NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Final appraisal determination

Trastuzumab emtansine for treating HER2-positive, unresectable locally advanced or metastatic breast cancer after treatment with trastuzumab and a taxane

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

1 Guidance

1.1 Trastuzumab emtansine is not recommended, within its marketing authorisation, for treating adults with human epidermal growth factor receptor 2 (HER2) positive, unresectable locally advanced or metastatic breast cancer previously treated with trastuzumab and a taxane.

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

2 The technology

2.1 Trastuzumab emtansine (Kadcyla, Roche) is an antibody–drug conjugate consisting of trastuzumab linked to maytansine, which is a cytotoxic agent. Because the antibody targets human epidermal growth factor receptor 2 (HER2), and HER2 is overexpressed in breast cancer cells, the conjugate delivers the toxin directly to the cancer cells. Trastuzumab emtansine, as a single agent, has a UK marketing authorisation 'for the treatment of adult patients with

HER2-positive, unresectable locally advanced or metastatic breast cancer who previously received trastuzumab and a taxane, separately or in combination. Patients should have either:

- received prior therapy for locally advanced or metastatic disease, **or**
- developed disease recurrence during or within 6 months of completing adjuvant therapy.'

Trastuzumab emtansine is administered intravenously. The recommended dose of trastuzumab emtansine is 3.6 mg/kg body weight administered every 3 weeks (21-day cycle). Patients should have treatment until the disease progresses or unacceptable toxicity occurs.

2.2 The summary of product characteristics includes the following adverse reactions for trastuzumab emtansine: increase in serum transaminases, left ventricular dysfunction, infusion-related reactions, hypersensitivity reactions, decreased platelet counts, an immune response to trastuzumab emtansine, and reactions secondary to the accidental administration of trastuzumab emtansine around infusion sites. For full details of adverse reactions and contraindications, see the summary of product characteristics.

2.3 Trastuzumab emtansine costs £1641.01 per 100 mg vial and £2625.62 per 160mg vial (excluding VAT; MIMS, March–May 2014). The company estimated that the average cost of a course of treatment with trastuzumab emtansine is £90,831 (excluding administration costs), assuming a 3-weekly dose of 3.6 mg/kg, a patient weight of 70.1 kg and an average length of treatment of 14.5 months. Roche has agreed a patient access scheme with the Department of Health. If trastuzumab emtansine had been recommended, this scheme would provide a simple discount to the

list price of trastuzumab emtansine, with the discount applied at the point of purchase or invoice. The level of the discount is commercial in confidence. The Department of Health considered that this patient access scheme does not constitute an excessive administrative burden on the NHS.

3 The company's submission

The Appraisal Committee (section 7) considered evidence submitted by Roche and a review of this submission by the Evidence Review Group (ERG; section 8).

Clinical-effectiveness evidence

3.1 The company's systematic review of clinical evidence identified 2 relevant randomised controlled trials for inclusion in its submission: EMILIA and TH3RESA. Both trials were international, open-label trials evaluating the safety and efficacy of trastuzumab emtansine (3.6 mg/kg every 3 weeks) for human epidermal growth factor receptor 2 (HER2) positive, unresectable, locally advanced or metastatic breast cancer. EMILIA compared trastuzumab emtansine with lapatinib plus capecitabine, and TH3RESA compared it with treatment of physician's choice (defined in section 3.3). Both trials were ongoing at the time of the company's submission to NICE. The company used 4 additional randomised controlled trials, together with EMILIA, to perform a mixed treatment comparison between trastuzumab emtansine and the other comparators listed in the scope (that is, an analysis combining direct and indirect evidence for particular pairwise comparisons).

3.2 Patients in EMILIA had documented progression of unresectable, locally advanced or metastatic HER2-positive breast cancer previously treated with trastuzumab, alone or in combination with another agent, and a taxane, alone or in combination with another

agent. The trial's inclusion criteria stipulated that disease progression must have occurred:

- during or after at least 1 line of therapy for locally advanced or metastatic disease, **or**
- within 6 months after completing adjuvant therapy for early-stage disease.

Patients were randomised in a 1:1 ratio to trastuzumab emtansine (n=495) or lapatinib plus capecitabine (n=496). More than 50 patients were randomised from the UK. Stratification factors were geographical region (USA, Western Europe, or other), the number of previous chemotherapy regimens for unresectable, locally advanced or metastatic disease (0 or 1 compared with more than 1), and disease involvement (visceral compared with non-visceral). The study investigators and an independent review committee assessed the tumour at baseline and then every 6 weeks until disease progressed according to the investigators' assessment. Patients continued to receive study treatment until investigators established disease progression or unmanageable toxic effects developed.

3.3 TH3RESA enrolled patients with HER2-positive unresectable, locally advanced or metastatic breast cancer whose disease had progressed after at least 2 HER2-targeted regimens, including trastuzumab and lapatinib, and a taxane. Disease progression had to have occurred on both trastuzumab- and lapatinib-containing regimens (unless lapatinib was not tolerated by the patient). Patients were randomised 2:1 to trastuzumab emtansine (n=404) or treatment of physician's choice (n=198), which could be any of the following:

- single-agent chemotherapy

- hormonal therapy as a single agent (for example, tamoxifen or an aromatase inhibitor) or a dual agent (for example, an aromatase inhibitor plus a luteinizing hormone-releasing hormone agonist)
- HER2-targeted therapy alone (for example, trastuzumab or lapatinib) or in combination with 1 of the following:
  - another HER2-targeted therapy (for example, trastuzumab plus lapatinib)
  - single-agent chemotherapy (for example, lapatinib plus capecitabine)
  - single-agent hormonal therapy (for example, lapatinib plus letrozole).

Patients randomised to treatment of physician's choice could switch to trastuzumab emtansine when their disease progressed. This was allowed after results from EMILIA were published.

3.4 The co-primary efficacy end points in both EMILIA and TH3RESA were progression-free survival and overall survival. In EMILIA, progression-free survival was assessed by independent review (progression-free survival assessed by study investigators was a secondary end point), and in TH3RESA it was assessed by study investigators. Progression-free survival was defined as the time from randomisation to disease progression or death from any cause. The independent review committee in EMILIA and the study investigators in TH3RESA assessed disease progression based on Response Evaluation Criteria in Solid Tumours (RECIST). Overall survival was defined as the time from randomisation to death from any cause. Pre-specified secondary end points in both trials included objective response rate, duration of response, and time to symptom progression (which was used as a proxy for health-related quality of life in EMILIA). TH3RESA collected EQ-5D utility data.

3.5 Patients with an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1 were eligible for inclusion in EMILIA. TH3RESA enrolled patients with an ECOG performance status of 0, 1 or 2 (6.2% of the trial's population had an ECOG performance status of 2). For patients randomised to trastuzumab emtansine in EMILIA, the median age was 53 years, 99.8% were female, and 57% had oestrogen- or progesterone-receptor-positive disease. EMILIA included patients whose disease had progressed on trastuzumab and a taxane received as an adjuvant treatment or as a treatment for locally advanced or metastatic disease. Because of this, patients received treatment as first- (12%), second- (36%), or third- or subsequent-line (52%) therapy for locally advanced or metastatic disease. In contrast, patients in TH3RESA had previously received, on average, 4 lines of therapy for locally advanced or metastatic disease. The company stated that patient and disease characteristics at baseline were well balanced between study groups in EMILIA and TH3RESA.

3.6 For EMILIA the company presented the primary analysis of progression-free survival and 2 interim analyses of overall survival that were performed 6 months apart. For TH3RESA it presented the primary analysis of progression-free survival and 1 interim analysis of overall survival. All efficacy end points in EMILIA and TH3RESA were assessed in the intention-to-treat population (that is, in all patients randomised at baseline). Patients in TH3RESA who initially received treatment of physician's choice but then switched to trastuzumab emtansine were included in the analyses as originally randomised.

3.7 In EMILIA, median follow-up was 13 months at the time of the primary analysis of progression-free survival and the first interim analysis of overall survival. Treatment with trastuzumab emtansine improved median progression-free survival as assessed by

independent review by 3.2 months (trastuzumab emtansine 9.6 months, lapatinib plus capecitabine 6.4 months), with a hazard ratio stratified on randomisation factors of 0.65 (95% confidence interval [CI] 0.55 to 0.77, p<0.001). Investigator-assessed progression-free survival was similar (difference in median progression-free survival 3.6 months; hazard ratio [HR] 0.66, 95% CI 0.56 to 0.78). When the second interim analysis of overall survival was performed, median follow-up was 19 months. At that time, 149 (30%) and 182 (37%) of patients randomised to trastuzumab emtansine and lapatinib plus capecitabine, respectively, had died. Trastuzumab emtansine increased median overall survival by 5.8 months (trastuzumab emtansine 30.9 months, lapatinib plus capecitabine 25.1 months), and the hazard ratio was 0.68 (95% CI 0.55 to 0.85, p<0.001). Estimated 1-year survival rates were 85.2% in the trastuzumab emtansine group compared with 78.4% in the lapatinib plus capecitabine group, and rates at 2 years were 64.7% in the trastuzumab emtansine group and 51.8% in the lapatinib plus capecitabine group. For the secondary end points, trastuzumab emtansine increased objective response rate by 12.7% and prolonged the duration of response by 6.1 months compared with lapatinib plus capecitabine.

3.8 In TH3RESA, a total of 44 patients (22.2%) switched from treatment of physician's choice to trastuzumab emtansine after their disease progressed. Of patients randomised to treatment of physician's choice, 83.2% received HER2-targeted regimens and 16.8% received single-agent chemotherapy. After 16 months of follow-up and 348 events of investigator-assessed disease progression (219 with trastuzumab emtansine, 129 with treatment of physician's choice), median progression-free survival was 6.2 months with trastuzumab emtansine and 3.3 months with treatment of physician's choice, a difference of 2.9 months (hazard

ratio 0.53; 95% CI 0.42 to 0.66, p<0.0001). Median overall survival had not been established in the trastuzumab emtansine group by the time of the interim analysis (less than 50% of patients had died). The hazard ratio for overall survival was 0.55 (95% CI 0.37 to 0.83, p=0.0034), but the company did not consider it statistically significant because it had not crossed the stopping boundary (that is, the number of deaths that had accumulated at that time was not enough to come to a conclusion about overall survival).

