

# NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

## Appraisal consultation document

# Eribulin for the treatment of locally advanced or metastatic breast cancer

The Department of Health and the Welsh Government has asked the National Institute for Health and Clinical Excellence (NICE) to produce guidance on using eribulin in the NHS in England and Wales. The Appraisal Committee has considered the evidence submitted by the manufacturer and the views of non-manufacturer consultees and commentators, and clinical specialists and patient experts.

**This document has been prepared for consultation with the consultees.**

It summarises the evidence and views that have been considered, and sets out the draft recommendations made by the Committee. NICE invites comments from the consultees and commentators for this appraisal (see appendix B) and the public. This document should be read along with the evidence base (the evaluation report), which is available from [www.nice.org.uk](http://www.nice.org.uk)

The Appraisal Committee is interested in receiving comments on the following:

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

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

After consultation:

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

For further details, see the 'Guide to the technology appraisal process' (available at [www.nice.org.uk](http://www.nice.org.uk)).

**The key dates for this appraisal are:**

Closing date for comments: 9 August 2011

Second Appraisal Committee meeting: 25 August 2011

Details of membership of the Appraisal Committee are given in appendix A, and a list of the sources of evidence used in the preparation of this document is given in appendix B.

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The recommendations in section 1 may change after consultation.**

## **1 Appraisal Committee's preliminary recommendations**

- 1.1 Eribulin is not recommended for the treatment of locally advanced or metastatic breast cancer in people whose disease has progressed after at least two chemotherapeutic regimens for advanced disease.
- 1.2 People currently receiving eribulin 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/m<sup>2</sup> (equivalent to 1.4 mg/m<sup>2</sup> eribulin mesylate), which is administered intravenously over 2–5 minutes on days 1 and 8 of every 21-day cycle. 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.
- 2.2 The manufacturer's submission stated that the cost of a vial of 1.0 mg of eribulin mesylate (equivalent to 0.88 mg eribulin) is £313.

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 this submission by the Evidence Review Group (ERG; appendix B).

- 3.1 The manufacturer's submission presented clinical-effectiveness data 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 patients (508 randomised to the eribulin arm, 254 randomised to the TPC arm) and was conducted at 135 centres in 19 countries, with 51 patients 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/m<sup>2</sup> 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 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, conducted when 77% of patients had died, the median overall survival remained 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 (when 55% of the patients had died). The analysis of progression-free survival indicated that median

progression-free survival was 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 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 people 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 the primary analysis, a

statistically significant 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/399 days [95% CI 360 to 434] versus 10.6 months/324 days [95% CI 282 to 380];  $p = 0.041$ ). In the updated analysis, the survival gain of 3.1 months for patients treated with eribulin rather than TPC remained statistically significant (13.2 months/403 days [95% CI 367 to 438] versus 10.5 months/321 days [95% CI 281 to 365];  $p = 0.014$ ). 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 utilised 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 people whose disease responded and those whose disease did not respond to eribulin therapy. However, 57% of people whose disease responded to eribulin showed an increased quality of life compared with 45% of those whose disease did not respond. None of the people 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, the majority of 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 development of CTCAE grade 3 or 4 adverse events of neutropenia occurred in 21.1% and 24.1% of patients receiving eribulin, respectively. However, it led to discontinuation in 0.6% of these patients, and 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 chemotherapeutic 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 utilities 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 employed in the model. This meant that no extrapolation of trial outcomes was undertaken 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 composed of the underlying state utility 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 'British national formulary' edition 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 considered its formulation as oral capsules. The intravenous infusion formulation was considered as part of the sensitivity analysis. The costs of the individual TPCs were assumed to be 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 consumed in all three health states included chemotherapy support medication, scans and laboratory tests, hospitalisations 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 m<sup>2</sup> 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 comparisons 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 utilities 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. First, 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 Second, 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 Third, 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 the majority 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 employed in the EMBRACE trial was generally appropriate, but raised concerns about post-hoc analyses conducted by the manufacturer by splitting 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 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 accordance 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 dosed on the basis of the body surface area of the individual patient. However, the model used a fixed average value for all patients (1.74 m<sup>2</sup>) 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 battery 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, the hospital critical care daily costs were used as a proxy. 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 that the age parameter in the published paper refers to the age of 100 participants in the valuation exercise, and not to the age of patients. For consistency with the standard UK EQ-5D tariff scores, the ERG commented that the mean age should be set to 47 – the mean age of the original York study – 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 utilities 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 where 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 individuals 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 the behaviour of 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 the bulk of the trial population. The ERG noted that the manufacturer's model did not make any adjustments to ameliorate 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 undertook 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 by comparing the times at which the last recorded trial event (that is, death in the case of overall survival) occurred in the two trial arms, and truncating the analysis at the earlier of these values. 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 exponential parameter values were estimated 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 achieved 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.

