated that altering the population under consideration for treatment with eribulin to patients who had relapsed after prior treatment with capecitabine and consequently modifying the comparator to vinorelbine was reasonable and realistic in the UK context. However, the ERG noted that this would result in a large reduction of the overall admissible trial data by firstly excluding approximately 25% of patients (by including the prior capecitabine-treated subgroup only) and secondly by restricting the comparator (vinorelbine) to less than 25% of the overall trial population. Both of these limitations would increase uncertainty.
- 3.40 The ERG noted the manufacturer's argument that region 1 data were preferred because regions 2 and 3 began recruiting at a later date and the greater degree of censoring would bias survival estimates and hazard ratios. However, the ERG was of the opinion that techniques such as Kaplan-Meier and Cox regression analysis were specifically designed to take account of differing proportions of censoring within data sets. The ERG applied Cox regression analysis to the overall survival data for the prior capecitabine-treated patients and thereafter concluded that there were no grounds for distinguishing between subgroups on the basis of HER2 status or geographical region. The ERG therefore noted that, if eribulin was to be compared with vinorelbine, the most appropriate base-case analysis would compare eribulin with vinorelbine in prior capecitabine-treated patients from the ITT population of the EMBRACE trial. The ERG identified that the ICER presented in the manufacturer's submission for the comparison of eribulin with vinorelbine in prior capecitabine-treated patients from the overall ITT population was £38,005 per QALY gained and noted this was based on using Kaplan-Meier values combined with long-term projected modelling. No equivalent scenarios based on

proportional hazards modelling were presented for this comparison of eribulin versus vinorelbine in the prior capecitabine-treated subgroup. The ERG also examined the updated economic model to check whether logic errors had been corrected and amendments recommended in the original report made. If the changes had not been incorporated, the necessary modifications were made by the ERG, which resulted in an increase in the ICER to £38,737 per QALY gained.

- 3.41 The ERG noted that although the exclusion of patients not previously treated with capecitabine and the restriction of patients to those initially identified for treatment with vinorelbine would result in reduced patient numbers, it would also reduce heterogeneity. Therefore different methods to estimate patient outcomes might be necessary. The ERG examined the overall survival Kaplan-Meier plot comparing eribulin with vinorelbine for the prior capecitabine-treated subgroup and noted that the survival of patients receiving vinorelbine and eribulin may converge after approximately 2 years. Given the small numbers involved in this comparison, the ERG acknowledged that this effect could be caused by chance and explored the possibility of supplementing the vinorelbine data with additional gemcitabine data to test for convergence using increased numbers of patients. The ERG noted that the vinorelbine and gemcitabine subgroups showed a similar mean overall survival and statistically significant survival gain. A log rank test and examination of Kaplan-Meier plots indicated close correspondence between the vinorelbine and gemcitabine planned treatment cohorts for both arms of the trial for overall survival and progression-free survival. The ERG therefore concluded that it was appropriate to supplement the vinorelbine data with additional gemcitabine data and that this would increase the numbers available for analysis by 80%. The ERG then examined the overall

survival Kaplan-Meier plots for this pooled group and confirmed that the survival of patients receiving vinorelbine and eribulin converged after approximately 2 years. The ERG highlighted that, as a result, survival gain could be estimated directly from the Kaplan-Meier analysis without the need for parametric modelling. The ERG estimated Kaplan-Meier survival estimates using the area under the curve (AUC) difference until the survival curves converged. This resulted in a non-statistically significant mean overall survival gain of 2.79 months (95% CI 0.99 to 4.59) for eribulin compared with vinorelbine.

3.42 The ERG also explored the impact of incorporating the utility value of 0.69 for pre-progression survival obtained from EQ-5D data collected in the EFG100151 clinical trial because this came from a similar population of patients with heavily pre-treated advanced breast cancer. This resulted in a small increase in the ICER from £38,737 to £39,137 per QALY gained. The effect of including the ERG's new survival analysis estimates on the ICER per QALY gained was explored by incorporating survival estimates from the vinorelbine subgroup as an alternative to the manufacturer's overall survival and progression-free survival data. This resulted in an increase in the ICER from £39,137 per QALY gained to £53,538 per QALY gained for eribulin compared with vinorelbine in the prior capecitabine-treated subgroup.

3.43 Full details of all the evidence are in the manufacturer's submission and the ERG report, which are available from www.nice.org.uk/guidance/TAXXX

4 Consideration of the evidence

4.1 The Appraisal Committee reviewed the data available on the clinical and cost effectiveness of eribulin, having considered evidence on the nature of locally advanced or metastatic breast

cancer and the value placed on the benefits of eribulin 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 considered the clinical-effectiveness data from the EMBRACE trial for the comparison of eribulin with TPC. It noted that this formed most of the clinical-effectiveness evidence in the manufacturer's submission. The Committee was aware that patients in the trial had previously been treated with anthracyclines, taxanes and at least two chemotherapy regimens for locally advanced or metastatic breast cancer. The clinical specialist confirmed that this reflected clinical practice in the UK and that palliative chemotherapy after anthracyclines and taxanes was usually sequential monotherapy (vinorelbine, capecitabine and, more rarely, gemcitabine). The clinical specialist also highlighted that because of its toxicity profile, eribulin was unlikely to displace capecitabine or vinorelbine in the established sequential pathway and would be likely to be given as a third- or fourth-line treatment for advanced or metastatic breast cancer after treatment with capecitabine and vinorelbine. The Committee also heard from the clinical specialist that the treatments included in the TPC arm of the trial were a reasonable reflection of clinical practice in the UK, although the use of gemcitabine monotherapy was less common than in the EMBRACE trial. The Committee noted that submissions from professional groups in the UK reinforced this view. The Committee was aware that the dose of eribulin had been pre-specified in the EMBRACE trial, whereas the doses of the TPCs had not. However, the clinical specialist stated that it was unlikely that the uncontrolled dose of the treatments in the TPC arm would skew the results because it was common for patients in clinical practice to receive different starting doses and subsequent dose

reductions during the course of their treatment. The Committee concluded that the trial broadly reflected clinical practice in the UK.