3.9 Time to symptom progression was used as a proxy for health-related quality of life in EMILIA. It was defined as the time from randomisation to the first decrease of 5 points or more from baseline scores on the Trial Outcome Index of the patient-reported Functional Assessment of Cancer Therapy–Breast (FACT-B), which is scored from 0 to 92, with higher scores indicating a better quality of life. Trastuzumab emtansine delayed time to symptom progression by 2.5 months compared with lapatinib plus capecitabine (trastuzumab emtansine 7.1 months, lapatinib plus capecitabine 4.6 months; HR 0.796, p=0.0121). Of patients treated with trastuzumab emtansine or lapatinib plus capecitabine, 53.3% and 49.4% respectively had a clinically significant improvement in symptoms from baseline (p=0.0842). TH3ERSA, which collected EQ-5D data, reported utility values of 0.71 and 0.69 for patients who received trastuzumab emtansine or treatment of physician's choice respectively. In response to the appraisal consultation document, the company provided further health-related quality of life data from EMILIA obtained using the FACT-B and Diarrhoea Assessment Scale tools. Patients in the trastuzumab emtansine group reported being 'less bothered' by side effects than those in the lapatinib plus capecitabine group. In addition, the number of patients reporting diarrhoea symptoms increased 1.5- to 2-fold during treatment with lapatinib plus capecitabine but remained near baseline levels during treatment with trastuzumab emtansine.

3.10 The company provided pre-specified subgroup analyses of EMILIA and TH3RESA for progression-free survival and overall survival. For patients who received study treatment as first, second, or third or subsequent line, the hazard ratios for overall survival were 0.61 (95% CI 0.32 to 1.16), 0.88 (95% CI 0.61 to 1.27) and 0.62 (95% CI 0.46 to 0.84) respectively. The company indicated that no subgroups were of particular clinical interest for this appraisal.

3.11 The company performed a mixed treatment comparison between trastuzumab emtansine and the other comparators listed in the scope (capecitabine, vinorelbine, trastuzumab plus capecitabine, and trastuzumab plus vinorelbine) because no head-to-head data were available from randomised controlled trials. It used the following randomised controlled trials, which it identified from a review of the literature:

- EMILIA
- CEREBEL: an open-label trial comparing the incidence of central nervous system metastases in patients with HER2-positive metastatic breast cancer, treated with lapatinib plus capecitabine or trastuzumab plus capecitabine. Patients must have received either an anthracycline or a taxane as an adjuvant treatment and they may or may not have received trastuzumab. Randomisation in CEREBEL was stratified by whether or not the patient had received previous trastuzumab. For the mixed treatment comparison, the company used the results of the subgroup that had received trastuzumab.
- EGF100151: a comparison of lapatinib plus capecitabine with capecitabine alone in patients with HER2-positive, locally advanced or metastatic breast cancer previously treated with anthracycline-, taxane- and trastuzumab-containing regimens. Some patients initially randomised to capecitabine alone

switched to lapatinib plus capecitabine. The company excluded those patients from the analysis.

- Martin et al.: an open-label study of neratinib compared with lapatinib plus capecitabine for the second- or third-line treatment of HER2-positive locally advanced or metastatic breast cancer. Eligible patients had received up to 2 previous trastuzumab regimens and a taxane. Martin et al. did not report results for overall survival, so the company did not use this study for the analysis of overall survival.
- GBG26: a study in patients with HER2-positive, advanced breast cancer whose disease had progressed while being treated with trastuzumab. In this study, adding capecitabine to continued trastuzumab therapy was compared with capecitabine alone.

The company did not include TH3RESA in the analysis, even though it was the only study that would have allowed the comparison of trastuzumab emtansine with trastuzumab plus vinorelbine (one of the comparators in the scope) received as a treatment of physician's choice. In response to a request for clarification from the ERG about why TH3RESA was not included, the company indicated that the treatment of physician's choice was determined after patients had been randomised and considering each patient's characteristics. The company explained that because of this, a comparison of trastuzumab emtansine with trastuzumab plus vinorelbine separately would break the randomisation in the trial and result in a biased comparison.

3.12 The company did a qualitative but not a statistical assessment of heterogeneity. It stated that the 5 included studies were comparable for age, ECOG performance status, disease stage and the number of sites with disease metastases. All studies apart from CEREBEL included patients who had received trastuzumab, of whom 71 to 95% received it for metastatic disease. In GBG26, only

70% of patients had received a taxane but the company considered this proportion large enough to include the study. The company stated that CEREBEL and Martin et al. seemed more heterogeneous than the other 3 trials. For CEREBEL, although the company used the subgroup of patients who had received trastuzumab, an unknown proportion of these patients could have received trastuzumab plus an anthracycline, which does not match the population specified in the decision problem. Furthermore, CEREBEL and Martin et al. had limited information on patient characteristics at baseline. Because of this, the company presented the analysis with and without these 2 studies.

3.13 The company did the mixed treatment comparison from a Bayesian perspective using a fixed-effect model (that is, assuming that all trials estimate exactly the same treatment effect and that the variability between individual study results occurs by chance). It estimated hazard ratios and corresponding 95% credible intervals (CrI) for each pairwise comparison that was possible from the network of trials. The company also presented results using the Bucher method for the analysis that excluded CEREBEL and Martin et al. to compare the results obtained using different methods.

3.14 The trials used by the company allowed the comparison of trastuzumab emtansine with capecitabine and with trastuzumab plus capecitabine, but not with vinorelbine or with trastuzumab plus vinorelbine. In the analysis that included CEREBEL and Martin et al., the hazard ratio for progression-free survival was 0.39 (95% CrI 0.29 to 0.55) for trastuzumab emtansine relative to capecitabine, and 0.68 (95% CrI 0.50 to 0.91) for trastuzumab emtansine relative to trastuzumab plus capecitabine. For overall survival, the hazard ratio for trastuzumab emtansine was 0.55 (95% CrI 0.41 to 0.75) relative to capecitabine, and 0.68 (95% CrI

0.46 to 0.98) relative to trastuzumab plus capecitabine. Excluding CEREBEL and Martin et al. from the analysis resulted in trastuzumab emtansine being associated with a lower risk (lower hazard ratios) of both disease progression and death relative to capecitabine and to trastuzumab plus capecitabine than when the 2 studies were included. The results using the Bucher method were statistically significant and similar to those obtained using the Bayesian method.

3.15 The company estimated the probability of each treatment being the most effective with respect to progression-free survival and overall survival. Trastuzumab emtansine had a 99% probability of being the best treatment to reduce the risk of disease progression and a 98% probability of being the best treatment to reduce the risk of death.

3.16 In both EMILIA and TH3RESA, adverse events were analysed for a 'safety population', defined as patients who received at least 1 dose of study treatment. In addition, the company presented a pooled safety analysis of 884 patients who had received trastuzumab emtansine either in EMILIA or in 5 other phase I or II studies. Trastuzumab emtansine caused grade 3 or above adverse events in 45.0% of these patients, serious adverse events in 19.8%, treatment discontinuation in 7.0% and death in 1.4%. The most common adverse events in the pooled analysis (occurring in 25% or more of patients) were fatigue (46.4%), nausea (43.0%), decreased platelet counts (29.6%), headache (29.4%), constipation (26.5%) and nosebleeds (25.2%). Serious adverse events reported by more than 5 patients were pneumonia (1.7%), fever (1.4%), cellulitis (1.1%), vomiting (0.9%), decreased platelet counts (0.9%), convulsion (0.8%), shortness of breath (0.8%), abdominal pain (0.7%), blood poisoning (0.7%), back pain (0.7%) and accumulation of fluid on the lungs (0.6%). The company considered that

trastuzumab emtansine is well tolerated and that the additional toxicity can be managed.

Evidence Review Group critique and exploratory analyses

3.17 The ERG considered that the company's search of clinical evidence was well-developed and unlikely to have missed any relevant studies. It also considered that EMILIA, TH3RESA and the trials used in the mixed treatment comparison were described in sufficient detail by the company.

3.18 The ERG considered that although in principle EMILIA and THE3ERA were generally at low risk of bias, the lack of blinding in both trials could have introduced bias, especially for the outcomes reported by patients. For progression-free survival, the ERG noted that the independent review committee in EMILIA was blinded to the intervention the patient had received, but study investigators in TH3RESA were not, which may have increased the risk of bias for progression-free survival in TH3RESA.

3.19 The ERG stated that the populations in EMILIA and TH3RESA were broadly similar to the population in UK clinical practice. However, it highlighted the following differences:

- Most patients in EMILIA and TH3RESA received study treatment as a third or subsequent line, whereas the company suggested that trastuzumab emtansine would be used second line in clinical practice.
- The ERG noted that because EMILIA and TH3RESA were international trials, not all patients would have received previous treatment according to UK practice.
- The ERG suggested that in clinical practice around one-third of patients would have an ECOG performance status of 2, whereas in EMILIA and TH3RESA, 0% and 6.2% of patients respectively had an ECOG performance status of 2.

3.20 The ERG noted the following differences between the trials used in the company's mixed treatment comparison:

- Not all patients had received a taxane in GBG26. The ERG's clinical experts believed that previous taxane therapy can modify the effect of subsequent treatment.
- The assessment of disease progression or time to progression was blinded to the intervention the patient had received in EMILIA and EGF100151 but not in the other trials included in the analysis.
- RECIST was used in EMILIA, EGF100151 and Martin et al. to assess disease progression, but it was unclear whether it was used in CEREBEL and GBG26.
- The sites of disease metastases differed between CEREBEL and the remaining studies because CEREBEL excluded patients with brain metastases.

