All Wales Therapeutics and Toxicology Centre
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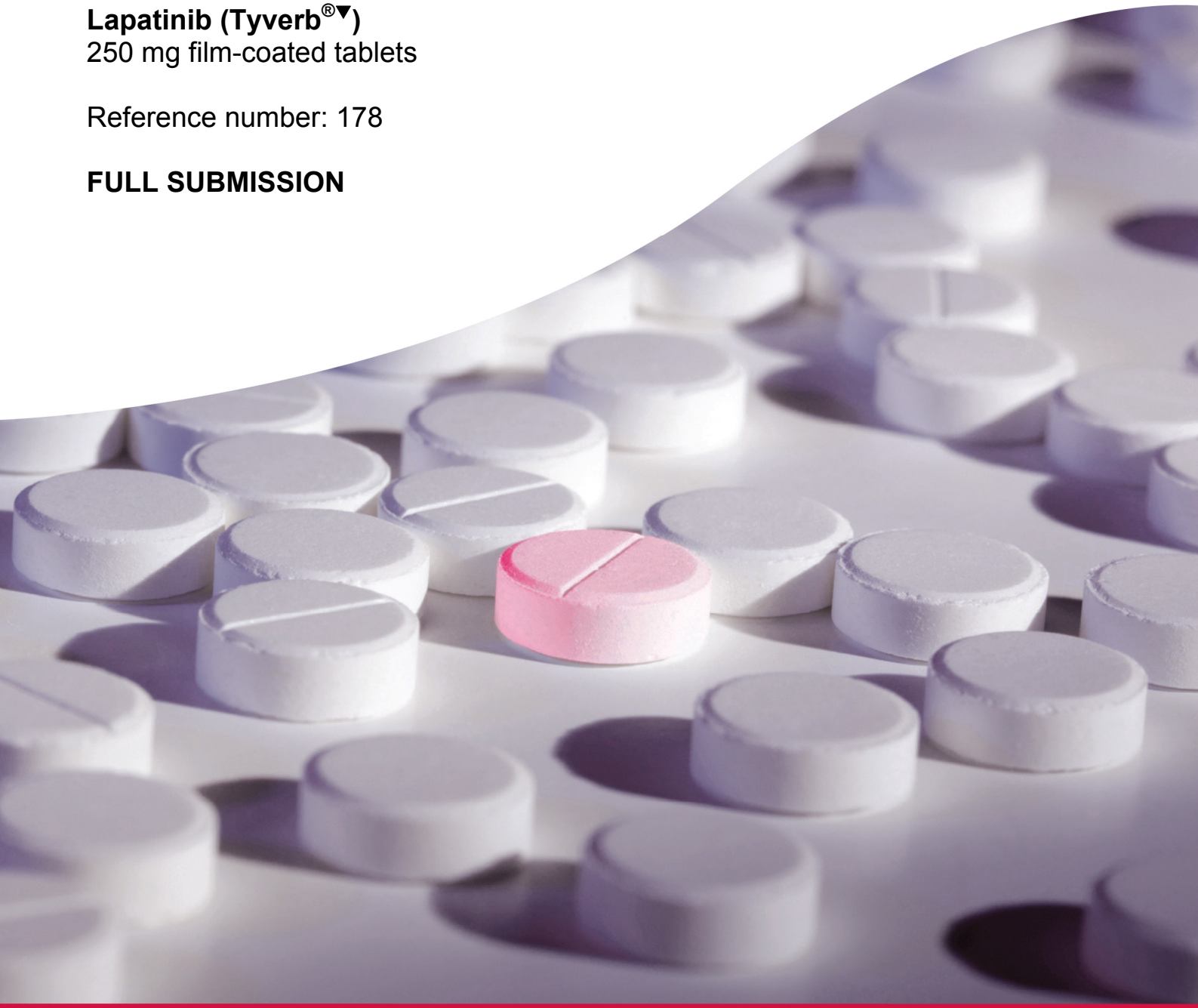
AWMSG SECRETARIAT ASSESSMENT REPORT

Lapatinib (Tyverb®▼)
250 mg film-coated tablets

Reference number: 178

FULL SUBMISSION



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This report should be cited as:
All Wales Therapeutics and Toxicology Centre. AWMSG Secretariat Assessment Report. Lapatinib (Tyverb®) 250 mg film-coated tablets. Reference number: 178. June 2013.

AWMSG Secretariat Assessment Report
Lapatinib (Tyverb®) 250 mg film-coated tablets

This assessment report is based on evidence submitted by GlaxoSmithKline on 14 February 2013[1].

1.0 PRODUCT DETAILS

Licensed indication under consideration	Lapatinib (Tyverb®) is indicated for the treatment of adult patients with breast cancer, whose tumours overexpress HER2 (ErbB2) in combination with capecitabine for patients with advanced or metastatic disease with progression following prior therapy, which must have included anthracyclines and taxanes and therapy with trastuzumab in the metastatic setting[2].
Dosing	The recommended dose of lapatinib is 1,250 mg (i.e. five tablets) once daily continuously, and should be taken either at least one hour before, or at least one hour after food. The recommended dose of capecitabine is 2,000 mg/m^2/day taken in two doses 12 hours apart on days 1–14 for a 21 day cycle. Capecitabine should be taken with food or within 30 minutes after food. Refer to the Summaries of Product Characteristics (SPCs) for further information[2,3].
Marketing authorisation date	10 June 2008[2].

2.0 DECISION CONTEXT

2.1 Background

Breast cancer is the most common cancer in women, affecting 24,133 patients in Wales in 2008 with 2,585 new cases diagnosed in 2009[4,5]. Estimates of the number of patients with metastatic breast cancer vary[6], but regional UK data suggests that around 5% of patients diagnosed have metastases at the time of diagnosis, with a further 35% developing metastatic cancer in the ten years following diagnosis[7]. Approximately 15–20% of metastatic breast cancers overexpress human epidermal growth factor receptor 2 (HER2)[8], which is associated with poor prognosis and reduced survival in breast cancer patients[9].

Guidelines issued by the National Institute for Health and Care Excellence (NICE) advise that in patients with advanced breast cancer who are not suitable for anthracyclines (because they are contraindicated or because of prior anthracycline treatment either in the adjuvant or metastatic setting), docetaxel should be offered first-line, followed by capecitabine (Xeloda®) or vinorelbine[10]. NICE also recommends that trastuzumab (Herceptin®) is used in combination with paclitaxel for women with tumours with excessive HER2 who have not had chemotherapy for metastatic breast cancer and for whom anthracycline treatment is inappropriate. There is no standard treatment for patients whose disease progresses after treatment with trastuzumab[11]. NICE recommends discontinuation of trastuzumab therapy at the time of disease

progression outside the central nervous system (CNS); continuation of treatment is recommended only where disease progression is within the CNS[10]. However, the company has highlighted, and NICE has acknowledged, that in clinical practice trastuzumab use may continue in patients whose disease has progressed beyond the CNS[1,11]. This is supported by market research conducted by the company and by local clinical expert opinion, which suggests that trastuzumab in combination with capecitabine or vinorelbine is used following progression in metastatic breast cancer[1]. It should be noted that the licensed indication for trastuzumab treatment of metastatic breast cancer does not include its use in combination with capecitabine or vinorelbine[12].

