Response to Appraisal Consultation Document on lapatinib in previously treated women with advanced or metastatic breast cancer

GlaxoSmithKline 28 July 2008

1. Do you consider that all of the relevant evidence has been taken into account?

There are two significant aspects of the evidence base that we do not believe have been fully considered.

Firstly, we believe that the ACD fails to take sufficiently into account reports provided by clinical and patient groups, nominated experts, and clinical experts advising the Evidence Review Group (ERG) as part of the STA process, which support GSK's evidence that trastuzumab is continued beyond progression in this setting. Further details are provided in Section 1.1 below.

Secondly, since our original submission in April 2007 there have been considerable and fundamental changes to the evidence base that address areas of uncertainty highlighted by the Appraisal Committee. GlaxoSmithKline submitted a dossier to NICE for lapatinib on 17 April 2007. At this time it was anticipated that marketing authorisation would be forthcoming from the EMEA during Quarter 3 2007. Due to several regulatory delays, CHMP positive opinion was first granted on 13 December 2007 and again on 24 April 2008, with marketing authorisation following on 10 June 2008. Therefore there has been a significant interval between GSK's submission in April 2007 and its review by the Evidence Review Group during May 2007, the Appraisal Committee meeting at which the evidence was considered on 22 January 2008, and the current consultation period in July 2008.

Whilst we acknowledge that the STA process is intended to provide guidance to the NHS on technologies as soon as possible after they become available on the market, the resulting need to perform the evidence review in parallel with licensing can cause significant issues when the process is delayed and the evidence base for the technology and its comparators develops significantly over time, as is the case for lapatinib. We strongly believe that these changes in the evidence base should be considered by the Appraisal Committee before issuing final guidance, and therefore we are submitting them for consideration as part of our response to the ACD.

1.1. Evidence for continuation of trastuzumab beyond progression

The ACD states that there was a lack of evidence to support the justification of trastuzumab containing regimens beyond progression as comparators in this setting (Section 4.9, Consideration of the Evidence). GSK provided in its original submission results from two key market research studies performed in the UK to determine current service provision for patients with advanced or metastatic breast cancer (IMS Oncology Analyzer study, independently collected patient record data from January 2004 to September 2006; Dendrite Docscan Oncology Survey, physician-based survey of prescribing behaviour undertaken in August 2006). These studies suggested that trastuzumab was used widely beyond disease progression in UK clinical practice at that time (in 40-45% of patients).

We acknowledge the limitations of the analyses highlighted by the ERG and in the ACD, in particular the small sample size that was included in the IMS Oncology Analyzer study (24 patients who fitted the criteria for inclusion). However, the data are in the form of patient-level notes reviews, provided anonymously by physicians. The 24 eligible patients were identified from 1,410 patients with metastatic breast cancer in the database. We believe that despite the limited numbers these anonymously submitted patient-level results are possibly more reflective of real practice than anecdotal evidence which will be influenced by concerns about highlighting the unlicensed use of trastuzumab beyond progression. These data are

supported by the ERG's clinical advisors who confirmed that trastuzumab is continued beyond progression in conjunction with either capecitabine or vinorelbine, whereas trastuzumab monotherapy is rarely used beyond disease progression (Section 2.3.3, ERG report), and concluded that the selected comparators in GSK's evaluation were appropriate (Section 3.1.2, ERG report). This is also consistent with statements by patient and physician groups, as well as nominated experts which formed part of the Evaluation Report underpinning the Appraisal Committee's deliberations. These written comments are particularly relevant as from the ACD documentation it would appear that a medical oncologist did not attend the Appraisal Committee discussions. Whilst trastuzumab is only licensed for use up to disease progression in the metastatic setting, it is our understanding that this practice has come about due to the acceptance of the importance of continuing to suppress the ErbB2 receptor and the lack of alternative ErbB2-targeted treatments. The ACD refers to the view of clinical experts that the practice varies considerably across England and Wales. Whilst we acknowledge that variability does exist, the written expert submissions do support that it is used and with almost 50% of patients receiving this option it should not be discounted as a valid comparator from the appraisal. Further, we note that the ACD highlights the requirement for research to compare lapatinib with trastuzumab in this setting, which would not be appropriate if this was not a relevant comparator. We acknowledge that capecitabine regimens are also a valid comparator although updated data (reported below) would question whether these remain the most commonly used.

GSK therefore defends the original assumption that at that time of our original submission, trastuzumab-containing regimens were routinely continued beyond progression, in nearly half of patients in this setting.

1.1.1. *New market research data supporting the use of trastuzumab beyond progression*

Since the original market research studies were performed in 2004-2006 there are more data available in the IMS Oncology Analyzer database on which to base conclusions regarding clinical practice. The original analysis has been expanded to a 2 year period covering 2006-2007, which is more up-to-date and therefore more reflective of current practice, and includes a greater number of relevant patient records (n=98) from a larger pool of metastatic breast cancer patients (n=2,815). In response to the original IMS data the ACD noted that it was not clear which hospitals the data relate to, and whether different regions or specialist hospitals could be over- or under-represented. Full details of the regional distribution, as well as the respondents' description of their place of work (university hospital, non-university hospital, or both) are given in Appendix 1 for these new market research data. We believe that the data are not over-representative of any particular UK region, or any particular type of hospital.