3.21 The ERG agreed that it was appropriate for the company to have excluded TH3RESA from the mixed treatment comparison. However, it did not agree that using a fixed-effect model was appropriate because heterogeneity between trials was likely to exist. Therefore, the ERG requested that the company performs the analysis using a random-effects model (that is, a model that attempts to account for any unexplained variability between study results). However, when this was provided, the ERG stated that the company did not describe the analysis in sufficient detail, so the ERG repeated the analysis that included CEREBEL and Martin et al. using a random-effects model. It reported similar results to the company, but the ERG's results had wider credible intervals which crossed 1 (1 being the equivalent of no treatment effect). In the ERG's analysis, the probability of trastuzumab emtansine being the best treatment to reduce the risk of disease progression was 87%,

and the probability of it being the best treatment to reduce the risk of death was 84%.

Cost-effectiveness evidence

3.22 The company submitted a de novo economic model to estimate the cost effectiveness of trastuzumab emtansine in adults with HER2-positive, unresectable, locally advanced or metastatic breast cancer who previously received trastuzumab and a taxane, separately or in combination. The company conducted the analysis from the perspective of the NHS and personal social services. It chose a time horizon of 10 years and a cycle length of 1 week. Costs and health effects were discounted at an annual rate of 3.5%.

3.23 The company's model was a state-transition Markov cohort model simulating 3 states: progression-free, progressed disease and death. All patients entered the model in the progression-free state and received trastuzumab emtansine or one of its comparators either as first, second or third line (based on the proportions in EMILIA, see section 3.5). They could then remain in this state, move to the progressed-disease state or die. Once patients transitioned in the model, they could not return to their previous state. The company's model assumed that patients whose disease progressed stopped treatment and received capecitabine, vinorelbine or best supportive care, in line with Advanced breast cancer: diagnosis and treatment (NICE guideline CG81).

3.24 The company obtained the clinical-effectiveness data for trastuzumab emtansine and the comparator lapatinib plus capecitabine from EMILIA. Progression-free survival in the model was based on the assessment by study investigators (secondary end point) rather than the assessment by independent review (primary end point). To model the clinical effectiveness of the

comparators for which there was no head-to-head evidence, the company used the results of its Bayesian mixed treatment comparison that included CEREBEL and the study by Martin et al. It assumed that vinorelbine and trastuzumab plus vinorelbine, which could not be compared with trastuzumab emtansine in the mixed treatment comparison, were clinically equivalent to capecitabine and trastuzumab plus capecitabine respectively. This was because NICE guideline CG81 recommends capecitabine or vinorelbine as second- or third-line treatment for advanced breast cancer, and the All Wales Medicines Strategy Group recommends lapatinib plus capecitabine as an alternative to trastuzumab plus capecitabine or trastuzumab plus vinorelbine. The company suggested that this implies that capecitabine and vinorelbine, alone or in combination with trastuzumab, can be used interchangeably.

3.25 To estimate progression-free survival and overall survival for trastuzumab emtansine and lapatinib plus capecitabine, the company produced log-cumulative hazard plots to examine how the risks of disease progression and death change over time with each treatment. It then fitted alternative parametric functions to Kaplan–Meier data for each of EMILIA's treatment groups, and extrapolated the curves beyond the end of the trial. The company chose the base-case survival functions for trastuzumab emtansine and lapatinib plus capecitabine based on statistical tests, on visually inspecting the curves' fit to the data and on the clinical plausibility of the extrapolation. It then applied the hazard ratios from the mixed treatment comparison to the survival function of trastuzumab emtansine to estimate progression-free survival and overall survival for each of the other comparators. The company's model assumed that the treatment effect of trastuzumab emtansine was maintained during the entire time horizon (that is, the hazard ratios for progression-free survival and overall survival remained below 1).

3.26 The company noted that the risk of disease progression with trastuzumab emtansine and lapatinib plus capecitabine was relatively constant during the first 17 months (72 weeks) after starting treatment, then started changing irregularly. It stated that although this might have a clinical explanation, it could be spurious because there were few patients at risk of developing disease progression after 17 months. According to statistical tests, the log-normal function provided the best fit to the Kaplan–Meier data for trastuzumab emtansine and lapatinib plus capecitabine. However, on visual inspection the company noted a poor fit. Because of this and the small effect progression-free survival had in the model compared with overall survival (see sections 3.33 and 3.34), the company chose to use in its base case the Kaplan–Meier data for each treatment group up to 17 months after starting treatment, the point at which the risk of disease progression starts changing irregularly, and fit the log-normal function beyond 17 months.

3.27 For overall survival, the log-logistic and gamma functions provided the best fit to the Kaplan–Meier data according to statistical tests. However, the company chose the gamma function, which it fitted to the entire curves to model overall survival. This was because the gamma function produced survival curves that were more biologically plausible and more comparable with the Kaplan–Meier curves and with external registry data than those produced by the log-logistic function. The difference in mean overall survival between trastuzumab emtansine and lapatinib plus capecitabine with the gamma function was 7.6 months.

3.28 The company could not transform the FACT-B Trial Outcome Index data collected from EMILIA to EQ-5D, and it did not use the utility values from TH3RESA because patients in TH3RESA received treatment as third- or subsequent-line therapy and would be expected to have a lower quality of life than patients with fewer

recurrences. The company stated that the best available source of health-related quality of life data was a study by Lloyd et al., which has been used in previous NICE technology appraisals for metastatic breast cancer. The company used the model by Lloyd et al. to estimate treatment-specific utility values in the progression-free state based on the objective response rate reported for the treatment in trials. For trastuzumab emtansine and lapatinib plus capecitabine the company obtained response rates from EMILIA, estimating utility values of 0.78 and 0.74 respectively. It considered that the FACT-B and Diarrhoea Assessment Scale data from EMILIA and the favourable safety profile of trastuzumab emtansine support using a higher utility value for trastuzumab emtansine than for lapatinib plus capecitabine. The company estimated a utility value of 0.72 for capecitabine based on response rates from EGF100151 and a utility value of 0.73 for trastuzumab plus capecitabine based on response rates from GBG26. Because the company assumed clinical equivalence between capecitabine and vinorelbine (see section 3.24), it used the same utility value for vinorelbine as that for capecitabine (0.72) and the same value for trastuzumab plus vinorelbine as that for trastuzumab plus capecitabine (0.73). For the progressed-disease state, the company applied a single utility value of 0.50 for all patients, which it estimated based on the Lloyd et al. model. To capture the decrease in utility associated with adverse events, the company included utility decrements for 3 adverse events: diarrhoea and vomiting, fatigue and hand-foot syndrome. For capecitabine, trastuzumab plus capecitabine, vinorelbine, and trastuzumab plus vinorelbine, the company applied the same adverse events as for lapatinib plus capecitabine based on EMILIA, with the same frequency.

3.29 The company included the following costs in the model: drug costs, the costs of preparing and administering drugs, the costs of 2

adverse events (diarrhoea and fatigue) and supportive care costs. It calculated the doses of drugs that are dosed by body weight or body surface area based on the average body weight and body surface area of patients in EMILIA. The company assumed that any unused drug in a vial was discarded (wasted) for trastuzumab emtansine and trastuzumab, but not for vinorelbine (lapatinib and capecitabine are oral drugs, and so are not associated with wastage). The company assumed that each treatment the patient received in the progressed-disease state (capecitabine and/or vinorelbine) was received for 4.3 months, based on a study by Cameron et al. To capture the costs likely to be incurred at the end of life, the company incorporated a palliative care cost of £3916 per patient as a transition cost to the death state.

3.30 The company's deterministic base-case results (without the patient access scheme) suggested that trastuzumab emtansine was more costly and more effective than all of its comparators. In an incremental analysis, vinorelbine, trastuzumab plus capecitabine and trastuzumab plus vinorelbine were dominated and excluded from the analysis; that is, vinorelbine was more costly than capecitabine and equally effective, and trastuzumab plus capecitabine and trastuzumab plus vinorelbine were more costly and less effective than lapatinib plus capecitabine. Among the remaining alternatives, capecitabine was the cheapest, followed by lapatinib plus capecitabine, then trastuzumab emtansine. The incremental cost-effectiveness ratio (ICER) for lapatinib plus capecitabine compared with capecitabine alone was £49,798 per quality-adjusted life year (QALY) gained (incremental costs £20,997, incremental QALYs 0.42). The ICER for trastuzumab emtansine compared with lapatinib plus capecitabine was £167,236 per QALY gained (incremental costs £76,992, incremental QALYs 0.46). The company stated that lapatinib plus capecitabine should be excluded from the analysis because the ICER for lapatinib plus

capecitabine compared with capecitabine alone is above the normally acceptable maximum ICER. In a pairwise comparison of trastuzumab emtansine with capecitabine the ICER was £111,095 per QALY gained (incremental costs £97,989, incremental QALYs 0.88).

3.31 In the company's base case, which used a 10-year time horizon, 3% of patients were alive at 10 years. In response to a request for clarification from the ERG, the company presented cost-effectiveness results using a 15-year time horizon. In an incremental analysis the ICER for trastuzumab emtansine compared with lapatinib plus capecitabine was £160,070 per QALY gained. At the end of the 15 years 1% of patients were alive.

3.32 The company presented 1-way sensitivity analyses in its base case that used a 10-year time horizon in which it varied most parameters to the lower and upper limit of their 95% confidence intervals. In addition, it explored alternative approaches to model progression-free survival and overall survival (see sections 3.33 and 3.34). The company performed all these analyses only on the pairwise ICER for trastuzumab emtansine compared with capecitabine (£111,095 per QALY gained). It found that this ICER was most sensitive to the utility value applied for trastuzumab emtansine in the progression-free state. When the utility value varied, this resulted in ICERs ranging from £94,909 to £179,337 per QALY gained. The company stated that, compared with capecitabine, the cost effectiveness of trastuzumab emtansine was most sensitive to how progression-free survival and overall survival were extrapolated in the model, the hazard ratios estimated from the mixed treatment comparison, and the utility values used.

