NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

Final appraisal determination

Lapatinib for the treatment of women with previously treated advanced or metastatic breast cancer

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

1 Guidance

1.1 Lapatinib (in combination with capecitabine), within its licensed indication, is not recommended for the routine treatment of women with previously treated advanced or metastatic breast cancer whose tumours overexpress HER2, except in the context of clinical trials.

1.2 Women currently receiving lapatinib should have the option to continue therapy until they and their clinicians consider it appropriate to stop.

2 The technology

2.1 Lapatinib (Tyverb, GlaxoSmithKline) is an inhibitor of the intracellular tyrosine kinase domains of ErbB1 (EGFR) and ErbB2 (HER2) receptors. Lapatinib, in combination with capecitabine, has a marketing authorisation for the treatment of patients with advanced or metastatic breast cancer whose tumours overexpress ErbB2 (HER2). Patients should have progressive disease following prior therapy which must include anthracyclines, taxanes and therapy with trastuzumab in the metastatic setting. The marketing authorisation was granted conditional on the manufacturer

performing and submitting an updated analysis of survival data for study EGF100151 (now completed) and conducting a phase III randomised, controlled clinical study to evaluate the incidence of brain metastases as the site of relapse with a lapatinib-containing therapy compared with an appropriate trastuzumab-containing therapy. Lapatinib is administered orally. The recommended dosage of lapatinib is 1250 mg/day to be taken continually. The recommended dosage of capecitabine, when taken with lapatinib, is 2000 mg/m^2 per day taken on days 1–14 of a 21-day cycle.

2.2 The summary of product characteristics (SPC) states that lapatinib has been associated with decreases in left ventricular ejection fraction. Caution should be taken if lapatinib is to be administered to patients with conditions that could impair left ventricular function. Left ventricular ejection fraction should be evaluated in all patients before initiation of treatment and continue to be evaluated during treatment with lapatinib. The SPC also states that diarrhoea, including severe diarrhoea, has been reported with lapatinib treatment. It therefore recommends proactive management of diarrhoea with anti-diarrhoeal agents. The SPC further warns of toxicity to the liver and recommends that liver function should be monitored before initiation of treatment and monthly thereafter or as clinically indicated. Lapatinib should be discontinued if changes in liver function are severe and patients should not be re-treated. For full details of side effects and contraindications, see the SPC.

2.3 The acquisition cost for lapatinib is £11.49 per 250-mg tablet (excluding VAT; 'British national formulary' [BNF] edition 56). The cost of lapatinib treatment is £57.45 per day, or £20,969 per year. The acquisition cost for capecitabine is £0.74 per 150-mg tablet and £2.46 per 500-mg tablet. The cost of 60 x 150-mg tablets of capecitabine is £44.47 and 120 x 500-mg tablets is £295.06 (excluding VAT; BNF edition 56). The cost of a 21-day cycle of

capecitabine treatment, based on a person with a body surface area of 1.77 m^2, is £244.00 per cycle or £4238 per year. This gives a combined cost of lapatinib plus capecitabine of approximately £25,207 per year. Costs may vary in different settings because of negotiated procurement discounts.

3 The manufacturer's submission

The Appraisal Committee (appendix A) considered evidence submitted by the manufacturer of lapatinib and a review of this submission by the Evidence Review Group and the Decision Support Unit (ERG and DSU; appendix B).

3.1 The manufacturer's analysis included several different comparators including capecitabine monotherapy, vinorelbine monotherapy, trastuzumab monotherapy and trastuzumab combination therapy. The manufacturer stated that because of the absence of an alternative HER2-suppressing agent some patients continue to receive trastuzumab following progression of disease, either alone, or in combination with cytotoxic chemotherapy. The manufacturer also reported that those patients who are most likely to receive trastuzumab following progression of disease are those in whom the drug still appears to be having some effect despite progression and that they could receive lapatinib instead. The manufacturer presented the results of market research (n = 24 patients) that identified which treatments were used following progression of disease after treatment with trastuzumab. The data showed that 17% of these patients continued to receive trastuzumab with the addition of vinorelbine, 17% continued to receive trastuzumab with the addition of capecitabine, and 7% continued to receive trastuzumab without the addition of further treatments. The other 59% of patients switched treatment to non-trastuzumab-containing regimens.

Clinical effectiveness

3.2 The manufacturer reported details of one randomised controlled trial (RCT). This open-label trial enrolled women with HER2-overexpressing advanced or metastatic breast cancer, who had received prior therapy, which included anthracyclines, taxanes and trastuzumab in the advanced or metastatic setting. Patients were randomised to receive treatment with lapatinib plus capecitabine or capecitabine alone. Enrolment in the trial was halted early after a recommendation from the Independent Data Monitoring Committee because an interim analysis showed an improvement in time to progression in the lapatinib plus capecitabine group compared with the capecitabine monotherapy group. Therefore, the trial may have been underpowered to detect a statistical difference in some of the specified secondary outcomes. At the time enrolment was ended, 198 patients were enrolled in the lapatinib plus capecitabine group and 201 patients in the capecitabine monotherapy group.

3.3 The primary outcome measure was time to progression, and the secondary outcomes were overall survival, progression-free survival, overall tumour response rate, clinical benefit rate and duration of response. The results reported here all relate to the analysis done using data for the April 2006 cut-off date unless otherwise stated. Statistically significant results in favour of the combined treatment group were reported for median time to progression, which was 27.1 weeks for lapatinib plus capecitabine compared with 18.6 weeks for capecitabine monotherapy (hazard ratio [HR] 0.57; 95% confidence interval [CI] 0.43 to 0.77, $p < 0.001$). Similarly, a statistically significant difference was reported for median progression-free survival, which was 27.1 weeks for the lapatinib plus capecitabine group compared with 17.6 weeks for the capecitabine monotherapy group (HR 0.55; 95% CI 0.41 to 0.74, $p < 0.001$). There was no statistically significant difference in median overall survival: 67.7 weeks for lapatinib plus

capecitabine and 66.6 weeks for capecitabine monotherapy (HR 0.78; 95% CI 0.55 to 1.12, p = 0.177).

