NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Final appraisal determination

Trastuzumab emtansine for treating HER2-positive advanced breast cancer after trastuzumab and a taxane

1 Recommendations

1.1 Trastuzumab emtansine is recommended, within its marketing authorisation, as an option for treating human epidermal growth factor receptor 2 (HER2)-positive, unresectable, locally advanced or metastatic breast cancer in adults 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 recommended only if the company provides it in line with the commercial access agreement with NHS England.

2 The technology

Description of the technology	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.
Marketing authorisation	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'.
Adverse reactions	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.
Recommended dose and schedule	Trastuzumab emtansine is administered as an intravenous infusion. The recommended dose is 3.6 mg/kg bodyweight every 3 weeks (21-day cycle). Patients should have treatment until the disease progresses or unacceptable toxicity occurs.

Price	The list price for trastuzumab emtansine is £1,641.01 for a 100 mg vial and £2,625.62 for a 160 mg vial (excluding VAT, British national formulary online, accessed February 2017). The company estimates that the average cost of a course of treatment is £91,614, using the list price, and based on 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. The pricing arrangement considered during guidance development was one in which the company (Roche) had agreed a complex patient access scheme with the Department of Health. At the end of the appraisal process, the patient access scheme was replaced with a commercial access agreement between Roche and NHS England. The commercial access agreement provides similar reductions in the total costs of treatment to the latest patient access scheme offer, and a simpler operational approach. The details of the agreement are commercial in confidence.

3 Evidence

3.1 The appraisal committee (section 7) considered evidence submitted by Roche and a review of this submission by the evidence review group. The appraisal was a Cancer Drugs Fund reconsideration of NICE's technology appraisal guidance on trastuzumab emtansine for the treatment of HER2-positive, unresectable locally advanced or metastatic breast cancer after treatment with trastuzumab and a taxane. The committee also considered the updated cost-effectiveness analyses submitted by Roche after consultation and its critique by the evidence review group.

3.2 Sections 4.1 to 4.26 reflect the committee's consideration of the evidence submitted in December 2013 for the original appraisal and the subsequent responses to consultation received during the development of TA371. The company included 2 randomised controlled trials in its original 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 the clinician's choice of treatment. The company used 4 additional randomised controlled trials, together with EMILIA, in a mixed treatment comparison of trastuzumab emtansine and the other comparators listed in the scope. Sections 4.27 to 4.35 reflect the committee's consideration of the evidence submitted for the Cancer Drugs Fund reconsideration. The new evidence included additional follow-up data from EMILIA, which was used to model overall survival. New cost-effectiveness analyses were done using a complex patient access scheme. The patient access scheme considered by the committee was subsequently replaced by a commercial access agreement between Roche and NHS England. The commercial access agreement provides similar reductions in the total costs of treatment to the latest patient access scheme offer, and a simpler operational approach. The details of the agreement are commercial in confidence.

3.3 See the committee papers for full details of the Cancer Drugs Fund reconsideration evidence, and the history for full details of the evidence used in NICE's original technology appraisal guidance on trastuzumab emtansine.

4 Committee discussion

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.

Clinical effectiveness (NICE technology appraisal guidance 371)

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 experts 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 experts 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 (see NICE's guidance on the use of trastuzumab for the treatment of advanced breast cancer). 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 (see NICE's guideline on advanced breast cancer). The committee heard from the clinical experts 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 plus 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 experts 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 experts 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 has 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 this stage of the disease.

4.4 The committee discussed which sources of trial data were appropriate for the second-line setting, in which trastuzumab emtansine is likely to be used. The committee was aware that 36% of patients in EMILIA and 0% of patients in TH3RESA received trastuzumab emtansine 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 experts that there was no evidence on whether or not pertuzumab can modify the effect of subsequent treatment with trastuzumab emtansine. However, the clinical experts 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'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 appreciated that patients enrolled in clinical trials may be younger and with better performance status than those in routine clinical practice, and so might have better outcomes. The committee agreed that the population in EMILIA was otherwise reasonably

representative of patients in the UK. It concluded that the results of EMILIA were suitable for assessing 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 had improved survival compared with patients in the lapatinib plus 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. The committee was aware that the analysis may not have been powered to show a difference in treatment effect in the subgroup. In addition, the committee heard from the clinical experts 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, 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, and the study by Martin et al. (2011), 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 (NICE technology appraisal guidance 371)