- 4.3 The Committee noted that the results from the primary and updated analyses in the overall ITT population demonstrated a statistically significant median overall survival benefit of 2.5 and 2.7 months respectively for eribulin compared with TPC. The Committee heard from the clinical specialist and patient expert that it is unusual for a technology to show an overall survival benefit in advanced breast cancer at this stage of the clinical pathway, and also of the importance of having a further treatment option for patients whose previous chemotherapy has failed. In addition, it heard from the clinical specialist that the trial data indicated that eribulin is less well tolerated than capecitabine and vinorelbine, and in particular is associated with peripheral neuropathy and alopecia (hair loss). It heard that alopecia is a very important consideration for patients at this stage of treatment for their advanced breast cancer, because they may already have experienced hair loss earlier in the treatment pathway. The Committee noted that no health-related quality of life data were collected during the EMBRACE trial and that data were presented from two phase II trials in which there was no comparator arm. The Committee considered quality of life to be an important outcome measure in advanced cancer and that this was an important omission from the phase III trial. It also noted that the use of bone marrow colony stimulating factors to reduce the risk of febrile neutropenia was much higher in those treated with eribulin (18%) than those in the TPC arm (8%). The Committee concluded that eribulin was associated with a greater overall survival benefit compared with TPC but with a less favourable toxicity profile, and that its effects on health-related quality of life had not been adequately captured.

4.4 The Committee was aware that the manufacturer had presented results for the region 1 population (North America, Western Europe and Australia) separately, stating that this group would be most generalisable to clinical practice in the UK. The Committee noted that the median overall survival gain for eribulin compared with TPC was higher in patients from region 1 than in the overall ITT population (3.1 months compared with 2.7 months). However, the Committee questioned how relevant the region 1 group was to clinical practice in the UK. Firstly, the Committee noted that differences in survival between the region 1 and overall ITT populations were only evident for the comparator arm and not for the eribulin arm and that this may be attributable to the small numbers in the region 1 group (because of the 2:1 randomisation ratio of eribulin to TPC). Second, the Committee was aware that the results of the ERG's analysis, which compared the mean overall survival for region 1 with the mean overall survival for regions 2 and 3 combined (see section 3.24), suggested that patients in region 1 did not differ in terms of prognosis from the patients in the remainder of the trial population. Third, the Committee heard from the clinical specialist that UK practice in the management of advanced breast cancer differs considerably from some areas of region 1 and that the results from the overall ITT population were therefore the most appropriate. The Committee noted that the trial should be evaluated as a whole as this was how the study had been designed and powered. The Committee was therefore not persuaded that the region 1 population was more applicable to the UK and concluded that it would be most appropriate to base its recommendations on the results from the overall ITT population which indicated a median overall survival gain of 2.7 months for eribulin compared with TPC.

- 4.5 The Committee examined the subgroup analyses conducted by the manufacturer comparing eribulin with the individual drugs that comprised the TPC arm of the trial. The Committee agreed with the ERG's critique that the results should be treated with caution because the analyses were defined post hoc, and the results were based on small numbers, had wide confidence intervals and did not include appropriate adjustment for multiple testing, therefore increasing the risk of chance findings. In addition, the Committee was aware that the trial was not powered to detect differences between individual treatment groups. The Committee concluded that it was not appropriate to consider the results from these individual TPC comparisons.
- 4.6 The Committee considered the manufacturer's economic model and the ERG's critique of this model. The Committee agreed with the ERG that the manufacturer's model was generally well constructed and in line with the scope issued by NICE. The Committee was aware that the Department of Health had approved a patient access scheme for eribulin and that these discounted costs were incorporated into the manufacturer's analysis. The Committee noted that data from the region 1 population was used in the manufacturer's base-case economic evaluation but that data from the overall ITT population (judged by the Committee to be more appropriate than region 1 data, see section 4.4), was used in a sensitivity analysis. The Committee noted that the manufacturer's estimate of the incremental cost per QALY gained of eribulin compared with TPC in the overall ITT population was £50,100 and that the ERG's minor corrections to the manufacturer's estimate reduced this to £48,500 per QALY gained.
- 4.7 The Committee discussed the ERG's concerns about the methods of costing adopted in the manufacturer's model and understood that these were key drivers of cost effectiveness. Firstly, the