3.4 The manufacturer provided updated overall survival data for a September 2007 cut-off from the main RCT. In both groups the median overall survival was longer when compared with the April 2006 cut-off data (see section 3.3). However, the difference between the two groups remained statistically non-significant. Median overall survival for the lapatinib plus capecitabine group for the September 2007 data was 74.0 weeks compared with 65.9 weeks for the capecitabine monotherapy group (HR 0.90; 95% CI 0.71 to 1.12, p = 0.3). These data may be subject to confounding because some patients in the capecitabine monotherapy group crossed over to the lapatinib plus capecitabine group during the trial.

3.5 The manufacturer also provided updated clinical-effectiveness data for trastuzumab. The original pooled estimate of time to progression data from eight studies (described in section 3.7) was updated with four newly available studies, including one RCT of trastuzumab plus capecitabine compared with capecitabine monotherapy. The updated pooled estimate of median time to progression was 27 weeks (95% CI 23.3 to 31.1) with an HR of 0.70 (95% CI 0.61 to 0.81). In addition to the pooled estimate, the manufacturer also provided data separately for the RCT of trastuzumab plus capecitabine compared with capecitabine monotherapy. The median time to progression for trastuzumab plus capecitabine was 8.2 months (95% CI 7.3 to 11.2) compared with 5.6 months (95% CI 4.2 to 6.3) for capecitabine monotherapy (HR 0.69; p = 0.034). The median overall survival for trastuzumab plus capecitabine was 25.5 months (95% CI 19.0 to 30.7) compared with 20.4 months (95% CI 17.8 to 24.7) for capecitabine monotherapy (HR 0.76; p = 0.26).

3.6 Diarrhoea was more common in the lapatinib plus capecitabine group compared with the capecitabine monotherapy group (affecting 65% and 40% of women in the two treatment groups, respectively). Palmar-plantar erythrodysaesthesia, a well-recognised side effect of capecitabine treatment, was also a common adverse event in the RCT, reported by 53% of women in the lapatinib plus capecitabine group and 51% in the capecitabine monotherapy group. In addition, seven (4%) women in the lapatinib plus capecitabine group and two (1%) women in the capecitabine monotherapy group experienced a decreased left ventricular ejection fraction; five of the seven women receiving combination therapy were asymptomatic. For other commonly reported adverse events (rash, vomiting, nausea and fatigue), the incidences were similar in both treatment groups. The European Medicines Agency (EMEA) scientific discussion showed that 24% of patients in the lapatinib plus capecitabine group and 23% in the capecitabine monotherapy group discontinued treatment because of adverse events.

Cost effectiveness

3.7 The manufacturer's submission included an economic model. The model compared lapatinib plus capecitabine versus: capecitabine monotherapy, vinorelbine monotherapy, trastuzumab in combination with vinorelbine or capecitabine, and trastuzumab monotherapy. The economic model used clinical-effectiveness data for lapatinib and capecitabine from the RCT. A further systematic review carried out by the manufacturer did not identify any studies comparing lapatinib plus capecitabine against trastuzumab-containing regimens. However, the review did identify non-comparative data for trastuzumab-containing regimens. Therefore, the manufacturer pooled median time-to-progression data from eight non-RCTs of trastuzumab-containing regimens, and this was assumed to be equivalent to median progression-free survival for

the trastuzumab-containing regimens. Similarly, the manufacturer's systematic review did not identify studies of vinorelbine clinical effectiveness. The manufacturer assumed that the clinical effectiveness of vinorelbine was identical to that of capecitabine, as obtained from the control group of the RCT.

3.8 The principal determinant of patients' health-related quality of life in the model was assumed to be disease progression. In the main RCT, the pre-progression health-related utility value (0.69) was obtained using the EQ-5D in all patients, regardless of treatment group. The value following disease progression included in the model (0.47) was based on a separate study. Quality-adjusted life years (QALYs) were estimated by applying these values to the mean progression-free and post-progression survival durations for each regimen considered. The manufacturer's model assumed that health utilities did not differ according to treatments received and did not explicitly include the impact of treatment-related adverse events on quality of life.

3.9 The cost-effectiveness model distinguished between the cost of care incurred while patients were free from disease progression (and receiving active treatment) and the cost of care after disease progression. These costs included drug acquisition costs, hospital resources for chemotherapy administration, pharmacy costs, diagnostic and laboratory costs and other related costs. The base-case economic analysis was based on a price of £11.00 per tablet. The model also included relative dose adjustment factors to account for differences between planned dose and actual dose prescribed in the main RCT, and to account for differences between independent and investigator-led analyses of progression-free survival. The costs of trastuzumab were based on an assumption that treatment would be administered as a weekly

infusion as stated in the SPC and that all excess trastuzumab would be wasted.

3.10 The base-case analysis showed that when lapatinib plus capecitabine was compared with capecitabine monotherapy, the QALY gain was 0.171 at an incremental cost of £13,873, giving an incremental cost-effectiveness ratio (ICER) of £81,251 per QALY gained. When compared with vinorelbine monotherapy, the QALY gain was 0.171 at an incremental cost of £11,584, giving an ICER of £67,847 per QALY gained. The model suggested that lapatinib plus capecitabine dominated trastuzumab-containing regimens (that is, it was both more effective and less costly).

3.11 The manufacturer presented a range of sensitivity analyses for the comparisons with trastuzumab-containing regimens. When wastage was excluded in the analysis for all medicines, the ICER for lapatinib plus capecitabine changed from being dominant to £1650 per QALY gained in comparison with trastuzumab plus capecitabine, and to £6772 per QALY gained in comparison with trastuzumab monotherapy. In addition, when trastuzumab administration was assumed to be on the basis of a 3-weekly schedule rather than weekly as in the base case, the ICER for lapatinib plus capecitabine changed from being dominant to £20,248 per QALY gained in comparison with trastuzumab plus capecitabine, and to £27,532 per QALY gained in comparison with trastuzumab monotherapy. When the progression-free survival for trastuzumab-containing regimens was assumed to be equal to that of capecitabine, the ICER for lapatinib plus capecitabine changed from being dominant to £1428 per QALY gained in comparison with trastuzumab plus capecitabine, and to £7099 per QALY gained in comparison with trastuzumab monotherapy. A similar trend was seen when the costs of adverse events associated with lapatinib were included in the analysis.