The results suggest that trastuzumab is now used beyond progression in around 55% of patients, the main regimens being in combination with either capecitabine or vinorelbine (Table 1.1).

These patient-level results are supported with striking consistency by a market research survey undertaken with Cegedim Dendrite (fielded April-June 2008), at oncology consultant-level, to provide insight into current practice (Table 1.1; see Appendix 1 for further details).

Table 1.1 Updated IMS Oncology Analyzer and Cegedim Dendrite Market research results*

	IMS Oncology Analyzer (2006-7) n=98 records from 2,815 metastatic breast cancer patients	**Cegedim Dendrite Survey (2008) n=92 respondents**
All patients (n=98)**	100%	100%
Capecitabine monotherapy	32%	33%
Vinorelbine monotherapy	5%	11%

Trastuzumab/vinorelbine	20%	12%
Trastuzumab/capecitabine	21%	23%
Trastuzumab monotherapy	2%	2%
Other trastuzumab regimens	11%	12%
Other non-trastuzumab regimens	9%	7%
Any trastuzumab beyond progression	**55%**	**48%**

***All patients who have progressed on trastuzumab for metastatic breast cancer, after prior anthracycline and taxane treatment**

The recent revised NICE methods guide states that unlicensed comparator technologies may be considered if they are used routinely in the NHS. Available evidence updated in this response demonstrates that currently regimens containing trastuzumab are the most likely therapeutic option for patients in the UK, in the absence of an alternative ErbB2-targeted therapy; the use of this option is clearly recognised by patient groups and clinicians in their advice and submissions to this appraisal.

Furthermore, the recent publication of the first phase III randomised controlled clinical trial data supporting the effectiveness of trastuzumab used in this setting (GBG 26/BIG 3-05) is likely to support the continued use of this therapeutic approach (see below). Indeed, our clinical advisers suggest that such practice will continue to increase over time on the basis of this trial.

In conclusion, we believe that the more recent evidence improves the robustness of our assumption that trastuzumab containing regimens are relevant comparators in this setting, and are now used in around 55% of patients. We believe that this evidence should be considered by the Appraisal Committee.

1.2. Evidence on the clinical effectiveness of trastuzumab beyond progression

The ACD highlighted the lack of randomised trial evidence on the use of trastuzumab beyond progression as a significant concern in their consideration of the evidence, concluding that the clinical effectiveness of trastuzumab in patients who have disease progression on treatment was unproven, and that the unadjusted indirect comparison method used resulted in uncertainty surrounding the cost-effectiveness estimates. Whilst we would argue that there was some evidence of trastuzumab efficacy in this setting at the time of our original submission, we recognise that the quality of evidence was limited by the nature of the uncontrolled studies that provided the only data at the time. Further, as acknowledged by the ERG, the use of these data in an unadjusted indirect comparison was unavoidable due to the lack of randomised data.

However, on 3 June 08 the statistical results of the only randomised controlled trial (GBG 26 / BIG 3-05)[1,2] investigating continuation of trastuzumab beyond progression in a setting similar to the current indication for lapatinib (i.e. following progression on trastuzumab administered for metastatic disease),were presented at the American Society of Clinical Oncology Annual Meeting (ASCO). These results now allow a more robust comparison with lapatinib than was possible at the time we submitted in April 2007. This study was identified by the ERG (see p25 of their report) as an ongoing study, and was also identified in GSK's systematic review which was updated to March 2008 (Appendix 2, section 2.1).

Given that the evidence base for the efficacy and extent of use of trastuzumab beyond progression was stated to be a key consideration for the Appraisal Committee in making their decision, we offered NICE the opportunity to consider the above additional evidence (together with an extended pooled analysis of uncontrolled trastuzumab studies identified by an updated literature search, as well as the most recent lapatinib overall survival data cited in the Summary of Product Characteristics, for completeness) prior to releasing the ACD to aid a more productive consultation. This offer was rejected in order to maintain the planned

timelines for the appraisal.

We believe that, in order to make a decision on the appropriate use of lapatinib in the context of regulatory delays and a rapidly evolving evidence base, the most up-to-date evidence should be considered by the Appraisal Committee.

These new data and their implications are summarised below.

1.2.1. New randomised data comparing trastuzumab plus capecitabine with capecitabine alone - study GBG 26 / BIG 3-05

Summary results from the GBG 26 study are presented in Table 1.2 alongside those from the latest results for the lapatinib pivotal study (EGF100151). Further details of the GBG 26 study design can be found in Tables 1-5, Appendix 2.