3.33 In its base case, the company modelled progression-free survival by using the Kaplan–Meier data for each treatment group up to 17 months (72 weeks) after starting treatment and fitting the log-

normal function beyond 17 months. The company explored the uncertainty around this approach by:

- Using the Kaplan–Meier data up to 17 months after starting treatment and fitting alternative parametric functions (Weibull, exponential, log-logistic and gamma) beyond 17 months instead of the log-normal function.
- Using the Kaplan–Meier data for each treatment group up to 3.5 months (14 weeks) after starting treatment, and fitting the exponential function to each group separately beyond 3.5 months. The company explored this approach because the risk of disease progression with trastuzumab emtansine and lapatinib plus capecitabine was similar during the first 3.5 months. The company stated that this might have biological plausibility, by which the true risk of disease progression with each treatment only becomes observed after 3.5 months.

In the first analysis, the ICERs ranged from £100,365 per QALY gained (Weibull) to £114,826 per QALY gained (log-logistic). In the second analysis, the ICER was £106,211 per QALY gained.

3.34 The company also investigated the uncertainty around how it modelled overall survival in its base case (gamma function fitted to the entire survival curves) by exploring the following approaches:

- Fitting alternative parametric functions (Weibull, log-logistic and log-normal) instead of the gamma function to the entire survival curves.
- Using the Kaplan–Meier data for each treatment group up to 7.3 months (29 weeks) after starting treatment, and fitting the exponential function to each treatment group separately beyond 7.3 months. The company explored this approach because the risk of death with trastuzumab emtansine and lapatinib plus capecitabine was similar during the first 7.3 months.

- Using the Kaplan–Meier data for each treatment group up to 7.3 months (29 weeks) after starting treatment, and fitting the exponential function to each treatment group separately beyond 7.3 months, but assuming no treatment effect (hazard ratio of 1) beyond 23.8 months (95 weeks) after starting treatment. The company explored this approach because there were few patients at risk of dying after 23.8 months and the treatment effect of trastuzumab emtansine beyond that time was uncertain.

The first analysis resulted in ICERs ranging from £111,004 per QALY gained (log-normal) to £151,208 per QALY gained (Weibull). The second and third analyses resulted in ICERs of £138,286 and £153,319 per QALY gained respectively.

3.35 To characterise the uncertainty in the base-case ICER the company performed a probabilistic sensitivity analysis, varying parameters simultaneously with values from a probability distribution. There was a 0% probability of trastuzumab emtansine being the most cost-effective treatment at a maximum acceptable ICER of £30,000 per QALY gained.

3.36 In response to the appraisal consultation document, the company submitted a patient access scheme. Including the confidential discount in the patient access scheme, the probability of trastuzumab emtansine being cost effective compared with lapatinib plus capecitabine at a maximum acceptable ICER of £30,000 per QALY gained remained 0%. Other cost-effectiveness estimates incorporating the patient access scheme are commercial in confidence and cannot be reported here because, having previously released the estimates without the patient access scheme, the estimates with the patient access scheme could reveal the confidential discount agreed between the company and the Department of Health. However, the estimates including the patient access scheme were fully taken into account during the appraisal.

Evidence Review Group critique and exploratory analyses

3.37 The ERG stated that the company's model was clinically appropriate for the decision problem defined in the scope, and generally well described and justified in the company's submission.

3.38 The ERG indicated that the company's modelling of progression-free survival and overall survival in the base case provided the most clinically plausible extrapolation. However, it noted that in the model the benefit of trastuzumab emtansine on progression-free survival and overall survival was assumed to be maintained during the entire time horizon (that is, the hazard ratio remained below 1). The ERG considered this subject to uncertainty and explored in a 1-way sensitivity analysis the conservative assumption of no treatment benefit with trastuzumab emtansine (hazard ratio of 1) beyond the time points at which the treatment effect was uncertain (see section 3.47).

3.39 The ERG stated that the utility values used in the model were consistent with values reported from a literature review of health-state utility values for breast cancer. In addition, the ERG's clinical advisers considered that it was reasonable to assume higher utility with trastuzumab emtansine than with its comparators because trastuzumab emtansine has a better safety profile.

3.40 The ERG noted that the model incorporated utility decrements for 3 adverse events only and costs for 2 adverse events only. It stated that this did not capture the decrease in utility and costs associated with many grade 3 or above adverse events that occurred frequently in EMILIA. The ERG included the costs of those adverse events in exploratory analyses (see section 3.45) and doubled the costs associated with adverse events in a 1-way sensitivity analysis (see section 3.47).

3.41 The company calculated the doses of trastuzumab emtansine, trastuzumab, capecitabine and vinorelbine based on the average body weight and body surface area of patients in EMILIA (this assumed that all patients receive the same treatment dose). The ERG indicated that the company, having assumed that any unused drug in a vial was discarded for trastuzumab emtansine and trastuzumab, calculated costs inaccurately. This was because patients' weight varies, so the combination of vial sizes patients would receive to administer the drug efficiently would also vary. In its exploratory analyses (see section 3.45), the ERG applied alternative costs for trastuzumab emtansine, trastuzumab and capecitabine based on an approximated weight distribution, rather than an average weight, of patients with HER2-positive metastatic breast cancer to account for the variation in patients' body weight.

3.42 The ERG identified an error in the model relating to how the cost of administering trastuzumab plus vinorelbine was implemented, which it corrected in exploratory analyses (see section 3.45).

3.43 In the model, some patients remained in the progressed-disease state longer than others, depending on the treatment they had received in the progression-free state, but most patients who received treatment in the progressed-disease state (capecitabine or vinorelbine) received it for 4.3 months. The ERG noted that, in the company's model, patients who spent more time in the progressed-disease state incurred more treatment costs than those who spent less time despite receiving treatment for the same duration. The ERG corrected this in its exploratory analyses by calculating the average cost of each treatment received in the progressed disease-state independently (see section 3.45).

3.44 The company performed 1-way sensitivity analyses only on the pairwise ICER for trastuzumab emtansine compared with capecitabine. The ERG did not consider this to have established

the robustness of the model or to have determined the key drivers of cost effectiveness. The ERG explained that it was important to include all the comparisons because the appropriate incremental comparison may change with each analysis. Furthermore, the ERG stated that the company did not present or justify the parameters it varied in the probabilistic sensitivity analysis, appeared to have selected the parameters arbitrarily and did not reflect the uncertainty around certain parameters.

3.45 To address its concerns about the company's model, the ERG performed the following exploratory analyses:

- Analysis 'a': including the costs of all adverse events that occurred in more than 2% of patients in either treatment group of EMILIA.
- Analysis 'b': correcting the error relating to how the cost of administering trastuzumab plus vinorelbine was implemented, and calculating the average cost of each treatment received in the progressed disease-state independently, together with analysis 'a'.
- Analysis 'c': applying the hazard ratios for progression-free survival and overall survival from the ERG's mixed treatment comparison that used a random-effects model, together with analysis 'b'.
- Analysis 'd': using a 15-year time horizon, together with analysis 'c'.
- Analysis 'e': calculating the cost of trastuzumab emtansine, trastuzumab and capecitabine based on an approximated weight distribution of patients with HER2-positive metastatic breast cancer, together with analysis 'd' (that is, applying all individual changes simultaneously).

3.46 In the above-listed analysis 'e' (hereafter 'the ERG's base case'), trastuzumab plus capecitabine, vinorelbine and trastuzumab plus vinorelbine were dominated and excluded from the analysis. In an incremental analysis, the ICER for trastuzumab emtansine compared with lapatinib plus capecitabine was £166,429 per QALY gained (incremental costs £80,971, incremental QALYs 0.49), which was very similar to the company's ICER of £167,236 per QALY gained. The ERG explained that this was because the changes it applied did not act on the ICER in the same direction (all changes, except applying revised drug costs, decreased the ICER). The incremental ICERs for trastuzumab emtansine compared with lapatinib plus capecitabine from the above-listed analyses were £167,229 per QALY for 'a', £166,701 for 'b', £166,701 for 'c' and £159,486 for 'd'.

3.47 Based on key areas of uncertainty it identified, the ERG repeated within its base case selected sensitivity analyses performed by the company. It also explored the following:

- Applying equal utility values of 0.74 for all treatments in the progression-free state, which was the value used for lapatinib plus capecitabine in the company's base-case analysis.
- Assuming that, compared with lapatinib plus capecitabine, trastuzumab emtansine had no effect on progression-free survival beyond 17.0 months after starting treatment and no effect on overall survival beyond 23.8 months after starting treatment (that is, beyond the points at which the treatment effect of trastuzumab emtansine was uncertain; see sections 3.33 and 3.34).
- Doubling the costs associated with adverse events.
- Decreasing the drug and administration cost of trastuzumab to investigate the impact of administering trastuzumab in its alternative form as a fixed subcutaneous dose.

Compared with the ERG's base-case ICER of £166,429 per QALY gained for trastuzumab emtansine compared with lapatinib plus capecitabine, the ICERs from the above-listed analyses were £185,623, £449,554, £165,858 and £166,429 per QALY gained respectively. The ICER remained above £147,000 per QALY gained in all the other sensitivity analyses. The key drivers in the model were the relative treatment effect of trastuzumab emtansine on overall survival, the utility values, and the assumptions about drug wastage. The ERG indicated that, given the uncertainty in the results of its mixed treatment comparison, if any of the comparators were equally effective as trastuzumab emtansine, the comparator would dominate trastuzumab emtansine because it would be cheaper.