3.12 The ERG reported that, although the evidence from the main RCT was of reasonable methodological quality, this was the only evidence on the clinical effectiveness of lapatinib used in the cost-effectiveness analysis. The ERG noted that in the original submission, there was a lack of appropriate RCT data for the clinical effectiveness of trastuzumab using an adjusted indirect comparison. The ERG stated that the unadjusted indirect comparison method used resulted in uncertainty surrounding the cost-effectiveness estimates comparing lapatinib plus capecitabine with trastuzumab-containing regimens. It also noted that the clinical effectiveness of vinorelbine was based on an assumption of equivalence with capecitabine rather than empirical data. The ERG highlighted that the manufacturer's market research analysis to determine current service provision for patients with advanced or metastatic breast cancer had limitations in terms of details of data collection and characteristics of respondents and non-respondents.

3.13 The ERG conducted an exploratory analysis to ascertain the cumulative impact of the assumptions listed below on the cost-effectiveness modelling in the manufacturer's submission:

- Administering trastuzumab every 3 weeks, rather than weekly.
- Changing the cost for administering chemotherapy infusion for trastuzumab from £207 per infusion used in the manufacturer's submission to £117 per infusion based on a published assessment report for a previous appraisal.
- Basing the mean HR for progression-free survival with trastuzumab-containing regimens on the minimum estimate of median time to progression from the pooled studies.
- Including the distributions of body surface area and weight used to estimate drug use from the main clinical trial.

The ERG results showed that, when these assumptions were considered cumulatively, the ICER for lapatinib plus capecitabine changed from being dominant to up to £37,336 per QALY gained when compared with trastuzumab-containing regimens.

Additional cost-effectiveness data provided by the manufacturer

3.14 The manufacturer presented updated results of the market research data (described in section 3.1). The updated data included 98 patients and reported that 21% of patients had continued to receive trastuzumab with the addition of capecitabine, 20% continued to receive trastuzumab with the addition of vinorelbine, 2% continued to receive trastuzumab alone and 11% had continued to receive trastuzumab with the addition of other treatments. Data showed that 46% of patients had switched treatment to non-trastuzumab-containing regimens, most frequently capecitabine monotherapy (32%). The manufacturer also provided data from an alternative survey of clinical oncologists (n = 92), which provided a slightly lower but comparable estimate that approximately 48% of patients switched treatment to non-trastuzumab-containing regimens.

3.15 The manufacturer provided a revised base-case economic analysis using updated median overall survival data for lapatinib plus capecitabine and updated progression-free survival and overall survival for trastuzumab plus capecitabine from the trastuzumab RCT. In the revised analyses, it was assumed that 15% of trastuzumab was wasted and that trastuzumab was administered once every 3 weeks in 88% of the patients receiving treatment. The 15% trastuzumab wastage was based on the results of market research commissioned by the manufacturer of lapatinib involving 24 oncology pharmacists from 17 cancer networks, which showed that on average, respondents estimated that 15% of trastuzumab is wasted because of factors such as unfinished vials (range 5% to

60%). In addition, respondents from the same market research said that an average of 11.6% of trastuzumab is administered weekly with the remainder of 88.4% administered every 3 weeks. The updated analysis also used the actual list price of £11.49 per lapatinib tablet.

3.16 The revised base-case analysis showed that when lapatinib plus capecitabine was compared with capecitabine monotherapy, the incremental QALY gain was 0.15 at an incremental cost of £14,015, giving an ICER of £93,825 per QALY gained. When compared with vinorelbine monotherapy, the incremental QALY gain was 0.15 at an incremental cost of £11,726, giving an ICER of £78,503 per QALY gained. When compared with trastuzumab monotherapy, the incremental QALY gain was 0.26 at an incremental cost of £638, giving an ICER of £24,227 per QALY gained. When compared with trastuzumab plus capecitabine, the incremental QALY gain for lapatinib plus capecitabine was 0.03 at an incremental cost of −£1075 meaning that it was dominant (that is, it was more effective and less costly). When compared with trastuzumab plus vinolrelbine, assuming the same incremental QALY gain of 0.03 at an incremental cost of −£3583, lapatinib plus capecitabine was dominant.

3.17 The manufacturer also presented an economic analysis that compared lapatinib plus capecitabine with a 'blended comparator', using the same data that were used in the revised base case. This analysis was carried out in recognition of the uncertainties in identifying a subgroup of patients who would be likely to have trastuzumab combination therapies in clinical practice. The blended comparator consisted of a weighted average of both the costs and QALYs of the three main treatment options: capecitabine monotherapy (estimated to be provided in 44% of patients), and trastuzumab in combination with either capecitabine (provided in

29% of patients) or vinorelbine (provided in 27% of patients). The proportions used were based on the results of the updated market research (described in section 3.14) with further adjustments made to re-allocate treatment regimens not included in the decision problem. The QALY gain for lapatinib plus capecitabine compared with the blended comparator was 0.080 at an incremental cost of £4887, giving an ICER of £60,730 per QALY gained.

3.18 The manufacturer further provided details of a proposed patient access scheme in which the acquisition costs of lapatinib for patients who qualified for treatment were paid by the manufacturer for up to 12 weeks. For those patients whose disease responded to lapatinib therapy, the NHS would pay for the costs of continued treatment with lapatinib beyond 12 weeks. Criteria for continuation of therapy beyond 12 weeks would be determined by the patient's clinician, based on reduction in size of lesion, presence of stable disease or improvement in other response criteria such as symptoms. The manufacturer reported that the scheme would continue until the release of updated guidance from NICE.

3.19 Incorporating the patient access scheme into the economic model suggested that the ICER for lapatinib plus capecitabine against the blended comparator would be reduced from £60,730 to £16,384 per QALY gained. Against the individual comparators, the ICER for lapatinib plus capecitabine compared with capecitabine would be reduced from £93,825 to £69,932 per QALY gained and against vinorelbine would be reduced from £78,503 to £54,610 per QALY gained. Lapatinib plus capecitabine dominated trastuzumab combination regimens (that is, it was more effective and less costly).