Committee agreed that the ERG's approach to estimating the costs of chemotherapy drugs per cycle by using body surface area values from the Sacco et al. (2010) study was more sophisticated and relevant than the manufacturer's method of assuming a fixed average value for all patients, because it allowed for appropriate vial size selection and reduced drug wastage. Secondly, the Committee accepted that the ERG's approach to estimating supportive care and state-based costs was more realistic and in line with the recommendations in NICE clinical guideline 81. Third, the Committee agreed that costs of administration should take into account chemotherapy day-case unit costs rather than outpatient department costs and that healthcare resource group costs appropriate to the first administration of a course of therapy should be included alongside costs for subsequent cycles. The Committee also supported the ERG's use of the most recent NHS Reference Costs. In addition, the Committee noted that the manufacturer's model incorporated the median of the listed drug prices (if branded and generic formulations were available) as an estimate of the price of the comparators. The Committee considered it unlikely that the NHS would pay the full list price for branded products if generic options were available. Moreover, the Committee heard from the clinical specialist that intravenous vinorelbine, which is available generically, is more frequently used in UK clinical practice than the more expensive, branded, oral vinorelbine assumed in the manufacturer's base-case model. The Committee also heard that vinorelbine administered weekly, as assumed in the manufacturer's model in line with the product's summary of product characteristics, is rarely tolerated in practice and tends to be given on day 1 and day 8 of a 21-day cycle. The Committee considered that this was an important issue as vinorelbine is the most commonly used comparator and accounted for 24% of the comparators used in the TPC analysis. The Committee concluded that the effect of these

factors in the manufacturer's model was to overestimate the costs of the comparators and to underestimate administration, supportive care and state-based costs.

4.8 The Committee noted that, because there were no data on health-related quality of life collected in the EMBRACE trial, the manufacturer's model incorporated utility values from previously published studies. The Committee was disappointed that quality of life data from the trial had not been recorded to inform the modelling. In addition, the Committee was concerned that the manufacturer's base-case model included only grade 3 and 4 adverse events that occurred in at least 10% of patients. The Committee considered that this potentially excluded some important adverse events such as febrile neutropenia and peripheral neuropathy. The Committee was further concerned that the disutility associated with alopecia had been omitted from the manufacturer's model. The Committee concluded that the manufacturer's model underestimated the costs and disutilities of adverse events associated with eribulin.

4.9 The Committee noted that, in the analysis of eribulin compared with TPC, rather than projecting trial outcomes when the trial ended, the manufacturer's original model assumed that all patients who were alive transitioned into a 'terminal' state. The Committee agreed that, for this population of patients, it was more appropriate to use the ERG's exploratory analysis that projected survival trends to the end of life in line with the lifetime time horizon recommended in the NICE 'Guide to the methods of technology appraisal'.

4.10 The Committee agreed that the ERG's exploratory analyses of the manufacturer's model for the overall ITT population in the comparison of eribulin versus TPC, which included the ERG's projection of overall survival and re-estimation of costs (see section

3.35), resulted in a more plausible estimate for the cost effectiveness of eribulin compared with TPC (that is, £68,600 per QALY gained) than the manufacturer's estimate. However, the Committee considered that this figure was likely to underestimate the true cost per QALY gained of eribulin relative to TPC because it did not incorporate the full toxicity profile of eribulin, including the disutility associated with alopecia. In addition, significant uncertainties remained about health-related quality of life associated with eribulin. Furthermore, the Committee was aware that some of its concerns about costs (see section 4.7) were not accounted for in the ERG's exploratory analyses, including less frequent administration of vinorelbine and the use of generic prices to estimate the price of the comparators. The Committee also noted that vinorelbine was available to the NHS with discounts in the region of 80–90% from the list prices (as issued by the NHS Commercial Medicines Unit), which would result in a further increase in the ICERs per QALY gained. Therefore, the Committee concluded that the ICER of £68,000 per QALY gained for eribulin compared with TPC from the ERG's analysis was the most optimistic estimate.

- 4.11 The Committee discussed the additional evidence presented by the manufacturer in response to consultation. The Committee noted that the population had firstly been changed by the manufacturer to the subgroup of patients who had previously been treated with capecitabine. The Committee was aware that a major stratification factor in the EMBRACE trial was pre-treatment with capecitabine (73.4% of patients) and agreed that this was potentially relevant to clinical practice. Secondly the Committee noted the manufacturer's statement that vinorelbine would be the most appropriate comparator for this subgroup in line with the sequential treatment recommended in NICE clinical guideline 81. The Committee agreed

that this would reflect UK clinical practice and concluded that consideration of this new decision problem was reasonable.

4.12 The Committee noted that the manufacturer presented overall survival estimates using survival projection methods adopted in the original ERG report as well as using several proportional hazards methods. However, the Committee expected the manufacturer to have investigated which method of extrapolation was most appropriate for the data before carrying out the analysis. The Committee was aware that the manufacturer had stated their preference for using proportional hazards methods to estimate overall survival and their reasoning was that these placed equal weight on all data points, while a Kaplan-Meier approach placed greater weight on data points at the end of the survival curves, resulting in a bias caused by truncation of the data. The Committee observed that the manufacturer had estimated progression-free survival using the Kaplan-Meier method despite 15% censoring, although it did not consider this appropriate for the estimation of overall survival, which was associated with 20% censoring. The Committee noted that no results had been presented for the comparison of eribulin with vinorelbine in the prior capecitabine-treated subgroup using proportional hazards of estimating survival. The Committee noted that, as discussed in section 4.5, it was not appropriate to consider the results from the individual TPC comparisons presented in the original submission. The Committee was not convinced that the proportional hazards assumption of a constant difference in survival for the extrapolated data was valid, given the survival curves from the primary analysis of the EMBRACE trial ITT population and the ERG's additional analysis showing convergence of the survival curves for eribulin versus vinorelbine in the prior capecitabine-treated subgroup. The Committee noted that the manufacturer also clarified that the

proportional hazards assumption had not been tested. In addition, the Committee noted that the manufacturer had only provided point estimates for the survival estimates and had not provided any confidence intervals. This was particularly important given the small number of patients considered in the analysis, and therefore added further uncertainty around the robustness of these estimates. The Committee agreed that there is often a need to extrapolate and there is no 'correct' model, but there is an expectation of a systematic, scientific approach that can be applied to selecting an appropriate model. The Committee expressed concern about the manufacturer's method, noting that it was unclear which patients were included in any of the analyses, there was a lack of justification for the assumptions and an incomplete analysis was presented, which all contributed to a lack of transparency. The Committee also considered that the discrepancies between the different methods of handling the data were evidence of the lack of robust long-term data to inform estimates of overall survival. Consequently the Committee was not convinced that the manufacturer's approach to modelling projected survival for the prior capecitabine-treated subgroup was appropriate, or that the results were robust.