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

4 Consideration of the evidence

The Appraisal Committee reviewed the data available on the clinical and cost effectiveness of trastuzumab emtansine, having considered evidence on the nature of human epidermal growth factor receptor 2 (HER2) positive, unresectable locally advanced or metastatic breast cancer and the value placed on the benefits of trastuzumab emtansine by people with the condition, those who represent them, and clinical experts. It also took into account the effective use of NHS resources.

4.1 The Committee discussed with patient experts the nature of the condition and the perceived benefits of trastuzumab emtansine for patients. It heard that metastatic breast cancer is a debilitating condition that can affect women of all ages and leads to premature death. The Committee heard from the patient experts that patients and their families often highly value what may seem to others even relatively short extensions to life, as long as the person's quality of

life is maintained. The Committee noted that patients are particularly concerned about unpleasant side effects associated with treatment. The clinical specialists explained that trastuzumab emtansine is both an effective treatment and also well tolerated, with fewer side effects than some of the other options. The Committee recognised that patients value the availability of more treatment options and that trastuzumab emtansine would be welcomed by patients and their families.

4.2 The Committee discussed with the clinical specialists the current clinical management of HER2-positive metastatic breast cancer. It was aware that NICE recommends trastuzumab plus paclitaxel as a first-line treatment for people who have not received chemotherapy for metastatic breast cancer and in whom anthracycline treatment is inappropriate (NICE technology appraisal guidance 34). After disease progression, NICE recommends second- and third-line treatment with non-targeted therapies such as capecitabine or vinorelbine, which can be combined with continued trastuzumab therapy if disease progression is within the central nervous system alone (NICE guideline CG81). The Committee heard from the clinical specialists that trastuzumab plus chemotherapy has become the standard first-line treatment in clinical practice, but more recently in England patients may receive pertuzumab in addition to trastuzumab and docetaxel, which is funded by the Cancer Drugs Fund. It further heard that after disease progression on trastuzumab (that is, in the second-line setting) clinical practice varies, but most patients will continue trastuzumab therapy combined with chemotherapy (capecitabine or vinorelbine) or receive lapatinib plus capecitabine. The Committee noted that continued trastuzumab therapy was not offered by all cancer centres, and that lapatinib plus capecitabine was available in England through the Cancer Drugs Fund. The Committee heard from the clinical specialists that contrary to NICE

guidance, single-agent chemotherapy (for example, capecitabine or vinorelbine) is not routinely used for patients whose disease progressed on first-line treatment. The Committee concluded that local access to treatments and the availability of treatments through the Cancer Drugs Fund led to some variation in clinical practice so that no single pathway of care could be defined.

4.3 The Committee considered the likely position of trastuzumab emtansine in the treatment pathway of HER2-positive, unresectable locally advanced or metastatic breast cancer and the key comparators for trastuzumab emtansine in clinical practice. It noted that the clinical specialists expect that trastuzumab emtansine would be used as second-line therapy (that is, instead of continued trastuzumab plus chemotherapy or lapatinib plus capecitabine) because trastuzumab emtansine had been shown to be more clinically effective than the alternative second-line agent, lapatinib plus capecitabine, in EMILIA. The Committee concluded that based on current clinical practice trastuzumab plus capecitabine, trastuzumab plus vinorelbine and lapatinib plus capecitabine were relevant comparators at that stage of the disease.

Clinical effectiveness

4.4 The Committee discussed which sources of trial data were appropriate for the place in therapy in which trastuzumab emtansine is likely to be used (that is, the second-line setting). The Committee was aware that 36% of patients in EMILIA and 0% of patients in TH3RESA received treatment as second-line therapy for locally advanced or metastatic disease. Given these proportions, the Committee concluded that EMILIA was the most relevant source of clinical evidence for its decision-making in this appraisal.

4.5 The Committee discussed whether the results from EMILIA were generalisable to clinical practice, noting that patients in England

may receive pertuzumab plus trastuzumab plus docetaxel in the first-line setting. It heard from the company that 9.5% of patients in EMILIA had previously received pertuzumab therapy (10.3% of patients in the trastuzumab emtansine group, 8.7% of patients in the lapatinib plus capecitabine group) but the Committee considered this proportion too small to determine whether the effect of trastuzumab emtansine differed in patients who had previously received pertuzumab. In addition, the Committee heard from the clinical specialists that there was no evidence on whether or not pertuzumab can modify the effect of subsequent treatment with trastuzumab emtansine. However, the clinical specialists indicated that trastuzumab emtansine demonstrated a clinical benefit after trastuzumab, and that trastuzumab and pertuzumab have similar mechanisms of action, so the effect of trastuzumab emtansine would not be expected to differ after trastuzumab or after pertuzumab plus trastuzumab. The Committee concluded that it was currently unknown whether previous pertuzumab would alter the clinical effectiveness of subsequent treatment with trastuzumab emtansine, but there was no positive evidence that this was the case.

4.6 The Committee also noted the Evidence Review Group's (ERG) concern that none of the patients in EMILIA had an Eastern Cooperative Oncology Group (ECOG) performance status of 2, whereas in clinical practice around one-third of patients would have an ECOG performance status of 2. The Committee appreciated that patients enrolled in clinical trials may be younger and with better performance status than those in routine clinical practice, and so might experience better outcomes. The Committee agreed that the population in EMILIA was otherwise reasonably representative of patients in the UK and concluded that the results of EMILIA were suitable for the assessment of the clinical effectiveness of trastuzumab emtansine in clinical practice.

4.7 The Committee considered the clinical effectiveness of trastuzumab emtansine as a second-line treatment. It was aware that in EMILIA, patients in the trastuzumab emtansine group experienced improved survival compared with patients in the lapatinib–capecitabine group, irrespective of the line of therapy. However, the Committee noted that subgroup analyses suggested a lesser benefit in patients who received second-line treatment (in whom the difference in effect was not statistically significant) than in the overall population (see section 3.10). The Committee was aware that the analysis may not have been powered to demonstrate a difference in treatment effect in the subgroup. In addition, the Committee heard from the clinical specialists that there is no biologically plausible reason for the effect to differ according to the number of previous treatments patients had received. The Committee concluded that the subgroup analysis was not reliable enough to inform a decision about the clinical effectiveness of trastuzumab emtansine as a second-line treatment.

4.8 The Committee took note of the patient expert's concern about the tolerability of treatment and discussed the adverse events in EMILIA that led patients to stop treatment, which it considered to be a reasonable proxy for tolerability. The Committee understood that fewer patients stopped treatment because of an adverse event in the trastuzumab emtansine group than in the lapatinib plus capecitabine group (5.9% and 17% of patients respectively). It also heard from the company that the most common adverse event that resulted in patients stopping trastuzumab emtansine was a decreased platelet count (2% of patients). The Committee concluded that trastuzumab emtansine had been shown to have a satisfactory adverse-event profile in EMILIA.

4.9 The Committee considered the Bayesian mixed treatment comparison used by the company to estimate hazard ratios for trastuzumab emtansine relative to the comparators for which no head-to-head evidence existed. The Committee agreed that CEREBEL and the study by Martin et al. should be included in the base-case analysis to use all available evidence and that the ERG's random-effects model would better reflect the heterogeneity between the trials than the company's fixed-effect model.

Cost effectiveness

4.10 The Committee considered the company's economic model used to estimate the cost effectiveness of trastuzumab emtansine and how it captured the main aspects of the condition. It noted that the company used a 3-state model and chose a time horizon of 10 years for its base case. The Committee agreed that the model structure was consistent with other models used for the same disease. The Committee noted that the ERG preferred a 15-year time horizon because a small proportion of patients were still alive at 10 years and data relating to these patients would not be included in a model with a 10-year horizon. The Committee agreed that in principle a lifetime horizon should be used to capture all long-term costs and health effects and concluded that the company's model was appropriate to estimate the cost effectiveness of trastuzumab emtansine, but that a 15-year time horizon should be used.

4.11 The Committee considered the utility values used in the company's model. It noted that in the progression-free state, the company applied a higher utility value for trastuzumab emtansine than for its comparators. The company considered that the favourable side effect profile of trastuzumab emtansine supports using a distinct utility value for trastuzumab emtansine. The Committee questioned whether utility values should differ for each treatment because the

clinical specialists indicated that most adverse events resolve within a few weeks, whereas in the model the utility values were applied throughout the entire progression-free state. In addition, the Committee considered that applying a higher utility value for trastuzumab emtansine could result in the benefit of treatment being double-counted and overestimated, because the utility decrements for adverse events already capture part of this benefit. In response to the appraisal consultation document, the company clarified that the utility decrements for adverse events were not applied separately in the model, but were incorporated into the utility values in the progression-free state, and therefore were applied only once. The Committee heard from the ERG that, although the modelling of adverse events had limitations (see section 3.40), the benefit of trastuzumab emtansine from reducing adverse events was not double-counted in the model. The Committee acknowledged the additional evidence submitted by the company in response to the appraisal consultation document (see section 3.9). It noted that the evidence suggested that in EMILIA, patients who received trastuzumab emtansine felt better and reported being less troubled by side effects than those who received lapatinib plus capecitabine. The Committee was aware that EMILIA was an open-label trial, which may have introduced bias in the outcomes reported by patients, but noted the additional evidence on wellbeing and side effects presented by the company. The Committee concluded that a marginally higher utility value for trastuzumab emtansine in the progression-free state could be accepted in this appraisal.

4.12 The Committee noted that in its cost-effectiveness analysis, the company assumed clinical equivalence between capecitabine and vinorelbine, and between trastuzumab plus capecitabine and trastuzumab plus vinorelbine. The Committee discussed with the clinical specialists whether this assumption was clinically plausible.

The clinical specialists indicated that any chemotherapy would produce additional benefit when combined with trastuzumab. They stated that the precise clinical difference between capecitabine and vinorelbine had not been established in clinical trials, although in their opinion it would be reasonable to assume no difference. The Committee concluded that, although it would be preferable to base the comparison on data from well conducted clinical trials, the assumption of no difference between capecitabine- and vinorelbine-based regimens in the model could be justified for this appraisal.