Evaluation of additional data and economic analysis by the Decision Support Unit (DSU)

3.20 The DSU evaluated the additional clinical-effectiveness data and the updated economic analysis from the manufacturer. The DSU was requested to comment on the use of trastuzumab following progression of disease and the appropriateness of the indirect comparison methodology used by the manufacturer to compare lapatinib plus capecitabine with trastuzumab-containing regimens. In addition, the DSU was asked to provide a critique of the methodology used to obtain the blended comparator proposed by the manufacturer and to establish that the model had been updated appropriately.

3.21 The DSU noted that the updated lapatinib clinical-effectiveness data were for overall survival and that time to progression data were not provided. The DSU reported that the same methodological limitations applied to the updated pooled estimate of trastuzumab efficacy as had applied to the original pooled estimate (see section 3.12). The DSU also noted that the RCT comparing trastuzumab plus capecitabine with capecitabine monotherapy reported results for overall survival and time to progression that favoured trastuzumab. However, the DSU stated that neither lapatinib nor trastuzumab had demonstrated a statistically significant increase in overall survival. The DSU commented that although the HR for time to progression for trastuzumab-containing regimens in comparison with lapatinib in combination with capecitabine derived from pooling non-RCT data was similar to that derived from the trastuzumab plus capecitabine trial, both methods were associated with methodological limitations because neither maintained randomisation.

3.22 The DSU stated that the updated assumptions in the economic analysis were implemented as described by the manufacturer. The

DSU provided analyses that explored the sensitivity of the ICERs to the assumptions about trastuzumab wastage and administration. These showed that if the wastage was 10% rather than 15%, then lapatinib plus capecitabine would still dominate trastuzumab combination therapies, but the incremental costs would be reduced. For example, the incremental costs of trastuzumab plus capecitabine compared with lapatinib plus capecitabine would be reduced from £1075 to £478. Alternatively, if 92% of patients had trastuzumab administered every 3 weeks rather than 88%, then the incremental cost for the trastuzumab plus capecitabine combination compared with lapatinib plus capecitabine would be reduced from £1075 to £952.

3.23 The DSU commented that the blended comparator assumed that all the comparator treatments were used in routine practice and that it would be appropriate for each of them to be displaced from NHS practice. The DSU provided analyses that explored how the ICERs changed if the proportion of trastuzumab use changed using a variety of market research estimates provided by the manufacturers of lapatinib and trastuzumab. Using estimates from the manufacturer of lapatinib, if trastuzumab was used to treat 49% of patients rather than 56%, then the ICER increased from £60,730 to £67,050 per QALY gained. If trastuzumab was used to treat 12% of patients, as suggested by the manufacturer of trastuzumab, the ICER increased further to £89,545 per QALY gained. The DSU also explored how the ICERs would change when the patient access scheme was applied to the different estimates of the proportion of trastuzumab use that was continuing following progression of disease. The DSU showed that when the proportion of women continuing trastuzumab-containing regimens following disease progression was estimated to be 56% (as in the manufacturer base case), the ICER was £16,387 per QALY gained. When the estimate was 54%, the ICER was £19,108 per QALY gained, an estimate of

49% gave an ICER of £26,993 per QALY gained and an estimate of 12% gave an ICER of £63,034 per QALY gained.

3.24 The DSU commented that a more appropriate approach to economic analysis in the context of the NICE 'Guide to the methods of technology appraisal' and general economic literature would have been to consider all treatment options in a single incremental analysis comparing each successive alternative from the least costly to the most costly. Using this methodology and the data provided by the manufacturer of lapatinib, the DSU estimated that the most cost-effective treatment option was capecitabine monotherapy. Vinorelbine monotherapy was dominated by capecitabine, that is, it had greater costs and the same QALYs. The ICER for lapatinib plus capecitabine in comparison with capecitabine monotherapy was £93,825 per QALY gained. Trastuzumab monotherapy compared with capecitabine monotherapy gave an ICER of £108,748 per QALY gained. Trastuzumab combination regimens were dominated by trastuzumab monotherapy. The ICER for lapatinib plus capecitabine compared with trastuzumab monotherapy was £24,227 per QALY gained. The DSU also carried out a probabilistic sensitivity analysis to determine the probability of each treatment being cost effective across a range of thresholds. The analysis showed that capecitabine monotherapy is likely to be the most cost-effective treatment option up to a threshold of approximately £80,000 per QALY gained.

3.25 Full details of all the evidence are in the manufacturer's submission, the manufacturer's response to the appraisal consultation document (ACD), the ERG report and DSU report, which are available from www.nice.org.uk/TAxxx

4 Consideration of the evidence

4.1 The Appraisal Committee reviewed the data available on the clinical and cost effectiveness of lapatinib, in combination with capecitabine, having considered evidence on the nature of the condition and the value placed on the benefits of lapatinib plus capecitabine by women with advanced or metastatic breast cancer, those who represent them, and clinical specialists. It was also mindful of the need to take account of the effective use of NHS resources.

4.2 The Committee considered current clinical practice in the treatment of advanced or metastatic breast cancer following progression after treatment with anthracycline-based regimens, taxanes and trastuzumab. The Committee noted inconsistency in the evidence provided, which suggested a range of estimates of continued trastuzumab use following progression of disease from approximately 10% to 50% of patients. The Committee was aware of comments from the ERG that there was uncertainty in the market research data as set out in section 3.12. The Committee heard from clinical specialists that continued provision of trastuzumab following progression of disease varied considerably in England and Wales, but that they considered the higher estimates to be more appropriate. The Committee concluded that there is no agreed standard treatment for patients whose disease progresses after treatment with trastuzumab, but that this could include capecitabine-, vinorelbine- and trastuzumab-containing regimens.

4.3 The Committee noted the inclusion of trastuzumab-containing regimens in the decision problem from the manufacturer. The Committee accepted that the continued use of trastuzumab following progression of disease was not currently licensed, but was mindful of comments from clinical specialists that it was being

used in clinical practice. The Committee recognised that the NICE 'Guide to the methods of technology appraisal' allows unlicensed comparators in clinical use in the NHS to be considered in appraisals. The Committee was persuaded by the evidence of trastuzumab usage from consultees (described in section 4.2) and the testimony from clinical specialists that it should allow consideration of the clinical- and cost-effectiveness analyses that included trastuzumab as a comparator.