Lapatinib is a tyrosine kinase inhibitor that dually inhibits the activity of HER2 and epidermal growth factor receptor (EGFR). In June 2008, lapatinib received marketing authorisation for the indication under consideration[2]. An appraisal by NICE of lapatinib for this indication was suspended in October 2010[13] and for this reason, lapatinib in this indication is scheduled for appraisal by the All Wales Medicines Strategy Group (AWMSG).

2.2 Comparators

The comparators requested by the All Wales Therapeutics and Toxicology Centre (AWTTC) were:

- Trastuzumab plus capecitabine
- Trastuzumab plus vinorelbine.

2.3 Guidance and related advice

- European Society for Medical Oncology. Locally recurrent or metastatic breast cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up (2012)[14].
- NICE. Clinical Guideline 81. Advanced breast cancer: diagnosis and treatment (2009)[10].
- Scottish Intercollegiate Guidelines Network. Management of breast cancer in women (2005)[15].
- NICE. Guidance on Cancer Services: Improving outcomes in breast cancer (2002)[16].
- NICE. Technology Appraisal 34. Guidance on the use of trastuzumab for the treatment of advanced breast cancer (2002)[17].

3.0 SUMMARY OF EVIDENCE ON CLINICAL EFFECTIVENESS

3.1 Comparative effectiveness

The company submission presents five studies evaluating the effectiveness of chemotherapeutic regimens for the treatment of patients with metastatic breast cancer[1]. The submission includes phase III pivotal study, EGF100151, which compared a regimen containing lapatinib and capecitabine with capecitabine treatment alone, and a phase III confirmatory study, EGF111438 (CEREBEL), which evaluated lapatinib plus capecitabine versus trastuzumab plus capecitabine.

Additionally, the submission includes three supportive studies: two open-label single-arm phase II trials evaluating lapatinib as a monotherapy and an open-label single-arm phase IV study[1]. As these three studies do not provide evidence of the comparative effectiveness of lapatinib versus trastuzumab in the indication under consideration, the studies will not be discussed further.

To enable a comparison between lapatinib plus capecitabine and trastuzumab plus capecitabine or vinorelbine for the indication under consideration, a systematic review

and indirect comparison between study EGF100151 and the German Breast Group study (GBG 26) was also undertaken by the company[1].

3.1.1 Study EGF100151

This randomised, open-label, multicentre phase III study compared lapatinib and capecitabine combination therapy with capecitabine monotherapy in women with $HER2^+$ advanced or metastatic breast cancer that has progressed or relapsed after prior treatment, which must have included anthracyclines, taxanes and trastuzumab[18]. Patients (n = 399) were randomised 1:1 to receive lapatinib (1,250 mg once daily) in combination with capecitabine (2,000 mg/m^2 of body surface area [BSA] per day taken in two doses on days 1–14 of a 21-day cycle) or capecitabine monotherapy (2,500 mg/m^2/day in two doses on days 1–14 of a 21-day cycle)[19,20].

Eligible patients had to have received previous treatment with trastuzumab for at least six weeks, alone or in combination with chemotherapy for locally advanced or metastatic disease. Previous therapies also had to include, but were not limited to, at least four cycles of regimens that included both an anthracycline and a taxane (two cycles if the disease progressed during therapy), administered concurrently or separately as adjuvant therapy or for metastatic disease[18].

The primary endpoint was the time to progression (TTP) as established by an independent review committee (IRC) who were blinded to the study treatments; investigator-evaluated data was also collected as a secondary assessment. Secondary endpoints included progression-free survival (PFS), overall survival (OS), overall response rate and rate of clinical benefit[18]. See Glossary for endpoint definitions.

Study enrolment was halted early on 3 April 2006 due to a recommendation from the independent data monitoring committee following a planned interim analysis, which demonstrated a statistically significant advantage in TTP for the lapatinib with capecitabine group versus capecitabine monotherapy. Patients in the capecitabine monotherapy arm were given the opportunity to crossover and receive the combination of lapatinib and capecitabine[21].

Results are summarised in Table 1. Patients receiving lapatinib plus capecitabine had a significantly longer TTP than the capecitabine monotherapy group (primary endpoint analysis $p < 0.001$). This was supported by statistically significant improvements in other secondary endpoints, including PFS[20], with no evidence of a deleterious effect on the quality of life of these patients following addition of lapatinib to capecitabine chemotherapy[22]. However, no statistically significant difference in OS was observed[19,21].

Table 1. Overview of endpoint data from Study EGF100151[19–21].

Endpoint	Lapatinib plus capecitabine (n = 198)	Capecitabine monotherapy (n = 201)	Hazard ratio (95% confidence interval [CI])
Primary endpoint			
Number of IRC-evaluated TTP events	82	102	-
Median IRC-evaluated TTP (weeks)	27.1	18.6	0.57 (0.43–0.77) p < 0.001
Secondary endpoints			
Number of investigator-evaluated TTP events	121	126	-
Median investigator-evaluated TTP (weeks)	23.9	18.3	0.72 (0.56–0.92) p = 0.00762
Median PFS (weeks)	27.1	17.6	0.55 (0.41–0.74) p < 0.001
Median OS (weeks)[†]	75.0	64.7	0.87 (0.70–1.08) p = 0.206
[†] At the time of the final analysis (1 October 2008). Other endpoints assessed at 3 April 2006 data cut-off.			

3.1.2 Study EGF111438 (CEREBEL)

This randomised, open-label, multicentre phase III study compared lapatinib plus capecitabine with trastuzumab plus capecitabine in patients with $HER2^+$ metastatic breast cancer who had received prior treatment with anthracyclines or taxanes in the neo-adjuvant, adjuvant or metastatic setting[1,23]. Patients (n = 540) were randomised to one of two treatment groups: lapatinib (n = 271; 1,250 mg administered once daily) plus capecitabine (2,000 mg/m^2/day taken in two doses on days 1–14 of a 21-day cycle) or trastuzumab (n = 269; loading dose of 8 mg/kg on day 1 followed by 6 mg/kg every three weeks) plus capecitabine (2,500 mg/m^2/day in two doses on days 1–14 of a 21-day cycle)[1,23].

Prior treatment with taxanes or anthracyclines was required but patients who had not been treated for metastatic disease were eligible for the study, and 44% of randomised patients had not previously received treatment in the metastatic setting. Further, prior treatment with trastuzumab was permitted but not required. Additionally, patients must not have had any history of CNS metastases and must not have had any evidence of brain metastases on baseline magnetic resonance imaging (MRI) scan[1,23].

The primary endpoint was the incidence of CNS as site of first relapse as established by a blinded independent reviewer; this analysis was performed on the modified-intent-to-treat (M-ITT) population, which comprised all randomised patients who had no baseline CNS metastases (lapatinib: n = 251; trastuzumab: n = 250). Secondary endpoints, including PFS and OS, were analysed using the intent-to-treat (ITT) dataset, which comprised all randomised patients, regardless of whether treatment was administered[1,23]. See Glossary for endpoint definitions.