4.13 The Committee considered the adverse events associated with trastuzumab emtansine in relation to the economic modelling. It noted that the model incorporated utility decrements for only 3 adverse events and costs for 2 adverse events. The Committee was concerned that this did not capture many adverse events associated with trastuzumab emtansine including decreased platelet counts. The Committee was aware that when the ERG included the costs of the adverse events that occurred frequently in EMILIA, this had little impact on the cost-effectiveness estimates. However, it concluded that the model should have incorporated both the decrease in utility and the increased costs associated with adverse events.

4.14 The Committee considered the cost-effectiveness results for trastuzumab emtansine. It noted the company's suggestion that lapatinib plus capecitabine should be excluded from the analysis because the incremental cost-effectiveness ratio (ICER) for lapatinib plus capecitabine compared with capecitabine alone was £49,800 per quality-adjusted life year (QALY) gained, which the company considered to be above the acceptable maximum ICER normally regarded by NICE to represent cost-effective treatments (see section 3.30). The Committee was aware that excluding a

technology based on its cost effectiveness in relation to a maximum ICER does not comply with the NICE reference case, which recommends a fully incremental cost–utility analysis. The Committee agreed that there was no reason on this occasion to depart from the NICE reference case. It concluded that the cost effectiveness of trastuzumab emtansine should be evaluated in an incremental analysis comparing all technologies including lapatinib plus capecitabine.

4.15 The Committee discussed the most plausible ICERs for trastuzumab emtansine without the patient access scheme. It agreed that lapatinib plus capecitabine, trastuzumab plus capecitabine and trastuzumab plus vinorelbine were in routine use in clinical practice in the NHS and should be included in the analysis. It also agreed that the analysis should use a 15-year time horizon and incorporate the decrease in utility and increased costs associated with treating adverse events. The Committee noted that in both the company's and ERG's base case, trastuzumab plus capecitabine and trastuzumab plus vinorelbine were more costly and less effective than lapatinib plus capecitabine (that is, they were dominated). The company's base-case ICER for trastuzumab emtansine compared with lapatinib plus capecitabine was £167,200 per QALY gained. The Committee noted that the ERG's base-case ICER was very similar at £166,400 per QALY gained. At its first meeting, the Committee agreed that the most plausible ICER was above the ICER range that would normally be considered a cost-effective use of NHS resources.

4.16 At its second meeting, the Committee considered the revised cost-effectiveness results incorporating the patient access scheme submitted in response to the appraisal consultation document (which are commercial in confidence). It expressed disappointment that the patient access scheme did not reduce the ICER to a level

close to one that could be accepted as a cost-effective use of NHS resources. The Committee concluded that the size of the discount in the patient access scheme meant that it was still unable to recommend trastuzumab emtansine for treating HER2-positive, unresectable locally advanced or metastatic breast cancer previously treated with trastuzumab and a taxane.

4.17 The Committee considered whether trastuzumab emtansine represents an innovative treatment. It acknowledged that trastuzumab emtansine is a novel antibody–drug conjugate combining the HER2-targeted anti-tumour activity of trastuzumab with a cytotoxic agent. It also noted that trastuzumab emtansine prolonged survival, with less toxicity than lapatinib plus capecitabine. However, the Committee considered that all benefits of a substantial nature relating to treatment with trastuzumab emtansine had been captured in the QALY calculation, including the favourable adverse-event profile and increased progression-free and overall survival.

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 considered the criterion for short life expectancy. It agreed that the best estimate of expected survival using current standard NHS treatment was demonstrated in the control groups of the trials. The Committee noted that in EMILIA, the median overall survival of patients in the lapatinib plus capecitabine group was 25.1 months. The Committee noted the company's response to the appraisal consultation document suggesting that lapatinib plus capecitabine should not be considered a comparator in the context of life-extending treatments at the end of life because it is only available through the Cancer Drugs Fund. The Committee was aware that it should be guided by established practice in the NHS when identifying the appropriate comparators, irrespective of how these are funded. The Committee noted that lapatinib plus capecitabine was the comparator treatment in the EMILIA trial, and after discussion with clinical specialists the Committee had agreed that lapatinib plus capecitabine was a clinically relevant comparator in the second-line setting (see section 4.3). Lapatinib plus capecitabine was also the relevant comparator for trastuzumab emtansine in the incremental cost-effectiveness analysis. After further consideration, the Committee did not change its view that the evaluation of expected survival with current standard of care should be based on that of patients receiving lapatinib plus capecitabine. However, the Committee did note the comment from the company that if lapatinib plus capecitabine is to be a comparator, evidence on survival from sources other than the EMILIA trial should be taken into account. Specifically, the comment highlighted that in a clinical trial of lapatinib plus capecitabine compared with capecitabine alone (Cameron et al.)

the median survival with lapatinib plus capecitabine was 75 weeks (18.8 months). The Committee considered evidence from this trial, together with other trials for lapatinib plus capecitabine in patients with advanced breast cancer. It noted that patients who received lapatinib plus capecitabine in EMILIA appeared to have lived longer than those who received it in other trials, in which median survival on this treatment generally fell below 24 months. However, the Committee did not have details of the patient characteristics at baseline in these trials, so it could not compare them directly with EMILIA or determine the extent to which they were generalisable to clinical practice. The Committee also noted that the mean survival with lapatinib plus capecitabine estimated by the company in its cost-effectiveness analysis was 30.4 months. The Committee found it difficult to evaluate this conflicting evidence, but after review of the reported median survival from several trials of lapatinib plus capecitabine, it was prepared to accept that trastuzumab emtansine fulfilled this criterion. It also accepted that trastuzumab emtansine fulfilled the other 2 end-of-life criteria, namely a small patient population (approximately 1200) and a survival gain of at least 3 months. The Committee therefore concluded that trastuzumab emtansine fulfilled the criteria for end-of-life consideration.

4.20 Based on the considerations in section 4.19, the Committee discussed whether trastuzumab emtansine represents a cost-effective use of NHS resources. It agreed that, even taking into account additional weights applied to QALY benefits for a life-extending treatment at the end of life, the ICER incorporating the patient access scheme remained well above the range that could be considered a cost-effective use of NHS resources. The Committee concluded that trastuzumab emtansine could not be recommended for treating HER2-positive, unresectable locally

advanced or metastatic breast cancer previously treated with trastuzumab and a taxane.

Pharmaceutical Price Regulation Scheme (PPRS)

4.21 The Committee met after an appeal against the Final Appraisal Determination (FAD) for this appraisal, which was upheld. The Appeal Panel had concluded that 'the 2014 PPRS should have been taken into account, or, alternatively and sufficiently for this appeal, that the possibility of the PPRS being relevant had not been sufficiently considered and its irrelevance established'. The Committee noted that, after this appeal, NICE had sought a view from the Department of Health about whether it should take account the payment mechanism set out in the 2014 PPRS agreement in its technology appraisals. In the Department of Health's view, 'the 2014 PPRS does not place obligations on, nor create expectations of, NICE other than where these are explicitly stated in that agreement'. The Department of Health noted paragraph 4.9 of the PPRS which states that 'the basic cost-effectiveness threshold used by NICE will be retained at a level consistent with the current range and not changed for the duration of the scheme', and stated that 'the PPRS contains no other provisions which require NICE to adopt a particular approach or method for technology appraisals, or to make an adjustment to its considerations to take account of the payment arrangements set out in the Scheme agreement'. The Committee understood that, in response to the appeal decision, NICE developed a position statement about the relevance of the 'PPRS Payment Mechanism' of the 2014 PPRS to assessing the cost effectiveness of new branded medicines. This took into account the views obtained from the Department of Health. It was subsequently refined in a targeted consultation with the Department of Health, the Association of the British Pharmaceutical Industry (ABPI), and NHS England. The

NICE position statement concluded that 'the 2014 PPRS Payment Mechanism should not, as a matter of course, be regarded as a relevant consideration in its assessment of the cost effectiveness of branded medicines'. The Committee noted the response from the ABPI, an association with 57 pharmaceutical company members, which stated that the ABPI had no comments on the substance of the position statement, and welcomed the statement. The Committee also noted the ABPI comment that: 'Indeed, any other interpretation may increase the risk of legal challenge from other companies.' The Committee was, however, aware that the company continued to believe that it was 'unfair to disregard the consideration of PPRS payments within the appraisal process' and was 'deeply disappointed' by the conclusion of the position statement. Company representatives at the meeting stated that the company's opinion was that the NICE position statement should state that 'the 2014 PPRS Payment Mechanism *should*, as a matter of course, be regarded as a relevant consideration in its assessment of the cost effectiveness of branded medicines', and that it should apply to all technology appraisals, not just to the appraisal of trastuzumab emtansine. The Committee concluded that the 2 sole negotiators for the PPRS, that is the Department of the Health and the ABPI, fully supported the NICE position statement, but that the company disagreed with it.

4.22 The Committee discussed what the NICE position statement meant for its consideration of cost effectiveness. It noted the company's suggestion that the failure of NICE to identify a solution was not sufficient reason for the Committee to disregard the impact of the 2014 PPRS on its appraisal of trastuzumab emtansine. The company representatives stated that the company's view was that the Committee should disregard the NICE position statement, and either accept the 'pragmatic solution' suggested in the company's formal response (see section 4.25), or itself devise some other

mechanism to incorporate the PPRS into its evaluation of cost effectiveness. The Committee reminded itself that its role was limited to making recommendations to NICE about the clinical and cost effectiveness of treatments for use within the NHS, in line with the Guide to the methods of technology appraisals 2013. This states that the Committee should not recommend treatments that are not cost effective. It also recalled paragraph 6.4.14 of the Guide to the methods of technology appraisal 2013, which states that: 'The potential budget impact of the adoption of a new technology does not determine the Appraisal Committee's decision.' The Committee concluded that it was not responsible for devising new methods for estimating cost effectiveness and, further, it had neither the remit nor the expertise to do so. Furthermore, it understood that the position statement had been issued as guidance to all NICE technology appraisal committees to ensure consistency of decision-making. It therefore took the view that the NICE position statement should not be disregarded without clear and coherent reasons for doing so.