- 4.13 The Committee then discussed the alternative survival estimation presented in the ERG critique of the additional analysis. The Committee heard that because of the change to the decision problem by the manufacturer to the comparison of eribulin versus vinorelbine in the prior capecitabine-treated subgroup and the resulting reduction in patient numbers in this analysis (albeit with potentially less heterogeneity), the ERG had examined the data to see whether the patterns of survival had changed. The Committee noted the overall survival Kaplan-Meier plot comparing eribulin with vinorelbine for the subgroup previously treated with capecitabine

and observed that the survival of patients receiving vinorelbine and eribulin appeared to converge after approximately 2 years. The Committee was aware that this convergence had been confirmed by the ERG by pooling the vinorelbine and gemcitabine data thereby increasing patient numbers. The Committee was aware that this convergence eliminated the need for parametric modelling, and it concluded that the survival gain could be estimated directly from the Kaplan-Meier analysis.

- 4.14 The Committee noted the manufacturer's comment that convergence would imply that longer term survivors would benefit less from treatment and that this lacked face validity. However, the Committee agreed that convergence was scientifically plausible and consistent with both the overall survival and the progression-free survival data. The Committee also heard from the manufacturer that Kaplan-Meier estimates based on censored data systematically underestimated the benefit. The Committee heard that if the area under a Kaplan-Meier curve is used to estimate mean survival, it will underestimate mean survival if patients remain alive at the end of the study. However, given that in this instance only the difference between the areas under the Kaplan-Meier curves for eribulin and TPC are relevant, by using the area under the curve approach this difference could be overestimated or underestimated. The Committee concluded that in this instance the ERG method was preferable to assuming proportional hazards for survival estimation for this comparison of eribulin versus vinorelbine in the prior capecitabine-treated subgroup. The Committee noted that the ERG's method resulted in a non-statistically significant mean survival gain of 2.79 months (95% CI 0.99 to 4.59) for eribulin compared with vinorelbine. The Committee, however, was aware that this estimation was post hoc, and based on very small numbers. The Committee also noted the wide confidence intervals

of these estimates. Therefore it was not persuaded that the estimates of the extension to life were robust.

4.15 The Committee then discussed the base-case cost-effectiveness analysis put forward by the manufacturer for eribulin versus vinorelbine and noted that results for the region 1 population were presented as a proxy for patients who had received prior treatment with capecitabine, because 95% of those randomised to vinorelbine in region 1 had received prior capecitabine. The Committee noted that the manufacturer's preference for region 1 was based on the fact that regions 2 and 3 began recruiting at a later date and the greater degree of censoring would bias survival estimates and hazard ratios. However, the Committee noted the ERG's application of the Cox regression analysis to the overall survival data, which showed that there were no grounds for distinguishing between treatment regions and it concluded that there was no evidence to indicate that limiting the data to region 1 was appropriate. The Committee therefore agreed that it was appropriate for the ERG to use the ICER of £38,000 per QALY gained for eribulin compared with vinorelbine, based on prior capecitabine-treated patients from the overall ITT population from the manufacturer's submission as a starting point for further exploration.

4.16 The Committee agreed with the ERG logic error amendments and the revision of the utility value to that obtained from EQ-5D data collected in the EFG100151 clinical trial for pre-progression survival. The Committee noted that incorporating ERG survival estimates from the vinorelbine subgroup as alternatives to the manufacturer's overall survival and progression-free survival data resulted in an ICER of £53,500 per QALY gained for eribulin versus vinorelbine in the prior capecitabine-treated subgroup. The Committee considered that this ICER was the best estimate

presented for the prior capecitabine-treated subgroup. However, the Committee noted that the concerns discussed in section 4.10 about the toxicity profile of eribulin, the uncertainties about health-related quality of life, the less frequent administration of vinorelbine, the use of generic prices to estimate the price of the comparators and the national discounts available to the NHS for vinorelbine would also apply to this analysis and would result in a further increase in the ICER per QALY gained. The Committee noted that the efficiency savings to the NHS suggested by the manufacturer for eribulin because of it being a ready-to-use formulation, because it does not require routine pre-medication for hypersensitivity and because it has a quick 2–5 minute infusion period also largely applied to vinorelbine. In addition, given the uncertainty around the survival estimates (see section 4.14), the Committee concluded that no robust ICER had been presented for the prior capecitabine-treated subgroup.

4.17 In summary, the Committee considered that the most plausible estimate of the ICER for eribulin versus TPC in the whole EMBRACE population was above £68,600 per QALY gained; this ICER was regarded as a significant underestimate. The Committee considered that it had not been presented with a most plausible estimate of the ICER for eribulin versus vinorelbine in the prior capecitabine-treated subgroup because of the lack of a robust survival advantage in this setting. The Committee concluded that eribulin could not be recommended as a cost-effective use of NHS resources for the treatment of locally advanced or metastatic breast cancer that has progressed after at least two chemotherapy regimens for advanced disease, for the whole population as well as for people previously treated with capecitabine.