Due to a recommendation from the independent data monitoring committee, study enrolment was terminated early for two major reasons: it was unlikely that the primary endpoint would be met due to the low incidence of CNS metastases as the first site of progression (8 [3.2%] in the lapatinib group and 12 [4.8%] in the trastuzumab group) and median PFS was significantly in favour of the trastuzumab treatment arm (6.6 months and 8.1 months respectively; hazard ratio [HR]: 1.30; 95% confidence interval [CI]: 1.04–1.64)[1,23].

[Commercial in confidence information removed]

3.2 Systematic review and indirect comparison

A systematic review was undertaken by the company to identify available evidence that would enable a comparison of lapatinib plus capecitabine with trastuzumab plus capecitabine or vinorelbine as a treatment in patients with $HER2^+$ advanced or metastatic breast cancer that had progressed following prior therapy. This review identified study EGF100151 (see Section 3.1.1) and the GBG 26 study[24,25], which form the basis of the comparison between lapatinib plus capecitabine, trastuzumab plus capecitabine and trastuzumab plus vinorelbine when used beyond progression[1].

Two further studies were identified but did not meet criteria for inclusion into the indirect comparison[1]. Only 35% of patients enrolled in study EGF111438 had received prior trastuzumab therapy in the metastatic setting, and an analysis of this patient group was conducted post hoc (see Section 3.1.2). Further, around 20% of patients screened for enrolment into this study were found to have an asymptomatic CNS metastasis, which the applicant company concludes is not reflective of the patient population that will be eligible to receive lapatinib therapy in NHS Wales. VITAL/LAP112620 was excluded as it compared lapatinib plus capecitabine with an unlicensed treatment (lapatinib plus vinorelbine) and only 65% of patients enrolled had received therapy for metastatic disease before study entry[1].

3.2.1 GBG 26 study

This open-label, randomised, phase III study evaluated the continued use of trastuzumab plus capecitabine and capecitabine monotherapy in patients with $HER2^+$ metastatic breast cancer that had progressed following therapy with trastuzumab in the metastatic setting[24,25]. Following advice from the independent data-monitoring committee, recruitment to the trial was halted early due to slow patient accrual and the registration of lapatinib in the EU for this indication. Patients (n = 156) were randomised 1:1 to receive capecitabine (2,500 mg/m^2/day in two doses on days 1–14 of a 21-day cycle) with or without trastuzumab (6 mg/kg body weight as a 30-minute infusion every three weeks)[24,25].

Median TTP (primary endpoint) was 8.2 months in trastuzumab plus capecitabine arm, compared with 5.6 months in the capecitabine monotherapy arm (hazard ratio, 0.69; p = 0.0338). However, there was no significant difference in OS between the treatment arms (25.5 months in patients receiving both trastuzumab and capecitabine versus 20.4 months in the capecitabine only group)[24,25].

3.2.2 Indirect comparison with trastuzumab plus capecitabine

An indirect comparison between studies EGF100151 and GBG 26 was undertaken by the company to compare lapatinib plus capecitabine with trastuzumab plus capecitabine. Limitations of the indirect comparison included administration of differing doses of capecitabine in the combination arms of the studies (2,000 mg/m^2/day in study EGF100151 compared with 2,500 mg/m^2/day in the GBG 26 study); as the differing capecitabine doses were in the combination, not monotherapy, treatment groups, the company does not view this as a limitation. A comparison of the baseline characteristics of patients included in studies EGF100151 and GBG 26 found that the populations differed in several ways. Median patient age was older in the capecitabine monotherapy arm of the GBG 26 study (59 years versus 51 years); median ages for the combination arms of studies EGF100151 and GBG 26 were 54 and 52.5 years respectively[20,24]; however, the company is not aware of data to support an association between treatment outcomes and age among women with $HER2^+$ metastatic breast cancer[1]. Patients were more heavily pretreated in the EGF100151 study, as 82% had received three or more prior lines of chemotherapy[1], whereas the GBG 26 study included only patients who had previously received one prior chemotherapy for metastatic breast cancer[24]. Post-hoc analysis of EGF100151 demonstrated that the improvements in TTP observed in the lapatinib/capecitabine combination therapy group were greater in patients who had received one or two prior lines of chemotherapy than

in those who had received three or more[1]. Further, fewer patients in the GBG 26 had received therapy with anthracyclines or taxanes[20,24]. Patients also differed in the therapies administered following progression or halting of enrolment to the study[1].

The endpoints evaluated for the adjusted indirect comparison were investigator-assessed TTP and OS in the intent-to-treat populations of both studies, as other endpoints differed between the studies. There was no significant difference between lapatinib plus capecitabine and trastuzumab plus capecitabine for TTP (hazard ratio point estimate 1.05; 95% CI 0.68–1.62) or OS (hazard ratio point estimate 0.93; 95% CI 0.61–1.42)[1].

3.2.3 Indirect comparison with trastuzumab plus vinorelbine

The company was unable to identify randomised controlled trials for trastuzumab plus vinorelbine following progression of metastatic breast cancer. In the company submission, the company has assumed that the addition of vinorelbine to trastuzumab therapy is equivalent to the effect of adding capecitabine to trastuzumab therapy[1]. This is based on reports of the similar efficacy of capecitabine and vinorelbine as monotherapies after failure of first-line treatment of metastatic breast cancer[26]. Additionally, the company highlights NICE Clinical Guideline 81[10], where capecitabine and vinorelbine are used interchangeably as second or third line therapy for metastatic breast cancer patients who have progressed on an anthracycline or taxane in any setting and trastuzumab in the metastatic setting[1]. The company acknowledge that uncertainty is implicit within this assumption, but suggest that in the absence of evidence, these are likely to be amongst the assumptions made by clinicians when choosing to use trastuzumab plus vinorelbine in this patient group. The company conclude that the results of the indirect comparison of lapatinib plus capecitabine with trastuzumab plus capecitabine can be taken as a proxy for a comparison with trastuzumab plus vinorelbine[1].

3.3 Evidence of comparative safety

The company submission includes an evaluation of the safety profile following the addition of lapatinib to capecitabine based on data from the pivotal study (EGF100151)[1]. The incidence of adverse events (AEs) was 192/198 (97%) and 177/191 (93%) in patients treated with lapatinib plus capecitabine and capecitabine monotherapy, respectively. AEs of grade 3 or more were observed in 98 (49%) combination group patients and 88 (46%) patients receiving capecitabine monotherapy, while treatment-related serious AEs were observed in 23 (12%) and 18 (9%) patients, respectively[21]. The most commonly reported AEs were diarrhoea (65% of the combination therapy group versus 40% of the monotherapy group), palmar-plantar erythrodysaesthesia (PPE; 53% versus 51%), nausea (44% versus 43%), fatigue (23% versus 25%), vomiting (26% versus 21%) and rash (28% versus 14%)[20,21]. Eleven patients experienced 12 episodes of decreased left ventricular ejection fraction (LVEF), of which eight (four in each treatment arm) met the definition of serious AE; all were asymptomatic. Serious hepatobiliary AEs developed in four patients (1.9%) in the combination therapy group and three patients (1.6%) in the monotherapy group[19].