Table 1.2: Summary of key findings from EGF100151 and GBG 26 (Von Minckwitz 2008)

Study	Interventions	Median TTP (95% CI)	ORR (95% CI)	CBR (95% CI)	Median OS
EGF100151† (independent assessment)	lapatinib + capecitabine (N=198)	6.25 mths (4.02, 11.40)	23.7 % (18.0, 30.3)	29.3 % (23.1, 36.2)	17.08 mths (15.07, 19.59)
	capecitabine (N=201)	4.29 mths (2.10, 8.52)	13.9 % (9.5, 19.5)	17.4 % (12.4, 23.4)	15.21 mths (12.32, 17.31)
		p=0.00013 HR=0.57 (0.43, 0.77)	p=0.017 OR = 1.9 (1.1, 3.4)	p=0.008 OR=2.0 (1.2, 3.3)	p=NS HR=0.9 (0.71, 1.12)
GBG 26 (Von Minckwitz 2008)	trastuzumab + capecitabine (N=78)	8.2 mths (7.3, 11.2)	48.0 % (36.5, 59.7)	75.3 % (64.2, 84.4)	25.5 mths (19.0, 30.7)
	capecitabine (N=78)	5.6 mths (4.2, 6.3)	27.0 % (17.3, 38.6)	54.0 % (42.1, 65.7)	20.4 mths (17.8, 24.7)
		p=0.034 HR=0.69	p=0.011	p=0.00068	p=NS HR=0.76

TTP = Time to progression; ORR = Overall Response Rate; CBR = Clinical Benefit Rate; OS = Overall Survival. † Results for TTP, ORR and CBR for EGF100151 are for 03 April 2006 cut-off[3]; results for OS are updated for 28 September 2007 cut-off (lapatinib SmPC)

The primary endpoint of the GBG 26 study was time to progression; it was planned to recruit 241 patients per arm to show an improvement from 4 to 5.1 months by continuing trastuzumab. The study closed early on the advice of the study's Independent Data Monitoring Committee due to slow accrual, having recruited only a third of its planned patients (N =156 of 482-patient target); statistical analyses were carried out. Notably, the FDA registration of lapatinib was cited by the authors as a reason for the study not to reach target recruitment.

The results show that trastuzumab in combination with capecitabine is clinically effective when compared with capecitabine alone, with significantly improved median time to progression (TTP), overall response rate (ORR) and clinical benefit rate (CBR). Overall survival was not significantly different in the two treatment groups. Although the absolute values for the trastuzumab plus capecitabine combination appear to be numerically higher than those for lapatinib plus capecitabine, it should be noted that patients in the GBG 26 study were less advanced in the course of their disease having received a maximum of only one prior line of chemotherapy for metastatic disease[1], whereas more than 50% of patients in the EGF100151 study had previously received at least four prior lines of therapy in the metastatic setting. This also appears to be reflected in the higher efficacy results for the capecitabine monotherapy arm in the GBG 26 study compared with those for the capecitabine monotherapy arm at the same dosage in EGF100151. These results support the efficacy of trastuzumab in this setting, as suggested in GSK's original pooled analysis (weighted mean TTP 5.0 months (95%CI: 4,3, 5.8 months); HR 0.86 (95%CI: 0.74, 1.01)).

The GBG 26 study[1,2] is the first randomised controlled trial to have evaluated the continued use of trastuzumab beyond progression in a setting similar to the licensed setting for lapatinib. Whilst there are some limitations to the study, specifically relating to its early closure and the small number of patients recruited, it clearly confirms the value of continuing to suppress ErbB2 in receptor-positive patients and that, in the absence of an alternative ErbB2-targeted therapy, continuation of trastuzumab beyond progression is a reasonable clinical approach. In addition, it allows the use of more robust data to generate cost effectiveness estimates for the use of lapatinib plus capecitabine compared with trastuzumab beyond progression, and hence reduce the uncertainty around the estimates for consideration by the Appraisal Committee.

1.2.2. Additional, uncontrolled trastuzumab studies

The systematic review of clinical literature was updated from a cut-off of February 07 to March 2008. The review identified one new randomised controlled trial as meeting the eligibility criteria: the German Breast Group study (GBG 26) comparing trastuzumab plus capecitabine versus capecitabine monotherapy.[1,2] This study is described above.

An additional ten non-randomised studies[4-14] involving the use of trastuzumab beyond progression were identified as meeting the inclusion criteria in the updated systematic review conducted in March 2008. These studies were either single-arm phase II trials or observational studies, the majority of which were conducted retrospectively. Several of the studies involved small patient numbers and/or were conducted at single centres and in single countries. In addition, many are reported only as abstracts and therefore provide limited information on the participant characteristics. Further details on the individual study designs and baseline characteristics can be found in Tables 1 and 2 in Appendix 2.

The growing number of studies identified which involve the continuation of trastuzumab beyond disease progression supports the case that this has been a commonly employed therapeutic approach in the absence of alternative ErbB2-targeted agents.

The main efficacy and safety findings for the new non-randomised studies identified via the systematic review are summarised in Tables 3 to 5 in Appendix 2. Although the absence of a control group and lack of statistical dispersion data around the outcomes reported limit the validity of these study findings, their results support the rationale for continuing ErbB2-targeted therapy after progression on trastuzumab.