4.18 The Committee considered supplementary advice from NICE that should be taken into account when appraising treatments that may

extend the life of patients with a short life expectancy and that are licensed for indications that affect small numbers of people with incurable illnesses. For this advice to be applied, all the following criteria must be met:

- The treatment is indicated for patients with a short life expectancy, normally less than 24 months.
- There is sufficient evidence to indicate that the treatment offers an extension to life, normally of at least an additional 3 months, compared with current NHS treatment.
- The treatment is licensed or otherwise indicated for small patient populations.

In addition, when taking these criteria into account, the Committee must be persuaded that the estimates of the extension to life are robust and that the assumptions used in the reference case of the economic modelling are plausible, objective and robust.

- 4.19 The Committee discussed whether eribulin fulfilled the criteria for a life-extending, end-of-life treatment. The Committee agreed that eribulin is indicated for patients with a short life expectancy, of less than 24 months. The Committee also considered that it was likely that eribulin is licensed for a small patient population, because it is intended as a third- or fourth-line treatment option for advanced disease, but that the precise numbers of patients eligible for treatment were uncertain. However, the Committee considered that it had not seen sufficient evidence to indicate that eribulin offers an extension to life of at least 3 months; the only plausible estimate presented for the mean overall survival gain was 2.7 months from the overall ITT population. The Committee therefore concluded that eribulin did not fulfil all of the end-of-life criteria for the overall ITT population, or for the prior capecitabine-treated subgroup.
- Furthermore, given that the most optimistic ICER for the overall ITT

group was £68,600 per QALY gained, the Committee concluded that eribulin could not be considered a cost-effective use of resources for NHS use even if all of the criteria for being a life-extending, end-of-life treatment were met.

Summary of Appraisal Committee's key conclusions

TAXXX (STA)	Appraisal title: Eribulin for the treatment of locally advanced or metastatic breast cancer	FAD section
Key conclusion		
<p>Eribulin is not recommended, within its licensed indication, for the treatment of locally advanced or metastatic breast cancer that has progressed after at least two chemotherapy regimens for advanced disease.</p> <p>The Committee considered that the most plausible estimate of the ICER for eribulin versus TPC in the whole EMBRACE population was at least £68,600 per QALY gained.</p> <p>The most plausible estimate of the ICER for eribulin versus vinorelbine in the prior capecitabine-treated subgroup was at least £53,500 per QALY gained, but the Committee did not regard the assessment of survival advantage in this setting as being robust.</p> <p>Both these ICERS were regarded as significant underestimates because the concerns about the toxicity profile of eribulin, the uncertainties about health-related quality of life, the less frequent administration of vinorelbine, the use of generic prices to estimate the price of the comparators and the national discounts available to the NHS for vinorelbine would result in a further increase in the ICER per QALY gained for both the comparisons.</p>		1.1, 4.10, 4.17
Current practice		
Clinical need of patients, including the availability of alternative treatments	The Committee heard from the clinical specialist and patient expert of the importance of having a further treatment option for patients whose previous chemotherapy has failed.	4.3
The technology		
Proposed benefits of the technology	The Committee concluded that eribulin was associated with a greater overall survival benefit compared with treatment of physician's choice (TPC).	4.3
How innovative is the technology in its potential to make a significant and substantial impact on health-related benefits?	No specific claim for innovation was made.	
What is the position of the treatment in the pathway of care for	The Committee was aware that patients in the trial had previously been treated with anthracyclines, taxanes and at least two	4.2, 4.11

TAXXX (STA)	Appraisal title: Eribulin for the treatment of locally advanced or metastatic breast cancer	FAD section
the condition?	<p>chemotherapy regimens for locally advanced or metastatic breast cancer. The clinical specialist confirmed that this reflected clinical practice in the UK and that palliative chemotherapy after anthracyclines and taxanes was usually sequential monotherapy (vinorelbine, capecitabine and, more rarely, gemcitabine). The clinical specialist also highlighted that because of its toxicity profile, eribulin was unlikely to displace capecitabine or vinorelbine in the established sequential pathway and would be given as a third- or fourth-line treatment for advanced or metastatic breast cancer after treatment with capecitabine and vinorelbine.</p> <p>In the manufacturer’s additional evidence submission, the population had been changed to the subgroup of patients who had previously been treated with capecitabine. The Committee was aware that that a major stratification factor in the EMBRACE trial was pre-treatment with capecitabine (73.4% of patients) and agreed that this was potentially relevant to clinical practice. The Committee noted the manufacturer’s statement that vinorelbine would be the most appropriate comparator for this subgroup in line with the sequential treatment recommended in NICE clinical guideline 81. The Committee agreed that this would be reflect UK clinical practice.</p>	
Adverse effects	<p>The Committee heard from the clinical specialist that the trial data indicated that eribulin is less well tolerated than capecitabine and vinorelbine, and in particular is associated with peripheral neuropathy and alopecia (hair loss). It heard that alopecia is a very important consideration for patients at this stage of treatment for their advanced breast cancer as they may already have experienced hair loss earlier in the treatment pathway. The Committee concluded that eribulin was associated with a less favourable toxicity profile compared with TPC.</p>	4.3