In their submission, the applicant company also provided an assessment of the safety profile of trastuzumab in combination with capecitabine based on the GBG 26 study[1,24]. Grade 3 or 4 toxicities were reported in 49 (63.6%) patients receiving trastuzumab in combination with capecitabine and 49 (66.2%) patients receiving capecitabine monotherapy. A statistically significant difference in the incidence of anaemia was observed (48 [64%] patients in the combination therapy group versus 32 [44%] receiving capecitabine monotherapy, p = 0.0208). The most common grade 3–4 AEs in the combination arm included skin changes (includes PPE; 32% versus 24% in the monotherapy group), diarrhoea (16% versus 19%), neutropenia (5% versus 4%) and cardiovascular disorders (5% versus 3%). The severe cardiac events observed in four combination therapy patients included one patient (1.3%) with a decrease of LVEF[1,24].

The submission also includes data from the study EGF111438 safety population, only 35% of which were patients whose disease has progressed following prior therapy, including trastuzumab, in the metastatic setting[1,23]. In the overall safety population, the incidence of AEs was 245/269 (91%) and 245/267 (92%) in patients treated with lapatinib plus capecitabine and trastuzumab plus capecitabine, respectively. Serious AEs were observed in 34 (13%) and 45 (17%) patients respectively, while discontinuation due to AEs occurred in 29 (11%) patients in the lapatinib group and 35 (13%) patients receiving trastuzumab. Four fatal events occurred in the lapatinib plus capecitabine treatment group and were not considered related to study medication, while one fatality occurred in patients receiving trastuzumab; this was considered related to capecitabine therapy. The most commonly reported AEs were PPE (49% in the lapatinib group versus 58% in the trastuzumab group), diarrhoea (45% versus 39%), nausea (29% versus 18%) and rash (22% versus 7%)[1,23].

3.4 AWTTC critique

- The submission includes direct comparative data for lapatinib plus capecitabine versus capecitabine monotherapy (EGF100151) and lapatinib plus capecitabine versus trastuzumab plus capecitabine (EGF111438); however, only 35% of patients enrolled in study EGF111438 were patients whose disease has progressed following prior therapy, including trastuzumab, in the metastatic setting[1]. The applicant company has provided an indirect comparison of lapatinib plus capecitabine versus trastuzumab plus capecitabine (see Section 3.2.2), which is also assumed to be a proxy for a comparison with trastuzumab with vinorelbine (see Section 3.2.3). The company acknowledges in their submission that there are limitations with this approach, which could make it difficult to draw reliable conclusions. However, the applicant company reports that the comparison remains clinically informative in the absence of head-to-head evidence[1]. Any conclusions drawn from this comparison should be viewed in light of these limitations.
- The licensed indication for lapatinib use states that prior therapy must have included anthracyclines and taxanes and therapy with trastuzumab in the metastatic setting[2]. However, in study EFG111438, the inclusion criteria did not specify that eligible patients had received prior treatment with both an anthracycline and a taxane; patients who had not been treated for metastatic disease were eligible for the study and prior treatment with trastuzumab was permitted but not required[23]. A post hoc subgroup analysis is provided for patients treated with trastuzumab in the metastatic setting, but this analysis does not specify previous chemotherapies received by included patients[1]. It is therefore uncertain to what extent this post hoc subgroup analysis reflects outcomes in patients eligible for treatment with lapatinib in NHS Wales.
- The pivotal study, EGF100151, demonstrated that lapatinib in combination with capecitabine significantly improves TTP, PFS and overall tumour response in this patient population when compared with capecitabine monotherapy[20]. Although OS tended to be longer in combination group patients, this difference was not statistically significant[19]. The company suggest that the effect of lapatinib combination therapy on OS could be confounded by crossover from the monotherapy arm following termination of recruitment[1]. However, an oncology Scientific Advisory Group, convened following Committee for Medicinal Products for Human Use (CHMP) request, considered data from the 3 April 2006 data cut-off point and concluded it was unlikely that imbalances arising from patient crossover affected overall conclusions[21]. CHMP also considered that the IRC-assessed endpoints were likely to overestimate the difference in TTP between the study arms, due to non-confirmation of investigator-assessed progression events and the absence of follow-up imaging. It was suggested that a reasonable estimate of hazard ratio was approximately 0.7 and a median TTP difference of 6–8 weeks. The Scientific

Advisory Group suggested that an improvement of six weeks in median TTP was not clinically significant in the context of advanced breast cancer in late lines of treatment. However, following further consideration, CHMP considered that the benefit-risk balance of lapatinib in this indication was favourable and lapatinib received marketing authorisation[21].

- Lapatinib was associated with frequent, low grade diarrhoea and skin toxicity, as well as infrequent but significant cardiac and hepatic events (see Section 3.3)[1,21]. The company noted that the trastuzumab SPC also lists diarrhoea and skin toxicity as very common events, while hepatocellular injury is listed as common[1,12]. The submission also highlights grade 3–4 AEs, including neutropenia, leucopenia, constipation and febrile neutropenia, which are associated with trastuzumab/vinorelbine or trastuzumab/capecitabine treatment but not lapatinib/capecitabine treatment [1].
- At the time of licensing of lapatinib, CHMP noted that confirmatory studies should be designed to show survival benefit where survival is expected to be short and where there are no evidence-based next-line therapies available[21]. However, no statistically significant improvements in OS were observed in the EGF100151 and GBG 26 trials for the study medication (lapatinib plus capecitabine and trastuzumab plus capecitabine, respectively) versus capecitabine monotherapy[20,24,25].
- An exploratory analysis found that during study EGF100151 the incidence of CNS metastasis was significantly reduced in patients who received lapatinib plus capecitabine in comparison with those that received capecitabine monotherapy (2% versus 6%; p = 0.0445)[20]. This effect was noted by CHMP, and it was considered that it needed to be prospectively confirmed[21]. This was not supported by data from study EGF111438[23]; however, there were several differences in the patient populations of the two studies (see Sections 3.1.1 and 3.1.2).
- Lapatinib and capecitabine are administered orally[2,3], whereas the comparator regimens require intravenous infusion of trastuzumab[12]; therefore, lapatinib/capecitabine treatment may be preferred by patients and has the advantage that it does not require administration by a health care professional.

4.0 SUMMARY OF THE EVIDENCE ON COST-EFFECTIVENESS

4.1 Cost-effectiveness evidence

4.1.1 Context

The company submission describes a cost-utility analysis (CUA) of lapatinib in combination with capecitabine for the treatment of patients with breast cancer, whose tumours overexpress HER2, with advanced or metastatic disease with progression following prior therapy, which must have included anthracyclines and taxanes and therapy with trastuzumab in the metastatic setting[1]. The comparator treatments requested include trastuzumab in combination with either capecitabine or vinorelbine.