Five of the newly identified studies[2,4-7] report a time to second progression and these data have been included in an updated pooled analysis (with weighting applied to account for sample size) conducted in a similar manner to that undertaken for our original submission, to estimate a pooled median TTP for trastuzumab-based therapy beyond progression. The final number of studies included in this updated analysis was sixteen, since one of the original studies[7] was an update of data previously included in the original analysis, so the original study was omitted. Although it was not possible to differentiate between the efficacy of different trastuzumab-containing regimens, this yielded a pooled estimate of median TTP of 27.0 weeks (95% CI: 23.3, 31.1) [6.2 months (95%CI: 5.4, 7.2)], and a hazard ratio of 0.70 (95% CI: 0.61, 0.81). The addition of these studies increases the magnitude of efficacy in comparison with the original pooled analysis (see section 1.2.1 for original results). The disaggregated and pooled results from these studies can be found in section A2.2 in Appendix 2.

1.3. Evidence on the clinical effectiveness of lapatinib

The Summary of Product Characteristics (SmPC, section 5.1) now presents a later survival analysis than that presented in our original submission. This updated analysis for overall survival was conducted on 28 September 2007 (see Table 1.3 below for a comparison of the two analyses). These data were provided to NICE in the form of an addendum to the submission on 2 May 2008, which contained further detail of the analysis.

Table 1.3: Summary of overall survival (ITT population, April 2006 and September 2007 cut-offs)

Outcome Measure	Lapatinib + Capecitabine	Capecitabine	Hazard Ratio (95% CI)	Log-rank 2-sided p-value
April 2006 cut-off	**N=207**	**N=201**		
Deaths	53 (27%)	59 (29%)	-	-
Median Overall Survival (weeks)	67.7 (58.9, 91.6)	66.6 (49.1, 75.0)	0.78 (0.55, 1.12)	0.2
September 2007 cut-off	**N=198**	**N=201**		
Deaths	148 (71.5%)	154 (76.6%)	-	-
Median Overall Survival (weeks)	74.0 (65.3, 84.9)	65.9 (53.4, 75.0)	0.9 (0.71, 1.12)	0.3

Note: *n=36 of 39 patients on capecitabine monotherapy at the 03 April 2006 cut-off crossed over to receive lapatinib in addition to capecitabine

Despite an increase in the median overall survival benefit for lapatinib plus capecitabine versus capecitabine (8.1 weeks difference for the September 2007 cut-off; 1.1 weeks for the April 2006 cut-off), the hazard ratio has increased slightly, and the difference remains non-significant. The impact of these updated results on the cost effectiveness of lapatinib in combination with capecitabine is explored below in section 1.4.

1.4. Impact of developments in the evidence base on the cost effectiveness of lapatinib in combination with capecitabine

Having presented new and updated data we believe that it is important to show how these developments in the evidence base impact on the cost effectiveness results presented in GSK's original submission. Table 1.4 summarises the impact on costs and effects of lapatinib and comparators associated with the evolving evidence base, as well as the change from an assumed price of £11.00 per tablet (in the original submission) to the final list price of £11.49 per tablet. Due to some minor corrections to the economic model to address errors that were discovered after GSK made our original submission the original base case results have changed marginally (shown in Scenario 2; details of minor corrections to the model are included in Appendix 3). All analyses from Scenario 3 onwards have been performed using the corrected model. The assumptions for each scenario are described as follows:

Scenario 1 (original base case; original model):
- Lapatinib list price £11.00 per tablet
- Overall survival data April 2006 cut-off
- Efficacy for trastuzumab comparator regimens from original pooled analysis (11 studies)

Scenario 2 (original base case; corrected model):
- Lapatinib list price £11.00 per tablet
- Overall survival data April 2006 cut-off
- Efficacy for trastuzumab comparator regimens from original pooled analysis (11 studies)

Scenario 3
- Lapatinib list price £11.49 per tablet (current list price)
- Overall survival data April 2006 cut-off
- Efficacy for trastuzumab comparator regimens from original pooled analysis (11 studies)

Scenario 4
- Lapatinib list price £11.49 per tablet (current list price)
- Overall survival data April 2006 cut-off
- Efficacy for trastuzumab comparator regimens from updated pooled analysis (16 studies)

Scenario 5
- Lapatinib list price £11.49 per tablet

- Overall survival data September 2007 cut-off (most recent data cited in SmPC)
- Efficacy for trastuzumab comparator regimens from updated pooled analysis (16 studies)

Scenario 6 (fully updated price and clinical results)
- Lapatinib list price £11.49 per tablet
- Overall survival data September 2007 cut-off
- Efficacy for trastuzumab comparator regimens from Von Minckwitz study*

The methodology for estimating the hazard ratios for this study, for incorporation into the economic modelling, are detailed in Appendix 4.