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 for these patients would not be included in a model with a 10−year horizon. The committee agreed that in principle a lifetime time horizon should be used to capture all long-term costs and health effects. It 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 experts 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 treatment benefit 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 for NICE technology appraisal guidance 371, 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, 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. 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 experts whether this

assumption was clinically plausible. The clinical experts 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. 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 after 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 EMILIA, and after discussion with clinical experts the committee agreed that lapatinib plus capecitabine was a clinically relevant comparator in the second-line setting. 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 EMILIA 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. 2010) 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 1,200) 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 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 of 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 appraisal (2013). This states that the committee should not recommend treatments that are not cost effective. It also recalled paragraph 6.2.14 of the guide, 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 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 be 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 through 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.

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 overriding current guidance on the assessment of the cost effectiveness of health technologies and, by not applying its published methods of technology appraisal, 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 in line 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 NICE 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.

Cancer Drugs Fund reconsideration

4.27 This appraisal was a Cancer Drugs Fund reconsideration of NICE's technology appraisal guidance on trastuzumab emtansine for treating HER2-positive, unresectable, locally advanced or metastatic breast cancer after treatment with trastuzumab and a taxane. In its revised submission, the company included:

- an additional 2 years follow-up data from EMILIA, which was used to model overall survival
- a complex patient access scheme in which the NHS would pay for trastuzumab emtansine up to the first 14 months of treatment for each patient, and the company would pay for trastuzumab emtansine for any

patients remaining on treatment beyond 14 months (which was subsequently amended after the first committee meeting)[1] and

- an updated model incorporating new data and using some of the committee's preferred assumptions (see sections 4.10 to 4.20):
  - extending the model time horizon from 10 to 15 years
  - incorporating the follow-up costs of left ventricular ejection fraction monitoring
  - correcting the utility values for adverse events (although the ERG suggested that these may still be incorrect)
  - using the actual dose of trastuzumab emtansine and lapatinib plus capecitabine rather than the planned dose
  - revising the parameters for the probabilistic sensitivity analysis and
  - estimating the post-progression treatment costs.

Clinical management of HER2-positive advanced breast cancer

4.28 The committee heard from the clinical experts that trastuzumab emtansine is an effective treatment, which improves overall survival by several months compared with other HER2-directed treatments. The clinical experts recognised that trastuzumab emtansine is not suitable for everyone, but noted that it is particularly well tolerated in many people compared with other treatments. The committee heard that the other treatment options have a worse toxicity and side effect profile than trastuzumab emtansine. It also heard that, on average, after 6 months of capecitabine treatment people start to have major side effects, which reduce treatment effectiveness and cause people to stop treatment. This also applies to the combination therapies, trastuzumab plus capecitabine and lapatinib plus capecitabine. People whose disease responds well to trastuzumab emtansine have improved quality of life as well as longer life.

[1] The complex patient access scheme was subsequently replaced by a commercial access agreement. See section 2 for further details.

The clinical experts noted that they can assess whether trastuzumab emtansine is effective or limited by toxicity within 3 cycles. Treatment normally continues until disease progression. The clinical experts stated that the next line of treatment after trastuzumab emtansine would depend on the person's treatment history, but options were limited at this stage, and often this would be palliative care.

Patient experience

4.29 The patient experts described the benefits of treatment with trastuzumab emtansine. They stated that as well as the treatment stopping the progression of the condition, quality of life is better with trastuzumab emtansine than with other treatments. They noted that the side effects are minimal so they no longer need to be admitted to hospital or confined to bed after treatment. The patient experts stated that trastuzumab emtansine has removed some of the fear associated with their disease and has given them quality time with family and friends. They also emphasised that trastuzumab emtansine has helped them to live their lives fully and continue working, 2 factors that are very important and highly valued by patients, especially because many are relatively young women with caring responsibilities. They stated that if the drug were not available there would be no other suitable treatments for them.