The model uses a partitioned survival analysis to estimate the incremental costs and health outcomes based upon time spent in three health states: ‘alive prior to disease progression’, ‘alive following disease progression’ and ‘dead’. Patients enter the model in the ‘alive prior to disease progression’ state, which assumes that patients are progression-free for this line of treatment, although they have already experienced disease progression on prior therapies. The model assumes that patients will receive lapatinib/capecitabine, trastuzumab/capecitabine or trastuzumab/vinorelbine until they subsequently experience disease progression or death. Although in clinical practice patients may receive subsequent-line or salvage chemotherapies following disease progression, it is assumed that these would not differ between treatment groups included in the model and so these are excluded. The proportion of patients residing in

each health state using lapatinib/capecitabine and trastuzumab/capecitabine therapies was derived from an adjusted, indirect comparison of study EGF100151 (comparing lapatinib/capecitabine with capecitabine monotherapy) and study GBG 26 (comparing trastuzumab/capecitabine with capecitabine monotherapy). Due to a lack of randomised controlled trials for trastuzumab/vinorelbine in the relevant patient population, it was assumed that trastuzumab/vinorelbine is therapeutically equivalent to trastuzumab/capecitabine. See Appendix 1 for further details.

4.1.2 Results

Results of the base case analysis of lapatinib/capecitabine versus trastuzumab/capecitabine and trastuzumab/vinorelbine are summarised in Table 2. The analyses were conducted with and without a Patient Access Scheme Wales (PASW)-approved Wales Patient Access Scheme (WPAS), involving a confidential discount on the current list price of lapatinib. In both cases, treatment with lapatinib/capecitabine was estimated to be less costly and marginally more effective than trastuzumab-based regimens.

Table 2. Company-reported results of the base case analysis.

Base case	Lapatinib/ capecitabine	Trastuzumab/ capecitabine	Trastuzumab/ vinorelbine	Difference	
				lapatinib/capecitabine versus trastuzumab/ capecitabine	lapatinib/capecitabine versus trastuzumab/ vinorelbine
Anti-HER2 drug costs without WPAS	£11,944	£13,276	£13,276	−£1,332	−£1,332
Anti-HER2 drug costs with WPAS	*	£13,276	£13,276	*	*
Other chemotherapy drug costs	£1,884	£2,430	£2,147	−£546	−£263
Administration	£108	£2,726	£4,552	−£2,618	−£4,444
Total cost without WPAS	**£28,568**	**£32,146**	**£33,689**	**−£3,578**	**−£5,121**
Total cost with WPAS	*	**£32,146**	**£33,689**	*	*
Progression-free life years	0.682	0.705	0.705	−0.023	−0.023
Total life years	1.671	1.582	1.582	0.088	0.088
Total QALYs	**0.887**	**0.856**	**0.856**	**0.031**	**0.031**
Incremental cost per QALY gained	**Lapatinib/capecitabine is both less costly and more effective than the comparators**				

QALYs: quality-adjusted life-years; WPAS: Wales Patient Access Scheme, providing a confidential discount on the list price of lapatinib.
* commercial in confidence figures removed.

Based on the indirect treatment comparison, in which there were no statistically significant differences observed between lapatinib/capecitabine and trastuzumab/capecitabine with respect to TTP (HR 1.05; 95% CI 0.68–1.62) or OS (HR 0.93; 95% CI 0.61–1.42), the modelled progression-free life years are numerically lower for lapatinib/capecitabine compared with trastuzumab regimens. The modelled differences in QALYs are therefore driven by extended survival in the post-progression state, which is experienced at a lower health-related quality of life than in the progression-free state. A wide range of one-way sensitivity analyses have been conducted by the company to address uncertainty in model parameters, including dose intensity, drug wastage, costs associated with PFS and OS, adjusted hazard ratios to

account for patient crossover in the EGF100151 trial, utility weights and discount rates, use of vinorelbine capsules rather than IV solution, and all patients receiving trastuzumab once every three weeks. The sensitivity analyses indicated that lapatinib/capecitabine would remain the dominant strategy within the tested ranges of parameters while the WPAS discount price for lapatinib is assumed.

Scenario analyses have been conducted assuming equal efficacy of lapatinib/capecitabine and comparators, and, separately, restricting the population to those who had only received one prior line of trastuzumab therapy. Lapatinib/capecitabine treatment is reported to dominate both trastuzumab-based regimens in these analyses.

Probabilistic sensitivity analyses (PSA) undertaken for the base case scenario indicate that in the absence of the WPAS, the probability that lapatinib/capecitabine treatment is cost-effective compared to trastuzumab-based therapies is > 90% at a cost-effectiveness threshold of between £20,000 and £30,000 per QALY gained. With the WPAS in place, this probability approaches 100%.

4.1.3 AWTTC critique

Based on the limited evidence available, it would seem plausible that lapatinib plus capecitabine could have a similar efficacy to trastuzumab plus capecitabine and could be associated with lower overall costs when used in this patient population, particularly in the context of the discounted price of lapatinib offered via WPAS. However, there is significant uncertainty in the relative efficacy estimates. There is insufficient evidence to determine the effectiveness and costs of lapatinib in combination with capecitabine relative to trastuzumab in combination with vinorelbine. In addition, it is not possible to infer from the evidence presented by the company the cost-effectiveness of lapatinib in combination with capecitabine relative to any other potential comparators.

Strengths of the company's economic evidence include:

- In the absence of direct comparative data in the population for which lapatinib use is indicated, the company has made efforts to provide relevant data, by undertaking a detailed literature review of relevant trials and attempts to undertake an adjusted indirect comparison.

Limitations of the economic evidence include:

- The company has provided comparisons against trastuzumab in combination with either capecitabine or vinorelbine as requested by AWTTC; however, it would not be plausible to infer that the company's evidence on the cost-effectiveness of lapatinib/capecitabine relative to trastuzumab/capecitabine or trastuzumab/vinorelbine is applicable to any other potential treatment options (e.g. capecitabine monotherapy).
- There is a lack of direct comparative data for lapatinib/capecitabine and trastuzumab/capecitabine, and there are no data to inform the comparative effectiveness of lapatinib/capecitabine and trastuzumab/vinorelbine. The company has acknowledged heterogeneity between the studies included in the indirect comparison, particularly with regard to previous chemotherapy treatments received by participants. There is substantial uncertainty in the effectiveness estimates derived from the adjusted indirect comparison.
- Due to a reported lack of randomised controlled trials for trastuzumab/vinorelbine in the target patient population, the model assumes therapeutic equivalence of trastuzumab with capecitabine and trastuzumab plus vinorelbine regimens on the basis that capecitabine and vinorelbine are used interchangeably as second or third line therapy for metastatic breast cancer patients.
- The PSAs should be interpreted with some caution, as a good proportion (40%) of simulations indicated lapatinib/capecitabine to be less costly and less

effective than trastuzumab regimens, reflective of the uncertainty associated with the relative efficacy estimates.

4.2 Review of published evidence on cost-effectiveness

The company has highlighted one published CUA of lapatinib/capecitabine compared against capecitabine monotherapy and against trastuzumab/capecitabine[27]. This used data from the same pivotal trials of lapatinib/capecitabine and trastuzumab/capecitabine, but different approaches to modelling PFS and utility values, and earlier OS data for trastuzumab/capecitabine. The authors conclude that lapatinib/capecitabine has an ICER of £77,993 per QALY gained versus capecitabine monotherapy, and is dominant over (less costly and more effective than) trastuzumab/capecitabine in the base case deterministic analyses. In PSAs, lapatinib/capecitabine and trastuzumab/capecitabine were approximately equally likely to be cost effective over a wide range of cost effectiveness thresholds. This published analysis does not relate to the discounted price of lapatinib agreed via WPAS.