Table 1.4. Summary of impact of assumptions revised from original base case due to developing evidence base

Scenario	**Incremental cost per QALY gained for lapatinib plus capecitabine versus comparators**				
	Capecitabine	**Vinorelbine**	**Trastuzumab plus vinorelbine**	**Trastuzumab plus capecitabine**	**Trastuzumab monotherapy**
Scenario 1 (original base case)	£81,251 (QALYs= +0.17, costs=+£13,873)	£67,847 (QALYs= +0.17, costs=+£11,584)	Dominant (QALYs=+0.14, costs=-£4,452)	Dominant (QALYs=+0.14, costs=-£2,186)	Dominant (QALYs=+0.14, costs=-£1,075)
Scenario 2 (original base case, corrected model)	£81,239 (QALYs= +0.17, costs=+£13,872)	£67,836 (QALYs= +0.17, costs=+£11,584)	Dominant (QALYs=+0.14, costs=-£4,662)	Dominant (QALYs=+0.14, costs=-£2,555)	Dominant (QALYs=+0.14, costs=-£1,261)
Scenario 3	£84,330 (QALYs= +0.15, costs=+£14,400)	£70,927 (QALYs= +0.17, costs=+£12,111)	Dominant (QALYs=+0.14, costs=-£4,134)	Dominant (QALYs=+0.14, costs=-£2,027)	Dominant (QALYs=+0.14, costs=-£733)
Scenario 4	£84,330 (QALYs= +0.15, costs=+£14,400)	£70,927 (QALYs= +0.17, costs=+£12,111)	Dominant (QALYs=+0.05, costs=-£9,958)	Dominant (QALYs=+0.05, costs=-£7,246)	Dominant (QALYs=+0.05, costs=-£5,712)
Scenario 5	£93,825 (QALYs= +0.15, costs=+£14,015)	£78,503 (QALYs= +0.17, costs=+£11,726)	Dominant (QALYs=+0.05, costs=-£9,961)	Dominant (QALYs=+0.05, costs=-£7,249)	Dominant (QALYs=+0.05, costs=-£5,714)
Scenario 6 (fully updated price and clinical results)	£93,825 (QALYs= +0.15, costs=+£14,015)	£78,503 (QALYs= +0.17, costs=+£11,726)	Dominant (QALYs=+0.03, costs=-£8,958)	Dominant (QALYs=+0.03, costs=-£6,450)	Dominant (QALYs=+0.03, costs=-£4,993)

It is clear from these scenario analyses that incorporating the most recent and robust data sources into the cost effectiveness evaluation confirms the results of our original base case: lapatinib in combination with capecitabine remains highly cost effective compared with trastuzumab-containing regimens in this setting; lapatinib is not cost effective when compared with single agent chemotherapies (capecitabine or vinorelbine). We believe that Scenario 6 provides the most robust estimate as it is based on randomised trial data. However, if Scenario 5 was preferred (using efficacy for trastuzumab comparator regimens from the updated pooled analysis) the estimates would further favour lapatinib and hence the use of Scenario 6 also provides the more conservative approach.

Probabilistic sensitivity analysis (PSA) was performed on Scenario 6 with the same probability distributions, means and standard errors as used in our original submission. In summary these analyses suggest that the likelihood of lapatinib plus capecitabine having an incremental cost-utility ratio lower than £20,000/QALY when compared with capecitabine or vinorelbine monotherapies is negligible (under 1%); (2-6% for a threshold of £30,000/QALY). The likelihood that lapatinib plus capecitabine has an incremental cost-utility ratio lower than £20,000/QALY when compared with trastuzumab-containing regimens is over 90% (from 85-93% for the £30,000 threshold).

2. Do you consider that the summaries of clinical and cost effectiveness are reasonable interpretations of the evidence, and that the preliminary views on the resource impact and implications for the NHS are appropriate?

GSK believes that the interpretation of the pivotal clinical trial EGF100151 is reasonable. We agree with the ACD's conclusion that whilst lapatinib in combination with capecitabine is clinically effective when compared with capecitabine monotherapy, it is not cost effective in this comparison, nor when compared with vinorelbine monotherapy.

However, we have significant concerns about the interpretation of the cost effectiveness evidence versus trastuzumab-containing regimens submitted by GSK. The ACD refers to scenario analyses performed by the ERG to evaluate the impact of changing assumptions that relate to the lifetime costs of comparator regimens. Responses to these analyses are discussed individually below, and summarised thereafter.

2.1. Calculation of IV medication use/wastage

The ERG notes that it is not clear why the weight and BSA distributions from the main trial were not used directly, rather than inferring distributions based on the trial mean and standard deviation; they conducted an exploratory analysis on this issue, which we believe under-estimates the true level of wastage of trastuzumab.

The method used in GSK's model was intended to facilitate the use of alternative estimates of mean weight and BSA as user inputs, and also to facilitate switching between 'with wastage' and 'no wastage' scenarios. The assumption of lognormal distribution of weight and BSA was based on inspection of the two distributions, showing them to be truncated at zero and skewed to the right. The parameterized lognormal distributions fit the actual distributions remarkably well (see GSK's response to the ERG report for details). We believe that the use of the parameterized lognormal distributions rather than the actual weight distributions was a reasonable approach.