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Evidence for clinical effectiveness		
Availability, nature and quality of evidence	<p>The EMBRACE trial formed most of the clinical-effectiveness evidence in the manufacturer's submission.</p> <p>The Committee noted that no health-related quality of life data were collected during the EMBRACE trial and that data were presented from two phase II trials in which there was no comparator arm. The Committee considered quality of life to be an important outcome measure in advanced cancer and that this was an important omission from the phase III trial. The Committee concluded that the effects of eribulin on health-related quality of life had not been adequately captured.</p>	4.2, 4.3
Relevance to general clinical practice in the NHS	<p>The Committee heard from the clinical specialist that the treatments included in the TPC arm of the trial were a reasonable reflection of clinical practice in the UK, although the use of gemcitabine monotherapy was less common than in the EMBRACE trial. The Committee noted that submissions from professional groups in the UK reinforced this view. The Committee was aware that the dose of eribulin had been pre-specified in the EMBRACE trial, whereas the doses of the TPCs had not. However, the clinical specialist stated that it was unlikely that the uncontrolled dose of the treatments in the TPC arm would skew the results because it was common for patients in clinical practice to receive different starting doses and subsequent dose reductions during the course of their treatment. The Committee concluded that the trial broadly reflected clinical practice in the UK.</p>	4.2
Uncertainties generated by the evidence	Significant uncertainties remained about health-related quality of life associated with eribulin.	4.10
Are there any clinically relevant subgroups for which there is evidence of differential effectiveness?	The Committee was aware that the manufacturer had presented results for the region 1 population separately, stating that this group would be most generalisable to clinical practice in the UK. The Committee was not persuaded that the region 1	4.4, 4.5, 4.11,

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	<p>population was more applicable to the UK and concluded that it would be most appropriate to base its recommendations on the results from the overall ITT population.</p> <p>The Committee examined the subgroup analyses conducted by the manufacturer comparing eribulin with the individual drugs that comprised the TPC arm of the trial. The Committee agreed with the ERG's critique that the results should be treated with caution because the analyses were defined post hoc, and the results were based on small numbers, had wide confidence intervals and did not include appropriate adjustment for multiple testing, therefore increasing the risk of chance findings. In addition, the Committee was aware that the trial was not powered to detect differences between individual treatment groups. The Committee concluded that it was not appropriate to consider the results from these individual TPC comparisons.</p> <p>The Committee was aware that that a major stratification factor in the EMBRACE trial was pre-treatment with capecitabine (73.4% of patients) and agreed that this was potentially relevant to clinical practice.</p>	
<p>Estimate of the size of the clinical effectiveness including strength of supporting evidence</p>	<p>The Committee noted that the results from the primary and updated analyses in the overall ITT population demonstrated a statistically significant median overall survival benefit of 2.5 and 2.7 months respectively for eribulin compared with TPC.</p> <p>The Committee was not convinced that the manufacturer's approach to modelling projected survival for the prior capecitabine-treated subgroup was appropriate, or that the results were robust. The Committee concluded that in this instance the ERG method was preferable to assuming proportional hazards for survival estimation for this comparison of eribulin versus vinorelbine in the prior capecitabine-treated subgroup. The Committee noted that this method resulted in a non-statistically significant mean survival gain of 2.79 months (95% CI 0.99 to 4.59) for</p>	<p>4.3, 4.12, 4.14</p>

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	eribulin compared with vinorelbine. The Committee, however, was aware that this estimation was post-hoc, and based on very small numbers. The Committee also noted the wide confidence intervals of these estimates. It was not persuaded that the estimates of the extension to life were robust.	
Evidence for cost effectiveness		
Availability and nature of evidence	The Committee agreed with the ERG that the manufacturer's model was generally well constructed and in line with the scope issued by NICE.	4.6
Uncertainties around and plausibility of assumptions and inputs in the economic model	<p>The Committee agreed that it was more appropriate to use the ERG's exploratory analysis that projected survival trends to the end of life in line with the lifetime time horizon recommended in the NICE methods guide.</p> <p>The Committee agreed that the ERG's approach to estimating the costs of chemotherapy drugs per cycle by using body surface area values from the Sacco et al. (2010) study was more sophisticated and relevant than the manufacturer's method and that the ERG's approach to estimating supportive care and state-based costs was more realistic and in line with the recommendations in NICE clinical guideline 81.</p> <p>The Committee agreed that costs of administration should take into account chemotherapy day-case unit costs rather than outpatient department costs and that healthcare resource group costs appropriate to the first administration of a course of therapy should be included alongside costs for subsequent cycles. The Committee also supported the ERG's use of the most recent NHS Reference Costs.</p> <p>The Committee considered it unlikely that the NHS would pay the full list price for branded products if generic options were available. The Committee heard that intravenous vinorelbine, which is available generically, is more frequently used in UK</p>	4.7, 4.9, 4.10, 4.11, 4.16

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	<p>clinical practice rather than the more expensive, branded, oral vinorelbine assumed in the manufacturer's base-case model. The Committee also heard that vinorelbine administered weekly, as assumed in the manufacturer's model in line with the product's summary of product characteristics, is rarely tolerated in practice and tends to be given on day 1 and day 8 of a 21-day cycle. The Committee also noted that vinorelbine was available to the NHS with discounts in the region of 80–90% from the list prices (as issued by the NHS Commercial Medicines Unit), which would result in a further increase in the ICERs per QALY gained. The Committee concluded that the effect of these factors in the manufacturer's model was to overestimate the costs of the comparators and to underestimate administration, supportive care and state-based costs.</p> <p>The Committee discussed the base-case cost-effectiveness analysis put forward by the manufacturer for eribulin versus vinorelbine and noted that results for the region 1 population were presented as a proxy for patients who had received prior treatment with capecitabine, because 95% of those randomised to vinorelbine in region 1 had received prior capecitabine. However, the Committee noted the ERG's application of the Cox regression analysis to the overall survival data, which showed that there were no grounds for distinguishing between treatment regions and it concluded that there was no evidence to indicate that limiting the data to region 1 was appropriate. The Committee agreed with the ERG logic error amendments and the revision of the utility value to that obtained from EQ-5D data collected in the EFG100151 clinical trial for pre-progression survival.</p>	
<p>Incorporation of health-related quality of life benefits and utility values</p> <p>Have any potential significant and</p>	<p>The Committee noted that, because there were no data on health-related quality of life collected in the EMBRACE trial, the manufacturer's model incorporated utility values from previously published studies. The Committee was disappointed that quality of life data from the trial had not been</p>	<p>3.42, 4.8, 4.16</p>