5.0 SUMMARY OF EVIDENCE ON BUDGET IMPACT

5.1 Budget impact evidence

5.1.1 Context and methods

Based on Cancer Research UK incidence figures for 2008[28], the company assumes there are 2,624 new cases of breast cancer diagnosed every year in Wales[1]. To estimate the number of patients with $HER2^{+}$ tumours and advanced or metastatic disease with progression following prior therapy, a number of assumptions have been made based on data drawn from different sources, including NICE guidance Technology Appraisal 107 (2006)[29], a systematic review[30], and the company's own data (on file)[1]. According to these estimations, there are currently 96 patients eligible for treatment in Wales with lapatinib/capecitabine, of which 11 patients are already receiving this treatment (as estimated from company sales data). According to data provided by five medical oncologists in Wales, approximately 27% of the relevant population are currently receiving trastuzumab/capecitabine and 15% trastuzumab/vinorelbine (trastuzumab/paclitaxel regimen was excluded as a comparator, since patients who did not receive a taxane in the first line setting would not be eligible for lapatinib/capecitabine treatment), and collectively, 72.8% of patients are estimated to receive a trastuzumab-containing regimen[1]. The company assumes that lapatinib plus capecitabine will displace trastuzumab plus capecitabine and trastuzumab plus vinorelbine proportionally to their market share (64% and 36%, respectively). The uptake of lapatinib/capecitabine is anticipated to increase from 20% in year one to 60% in year five upon AWMSG endorsement. The number of patients prescribed lapatinib/capecitabine will therefore increase from 25 to 53 in five years. Drug acquisition, administration and monitoring costs are derived from the economic model discussed above[1].

5.1.2 Results

The estimated numbers of patients and the associated costs are summarised in Table 3. The total cost of lapatinib/capecitabine treatment includes a confidential discount on the list price as part of a PASW-approved WPAS. Net cost savings with the use of lapatinib/capecitabine are estimated, and include avoidance of hospital attendances for patients who would otherwise receive trastuzumab-based regimens.

Table 3. Company-reported costs associated with use of lapatinib in combination with capecitabine for the treatment of patients with HER2+ advanced or metastatic breast cancer.

	Year 1	Year 2	Year 3	Year 4	Year 5
Assuming no AWMSG endorsement					
Number of eligible patients	81	81	81	81	81
Trastuzumab/ capecitabine total cost (64%)	£1,720,606	£1,720,606	£1,720,606	£1,720,606	£1,720,606
Trastuzumab/ vinorelbine total cost (36%)	£1,003,427	£1,003,427	£1,003,427	£1,003,427	£1,003,427
Total costs	£2,724,033	£2,724,033	£2,724,033	£2,724,033	£2,724,033
Assuming AWMSG endorsement					
Lapatinib uptake	20%	30%	40%	50%	60%
Number of lapatinib-treated patients	25	32	39	46	53
Lapatinib/ capecitabine total cost with WPAS	†	†	†	†	†
Trastuzumab/ capecitabine total cost	£1,189,252	£1,040,595	£891,939	£743,282	£594,626
Trastuzumab/ vinorelbine total cost	£693,550	£606,857	£520,163	£433,469	£346,775
Total costs	†	†	†	†	†
Overall net costs with WPAS*	†	†	†	†	†

WPAS: Welsh Patient Access Scheme.
* NB: the company reports that lapatinib is already in use in Wales under a different discount scheme (not approved by PASW), and estimates that cost savings are already being realised. The anticipated cost savings estimated above take into account the discount price being utilised by NHS Wales at the time of appraisal.
† Commercial in confidence figures removed

The company reports that lapatinib is already in use in Wales under a different discount scheme (not approved by PASW), and estimates that cost savings are already being realised from its use compared with trastuzumab-regimens. The anticipated cost savings estimated above take into account the discount price being utilised by NHS Wales at the time of appraisal. Compared with current cost savings estimated by the company due to the current use of lapatinib in NHS Wales, endorsement of lapatinib by AWMSG (with its associated increase in uptake) is anticipated to deliver cost savings. [Commercial in confidence information removed]

Scenario analyses of resource implications presented by the company included cost of treating the most frequent AEs, including diarrhoea, vomiting, fatigue/asthenia, skin changes and LVEF events. The company states that this would reduce savings by approximately £1,000 in year one and £3,000 in year five[1].

5.1.3 AWTTC critique

- The company has adopted a pragmatic approach to estimate the eligible patient numbers, which is based on only incident cases of breast cancer and assumes no contribution of patients from prevalent cases. A range of assumptions have

been necessary, which has introduced a degree of uncertainty in these estimates.

- Cost estimates are derived from the economic model discussed in Section 4.0. The limitations and uncertainties in costs observed in the economic model would therefore feed through to the budget impact estimates.
- Estimates of actual net costs in practice are therefore subject to uncertainty.

5.2 Comparative unit costs

The estimation of comparative acquisition costs for chemotherapy regimens are complicated, as doses of individual components may be calculated on a body weight or BSA basis. The example costs of regimens for the treatment of patients with advanced or metastatic breast cancer shown in Table 4 assume an average body weight of 70 kg and a BSA of 1.73 m^2. Example acquisition costs over 21 days are provided, to facilitate comparison with regimens that are delivered in three-week cycles.

Table 4. Examples of cost per patient of anti-HER2 regimens for the treatment of patients with advanced or metastatic breast cancer.

Regimens	Example doses	Approximate 21-day costs
Capecitabine (Xeloda®) 150 mg and 500 mg tablets	1,250 mg/m^2 twice daily for 14 days followed by a seven-day rest period	£266
Trastuzumab (Herceptin®) 150 mg powder for concentrate for solution for infusion	6 mg/kg every three weeks (assuming loading dose already given)	£1,222
Vinorelbine (Navelbine®) 10 mg/ml solution for infusion 1 ml and 5 ml vial	25 mg/m² once weekly	£420
Vinorelbine (Navelbine® Capsules) 20 mg, 30 mg and 80 mg capsules	80 mg/m^2 once weekly (from week four onwards)	£924
Lapatinib (Tyverb®)/ Capecitabine (Xeloda®)	1,250 mg once daily 2,000 mg/m^2 for 14 days followed by a seven-day rest period	**£1,206 + £214 = £1,420 (assuming full list price for lapatinib)***
Trastuzumab (Herceptin®)/ Capecitabine (Xeloda®)	6 mg/kg every three weeks (assuming loading dose already given) 1,250 mg/m^2 twice daily for 14 days followed by a seven-day rest period	£1,222 + £266 = £1,488
Trastuzumab (Herceptin®)/ Vinorelbine (Navelbine®)	6 mg/kg every three weeks (assuming loading dose already given) 25 mg/m² once weekly	£1,222 + £420 = £1,642
Trastuzumab (Herceptin®)/ Vinorelbine (Navelbine® Capsules)	6 mg/kg every three weeks (assuming loading dose already given) 80 mg/m^2 once weekly (from week four onwards)	£1,222 + £924 = £2,146

Note: not all regimens may be licensed for use in this patient population. See relevant SPCs for full licensed indications and dosing details[2,3,12,31–33].
Costs are based on MIMS list prices as of March 2013[34], assuming vial wastage.
Costs of administration are not included.
* PASW-approved WPAS provides a confidential discount on the current list price for lapatinib.
This table does not imply therapeutic equivalence of drugs or the stated doses.