A comparison of the estimated mean dose for trastuzumab and vinorelbine assuming no wastage, assuming wastage based on the lognormal distribution, and assuming wastage based on the mean (ERG approach) in Table 2.1 suggests that the approach employed by the ERG generates an estimate of vinorelbine use that is similar to that generated by the original model. For trastuzumab the approach employed by the ERG generates estimates of use per dose that are greater than those obtained assuming no wastage, but less than those generated using the lognormal distribution.

Table 2.1. Comparison of estimated doses assuming no wastage, and wastage based on the lognormal distribution and ERG methodology

	Trastuzumab		**Vinorelbine**
	2 mg/kg weekly	**6 mg/kg 3-weekly**	**25 mg/m2 weekly**
Prescribed dose (adjusted for RDI)	1.98 mg/kg	5.94 mg/kg	22.25 mg/m^2
Expected medication used per dose (mg)			
No waste	136.422	409.26	39.38
With waste			
Using lognormal distribution	196.76	495.86	51.03
Using mean (ERG)	150.00	450.00	50.00

We acknowledge that attempts are made to batch-produce trastuzumab infusions and minimise drug wastage, but since the trastuzumab SmPC specifies that vials are for single use it would seem highly unlikely that wastage can be avoided altogether. Therefore to understand the extent of trastuzumab wastage we commissioned independent market research with 24 oncology pharmacists from 17 UK cancer networks (July 2008; Taylor Nelson Sofres) to understand the policies adopted regarding single use vials, and to quantify the proportion of trastuzumab for metastatic breast cancer that is wasted (further details are

presented in section 1.1.3 of Appendix 1). Results indicated that 46% of respondents have a policy relating to the repeat use of IV vials and consider all to be single use. Thirty three percent have a policy and consider some IV vials for multiple use (where possible). The remainder have no policy relating to repeat use of IV vials. Participants were asked to estimate the proportion of total trastuzumab that is discarded, i.e. wasted, in the treatment of metastatic breast cancer patients. On average respondents estimated that 15% of trastuzumab used for the treatment of metastatic breast cancer is wasted (range 5%-60%).

We believe that to exclude wastage would be extreme, and that the estimate of 15% trastuzumab wastage is most likely to reflect true clinical practice. We have therefore incorporated this level of wastage into scenario analyses presented below, by applying an inflation factor to the acquisition costs of trastuzumab (Section 2.5).

2.2. Trastuzumab administration costs

We strongly disagree with the use of the lower trastuzumab administration cost of £117 as suggested by the ERG.

Trastuzumab administration costs in GSK's original submission (£245.22) were taken from NHS Reference Costs 2006,[15] the most current available at the time. The cost includes the cost of an outpatient chemotherapy consultation £207.22 (interquartile range £171 to £277). In addition the handling cost of a complex IV infusion (£38) was added.[16]

The cost suggested by the ERG (£117) is referenced to a medical oncology outpatient consultation of £109 (Netten and Dennett 1999)[17] uplifted to 2006 prices.

We believe that the most recent costs published by the Department of Health at the time of the submission are far more robust than those calculated almost a decade ago, and we vigorously defend our original assumption of £245.22.

2.3. Three-weekly versus weekly trastuzumab administration

The ERG scenario analysis assumed that all patients receive trastuzumab on a three-weekly schedule (6mg/kg). Our original assumption was that trastuzumab is administered once-weekly (2mg/kg), in accordance with NICE guidance and the SmPC for trastuzumab treatment of metastatic breast cancer. However, in recognition of the use of the three-weekly administration schedule by some practitioners, despite this schedule being licensed only for early breast cancer, we supplied a deterministic sensitivity analysis in our original submission. To further address this issue, as highlighted by the ERG, we tested the assumption in the market research with oncology pharmacists described above (and in section 1.1.3 of Appendix 1). Respondents fed back that an average of 11.6% of trastuzumab in metastatic breast cancer is given weekly (range 0% to 100%; standard deviation of mean = 29.3%). Therefore we have applied the figure of 11.6% weekly/88.4% 3-weekly trastuzumab to the scenario analyses below (Section 2.5).