4.23 The Committee discussed whether the PPRS could potentially be relevant to assessing opportunity costs that underlie a NICE appraisal; that is, would NHS adoption of trastuzumab emtansine, or other branded medicines that were not cost effective, come without additional cost to society, and without reducing spending on other more cost-effective treatments. It noted that the rationale for the NICE position statement was that it was not clear how payments made under the 2014 scheme were being applied in providing NHS services. The payments were not mandated to be allocated to local drug budgets and so would not automatically or routinely allow local commissioners or NHS England to revise their assessment of the opportunity costs of branded medicines. The Committee also noted NHS England's 'Question and Answer document for the NHS on the Pharmaceutical Price Regulation

Scheme (PPRS)', which states that 'the agreement makes no provision for what happens to the PPRS payments, so there is no commitment for the DH [Department of Health] to make any additional payments to the NHS'. Moreover, the Committee was aware that any rebates for drug costs are paid quarterly, so even if the PPRS payments were repaid to the NHS, and directly to local commissioners, who have finite budgets, decisions would have to made to temporarily reduce funding other health services until the PPRS payments are received, which would incur opportunity cost. In addition, there would be no rebate for administration or other follow-on medical costs incurred from introducing a new technology. The Committee also understood that, under the terms of the 2014 PPRS, when the allowed growth rate is exceeded, companies will make a cash payment of a percentage applied to sales covered by the PPRS payment during the relevant quarter (excluding products launched after 1 January 2014), and that percentage will be equal for all companies. Therefore, the Committee considered that the opportunity cost would not only be borne by the NHS, but also by other companies who have joined the 2014 PPRS, and would have to contribute a larger share to the rebate based on how much the allowed spend was exceeded because of trastuzumab emtansine prescribing. The Committee concluded that, as it stands, the 2014 PPRS does not remove the opportunity cost from funding treatments that are not considered to be cost effective according to the normal methods of technology appraisals, and that the precise and full costs of introducing a new technology into the NHS were not covered or rebated via the PPRS.

4.24 The Committee noted that the essence of the position statement was that NICE did not consider that the 2014 PPRS enabled rebates to be transparently attributed to the acquisition cost of individual branded medicines at the time of the appraisal, and so

could not identify a way in which the 2014 PPRS could fit within NICE's framework of appraising cost effectiveness. However, the statement did provide for potential exceptions to the general position of NICE. The Committee referred to the guidance in the Guide to the methods of technology appraisal 2013 on considering prices for technologies in cost-effectiveness analyses. Specifically, it noted paragraph 5.5.2 which states that the public list prices for technologies should be used in the reference-case analysis or alternatively, and when nationally available, price reductions, provided that these are transparent and consistently available across the NHS, and the period for which the specified price is available is guaranteed. Because of the role of the Committee and the basis for the position statement, the Committee concluded that it would only be able to apply the exception provided for in the position statement if the PPRS mechanism could be shown to reduce the cost of the technology to the NHS, and still be in keeping with paragraph 5.5.2 of the Guide to the methods of technology appraisal 2013.

4.25 The Committee discussed the company's proposal that the Committee issues positive guidance on trastuzumab emtansine conditional on the following:

- The company remains within the 2014 PPRS scheme.
- The spend level within the 2014 PPRS scheme remains above the agreed growth levels.
- Guidance is reviewed at the start of the 2019 PPRS scheme.

The Committee noted that the company's proposal did not show how the PPRS rebate mechanism can be applied directly to the cost to the NHS of trastuzumab emtansine, in a way that could be incorporated into a cost-effectiveness analysis. It also heard from NICE that accepting this proposal would potentially be unlawful for

a number of reasons. Firstly, the Committee would be over-riding current guidance on the assessment of the cost effectiveness of health technologies and, by not applying its published methods of technology appraisals, this implies that NICE would not be fulfilling its statutory functions. This would also be incongruous with the 2014 PPRS itself, which states that 'the basic cost-effectiveness threshold used by NICE will be retained at a level consistent with the current range and not changed for the duration of the scheme', indicating that NICE should continue to assess cost effectiveness. Secondly, accepting the proposal would potentially impact on the financial position of other pharmaceutical companies, with the potential legal implications referred to in the ABPI's response to consultation on the NICE position statement (see section 4.21). Thirdly, there is already a mechanism within the existing process for companies to propose special pricing arrangements to be taken into account in technology appraisals – Patient Access Schemes. These have to be approved by the Department of Health, which is also responsible for the 2014 PPRS. The Committee noted that the company could have used this mechanism to apply a price discount commensurate with what it believed would be the true cost of trastuzumab emtansine to the NHS, in the context of the 2014 PPRS. Accepting the company's proposal would, therefore, transcend the existing framework. In summary, the Committee was not satisfied that the company's proposal demonstrated that the impact of the PPRS rebate could be traced back to the opportunity cost of trastuzumab emtansine within the existing Guide to the methods of technology appraisal 2013, and NICE's statutory functions. Because of this, the Committee concluded that the company's proposal did not represent an exception that might lead it to depart from the general position in the NICE statement.

4.26 In conclusion, the Committee did not hear anything that it could consider to be reasonable grounds to disregard the NICE position

statement in this appraisal. The Committee agreed that it may consider the 2014 PPRS if specific proposals are put forward, if these fit within the methods and processes of technology appraisal and are consistent with NICE's statutory functions. However, it did not consider that such proposals had been put forward in this appraisal. Therefore, the Committee concluded that the 2014 PPRS did not affect its previous recommendations about trastuzumab emtansine.

Summary of Appraisal Committee's key conclusions

TAXXX	**Appraisal title: Trastuzumab emtansine for treating HER2-positive, unresectable locally advanced or metastatic breast cancer after treatment with trastuzumab and a taxane**	**Section**
Key conclusion		
Trastuzumab emtansine is not recommended, within its marketing authorisation, for treating adults with human epidermal growth factor receptor 2 (HER2) positive, unresectable locally advanced or metastatic breast cancer previously treated with trastuzumab and a taxane. The Committee agreed that the most plausible incremental cost-effectiveness ratio (ICER) for trastuzumab emtansine (without the patient access scheme) was above the ICER range that would normally be considered a cost-effective use of NHS resources. The Committee concluded that the size of the discount in the patient access scheme meant that it was still unable to recommend trastuzumab emtansine. The Committee agreed that trastuzumab emtansine fulfilled the criteria for end-of-life consideration. However, it agreed that, even taking into account additional weights applied to QALY benefits for a life-extending treatment at the end of life and the patient access scheme, trastuzumab emtansine did not represent a cost-effective use of NHS resources. The Committee concluded that the 2014 Pharmaceutical Price Regulation Scheme (PPRS) did not affect its recommendations about trastuzumab emtansine.		1.1, 4.15, 4.16, 4.19, 4.20, 4.26
Current practice		
Clinical need of patients, including the availability of alternative treatments	The Committee recognised that patients value the availability of more treatment options and that trastuzumab emtansine would be welcomed by patients and their families. The Committee noted that some alternative treatments to trastuzumab emtansine were not offered by all cancer centres or were available in England through the Cancer Drugs Fund, which led to some variation in clinical practice so that no single pathway of care could be defined.	4.1, 4.2

The technology		
Proposed benefits of the technology How innovative is the technology in its potential to make a significant and substantial impact on health-related benefits?	The Committee heard from the clinical specialists that trastuzumab emtansine is both an effective treatment and also well tolerated, with fewer side effects than some of the other options. The Committee acknowledged that trastuzumab emtansine is a novel antibody-drug conjugate combining the HER2-targeted anti-tumour activity of trastuzumab with a cytotoxic agent. It also noted that trastuzumab emtansine prolonged survival, with less toxicity than lapatinib plus capecitabine.	4.1, 4.17
What is the position of the treatment in the pathway of care for the condition?	The Committee noted that the clinical specialists expect that trastuzumab emtansine would be used second line (that is, instead of continued trastuzumab plus chemotherapy or lapatinib plus capecitabine).	4.3
Adverse reactions	The Committee concluded that trastuzumab emtansine had been shown to have a satisfactory adverse-event profile in EMILIA.	4.8
Evidence for clinical effectiveness		
Availability, nature and quality of evidence	The Committee discussed which sources of trial data were appropriate for the place in therapy in which trastuzumab emtansine is likely to be used (that is, the second-line setting). Because 36% of patients in EMILIA and 0% of patients in TH3RESA received treatment as second-line therapy, the Committee concluded that EMILIA was the most relevant source of clinical evidence for its decision-making in this appraisal.	4.4
Relevance to general clinical practice in the NHS	The Committee noted that patients in England may receive pertuzumab plus trastuzumab plus docetaxel in the first-line setting, and that 9.5% of patients in EMILIA had previously received pertuzumab therapy. It also noted the Evidence Review Group (ERG's) concern that none of the patients in EMILIA had an Eastern Cooperative Oncology Group (ECOG) performance status of 2, whereas in clinical practice around one-third of patients would have an ECOG performance status of 2. The Committee agreed that the population in EMILIA was otherwise reasonably representative of patients in the UK, concluding that the results of EMILIA were suitable for the assessment of the clinical effectiveness of trastuzumab emtansine in clinical practice.	4.5, 4.6