6.0 ADDITIONAL INFORMATION

6.1 Appropriate place for prescribing

AWTTC is of the opinion that, if recommended, lapatinib (Tyverb®) is appropriate for specialist only prescribing within NHS Wales for the indication under consideration.

6.2 Ongoing studies

The company submission states that there are no ongoing studies from which additional evidence is likely to be available within the next 6–12 months[1].

6.3 AWMSG review

This assessment report will be considered for review three years from the date of Ministerial ratification (as disclosed in the Final Appraisal Recommendation).

6.4 Evidence search

Date of evidence search: 5 April 2013.
Date range of evidence search: No date limits were applied to database searches.

GLOSSARY

Clinical benefit rate
This was defined in study EGF100151 as the percentage of subjects with complete or partial response or stable disease for ≥ six months[35].

Overall response rate
This was defined in studies EGF100151 and GBG 26 as the percentage of patients achieving either a complete or partial response[18,24]. The response of tumour lesions was made according to RECIST[24].

Overall survival
This was defined in studies EGF100151, EGF111438 and GBG 26 as the time period between randomisation until death due to any cause[23,24,35].

Progression-free survival
This was defined in studies EGF100151 and EGF111438 as the time from randomisation to disease progression or death due to any cause[18,23].

Response Evaluation Criteria In Solid Tumors (RECIST)
These are a set of published rules that define disease response, progression and stable disease during treatments[36].

Time to progression
This was defined in studies EGF100151 and GBG 26 as the time from randomisation to disease progression or death due to breast cancer[18,24].

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Appendix 1. Additional health economic information.

Table 1. Health economic model detail.

	Base case model	Appropriate?
Comparator(s)	Lapatinib in combination with capecitabine is compared against trastuzumab in combination with capecitabine and trastuzumab in combination with vinorelbine.	As requested by AWTTC. According to the company's market research trastuzumab/capecitabine, trastuzumab/paclitaxel and trastuzumab/vinorelbine are the most commonly used regimens in the target population in Wales (together accounting for 42.5% of treatment regimens used in this setting, although trastuzumab is not specifically licensed for use in combination with capecitabine or vinorelbine in this patient group). Trastuzumab in combination with paclitaxel was excluded as a comparator, as the majority of patients who receive paclitaxel in the second-line setting will not have received a taxane in the first line setting and so would not be eligible for treatment with lapatinib/capecitabine.
Population	The model population includes female patients with breast cancer, whose tumours overexpress HER2 (ErbB2), with advanced or metastatic disease with progression following prior therapy, which must have included anthracyclines and taxanes and therapy with trastuzumab in the metastatic setting. The model assumes a mean patient weight of 68.87 kg based on the characteristics of the study population of the EGF100151 trial.	Yes, reflects the licensed indication under appraisal. The model employs data from the ITT populations enrolled in the EGF100151 study comparing lapatinib plus capecitabine versus capecitabine monotherapy. The company acknowledged that there were significant differences in population characteristics between the pivotal lapatinib/capecitabine trial and the GBG 26 trastuzumab/capecitabine trial. Patients in the lapatinib/capecitabine trial were more heavily pretreated than those in the trastuzumab/capecitabine trial, which the company suggests may lead to conservative estimates of relative efficacy for lapatinib/capecitabine.
Model type and description	Cost-utility analysis (CUA). The model uses a partitioned survival analysis to estimate the incremental costs and health outcomes based upon time spent in three health states: 'alive prior to disease progression', 'alive following disease progression' and 'dead'. For the purpose of economic analysis the patients entering the model are considered to be progression free, although they have already experienced disease progression on prior therapies. The patients are assumed to receive lapatinib/capecitabine or comparator treatments until they subsequently experience disease progression or death. Subsequent-line or salvage chemotherapies are assumed to be the same for all treatment groups included in the model.	Yes, CUA is an appropriate type of analysis. Due to the lack of a direct comparison of lapatinib/capecitabine against trastuzumab/capecitabine and trastuzumab/vinorelbine, time spent in each health state was estimated using time-to-event data from study EGF100151. The hazard ratios for lapatinib/capecitabine versus the comparators are based on an adjusted indirect comparison of TTP and OS data from EGF100151 and GBG 26 trials.
Perspective	NHS Wales.	Appropriate. The analysis considers direct medical costs from the perspective of NHS Wales. Personal and Social Services are not considered.
Time horizon	The analysis uses a ten-year time frame as a lifetime projection for patients with $HER2^+$ advanced or metastatic breast cancer.	Appropriate. According to the company's model-based estimations, 99% of patients receiving lapatinib plus capecitabine are expected to have died within ten years.
Discount rate	A 3.5% per annum discount rate was applied to both costs and outcomes. Scenario analyses include discount rates of 0% and 6%.	Appropriate.

Table 1A. Continued.

	Base case model	Appropriate?
Efficacy	Clinical outcomes used in the model included TTP (used as a proxy for PFS) and OS for patients receiving lapatinib plus capecitabine derived from the EGF100151 trial by fitting a Weibull function. TTP was estimated by using data from the independent review committee which assessed PFS from the April 2006 data cut-off for the EGF100151 study. OS was estimated using data from the October 2008 data cut-off for the EGF100151 study. TTP and OS for trastuzumab/capecitabine were estimated using hazard ratios derived from an adjusted indirect comparison of lapatinib/capecitabine with capecitabine monotherapy (EGF100151) and trastuzumab/capecitabine with capecitabine monotherapy (GBG 26) applied to the estimated Weibull distributions for lapatinib/capecitabine. Trastuzumab plus vinorelbine was assumed to be equally as effective as trastuzumab plus capecitabine, therefore PFS and OS estimated for trastuzumab/capecitabine combination therapy were used for both trastuzumab-based regimens. Scenario analysis has been conducted assuming equal efficacy for lapatinib plus capecitabine, trastuzumab plus capecitabine and trastuzumab plus vinorelbine.	There is a lack of direct comparative data for lapatinib/capecitabine therapy versus trastuzumab/capecitabine and trastuzumab/vinorelbine in the target population. Therefore, the company has undertaken an adjusted indirect comparison of two studies comparing lapatinib/capecitabine with capecitabine monotherapy (EGF100151) and trastuzumab/capecitabine with capecitabine monotherapy (GBG 26). The company acknowledged that patients recruited to the EGF100151 trial were more heavily pretreated than those recruited to the GBG 26 study, and that prior lines of chemotherapy were shown to impact on the treatment effect for lapatinib/capecitabine. The adjusted indirect comparison does not account for this. TTP in the capecitabine monotherapy arm of trial GBG 26 was somewhat longer than that in the EGF100151 trial; however, neither trial observed a statistically significant difference in OS for combination therapy over monotherapy. There was also a five-year difference in the median age between patients in EGF100151 and GBG 26 trials. There are therefore several differences between the trials, which would suggest that results of indirect comparison are associated with significant uncertainty. TTP is used as a proxy for PFS, due to a reported lack of PFS data in the GBG 26 trial. In the base case analysis, the hazard ratio for OS for lapatinib/capecitabine versus capecitabine monotherapy is not adjusted to account for crossover of patients to the lapatinib arm at early termination of the study, which the company considers to be a conservative approach. Due to a lack of trial data, efficacy with trastuzumab/vinorelbine is assumed equal to that with trastuzumab/capecitabine. There are, therefore, several sources of uncertainty around the comparative efficacy estimates. Modelled PFS was numerically longer for trastuzumab containing regimens, and modelled post progression survival was longer for lapatinib; however, these are based on point estimates for which there were no statistically significant differences observed for TTP and OS based on the indirect comparison, and confidence intervals around point estimates are wide. A range of sensitivity and scenario analyses have been undertaken around the approach to relative efficacy estimates, including assuming equal efficacy for lapatinib/capecitabine and the comparators. Lapatinib/capecitabine treatment remained the dominant strategy, based on lower costs.