4.30 The committee acknowledged the comments from patients after consultation, in particular that 115,000 people have signed a Breast Cancer Now petition urging NICE and Roche to ensure that trastuzumab emtansine remains available for patients in England. The committee appreciated how important it is for effective treatments for breast cancer to be available, but noted that its role was to consider the clinical and cost effectiveness of this technology at the price set by the company (including any nationally agreed access arrangements). Nevertheless, the committee acknowledged that it was relevant that the treatment had been provided to patients in the NHS in England for 3 years so that patients and

clinicians would view a negative recommendation as 'taking away' an existing NHS funded treatment. Although it could be argued that the opportunity cost issues are not the same for a previously-funded drug as for one that requires new NHS investment, the NICE methods guide does not have any specific mechanisms or advice which apply to this situation.

Comparators

4.31 The committee noted that the company had excluded some of the comparators listed in the original appraisal from the incremental analysis in the revised submission. The committee assumed that vinorelbine had been excluded because it was expected to be dominated (less effective and more costly) by capecitabine. The company also excluded lapatinib plus capecitabine from the cost-effectiveness analysis because lapatinib was removed from the Cancer Drugs Fund in January 2015. The company stated that it has independent audit data to suggest that lapatinib plus capecitabine no longer represents current practice in England. The committee heard that lapatinib was removed from the Cancer Drugs Fund because the evaluation score (which considers clinical effectiveness, toxicity and drug cost for the Cancer Drugs Fund) for lapatinib plus capecitabine was considered to be too low to keep it in the Fund. The committee heard from the Cancer Drugs Fund clinical lead that drugs that had been removed from the Cancer Drugs Fund were no longer commissioned in England. The committee noted that lapatinib plus capecitabine was removed after trastuzumab emtansine became available. Since then, trastuzumab emtansine has become part of NHS clinical practice, and has replaced the comparator treatments listed in the original scope. The committee noted the company's opinion that trastuzumab plus capecitabine should be considered as the main comparator for trastuzumab emtansine. Responses from other consultees and commentators supported this view. The committee heard from the clinical expert and the Cancer Drugs Fund clinical lead that if trastuzumab emtansine were not available, trastuzumab plus capecitabine was likely to

be offered to patients with HER2-positive advanced breast cancer who had relapsed after first-line trastuzumab-based therapy. The committee noted that trastuzumab plus capecitabine does not have a marketing authorisation for this indication but was aware that according to section 6.2 of the NICE guide to the methods of technology appraisal, comparators without a marketing authorisation for the relevant indication can be considered as comparators by the committee if they are part of established practice in the NHS. It also noted that based on the results of the network meta-analysis, trastuzumab plus capecitabine showed similar clinical effectiveness to lapatinib plus capecitabine. Overall the committee concluded that based on what it had heard from experts at the committee meeting and in light of the consultation comments, trastuzumab plus capecitabine is the most relevant comparator.

The company's revised economic model

4.32 The committee considered the company's updated economic model submitted for the cancer drugs fund reconsideration and the subsequent updates in response to the ERG's critique. It also considered the ERG's exploratory analyses. It acknowledged that the final version of the model from the company took into account the ERG's concerns about the plausibility of the methods used in the probabilistic sensitivity analysis in the model. The company:

- used patient level data to calculate vial use
- excluded an additional adjustment for wastage
- updated the patient access scheme[1] and
- updated the probabilistic sensitivity analysis in line with the ERG's suggestions.

The committee heard from the ERG that the patient access scheme and other amendments had been accurately incorporated in the model. The committee agreed that the company's changes were plausible. It also noted that the updated probabilistic sensitivity analysis in the final version

was validated by the ERG. In general the ERG was satisfied with the updated analysis, but it also tested alternative prior distributions to determine the sensitivity of the economic model. As a result, the cost-effectiveness results presented by the company and the ERG were very similar.