3.34 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](http://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.

### ***Clinical effectiveness***

- 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 the majority 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 composition of treatments included in the TPC arm of the trial was 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 as 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. 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 separately, stating that this group would be most generalisable to clinical practice in the UK. The Committee noted that the 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. First, 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-treated group and that this may be attributable to the small numbers in the region 1 group (as a consequence 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. For example, the Committee heard that in North America there is a greater reimbursement incentive for drugs that are administered intravenously, resulting in greater use of vinorelbine relative to capecitabine than in the UK. The Committee was also aware that the European marketing authorisation for eribulin was based on the results of the overall EMBRACE population. 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.

- 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 they were defined post-hoc, based on small numbers, had

wide confidence intervals and did not include appropriate adjustment for multiple testing thus 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. The Committee also noted from the European Public Assessment Report for eribulin, produced by the European Medicines Agency, that a major stratification factor in the trial was pre-treatment with capecitabine (73.4% of patients). The Committee considered that this was potentially relevant to clinical practice but was aware that the manufacturer had not submitted evidence on clinical or cost effectiveness for this subgroup.

### ***Cost effectiveness***

- 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 accordance 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.

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. First, 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, as it allowed for appropriate vial size selection and reduced drug wastage. Second, 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 for branded products if generic options were available. Moreover, the Committee heard from the clinical specialist that intravenous vinorelbine, which is generically available, is more frequently used in UK 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 on a weekly basis, as was 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, owing to the absence of data on health-related quality of life collected in the EMBRACE trial, the manufacturer's model incorporated utilities from previously published studies. The Committee was disappointed that 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 rather than projecting trial outcomes when the trial ended, the manufacturer's model assumed that all patients who were alive transitioned into a 'terminal' state. 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.
- 4.10 The Committee agreed that the ERG's exploratory analyses of the manufacturer's 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. 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, there remained significant uncertainties 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 as an estimate of the price of the comparators. The Committee concluded on the basis of these factors that treatment with eribulin did not represent a cost-effective use of NHS resources and that it could not be recommended for the treatment of locally advanced or metastatic breast cancer in people whose disease has progressed after at least two chemotherapeutic regimens for advanced disease.

4.11 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.

4.12 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 was aware that eribulin had not demonstrated an extension to life in the overall ITT population of at least an additional 3 months compared with TPC. The Committee therefore concluded that eribulin did not fulfil all of the end-of-life criteria. Furthermore, given that the ICER was likely to exceed £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 had been met.

***Summary of Appraisal Committee’s key conclusions***

<b>TAXXX (STA)</b>	<b>Appraisal title: Eribulin for the treatment of locally advanced or metastatic breast cancer</b>	<b>ACD section</b>
<b>Key conclusion</b>		
Eribulin is not recommended for the treatment of locally advanced or metastatic breast cancer in people whose disease has progressed after at least two chemotherapeutic regimens for advanced disease.		1.1
<b>Current practice</b>		
Clinical need of patients, including the availability of	The Committee heard from the clinical specialist and patient expert of the importance of having a further treatment	4.3

TAXXX (STA)	Appraisal title: Eribulin for the treatment of locally advanced or metastatic breast cancer	ACD section
alternative treatments	option for patients whose previous chemotherapy has failed.	
<b>The technology</b>		
<p>Proposed benefits of the technology</p> <p>How innovative is the technology in its potential to make a significant and substantial impact on health-related benefits?</p>	<p>The Committee concluded that eribulin was associated with a greater overall survival benefit compared with TPC.</p> <p>No specific claim for innovation was made.</p>	4.3
<p>What is the position of the treatment in the pathway of care for the condition?</p>	<p>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 given as a third- or fourth-line treatment for advanced or metastatic breast cancer after treatment with capecitabine and vinorelbine.</p>	4.2
<p>Adverse effects</p>	<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



TAXXX (STA)	Appraisal title: Eribulin for the treatment of locally advanced or metastatic breast cancer	ACD section
<b>Evidence for clinical effectiveness</b>		
Availability, nature and quality of evidence	<p>The EMBRACE trial formed the majority 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 composition of treatments included in the TPC arm of the trial was 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 advised the Committee that it was unlikely that the uncontrolled dose of the treatments in the TPC arm would skew the results as it was common for patients in clinical practice to receive different 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	<p>There remained significant uncertainties about health-related quality of life associated with eribulin.</p>	4.10
Are there any clinically relevant subgroups for which there is evidence of differential effectiveness?	<p>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</p>	4.4, 4.5