Table 1A. Continued.

	Base case model	Appropriate?
Adverse effects	It is assumed that AEs requiring management through other medication and hospitalisation differ only by pre-progression and post-progression states and are the same regardless of the treatment regimen. AEs considered in sensitivity analysis included diarrhoea, vomiting, fatigue/asthenia, skin changes, and LVEF events (Grade 3 and higher). Estimates of the incidence of AEs for lapatinib/capecitabine were taken from the EGF1000151 study, and for trastuzumab/capecitabine from the GBG 26 study. Due to a lack of studies using trastuzumab/vinorelbine in the target population, AE rates were derived from a study of trastuzumab/vinorelbine as first-line treatment of $HER2^+$ metastatic breast cancer.	The base case analysis effectively assumes there are no discernible differences in cost or HRQoL impacts of AEs between lapatinib/capecitabine and the comparators. It is uncertain if this is appropriate given the differences in administration routes, etc.
Utility values	Utility values for patients treated with lapatinib/capecitabine were obtained from the EGF100151 trial using EQ-5D (pre-progression health state only). Pre-progression utility values were assumed to be independent of treatment strategy. For the post-progression state utility values were estimated using utility decrement derived from a published study[37]. The impact of disutilities imposed by AEs and intravenous administration were explored by sensitivity analyses.	Appropriate to use trial-derived utility values where available, although utility values are only available for the PFS state; the trial stopped routine collection of data following disease progression. The use of alternative sources for post-progression state therefore adds a source of uncertainty. The transition of patients from PFS state to post-progression state generates an abrupt reduction in utility weights rather than a gradual decline that may be more realistic in such patients. Utility values are assumed to be state-related and are independent of treatments received in the base case model. Sensitivity/scenario analyses include incorporation of utility decrements associate with specific AEs and with intravenous administration of trastuzumab.
Resource use and costs	A WPAS involving a confidential discount on the current list price of lapatinib has been approved by PASW. Acquisition costs for lapatinib/capecitabine regimens were estimated based on mean doses used in the EGF1000151 study (1,250 mg lapatinib daily, 2,000 mg/m^2 capecitabine for 14 days in every three-week cycle). Trastuzumab costs were estimated using recommended monotherapy doses in the adjuvant setting, with administration scheduled based on company sought expert opinion (2 mg/kg once weekly in 11.6% of cases and 6 mg/kg every three weeks in 88.4%). When used in combination with trastuzumab, capecitabine was assumed to be given at the doses used in the GBG 26 trial (2,500 mg/m^2 daily for 14 days in every three-week cycle). Vinorelbine was assumed to be used at the lower end of the indicated dose range (25 mg/m^2 twice every three weeks). Relative dose intensity adjustments were undertaken to adjust for differences in daily doses and therapy duration between the EGF1000151 and GBG 26 studies. Treatment is assumed to continue until disease progression. Wastage of 15% for intravenous trastuzumab was included in the base case analysis. Variations in trastuzumab and vinorelbine dosage and administration costs were addressed by sensitivity analysis. Administration costs are based on published unit cost data. Costs of other medication, tests, clinical consultations, radiotherapy and other interventions were derived from a published UK study of the costs of stage IV breast cancer[38].	The company has provided analyses assuming the full list price of lapatinib, and the PASW-approved discounted price of lapatinib. The company has made a reasonable effort to estimate costs associated with lapatinib/capecitabine and comparator therapies. In the base case model, the company has assumed doses for lapatinib/capecitabine as per the EGF1000151 trial, (capecitabine 2,000 mg/m^2 daily) and for trastuzumab/capecitabine doses are based on study GBG 26, which employed a higher dose of capecitabine (2,500 mg/m^2 daily). One way sensitivity analyses demonstrate that the modelled cost savings are reduced when both regimens are assumed to use the lower (2,000 mg/m^2) daily dose of capecitabine, but lapatinib/capecitabine remains dominant over trastuzumab/capecitabine. Non-drug resource use and cost estimations used in the model are based on published study of costs from 2002, uplifted to 2011 values. It is unclear whether treatment practices for $HER2^+$ advanced and metastatic breast cancer have changed since the study was published.

Table 1A. Continued.

	Base case model	Appropriate?
Uncertainty	A range of one-way sensitivity analyses have been conducted to address the uncertainty associated with key parameters, including dose intensity, hazard ratios derived from difference approaches to handling cross-over of patients in the EGF100151 study, drug wastage, costs associated PFS and PPS health states, utilities, discount rate, AE costs, and use of oral vinorelbine. Scenario analyses assumed equal efficacy for lapatinib/capecitabine and comparator regimens.	A useful range of sensitivity analyses have been conducted. PSAs did not include all relevant costs (other medication, tests, hospitalisation, etc), assuming that these costs are identical for all treatment regimens. The spread of simulated estimates generated in the PSA reflects the uncertainty of the key efficacy parameter estimates, with a similar proportion falling in the south east quadrant (lapatinib less costly and more effective than trastuzumab regimens) and the south west quadrant (lapatinib less costly and less effective than trastuzumab regimens) of the cost-effectiveness plane.
Model Provided?	Yes.	Appropriate. Model appears to generate the outputs as reported in the company submission.
Other considerations	NICE, in its suspended appraisal of lapatinib, considered that its end of life policy was relevant on the basis that eligible patients numbers are small, their life expectancy is likely to be less than two years, and a small chance that lapatinib could extend life by three months or more compared with capecitabine monotherapy[29]. In contrast, the comparators assumed for the AWMSG submission[1] are limited to trastuzumab-containing regimens and, using relative efficacy estimates from the indirect treatment comparisons, the model generates a survival gain for lapatinib of around one month.	

AE: adverse event; AWTTC: All Wales Therapeutics and Toxicology Centre; CUA: cost-utility analysis; EQ-5D: EuroQoL - 5 Dimensions health outcome measure; HRQoL: health-related quality of life; ITT: intent-to-treat; NICE: National Institute for Health and Clinical Excellence; OS: overall survival; PASW: Patient Access Scheme Wales; PFS: progression-free survival; PSA: probabilistic sensitivity analysis; TTP: time to progression; WPAS: Welsh Patient Access Scheme.