2.4. Trastuzumab efficacy

In the absence of randomised comparative evidence on the efficacy of trastuzumab, the ERG performed an analysis whereby the hazard ratio for progression free survival with trastuzumab was based on a lower median TTP than that obtained from the original pooled analysis. It is not clear from the ERG's report what the actual hazard ratio fed into the model was. However, the impact on the ICER was considerable (increasing those for trastuzumab regimens to a range of £17,000-£25,000/QALY) when compared with the impact observed in GSK's original deterministic sensitivity analysis, which assumed a lower hazard ratio equal to that of capecitabine (ICERs ranged from dominant to around £7,000/QALY). This implies that the ERG used an extreme assumption that the efficacy of trastuzumab regimens is lower than that of capecitabine, i.e. trastuzumab impairs time to progression when compared with capecitabine. It is clear from the GBG 26 trial that trastuzumab in combination with

capecitabine significantly improves time to progression when compared with capecitabine, and this efficacy is supported by evidence from a number of uncontrolled studies as described in section 1.2.2. Therefore we believe that in the absence of randomised controlled data our use of the weighted pooled estimate from uncontrolled trials provided a more robust assessment of trastuzumab efficacy than the extreme assumption applied by the ERG. Further, the availability of the GBG 26 study data allows for a comparison with randomised data, albeit indirectly. We therefore believe that GBG 26 provides the most robust estimate, and we have used these data in our updated analyses.

2.5. Summary - impact of revised assumptions according to ERG on the cost effectiveness of lapatinib in combination with capecitabine

In order to address the Appraisal Committee's concerns about uncertainty around the above variables, we have run revised sensitivity analyses using the updated assumptions described above. Since these above revised assumptions affect only comparisons with trastuzumab-containing regimens the single agent chemotherapy comparisons have been excluded from the results (Table 2.2) for clarity. The ERG reports that trastuzumab monotherapy is rarely used in this setting, which is consistent with the recent market research data reported above. Therefore the trastuzumab monotherapy comparison is included for completeness, but is shaded in the table to allow focus on the most relevant comparator regimens – single agent chemotherapies and trastuzumab in combination with either capecitabine or vinorelbine.

Table 2.3. Scenario analyses using updated assumptions

Scenario	**Incremental cost per QALY gained for lapatinib plus capecitabine versus comparators**		
	Trastuzumab plus vinorelbine	**Trastuzumab plus capecitabine**	**Trastuzumab monotherapy**
Scenario 6 as above (fully updated price and clinical results)	Dominant (QALYs= +0.03, costs= -£8,958)	Dominant (QALYs= +0.03, costs= -£6,450)	Dominant (QALYs= +0.03, costs= -£4,993)
Scenario 7 (88.4% 6mg/kg trastuzumab 3-weekly)	Dominant (QALYs= +0.03, costs= -£4,141)	Dominant (QALYs= +0.03, costs= -£1,632)	Dominant (QALYs= +0.03, costs= -£288)
Scenario 8 (15% wastage)	Dominant (QALYs= +0.03, costs= -£6,610)	Dominant (QALYs= +0.03, costs= -£4,101)	Dominant (QALYs= +0.03, costs= -£2,968)
Scenario 9 (*New base case*: 88.4% 6mg/kg trastuzumab 3-weekly and 15% wastage)	Dominant (QALYs=+0.03, costs= -£3,583)	Dominant (QALYs=+0.03, costs= -£1.075)	£24,227 (QALYs= +0.03, costs= +£638)

These results show that in the new base case, lapatinib in combination with capecitabine remains a highly cost effective option when compared with the key trastuzumab-containing regimens.

Probabilistic sensitivity analysis performed on Scenario 9 suggests that the likelihood of lapatinib plus capecitabine being cost effective in the £20,000-£30,000/QALY range is just over 60% when compared with trastuzumab plus capecitabine; the likelihood of being in this range when compared with trastuzumab plus vinorelbine is 78%-82% (see Appendix 5 for further details).

3. Do you consider that the provisional recommendations of the Appraisal Committee are sound and constitute a suitable basis for the preparation of guidance to the NHS?

We recognise that, compared with capecitabine and vinorelbine monotherapies, lapatinib in combination with capecitabine is unlikely to be cost effective and therefore the current recommendations regarding these comparisons are reasonable.

However we have significant concerns with the Committee's decision not to consider trastuzumab, in the context of its use beyond progression, as a relevant comparator. Whilst we accept some limitations of the original evidence base, collectively the updated body of evidence firmly establishes the use of trastuzumab beyond progression as the most common treatment approach for patients in this setting in the UK. The recently revised NICE methods guide states that unlicensed comparator technologies may be considered if they are used routinely in the NHS. We believe that disregarding the current evidence on clinical practice, continuing to disregard trastuzumab regimens as an important element of the comparator base, and non-consideration of emerging comparative clinical evidence confirming the efficacy trastuzumab in this setting, would result in provision of guidance to the NHS which is out-dated, incomplete and not reflective of current clinical practice.

Having addressed the concerns regarding trastuzumab costs and incorporated the new evidence into the analysis, lapatinib in combination with capecitabine remains highly cost effective (dominant) when compared with the key trastuzumab-containing regimens used in these patients. We believe that lapatinib plus capecitabine should be recommended as a licensed and proven alternative treatment option, when trastuzumab is being considered for continuation beyond disease progression..