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<p>substantial health-related benefits been identified that were not included in the economic model, and how have they been considered?</p>	<p>recorded to inform the modelling. In addition, the Committee was concerned that the manufacturer's base-case model included only grade 3 and 4 adverse events that occurred in at least 10% of patients. The Committee considered that this potentially excluded some important adverse events such as febrile neutropenia and peripheral neuropathy. The Committee was further concerned that the disutility associated with alopecia had been omitted from the manufacturer's model. The Committee concluded that the manufacturer's model underestimated the costs and disutilities of adverse events associated with eribulin.</p> <p>For the comparison of eribulin versus vinorelbine in the prior capecitabine-treated subgroup of patients, the Committee agreed with the ERG revision of the utility value to that obtained from EQ-5D data collected in the EFG100151 clinical trial for pre-progression survival because this came from a similar population of patients with heavily pre-treated advanced breast cancer.</p>	
<p>Are there specific groups of people for whom the technology is particularly cost effective?</p>	<p>The Committee discussed the cost-effectiveness analysis for eribulin versus vinorelbine in the prior capecitabine-treated subgroup. The Committee did not regard the assessment of survival advantage in this subgroup as being robust. The Committee noted that incorporating ERG survival estimates from the vinorelbine subgroup as alternatives to the manufacturer's overall survival and progression-free survival data resulted in an ICER of £53,500 per QALY gained for eribulin versus vinorelbine in the prior capecitabine-treated subgroup. The Committee concluded that this ICER was the best estimate presented for this subgroup. However, given the uncertainty around the survival estimates, the Committee concluded that no robust ICER had been presented for the prior capecitabine-treated subgroup</p>	<p>4.14, 4.16</p>
<p>What are the key drivers of cost effectiveness?</p>	<p>The methods of costing adopted in the manufacturer's model were key drivers of cost effectiveness.</p>	<p>4.7</p>
<p>Most likely cost-effectiveness</p>	<p>The Committee agreed that the ERG's exploratory analyses of the manufacturer's</p>	<p>4.10, 4.16</p>

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estimate (given as an ICER)	<p>model for the overall ITT population, which included the ERG’s projection of overall survival and re-estimation of costs (see section 3.35), resulted in a more plausible estimate for the cost effectiveness of eribulin compared with TPC (that is £68,600 per QALY gained), than the manufacturer’s estimate.</p> <p>For the comparison of eribulin versus vinorelbine in the subgroup of prior capecitabine-treated patients, the Committee agreed with the ERG logic error amendments and the revision of the utility value to that obtained from EQ-5D data collected in the EFG100151 clinical trial for pre-progression survival. The Committee noted that incorporating ERG survival estimates from the vinorelbine subgroup as alternatives to the manufacturer’s overall survival and progression-free survival data resulted in an ICER of £53,500 per QALY gained for eribulin versus vinorelbine in the prior capecitabine-treated subgroup.</p> <p>However, the Committee considered that both these figures were likely to underestimate the true cost per QALY gained of eribulin relative to TPC and eribulin relative to vinorelbine because they did not incorporate the full toxicity profile of eribulin, including the disutility associated with alopecia. In addition, significant uncertainties remained about health-related quality of life associated with eribulin. Furthermore, the Committee was aware that some of its concerns about costs (see section 4.7) were not accounted for in the ERG’s exploratory analyses, including less frequent administration of vinorelbine, the use of generic prices to estimate the price of the comparators and the national discounts available to the NHS for vinorelbine.</p>	
Additional factors taken into account		
Patient access scheme (PPRS)	The manufacturer has agreed a patient access scheme with the Department of Health, which makes eribulin available at a discounted price. The size of the discount is commercial-in-confidence. These	2.3, 3.8, 4.6

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	discounted costs were incorporated in the manufacturer's analysis.	
End-of-life considerations	The Committee considered that it had not seen sufficient evidence to indicate that eribulin offers an extension to life of at least 3 months; the only plausible estimate presented for the mean overall survival gain was 2.7 months from the overall ITT population. The Committee therefore concluded that eribulin did not fulfil all of the end-of-life criteria for the overall ITT population, or for the prior capecitabine-treated subgroup. Furthermore, given that the most optimistic ICER for the overall ITT group was £68,600 per QALY gained, the Committee concluded that eribulin could not be considered a cost-effective use of resources for NHS use even if all of the criteria for being a life-extending, end-of-life treatment were met.	4.19
Equalities considerations and social value judgements	No equality issues were identified during the scoping process or the appraisal.	-

5 Implementation

5.1 The Secretary of State and the Welsh Assembly Minister for Health and Social Services have issued directions to the NHS in England and Wales on implementing NICE technology appraisal guidance. When a NICE technology appraisal recommends use of a drug or treatment, or other technology, the NHS must usually provide funding and resources for it within 3 months of the guidance being published. If the Department of Health issues a variation to the 3-month funding direction, details will be available on the NICE website. When there is no NICE technology appraisal guidance on a drug, treatment or other technology, decisions on funding should be made locally.