Calculation of treatment costs

4.33 The committee considered the company's economic model and the ERG's critique. The committee noted that the company initially estimated average vial use using the average dose from EMILIA, but also used patient level data to calculate vial use after a request from the ERG. The committee noted that using patient level data increased the ICER compared with the company's base case, but it recognised that this did not account for dose reductions or treatment breaks. The committee heard that there is vial sharing in oncology centres that have centralised intravenous drug preparation. This reduces the amount of wastage, but cannot stop it completely. The committee noted that the company's revised economic model assumed no wastage because it used patient level data to calculate vial use, although the previous version of the model assumed that 50% of any drug remaining in a vial after the dose is drawn up is re-used and 50% is wasted. The committee concluded that some wastage needs to be included in the calculation of trastuzumab emtansine treatment costs, because assuming no wastage is not plausible.

End-of-life considerations

4.34 The committee considered the advice about life-extending treatments for people with a short life expectancy in NICE's final Cancer Drugs Fund technology appraisal process and methods. The committee noted that the updated median overall survival in the EMILIA intention-to-treat population was 25.9 months for people randomised to lapatinib plus capecitabine (it was 25.1 months at the time of the original appraisal), and 29.9 months for those randomised to trastuzumab emtansine. The committee

recognised that during NICE's original appraisal of trastuzumab emtansine, evidence from other trials of lapatinib plus capecitabine in advanced breast cancer was also considered. The original appraisal committee noted that patients who received lapatinib plus capecitabine in EMILIA appeared to live longer than those who received it in other trials, in which median survival generally fell below 24 months. The committee also considered the evidence submitted by the company for life expectancy with trastuzumab plus capecitabine. It heard from the company that there are limited data available on the life expectancy of patients with metastatic breast cancer receiving trastuzumab with capecitabine as second-line treatment. However, data from the CEREBEL study (Pivot et al. 2015) suggests that it is likely to be around 24 months. The committee took into account that patients with metastatic disease who are eligible for trastuzumab emtansine had already progressed on first-line therapy and were in the advanced stages of the disease. Therefore the committee agreed to uphold the end-of-life decision from the original appraisal. It was aware that it was now looking at a different comparator from the one on which the original decision had been made (lapatinib plus capecitabine), but judged that any difference in survival between lapatinib plus capecitabine and trastuzumab and capecitabine was likely to be marginal, taking into account the results of the network meta–analysis (see section 4.31). The committee therefore concluded that trastuzumab emtansine fulfilled the criteria for a life-extending, end-of-life treatment for HER2-positive advanced breast cancer.

Conclusions

4.35 The committee noted that the updated evidence available since the original appraisal confirms that trastuzumab emtansine is clinically effective, with a statistically significant survival benefit compared with lapatinib plus capecitabine. Despite only indirect evidence of its effectiveness compared with trastuzumab plus capecitabine, there was no reason to consider that the relative benefits would not be comparable.

Based on what the committee heard from experts at the committee meeting and in light of the consultation comments, it concluded that trastuzumab plus capecitabine is the most relevant comparator. Based on the clinical and cost-effectiveness analyses, including the updated complex patient access scheme, the most plausible ICER for trastuzumab emtansine compared with trastuzumab plus capecitabine was within the range that would normally be considered cost effective if the end-of-life criteria apply. The committee therefore concluded that trastuzumab emtansine could be recommended for use in the NHS for treating HER2-positive advanced breast cancer.

Summary of appraisal committee's key conclusions

TAXXX	**Appraisal title: Trastuzumab emtansine for treating HER2-positive advanced breast cancer after trastuzumab and a taxane**	**Section**
Key conclusion (Cancer Drugs Fund reconsideration of TA371)		
Trastuzumab emtansine is recommended, within its marketing authorisation, as an option for treating human epidermal growth factor receptor 2 (HER2)-positive, unresectable, locally advanced or metastatic breast cancer in adults 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 recommended only if the company provides it in line with the commercial access agreement with NHS England. The updated evidence available since the original appraisal confirms that trastuzumab emtansine is clinically effective, with a statistically significant survival benefit compared with lapatinib plus capecitabine. Despite only indirect evidence of its effectiveness compared with trastuzumab plus capecitabine, there was no reason to consider that the benefits would not be comparable. Based on the clinical and cost-effectiveness analyses, including an updated complex patient access scheme (that was subsequently replaced by a commercial access agreement), the most plausible ICER for trastuzumab emtansine compared with trastuzumab plus capecitabine was within the range that would normally be considered cost effective if the end-of-life criteria apply.		1.1, 4.35