TAXXX (STA)	Appraisal title: Eribulin for the treatment of locally advanced or metastatic breast cancer	ACD section
	<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 they were defined post-hoc, based on small numbers, had wide confidence intervals and did not include appropriate adjustment for multiple testing thus 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 noted from the European Public Assessment Report for eribulin, produced by the European Medicines Agency, that a major stratification factor in the trial was pre-treatment with capecitabine (73.4% of patients). The Committee considered that this was potentially relevant but was aware that the manufacturer had not submitted evidence on clinical or cost effectiveness for this subgroup.</p>	
Estimate of the size of the clinical effectiveness including strength of supporting evidence	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.	4.3
<b>Evidence for cost effectiveness</b>		
Availability and nature of evidence	The Committee agreed with the ERG that the manufacturer's model was generally well constructed and in accordance with the scope issued by NICE.	4.6
Uncertainties around and plausibility of assumptions and inputs in the	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	4.9

<b>TAXXX (STA)</b>	<b>Appraisal title: Eribulin for the treatment of locally advanced or metastatic breast cancer</b>	<b>ACD section</b>
economic model	<p>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 of assuming a fixed average value for all patients, as it allowed for appropriate vial size selection and reduced drug wastage.</p> <p>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. 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 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 for branded products if generic options were available. Moreover, the Committee heard from the clinical specialist that intravenous vinorelbine, which is generically available, is more frequently used in UK 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 on a weekly basis, as was 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</p>	4.7

<b>TAXXX (STA)</b>	<b>Appraisal title: Eribulin for the treatment of locally advanced or metastatic breast cancer</b>	<b>ACD section</b>
	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>Incorporation of health-related quality of life benefits and utility values</p> <p>Have any potential significant and substantial health-related benefits been identified that were not included in the economic model, and how have they been considered?</p>	<p>The Committee noted that, owing to the absence of data on health-related quality of life collected in the EMBRACE trial, the manufacturer's model incorporated utilities from previously published studies. The Committee was disappointed that 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.</p>	4.8
<p>Are there specific groups of people for whom the technology is particularly cost effective?</p>	<p>No subgroups were discussed by the Committee to be particularly cost effective.</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>	4.7
<p>Most likely cost-effectiveness estimate (given as an ICER)</p>	<p>The Committee agreed that the ERG's revisions to the manufacturer's model for the overall ITT population, which included the ERG's projection of overall survival and re-estimation of costs (see section 3.33), 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>However, the Committee considered that this figure was likely to underestimate the</p>	4.10

TAXXX (STA)	Appraisal title: Eribulin for the treatment of locally advanced or metastatic breast cancer	ACD section
	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, there remained significant uncertainties 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 as an estimate of the price of the comparators.	
<b>Additional factors taken into account</b>		
Patient access scheme	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 discounted costs were incorporated in the manufacturer's analysis.	2.2, 3.8, 4.6
End-of-life considerations	The Committee concluded that eribulin did not fulfil all of the end-of-life criteria because it had not demonstrated an extension to life in the overall ITT population of at least an additional 3 months compared with TPC. Furthermore, given that the ICER was likely to exceed £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 had been met.	4.12
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 on implementing NICE technology appraisal guidance. When a NICE

technology appraisal recommends use of a drug or treatment, or other technology, the NHS must 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](http://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 Proposed 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](http://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](http://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](http://www.nice.org.uk/guidance/TA116)

### **Under development**

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

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

## **8 Proposed date for review of guidance**

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

Peter Clark  
Chair, Appraisal Committee  
July 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, The 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

**Alison Hawdale**

Lay member

**Professor John Hutton**

Professor of Health Economics, University of York

**Professor Peter Jones**

Emeritus Professor of Statistics, Keele University

**Dr Rachel Lewis**

Doctoral Researcher, Manchester Business School

**Dr Anne McCune**

Consultant Hepatologist, University Hospitals Bristol NHS Foundation Trust

**Professor Jonathan Michaels (Vice Chair)**

Professor of Vascular Surgery, University of Sheffield

**Professor Femi Oyebode**

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

**Dr John Radford**

Director of Public Health, Rotherham Primary Care Trust

**Dr Brian Shine**

Consultant Chemical Pathologist, John Radcliffe Hospital, Oxford

**Dr Murray D. Smith**

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

**Paddy Storrie**

Lay member

**Mike Wallace**

Health Economics & Reimbursement Director, Johnson & Johnson Medical Ltd

**C**      ***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**

Technical Adviser

**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. (2011) Eribulin for the treatment of locally advanced or metastatic breast cancer

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 & Implementation Group, University of Liverpool
- 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 are 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
- Ms 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