4.4 The Committee considered the evidence for the clinical effectiveness of trastuzumab-containing regimens following progression of disease in the advanced or metastatic settings. The Committee noted the availability of clinical-effectiveness data from an RCT of trastuzumab continued following progression of disease, as well as an updated review of the trastuzumab clinical-effectiveness evidence provided by the manufacturer of lapatinib. The Committee heard from clinical specialists that evidence for the effect of continuation with trastuzumab treatment following progression of disease was increasing but its effectiveness remained uncertain. The Committee noted that the NICE clinical guideline on the treatment and diagnosis of advanced breast cancer (NICE clinical guideline 81) recommends that treatment with trastuzumab should be discontinued at the time of disease progression outside the central nervous system. The clinical guideline further recommends that trastuzumab should not be discontinued if disease progression is only within the central nervous system. The Committee heard from clinical specialists that this recommendation reflects the lack of cost-effectiveness evidence for trastuzumab when used at this point in the care pathway. The Committee was persuaded that continuing trastuzumab following progression of disease may be of benefit, but considered that there remained considerable uncertainty about the size of the benefit.

4.5 The Committee discussed the clinical effectiveness of lapatinib plus capecitabine presented in the main RCT. It noted that lapatinib plus capecitabine was associated with an improved time to progression, progression-free survival and other secondary outcomes compared with capecitabine monotherapy. The Committee considered the manufacturer's assertion that lapatinib has the potential to be beneficial to patients who have brain metastases because its smaller molecular size may allow it to cross the blood–brain barrier and enter the central nervous system. However, the Committee noted that the evidence to support this in terms of clinical effectiveness was still limited and that the manufacturer was specifically requested by the EMEA to further investigate this potentially important effect of lapatinib. The manufacturer will conduct a phase III randomised, controlled clinical study to evaluate the incidence of brain metastases as the site of relapse with a lapatinib-containing therapy compared with an appropriate trastuzumab-containing therapy as part of the conditional approval of marketing authorisation. The Committee concluded that the data currently available were insufficient to consider patients with brain metastases as a separate subgroup.

4.6 The Committee noted that adverse events reported in the main RCT by patients in the lapatinib plus capecitabine group included diarrhoea and palmar-plantar erythrodysaesthesia. The lapatinib plus capecitabine group had a marginally higher incidence of diarrhoea and palmar-plantar erythrodysaesthesia than the capecitabine monotherapy group. Clinical specialists and patient experts commented that people at this stage of disease are often willing to accept side effects to have the benefits of lapatinib plus capecitabine treatment. The Committee also noted that, although the side effects were significant, they could be managed within routine clinical practice.

4.7 The Committee agreed that the evidence to show that lapatinib plus capecitabine had fewer side effects than trastuzumab was limited. The Committee also discussed the potential for cardiotoxicity associated with lapatinib treatment and noted the results in the main RCT. The Committee considered the manufacturer's assertion that lapatinib was less cardiotoxic compared with trastuzumab. The Committee was not persuaded that, in the situation of limited life expectancy associated with advanced or metastatic breast cancer, this would necessarily influence the choice of treatments. This was supported by the testimony of the clinical specialists and patient experts.

4.8 The Committee considered the evidence on the cost effectiveness of lapatinib plus capecitabine presented in the manufacturer's submission as well as the revised base-case analysis. The Committee discussed the comparisons presented in the submission, in which lapatinib plus capecitabine was compared with capecitabine monotherapy, vinorelbine monotherapy and trastuzumab-containing regimens. The Committee understood that the clinical-effectiveness data used for the comparison with capecitabine monotherapy were based on the main clinical trial and noted that the ICER presented in the revised base-case analysis by the manufacturer for this comparison was greater than £90,000 per QALY gained. The Committee concluded that this did not represent a cost-effective use of NHS resources.

4.9 The Committee noted that the comparisons with vinorelbine presented in the modelling were not based on data from RCTs and that the efficacy of vinorelbine was assumed to be the same as that of capecitabine. The Committee considered that the data supporting this comparison were subject to considerable uncertainty. It also noted that in the revised base-case analysis the results of lapatinib plus capecitabine compared with vinorelbine

monotherapy gave an ICER of approximately £79,000 per QALY gained and concluded that this did not represent a cost-effective use of NHS resources.

4.10 The Committee specifically considered the estimates of cost effectiveness that included the patient access scheme comparing lapatinib plus capecitabine against capecitabine and vinorelbine monotherapy. The Committee noted that the ICERs were approximately £70,000 and £55,000 per QALY gained, respectively. The Committee was mindful of the factors that inform judgements about the acceptability of a technology as an effective use of NHS resources within, and above, the £20,000 to £30,000 per QALY gained range to be accepted. However, it concluded that lapatinib plus capecitabine could not be judged to be a cost-effective use of NHS resources, even taking into account the proposed patient access scheme.

4.11 The Committee accepted that the economic analysis comparing lapatinib plus capecitabine with trastuzumab-containing regimens had been revised to reflect the new clinical-effectiveness data available. The Committee recognised that two estimates had been provided: one using the RCT of continued trastuzumab use after progression and another using an updated pooled analysis of trastuzumab studies (see section 3.5). The Committee noted that both were based on an unadjusted indirect comparison to derive the comparative efficacy of lapatinib plus capecitabine with trastuzumab-containing regimens used in the model. The Committee expressed concerns about the pooling of estimates from experimental and observational studies, and considered that the indirect estimate using trial data was more appropriate. The Committee noted that the characteristics of the patients enrolled in the two RCTs were somewhat different in terms of the extent of previous treatment. The Committee also noted that the results from

the two RCTs showed that the capecitabine monotherapy arm in the trastuzumab plus capecitabine trial had better efficacy results compared with the capecitabine monotherapy arm in the lapatinib plus capecitabine trial. In the absence of head-to-head comparisons of lapatinib and trastuzumab regimens, the Committee concluded that although the indirect estimate using data from the trastuzumab RCT was associated with considerable uncertainty, it formed an appropriate basis for considering the cost-effectiveness estimates presented by the manufacturer.