5.2 NICE has developed tools to help organisations put this guidance into practice (listed below). These are available on our website (www.nice.org.uk/guidance/TAXXX). [NICE to amend list as needed at time of publication]

- Slides highlighting key messages for local discussion.
- Costing template and report to estimate the national and local savings and costs associated with implementation.
- Implementation advice on how to put the guidance into practice and national initiatives that support this locally.
- A costing statement explaining the resource impact of this guidance.
- Audit support for monitoring local practice.

6 Recommendations for further research

6.1 Health-related quality of life studies comparing eribulin with vinorelbine and capecitabine should be conducted.

7 Related NICE guidance

Published

- Advanced breast cancer: diagnosis and treatment. NICE clinical guideline 81 (2009). Available from www.nice.org.uk/guidance/CG81
- Early and locally advanced breast cancer: diagnosis and treatment. NICE clinical guideline 80 (2009). Available from www.nice.org.uk/guidance/CG80
- Gemcitabine for the treatment of metastatic breast cancer. NICE technology appraisal guidance 116 (2007). Available from www.nice.org.uk/guidance/TA116

Under development

NICE is developing the following guidance (details available from www.nice.org.uk):

- Fulvestrant for the treatment of locally advanced or metastatic breast cancer. NICE technology appraisal guidance (publication expected December 2011).

8 Review of guidance

8.1 The guidance on this technology will be considered for review in November 2014. The Guidance Executive will decide whether the technology should be reviewed based on information gathered by NICE, and in consultation with consultees and commentators.

Peter Clark

Chair, Appraisal Committee

November 2011

Appendix A: Appraisal Committee members and NICE project team

A *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 four 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 Darren Ashcroft

Professor of Pharmacoepidemiology, School of Pharmacy and Pharmaceutical Sciences, University of Manchester

Dr Matthew Bradley

Value Demonstration Director, AstraZeneca

Professor Usha Chakravarthy

Professor of Ophthalmology and Vision Sciences, The Queen's University of Belfast

Professor Peter Clark (Chair)

Consultant Medical Oncologist, Clatterbridge Centre for Oncology

Dr Ian Davidson

Lecturer in Rehabilitation, University of Manchester

Professor Simon Dixon

Senior Lecturer in Health Economics, University of Sheffield

Dr Martin Duerden

Assistant Medical Director, Betsi Cadwaladr University Health Board

Dr Alexander Dyker

Consultant Physician, Wolfson Unit of Clinical Pharmacology, University of Newcastle

Gillian Ells

Prescribing Advisor, NHS Sussex Downs and Weald

Paula Ghaneh

Senior Lecturer and Honorary Consultant, University of Liverpool

Niru Goenka

Consultant Physician, Countess of Chester NHS Foundation Trust

Dr Susan Griffin

Research Fellow, Centre for Health Economics, University of York

Professor Carol Haigh

Professor in Nursing, Manchester Metropolitan University

Alison Hawdale

Lay member

Professor John Hutton

Professor of Health Economics, University of York

Professor Peter Jones

Emeritus Professor of Statistics, Keele University

Dr Vincent Kirkbride

Consultant Neonatologist, Regional Neonatal Intensive Care Unit, Sheffield

Dr Rachel Lewis

Advanced Nurse Practitioner, Manchester Business School

Dr Anne McCune

Consultant Hepatologist, University Hospitals Bristol NHS Foundation Trust

Professor Jonathan Michaels (Vice Chair)

Professor of Clinical Decision Science, University of Sheffield

Professor Femi Oyebode

Professor of Psychiatry and Consultant Psychiatrist, The National Centre for Mental Health

Dr John Radford

Director of Public Health, Rotherham Primary Care Trust

Dr Phillip Rutledge

GP and Consultant in Medicines Management, NHS Lothian

Dr Brian Shine

Consultant Chemical Pathologist, John Radcliffe Hospital

Dr Murray D Smith

Associate Professor in Social Research in Medicines and Health, University of Nottingham

Paddy Storrie

Lay member

Mike Wallace

Health Economics and Reimbursement Director, Johnson & Johnson Medical Ltd

Dr Lok Yap

Consultant in Acute Medicine and Clinical Pharmacology, Whittington Hospitals NHS Trust

B ***NICE project team***

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

Raisa Sidhu

Technical Lead

Zoe Charles and Bhash Naidoo

Technical Advisers

Kate Moore

Project Manager

Appendix B: Sources of evidence considered by the Committee

A The Evidence Review Group (ERG) report for this appraisal was prepared by Liverpool Reviews and Implementation Group (LRiG):

- Bagust A, Boland A, Davis H et al. Eribulin for the treatment of locally advanced or metastatic breast cancer (May 2011)

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 document (ACD). 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:

- Eisai

II Professional/specialist and patient/carer groups:

- Breakthrough Breast Cancer
- Breast Cancer Campaign
- Breast Cancer Care
- Macmillan Cancer Support
- Cancer Research UK
- Royal College of Nursing
- Royal College of Pathologists
- Royal College of Physicians

III Other consultees:

- Department of Health
- NHS Camden
- Welsh Government

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

- British National Formulary
- Commissioning Support Appraisal Service
- Department of Health, Social Services and Public Safety for Northern Ireland
- Health Improvement Scotland
- Pierre Fabre
- Roche Products
- National Cancer Research Institute
- Liverpool Reviews and Implementation Group
- National Institute for Health Research Health Technology Assessment Programme

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 eribulin by attending the initial Committee discussion and providing written evidence to the Committee. They were also invited to comment on the ACD.

- Dr Mark Beresford, Consultant Medical Oncologist, University Hospital Bristol NHS Trust, nominated by the Royal College of Physicians – clinical specialist
- Tara Beaumont, Clinical Nurse Specialist, nominated by Breast Cancer Care – 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.

- Eisai