Cancer Drugs Fund reconsideration of TA371	
The company's revised submission included: • an additional 2 years follow-up data from EMILIA, which was used to model overall survival and • a complex patient access scheme. After consultation an updated model was submitted, in which the company: • used patient level data to calculate vial use • excluded an additional adjustment for wastage and • updated the patient access scheme and • updated the probabilistic sensitivity analysis in line with the ERG's suggestions. The committee considered that based on what it heard from experts at the committee meeting and in light of the consultation comments, trastuzumab plus capecitabine is the only relevant comparator. It also recognised that during NICE's original appraisal on trastuzumab emtansine, the original appraisal committee noted that patients who received lapatinib plus capecitabine in EMILIA appeared to live longer than those who received it in other trials, in which median survival generally fell below 24 months. The committee also considered the evidence submitted by the company for life expectancy with trastuzumab plus capecitabine. It heard from the company that data from the CEREBEL study (Pivot et al. 2015) suggests that it is likely to be around 24 months. The committee took into account that patients with metastatic disease eligible for trastuzumab emtansine had already progressed on first-line therapy, and were in the advanced stages of the disease. Therefore the committee agreed to uphold the end-of-life decision from the original appraisal. The committee therefore concluded that trastuzumab emtansine fulfilled the criteria for a life-extending, end-of life treatment for HER2 positive advanced breast cancer. Taking into account all factors, including the end-of-life criteria and the commercial access agreement that replaced the updated complex patient access scheme, trastuzumab emtansine could be recommended for use in the NHS for treating HER2-positive advanced breast cancer.	4.27, 4.32, 4.34, 4.35

5 Implementation

5.1 Section 7 of the National Institute for Health and Care Excellence (Constitution and Functions) and the Health and Social Care Information Centre (Functions) Regulations 2013 requires clinical commissioning

groups, NHS England and, with respect to their public health functions, local authorities to comply with the recommendations in this appraisal within 3 months of its date of publication.

5.2 The Welsh Assembly Minister for Health and Social Services has issued directions to the NHS in Wales on implementing NICE technology appraisal guidance. When a NICE technology appraisal recommends the use of a drug or treatment, or other technology, the NHS in Wales must usually provide funding and resources for it within 3 months of the guidance being published.

5.3 When NICE recommends a treatment 'as an option', the NHS must make sure it is available within the period set out in the paragraphs above. This means that, if a patient has HER2-positive advanced breast cancer and the doctor responsible for their care thinks that trastuzumab emtansine is the right treatment, it should be available for use, in line with NICE's recommendations.

5.4 NHS England and Roche have agreed that trastuzumab emtansine will be available to the NHS with a commercial access agreement. It is the responsibility of the company to communicate details of the scheme to the relevant NHS organisations. Any enquiries from NHS organisations about the commercial access agreement should be directed to [NICE to add details at time of publication]

6 Review of guidance

6.1 The guidance on this technology will be considered for review by the guidance executive 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, TA371 appraisal committee, November 2015

Andrew Stevens
Chair, Cancer Drugs Fund reconsideration of TA371 appraisal committee, February 2017

Jane Adam
Chair, appraisal committee, May 2017

7 Appraisal committee members and NICE project team

Appraisal committee members

The technology appraisal committees are standing advisory committees of NICE. This topic was considered by members of the existing standing committees who have met to reconsider drugs funded by the Cancer Drugs Fund and by committee A. The names of the members who attended are in the minutes of the appraisal committee meeting, which are posted in the NICE website.

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.

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.

TA371

Ahmed Elsada
Technical Lead

Sally Doss and Zoe Charles

Technical Advisers

Bijal Joshi

Project Manager

Cancer Drugs Fund reconsideration of TA371

Janet Robertson

Associate Director

Boglarka Mikudina and Helen Powell

Technical Leads

Jenna Dilkes

Project Manager

ISBN: [to be added at publication]