4.12 The Committee next considered the cost effectiveness of lapatinib plus capecitabine compared with trastuzumab-containing regimens presented by the manufacturer. The Committee noted that in the manufacturer's revised base-case analysis the assumptions about trastuzumab wastage and administration had been updated, so that 15% of trastuzumab was wasted instead of all excess trastuzumab, and 88% of patients had trastuzumab administered once every 3 weeks, instead of once a week for all patients. The Committee heard from clinical specialists that they considered that an assumption of 15% trastuzumab wastage could still be an overestimate, because arrangements were usually made to treat patients in groups on the same day and therefore vial use was efficiently optimised. The Committee also heard that administration of trastuzumab once every 3 weeks was standard clinical practice. The Committee noted that the ICERs were very sensitive to changes in these assumptions and that if the level of trastuzumab wastage was assumed to be 10% rather than 15% the cost savings associated with lapatinib treatment compared with trastuzumab would be reduced from £1075 to £478. Slightly increasing the number of patients receiving trastuzumab every 3 weeks from 88% to 92% reduced the cost savings associated with lapatinib treatment compared with trastuzumab from £1705 to £952. The Committee concluded that although the manufacturer's base-case

analysis suggested that lapatinib plus capecitabine dominated trastuzumab-containing regimens, the differences in costs and modelled benefits were small. The Committee considered that under these circumstances the final ICERs were potentially subject to considerable variation on the basis of small changes in the assumptions made. In addition, the Committee concluded that based on the testimony from clinical specialists about trastuzumab wastage and administration, the differences in cost may be even smaller than those in the revised base-case analysis.

4.13 The Committee examined the incremental analysis to evaluate cost effectiveness provided by the DSU that used the data submitted by the manufacturer of lapatinib to compare the cost and effect of each technology successively from the least costly to the most costly. The Committee noted that in this analysis capecitabine monotherapy represented the most cost-effective use of NHS resources, and had the highest probability of being cost effective up to a willingness-to-pay threshold of approximately £80,000 per QALY gained. The Committee noted that the ICER for lapatinib plus capecitabine in comparison with trastuzumab monotherapy was approximately £24,000 per QALY gained, but that this did not take into account the comparison of trastuzumab monotherapy with capecitabine for which the ICER was approximately £109,000 per QALY gained. The Committee further noted that the DSU report suggested that, using the data from the manufacturer of lapatinib, the ICER for trastuzumab plus capecitabine versus capecitabine alone would be higher (approximately £122,000 per QALY) than that of trastuzumab monotherapy compared with capecitabine. The Committee considered that, although the analysis presented by the manufacturer suggested that lapatinib plus capecitabine compared with trastuzumab-containing regimens was cost effective in the base case, the incremental analysis demonstrated that it was based on a comparison of capecitabine with trastuzumab which

was not cost effective. The Committee was mindful that there was uncertainty about the effectiveness of trastuzumab-containing regimens, but considered that even if future evidence on the effectiveness of trastuzumab plus capecitabine demonstrated that it was more cost effective than had been assumed, this would only increase the ICERs for lapatinib plus capecitabine in comparison. Therefore, the Committee concluded that the results of the manufacturer's cost-effectiveness analysis in this situation were unsupportable, and the Committee could not, on this basis, recommend lapatinib plus capecitabine as a cost-effective use of NHS resources.

4.14 The Committee next examined the economic analysis from the manufacturer that used a blended comparator, which weighted the costs and QALYs of the lapatinib comparators (that is, capecitabine-, vinorelbine- and trastuzumab-containing regimens) to produce a single ICER of approximately £61,000 per QALY gained for lapatinib plus capecitabine in comparison with all comparators included in the economic analyses. The Committee noted that the analysis was completed because the manufacturer recognised that at present it was difficult to identify a group of patients who in current clinical practice would be likely to continue trastuzumab following progression of disease. The Committee noted that the blended comparator assumed that all comparators were in routine use and that it was appropriate for lapatinib to displace each of the comparators. The Committee was not persuaded that it was appropriate to combine independent health technologies to produce a single estimate of cost effectiveness nor that the economic analyses that compared lapatinib plus capecitabine with a blended comparator were appropriate. Specifically the Committee was not persuaded that it was acceptable to include treatments in the blended comparator approach which, when considered individually, were not cost

effective. Therefore, the Committee did not consider that the cost-effectiveness analyses using a blended comparator could form the basis of a decision on the appropriate use of NHS resources.

4.15 The Committee noted that the proposed patient access scheme (section 3.18) had been applied to the blended comparator. The Committee was aware that the manufacturer proposed to pay for the costs of lapatinib for the first 12 weeks of treatment for all people eligible for treatment, as part of this scheme. The Committee recognised that the patient access scheme reduced the ICER, using the blended comparator, from approximately £61,000 per QALY gained to approximately £16,000 per QALY gained. The Committee did not consider that applying the patient access scheme to the blended comparator was appropriate because of its views on the acceptability of the blended comparator as an appropriate basis for making recommendations about the cost effectiveness of lapatinib as detailed in section 4.14.

4.16 The Committee considered the wider benefits that may be associated with lapatinib. These include providing a range of technologies for the treatment of advanced or metastatic breast cancer and the fact that lapatinib is taken orally. The Committee recognised the importance of patient choice, but considered that lapatinib could not be recommended in the absence of evidence of cost effectiveness. Therefore, the Committee was not persuaded that the benefits associated with the mode of administration of lapatinib or the importance of patient choice should alter their decision about lapatinib being an appropriate use of NHS resources.

4.17 The Committee considered whether there were any subgroups of patients for whom treatment with lapatinib would be cost effective, such as patients with brain metastases. It considered that there

was insufficient evidence to recommend treatment with lapatinib for any patient subgroup, but concluded that further research would be beneficial to identify such subgroups. The Committee concluded that trials to establish the effectiveness of lapatinib in subgroups of patients that included all appropriate treatment comparisons should be considered.

4.18 The Committee considered supplementary advice from NICE that should be taken into account when appraising treatments which may extend the life of patients with a short life expectancy and which 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.
- No alternative treatment with comparable benefits is available through the NHS.
- The treatment is licensed or otherwise indicated for small patient populations.