Uncertainties generated by the evidence	The Committee considered the clinical effectiveness of trastuzumab emtansine as a second-line treatment. It noted that subgroup analyses of EMILIA suggested a lesser benefit in patients who received second-line treatment (in whom the difference in effect was not statistically significant) than in the overall population. The Committee was aware that the analysis may not have been powered to demonstrate a difference in treatment effect in the subgroup, and that there is no biologically plausible reason for the effect to differ by the number of previous treatments received. The Committee concluded that the subgroup analysis was not reliable enough to inform a decision about the clinical effectiveness of trastuzumab emtansine as a second-line treatment.	4.7
Are there any clinically relevant subgroups for which there is evidence of differential effectiveness?	The Committee noted that the clinical specialists expect that trastuzumab emtansine would be used as a second-line therapy. In EMILIA, 36% of patients received treatment as second-line therapy for locally advanced or metastatic disease.	4.3, 4.4
Estimate of the size of the clinical effectiveness including strength of supporting evidence	The Committee concluded that EMILIA was the most relevant source of clinical evidence for its decision-making in this appraisal. In EMILIA, trastuzumab emtansine increased median overall survival by 5.8 months (trastuzumab emtansine 30.9 months, lapatinib plus capecitabine 25.1 months), and the hazard ratio was 0.68 (95% confidence interval 0.55 to 0.85, $p<0.001$).	3.7, 4.4
Evidence for cost effectiveness		
Availability and nature of evidence	The Committee concluded that the company's model was appropriate to estimate the cost effectiveness of trastuzumab emtansine but that, instead of the 10-year time horizon used in the company's base case, a 15-year time horizon should be used.	4.10
Uncertainties around and plausibility of assumptions and inputs in the economic model	The Committee noted that the company assumed clinical equivalence between capecitabine and vinorelbine, and between trastuzumab plus capecitabine and trastuzumab plus vinorelbine. It heard from the clinical specialists that in their opinion it would be reasonable to assume no difference. The Committee concluded that the assumption of no difference between capecitabine- and vinorelbine-based regimens in the model could be justified for this appraisal.	4.12

Incorporation of health-related quality-of-life benefits and utility values Have any potential significant and substantial health-related benefits been identified that were not included in the economic model, and how have they been considered?	The Committee noted that in the progression-free state, the company applied a higher utility value for trastuzumab emtansine than for its comparators. It noted that evidence from EMILIA suggested that in the trial, patients who received trastuzumab emtansine felt better and reported being less troubled by side effects than those who received lapatinib plus capecitabine. The Committee was aware that EMILIA was an open-label trial, which may have introduced bias in the outcomes reported by patients, but concluded that a marginally higher utility value for trastuzumab emtansine in the progression-free state could be accepted in this appraisal. The Committee noted that the model incorporated utility decrements for only 3 adverse events and costs for 2 adverse events. It concluded that the model should have incorporated the decrease in utility and the increased costs associated with the adverse events that occurred frequently in EMILIA.	4.11, 4.13
Are there specific groups of people for whom the technology is particularly cost effective?	There are no specific groups of people for whom the technology is particularly cost effective.	
What are the key drivers of cost effectiveness?	There were no specific Committee considerations on the key drivers of cost effectiveness.	
Most likely cost-effectiveness estimate (given as an ICER)	The Committee noted that, without the patient access scheme, the company's base-case ICER for trastuzumab emtansine compared with lapatinib plus capecitabine was £167,200 per QALY gained, and that the ERG's base-case ICER was very similar at £166,400 per QALY gained. It agreed that the most plausible ICER was above the ICER range that would normally be considered a cost-effective use of NHS resources, and that the patient access scheme did not reduce that ICER to a level close to one that could be accepted as a cost-effective use of NHS resources.	4.15, 4.16

Additional factors taken into account		
Patient access schemes (PPRS)	Roche has agreed a patient access scheme with the Department of Health. If trastuzumab emtansine had been recommended, this scheme would provide a simple discount to the list price of trastuzumab emtansine, with the discount applied at the point of purchase or invoice. The level of the discount is commercial in confidence. The Committee concluded that the proposals put forward by the company to take into account the PPRS did not represent an exception that might lead it to depart from the general position in the NICE statement.	2.3, 4.25
End-of-life considerations	Although the median survival of patients in the lapatinib plus capecitabine group of EMILIA was 25.1 months and the mean survival with lapatinib plus capecitabine was 30.4 months, review of the reported survival times from several trials other than EMILIA suggested that life expectancy on lapatinib plus capecitabine generally fell below 24 months. The Committee could not compare those trials directly with EMILIA or determine the extent to which they were generalisable to clinical practice but, based on the reported median survival on lapatinib plus capecitabine in them, it was prepared to accept that trastuzumab emtansine fulfilled the criterion for short life expectancy. It also accepted that trastuzumab emtansine fulfilled the other 2 end-of-life criteria (a small patient population and a survival gain of at least 3 months). However, it agreed that, even taking into account additional weights applied to QALY benefits for a life-extending treatment at the end of life and the patient access scheme, trastuzumab emtansine did not represent a cost-effective use of NHS resources.	4.19, 4.20
Equalities considerations and social value judgements	No equality issues relevant to the Committee's preliminary recommendations were raised.	

5 Related NICE guidance

Details are correct at the time of consultation and will be removed when the final guidance is published. Further information is available on the NICE website.

Published

- Eribulin for the treatment of locally advanced or metastatic breast cancer. NICE technology appraisal guidance 250 (2012).
- Advanced breast cancer: diagnosis and treatment. NICE clinical guideline 81 (2009).
- Guidance on the use of trastuzumab for the treatment of advanced breast cancer. NICE technology appraisal guidance 34 (2002).

Under development

- Pertuzumab in combination with trastuzumab and docetaxel for treating HER2-positive metastatic or locally recurrent unresectable breast cancer. NICE technology appraisal. Publication date to be confirmed.

6 Review of guidance

6.1 The guidance on this technology will be considered for review 3 years after publication of the guidance. The Guidance Executive will decide whether the technology should be reviewed based on information gathered by NICE, and in consultation with consultees and commentators.

Jane Adam
Chair, Appraisal Committee
November 2015

7 Appraisal Committee members and NICE project team

Appraisal Committee members

The Appraisal Committees are standing advisory committees of NICE. Members are appointed for a 3-year term. A list of the Committee members who took part in the discussions for this appraisal appears below. There are 4 Appraisal Committees, each with a chair and vice chair. Each Appraisal

Committee meets once a month, except in December when there are no meetings. Each Committee considers its own list of technologies, and ongoing topics are not moved between Committees.

Committee members are asked to declare any interests in the technology to be appraised. If it is considered there is a conflict of interest, the member is excluded from participating further in that appraisal.

The minutes of each Appraisal Committee meeting, which include the names of the members who attended and their declarations of interests, are posted on the NICE website.

Dr Jane Adam (Chair)
Consultant Radiologist, Department of Diagnostic Radiology, St George's Hospital, London

Professor Iain Squire (Vice-Chair)
Consultant Physician, University Hospitals of Leicester

Dr Gerardine Bryant
General Practitioner, Swadlincote, Derbyshire

Dr Andrew England
Senior Lecturer, Directorate of Radiography, University of Salford

Mr Adrian Griffin
Vice President, HTA & International Policy, Johnson & Johnson

Dr Anne McCune
Consultant Hepatologist, University Hospitals Bristol NHS Foundation Trust

Professor John McMurray
Professor of Medical Cardiology, University of Glasgow

Dr Mohit Misra

General Practitioner, Queen Elizabeth Hospital, London

Ms Pamela Rees

Lay Member

Dr Brian Shine

Consultant Chemical Pathologist, John Radcliffe Hospital, Oxford

Dr Eldon Spackman

Research Fellow, Centre for Health Economics, University of York

Mr David Thomson

Lay member

Dr John Watkins

Clinical Senior Lecturer, Cardiff University; Consultant in Public Health Medicine, National Public Health Service Wales

Professor Olivia Wu

Professor of Health Technology Assessment, University of Glasgow

Dr Nerys Woolacott

Senior Research Fellow, Centre for Health Economics, University of York

NICE project team

Each technology appraisal is assigned to a team consisting of 1 or more health technology analysts (who act as technical leads for the appraisal), a technical adviser and a project manager.

Ahmed Elsada

Technical Lead

Sally Doss and Zoe Charles

Technical Advisers

Bijal Joshi
Project Manager

8 Sources of evidence considered by the Committee

A. The Evidence Review Group (ERG) report for this appraisal was prepared by the School of Health and Related Research (ScHARR), The University of Sheffield:

- Squires H, Simpson EL, Harvey R, et.al. T-DM1 for treating HER2-positive, unresectable locally advanced or metastatic breast cancer after treatment with trastuzumab and a taxane: A Single Technology Appraisal, February 2014

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. Company:

- Roche Products

II. Professional/specialist and patient/carer groups:

- Breakthrough Breast Cancer
- Breast Cancer Campaign
- Breast Cancer Care
- Royal College of Nursing
- Royal College of Physicians (NCRI/RCP/RCR/ACP/JCCO)
- United Kingdom Oncology Nursing Society

III. Other consultees:

- Department of Health
- NHS England
- Welsh Government

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

- Department of Health, Social Services and Public Safety for Northern Ireland
- GlaxoSmithKline (lapatinib)
- Healthcare Improvement Scotland
- Medicines and Healthcare products Regulatory Agency
- National Collaborating Centre for Cancer

C. The following individuals were selected from clinical specialist and patient expert nominations from the consultees and commentators. They gave their expert personal view on trastuzumab emtansine by attending the initial Committee discussion and providing written evidence to the Committee. They were also invited to comment on the ACD.

- Dr Anne Armstrong, Consultant Medical Oncologist, nominated by organisation representing Royal College of Physicians (NCRI/RCP/RCR/ACP/JCCO) – clinical specialist
- Dr Gianfilippo Bertelli, Consultant / Honorary Senior Lecturer in Medical Oncology, nominated by organisation representing Royal College of Physicians (NCRI/RCP/RCR/ACP/JCCO) – clinical specialist
- Elisabeth Segal, nominated by organisation representing Breakthrough Breast Cancer – patient expert
- Tara Beaumont, nominated by organisation representing Breast Cancer Care – patient expert

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

- Roche Products