4. Are there any equality related issues that need special consideration that are not covered in the ACD?

Patients with ErbB2-positive advanced or metastatic breast cancer, who progress on or following treatment with trastuzumab, represent a population with an unmet clinical need and very few therapeutic options available to them other than trastuzumab, which is unlicensed for use in this setting. As metastatic breast cancer is essentially incurable, effective treatment options that can delay progression or extend survival without negatively impacting quality of life and adding unacceptably to the toxicity burden are greatly needed in this patient group. For these women, who are relatively young, with good performance status, the modest gains associated with medicines at this stage of breast cancer can be disproportionately valuable; we believe that the value of additional progression-free time at the end of a patient's life is not fully represented in a cost utility analysis.

Lapatinib plus capecitabine provides superior outcomes in terms of progression-free life years, life years and QALYs versus single agent chemotherapies. For patients who are more likely to be continued on a trastuzumab regimen beyond progression, lapatinib plus capecitabine is a clinically and cost-effective alternative, even when assumptions are amended to address the trastuzumab dosing and wastage issues identified by the ERG. In its original submission, GSK presented an argument that the subset of patients that is more likely to receive treatment with trastuzumab beyond progression includes patients with progression at an isolated site, patients with few metastases in the soft tissues or bone, and patients who experienced a previous good response to trastuzumab. However, we acknowledge such an approach presents a number of challenges:

- The difficulty in creating clear and unambiguous clinical criteria with which to define such a subgroup creates potential equity issues – a view that has been confirmed by UK medical oncologists
- Equity issues may be compounded by the inability to identify whether such subgroups are associated with differential effectiveness. The only randomised trial to demonstrate

the effectiveness of trastuzumab used beyond progression (GBG 26) included a broad population of patients that had received one prior line of trastuzumab therapy, rather than a selected subgroup. In addition the pivotal lapatinib study also included a broader group of patients consistent with the license.

GSK strongly believes that lapatinib offers tangible benefits to the group of patients within its licensed indications which has limited treatment options. GSK is committed to a solution that ensures access to lapatinib for all patients with the potential to benefit within its licensed indication. To this end, we have performed an analysis to demonstrate the overall cost effectiveness of lapatinib plus capecitabine against the three major existing therapeutic options currently employed within the NHS (capecitabine monotherapy, and trastuzumab in combination with capecitabine or vinorelbine).

Using the revised "base case", as described above (Scenario 9), GSK has generated a cost effectiveness estimate for lapatinib plus capecitabine compared with a 'blended' comparator consisting of a weighted average of both the costs and effectiveness of the three key treatment options. To ensure that all patients, including those receiving less commonly used interventions identified in the IMS Oncology Analyzer study described above (Table 1.1) were represented in the analysis, the less common treatment regimens were re-allocated to the three key intervention groups (see Appendix 1 for methodology), generating final proportions of:

- 44% capecitabine monotherapy
- 27% trastuzumab in combination with vinorelbine
- 29% trastuzumab in combination with capecitabine

The results of the blended analysis are presented in Table 4.1 below.

Table 4.1 Overall cost effectiveness of lapatinib in combination with capecitabine

	Costs and effects and cost per QALY gained for lapatinib plus capecitabine versus a blended scenario of comparators					
		Comparators				
	Lapatinib + capecitabine	**Capecitabine (44% of total)**	**Trastuzumab + vinorelbine (27% of total)**	**Trastuzumab +capecitabine (29% of total)**	**Blended comparator (total)**	**Blended cost/QALY***
Scenario 3 (current lapatinib list price £11.49 per tablet; overall survival data April 2006 cut-off; efficacy for trastuzumab comparator regimens from original pooled analysis (11 studies))						
Costs	£26,206	£5,194	£8,192	£8,188	£21,574	£30,474
QALYs	0.856	0.302	0.194	0.209	0.704	
Scenario 6 (fully updated clinical results)						
Costs	£26,939	£5,687	£9,692	£9,683	£25,062	£23,463
QALYs	0.897	0.337	0.235	0.253	0.817	
Scenario 9 (new base case)						
Costs	£26,939	£5,687	£8,241	£8,124	£22,052	£61,088
QALYs	0.897	0.337	0.235	0.253	0.817	

These results show that, using the original (Scenario 3) and the updated clinical data (Scenario 6), with GSK's original assumptions regarding wastage and dosing schedule for trastuzumab, incremental cost effectiveness ratios for lapatinib plus capecitabine are £30,474/QALY (Scenario 3) and £23,463/QALY (Scenario 6), when compared with a 'blended' comparator base broadly representing current clinical practice. However, in addressing uncertainties raised in the ACD it is clear that issues such as drug wastage and dosing schedules for trastuzumab have an impact on the cost effectiveness results, and this is reflected in the higher ICER of around £61,000 when these are taken into account in the blended comparator analysis (Scenario 9).

In recognition of the need to address the risks associated with these uncertainties, and to demonstrate clearly the value that lapatinib offers the NHS, GSK proposes an access programme for lapatinib that will reduce the cost per QALY to a level which is within acceptable limits. The programme aims to facilitate equitable patient access to treatment and maximise value to the NHS by linking payment to clinical benefit.

This scheme will be outlined in an addendum to this response.

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