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

4.19 On this basis the Committee understood that the main RCT reported a median overall survival for patients receiving capecitabine monotherapy of approximately 15 months (65.9 weeks). It is estimated that approximately 2000 patients with HER2-overexpressing metastatic breast cancer per year are

receiving second- or third-line chemotherapy and are therefore eligible to be offered treatment with lapatinib. The Committee observed that the trial data suggest that lapatinib plus capecitabine extends survival relative to capecitabine alone. However, it noted that the main RCT reported a gain in overall survival of approximately 1.9 months which did not reach conventional levels of statistical significance (lapatinib plus capecitabine 17.1 months versus capecitabine alone 15.2 months, HR 0.90; 95% CI 0.71 to 1.12, p = 0.3). The Committee was also mindful of the results from the economic model, but noted that this provided an estimate of life years gained of 0.19 reflecting a gain in overall survival of approximately 2.3 months. Therefore, the Committee did not consider that the size of the possible benefit was in keeping with the supplementary advice from NICE for consideration of life-extending, end-of-life treatments.

4.20 In summary, the Committee accepted the estimates of clinical-effectiveness reported in the main lapatinib RCT. However, the Committee did not consider that lapatinib had demonstrated that it was cost effective in comparison with capecitabine or vinorelbine, either with or without the patient access scheme. The Committee was mindful that trastuzumab may be continued following progression of disease but considered that the data submitted by the manufacturer of lapatinib had demonstrated that trastuzumab was not cost effective compared with capecitabine. The Committee noted the blended comparator proposed by the manufacturer, which enabled the calculation of a single ICER comparing lapatinib with current standard care. The Committee considered it inappropriate to mix mutually exclusive healthcare technologies. Therefore the Committee did not accept the use of the blended comparator with the application of the patient access scheme. The Committee was not persuaded that lapatinib fulfilled the criteria described in the supplementary advice from NICE for consideration

of end of life treatments. The Committee concluded that the use of lapatinib was not a cost effective use of NHS resources, and recommended that lapatinib should only be used in the context of further research.

4.21 The Committee was informed by NICE that an additional subgroup analysis had been submitted by the manufacturer of lapatinib the day before the Appraisal Committee meeting. In line with the published process, the Committee was not required to consider the late submission. However, the Committee chose to look at the document submitted by the manufacturer in order to assess whether the data presented in the document would be likely to materially affect the conclusions already reached. In the document the manufacturer identified a group of patients from the main RCT who had received less than three prior treatment regimens. The manufacturer argued that these patients more appropriately matched those enrolled in the trastuzumab RCT and that the clinical- and cost-effectiveness results from this subgroup should therefore be considered. The Committee considered whether in principle that it was clinically possible that this subgroup of patients might respond to lapatinib differently. The Committee was concerned that the subgroup was based on a small number of patients, and that very little information was provided on how the subgroup was identified, and on the patients involved. The Committee also noted that there was no exploration of the possibility that the differences in the efficacy observed for this subgroup could have occurred by chance. The Committee considered that the data analysis could, at this stage, generate a useful hypothesis for future research but it could not materially affect the conclusion that lapatinib should only be used in the context of clinical trials.

5 Implementation

5.1 The Healthcare Commission assesses the performance of NHS organisations in meeting core and developmental standards set by the Department of Health in 'Standards for better health' issued in July 2004. The Secretary of State has directed that the NHS provides funding and resources for medicines and treatments that have been recommended by NICE technology appraisals normally within 3 months from the date that NICE publishes the guidance. Core standard C5 states that healthcare organisations should ensure they conform to NICE technology appraisals.

5.2 'Healthcare standards for Wales' was issued by the Welsh Assembly Government in May 2005 and provides a framework both for self-assessment by healthcare organisations and for external review and investigation by Healthcare Inspectorate Wales. Standard 12a requires healthcare organisations to ensure that patients and service users are provided with effective treatment and care that conforms to NICE technology appraisal guidance. The Assembly Minister for Health and Social Services issued a Direction in October 2003 that requires local health boards and NHS trusts to make funding available to enable the implementation of NICE technology appraisal guidance, normally within 3 months.

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

- Slides highlighting key messages for local discussion.
- Costing report and costing template to estimate the savings and costs associated with implementation.
- Implementation advice on how to put the guidance into practice and national initiatives which support this locally.

- Audit support for monitoring local practice.

6 Recommendations for further research

6.1 The Committee proposed the following research: a trial of lapatinib plus capecitabine compared with trastuzumab-containing regimens and other chemotherapy regimens used in the advanced or metastatic setting following progression of disease with trastuzumab. In this research, emphasis should be placed on identifying potential subgroups that may particularly benefit from this treatment.

6.2 The Committee recommended that a study of the clinical and cost effectiveness of the use of trastuzumab continued following progression of disease in patients with advanced or metastatic breast cancer should be carried out.

7 Related NICE guidance

Published

- Advanced breast cancer: diagnosis and treatment. NICE clinical guideline 81 (2009). Available from www.nice.org.uk/CG81
- Bevacizumab for the first-line treatment of metastatic breast cancer (terminated appraisal). NICE technology appraisal guidance 147 (2008). Available from www.nice.org.uk/TA147
- Gemcitabine for the treatment of metastatic breast cancer. NICE technology appraisal guidance 116 (2007). Available from www.nice.org.uk/TA116
- Familial breast cancer: the classification and care of women at risk of familial breast cancer in primary, secondary and tertiary care. NICE clinical guideline 41 (2006). Available from www.nice.org.uk/CG41
- Guidance on the use of capecitabine for the treatment of locally advanced or metastatic breast cancer. NICE technology appraisal guidance 62 (2003). Available from www.nice.org.uk/TA62

- Guidance on cancer services. Improving outcomes in breast cancer. NICE clinical guideline manual update (2002). Available from www.nice.org.uk/CSGBC
- Guidance on the use of vinorelbine for the treatment of advanced breast cancer. NICE technology appraisal guidance 54 (2002). Available from www.nice.org.uk/TA54
- Guidance on the use of trastuzumab for the treatment of advanced breast cancer. NICE technology appraisal guidance 34 (2002). Available from www.nice.org.uk/TA34
- Guidance on the use of taxanes for the treatment of breast cancer. NICE technology appraisal guidance 30 (2001). Available from www.nice.org.uk/TA30

Under development

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

- Bevacizumab in combination with non-taxane chemotherapy for the first line treatment of metastatic breast cancer. NICE technology appraisal guidance (publication date to be confirmed)

8 Review of guidance

8.1 The review date for a technology appraisal refers to the month and year in which the Guidance Executive will consider whether the technology should be reviewed. This decision will be taken in the light of information gathered by the Institute, and in consultation with consultees and commentators.

8.2 The guidance on this technology will be considered for review in May 2013 and will coincide with the anticipated publication of the extra work requested by the EMEA.

David Barnett

Chair, Appraisal Committee

February 2009

Appendix A: Appraisal Committee members, guideline representatives and NICE project team

A Appraisal Committee members

The Appraisal Committee is a standing advisory committee of the Institute. Its 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. The Appraisal Committee meets three times a month except in December, when there are no meetings. The Committee membership is split into three branches, each with a chair and vice chair. Each branch considers its own list of technologies, and ongoing topics are not moved between the branches.

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
Radiologist, St George's Hospital, London

Professor A E Ades
Professor of Public Health Science, Department of Community Based Medicine, University of Bristol

Dr Amanda Adler
Consultant Physician, Cambridge University Hospitals Trust

Dr Tom Aslan
General Practitioner, Stockwell, London

Professor David Barnett (Chair)
Professor of Clinical Pharmacology, University of Leicester

Dr Matt Bradley

Head of HTA and Business Environment, Sanofi-Aventis Ltd

Mrs Elizabeth Brain

Lay Member

Dr Robin Carlisle

Deputy Director of Public Health, Rotherham PCT

Mr David Chandler

Lay Member

Professor Karl Claxton

Professor of Health Economics, Department of Economics & Related Research, University of York

Dr Simon Dixon

Reader in Health Economics, University of Sheffield

Mrs Fiona Duncan

Clinical Nurse Specialist, Anaesthetic Department, Blackpool Victoria Hospital, Blackpool

Dr Paul Ewings

Statistician, Taunton & Somerset NHS Trust, Taunton

Professor John Geddes

Chief Executive, Barking, Havering and Redbridge Hospitals NHS Trust

Mr John Goulston

Director of Finance, Barts and the London NHS Trust

Mr Adrian Griffin

VP Strategic Affairs, LifeScan, Johnson & Johnson

Dr Richard Harling

Director of Health Policy, Worcestershire PCT and Worcestershire County Council

Dr Rowan Hillson

Consultant Physician, Diabeticare, The Hillingdon Hospital

Professor Philip Home (Vice Chair)

Professor of Diabetes Medicine, Newcastle University

Dr Vincent Kirkbride

Consultant Neonatologist, Regional Neonatal Intensive Care Unit, Sheffield

Dr Simon Maxwell

Senior Lecturer in Clinical Pharmacology and Honorary Consultant Physician, Queen's Medical Research Institute, University of Edinburgh

Dr Alec Miners

Lecturer in Health Economics, London School of Hygiene and Tropical Medicine

Dr Ann Richardson

Lay Member

Mrs Angela Schofield

Chairman, Bournemouth and Poole Teaching PCT

Mr Mike Spencer

General Manager, Clinical Support Services, Cardiff and Vale NHS Trust

Mr David Thomson

Lay Member

Mr William Turner

Consultant Urologist, Addenbrooke's Hospital, Cambridge

Dr Luke Twelves

General Practitioner, Ramsey Health Centre, Cambridgeshire

Dr Norman Vetter

Reader, Department of Epidemiology, Statistics and Public Health, College of Medicine, University of Wales, Cardiff

Dr Paul Watson

Director of Commissioning, East of England Strategic Health Authority

B Guideline representative

The following individual, representing the Guideline Development Group responsible for developing the Institute's clinical guideline related to this topic, was invited to attend the meeting to observe and to contribute as an adviser to the Committee.

- Dr Nick Murray, National Collaborating Centre for Cancer

C NICE project team

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

David Chandiwana
Technical Lead

Louise Longworth
Technical Adviser

Zoe Garrett (from July 2008)
Technical Adviser

Eloise Saile
Project Manager

Bijal Chandarana (from September 2008)
Project Manager

Appendix B: Sources of evidence considered by the Committee

A The Evidence Review Group (ERG) report for this appraisal was prepared by the Southampton Health Technology Assessment Centre:

- Jones J, Takeda A, Picot J et al. Lapatinib for HER2 over-expressing breast cancer, June 2007

B Evidence for this appraisal was also prepared by the NICE Decision Support Unit, Southampton Health Technology Assessment Centre and the University of Sheffield.

C The following organisations accepted the invitation to participate in this appraisal. 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 gave their expert views on lapatinib by providing a written statement to the Committee. Organisations listed in I and II have the opportunity to appeal against the final appraisal determination.

I Manufacturer/sponsor:

- GlaxoSmithKline

II Professional/specialist and patient/carer groups:

- Breakthrough Breast Cancer
- Breast Cancer Campaign
- Breast Cancer Care
- British Association of Surgical Oncology
- Cancerbackup
- Cancer Research UK
- National Collaborating Centre for Cancer
- Royal College of Nursing
- Royal College of Pathologists
- Royal College of Physicians (Medical Oncology Joint Special Committee)
- Welsh Assembly Government

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

- British National Formulary
- Department of Health, Social Services and Public Safety for Northern Ireland
- Eli Lilly and Company Ltd
- NHS Quality Improvement Scotland
- Pierre Fabre Ltd
- Roche

D The following individuals were selected from clinical specialist and patient advocate nominations from the non-manufacturer/sponsor consultees and commentators. They gave their expert personal view on lapatinib by attending the initial Committee discussion and providing written evidence to the Committee. They are invited to comment on the ACD.

- Professor Dudley Sinnett, nominated by British Association of Surgical Oncology
- Dr Justin Stebbing, nominated by Royal College of Physicians
- Dr Rob Stein, nominated by Royal College of Physicians
- Mrs Marie Wilby, patient expert, nominated by Breast Cancer Care
- Ms Carolyn Rogers, patient expert, nominated by Breast Cancer Care