BY E-MAIL

Meindert Boysen
Associate Director Centre for Health Technology Evaluation
MidCity Place
71 High Holborn
London
WC1V 6NA

29 August 2008

Re: Clarification letter 26 August 2008 – Lapatinib for the treatment of previously treated women with advanced, metastatic or recurrent breast cancer

Dear Meindert

Many thanks for your letter outlining points for clarification for the Decision Support Unit. I have listed our responses below:

1. ASCO poster

2. SABCS abstract and poster

3. Confirmation of any amendments to the dose adjustments (relative dose intensity) for trastuzumab in the updated model

I can confirm that the assumptions around relative dose intensity (RDI) in the updated model are the same as those used in the original submission. These are summarised in Table 6.7 in the original submission (page 87) which has been included below for information. The assumptions for the IV therapies are conservative with regard to costs, as it would be expected that concordance with IV regimens is higher than with a self administered oral regimen. For a more detailed discussion of the approach taken please see Section 6 in the original submission.

Table 6.7 (original submission): Relative dose intensity estimates used within the cost-effectiveness model

◊ **Treatment regimen**	◊ **Regimen component**	◊ **RDI for daily dosage**	◊ **RDI for days treated without disease progression**	◊ **Source**
◊ Lapatinib plus capecitabine	◊ Lapatinib	◊ 0.99 (0.004)	◊ 0.80 (0.077)	◊ Study EGF100151 ◊
	◊ Capecitabine	◊ 0.89 (0.017)	◊ 0.77 (0.075)	
◊ Capecitabine monotherapy	◊ Capecitabine	◊ 0.87 (0.014)	◊ 0.94 (0.072)	
◊ Vinorelbine monotherapy	◊ Vinorelbine	◊ 0.87 (0.014)	◊ 0.94 (0.072)	◊ Assumption: RDI parameters are the same as for capecitabine monotherapy in EGF100151
◊ Trastuzumab plus vinorelbine	◊ Trastuzumab	◊ 0.99 (0.004)	◊ 0.80 (0.077)	◊ Assumptions: ◊ RDI parameters for trastuzumab are the same as those for
	◊ Vinorelbine	◊ 0.89 (0.017)	◊ 0.77 (0.075)	
◊ Trastuzumab	◊ Trastuzumab	◊ 0.99	◊ 0.80	

◊ **Treatment regimen**	◊ **Regimen component**	◊ **RDI for daily dosage**	◊ **RDI for days treated without disease progression**	◊ **Source**
		(0.004)	(0.077)	lapatinib in EGF100151.
plus capecitabine	◊ Capecitabine	◊ 0.89 (0.017)	◊ 0.77 (0.075)	◊ RDI parameters for adjunctive chemotherapy are the same as those for capecitabine in the lapatinib plus capecitabine combination in EGF100151.
◊ Trastuzumab monotherapy	◊ Trastuzumab (monotherapy)	◊ 0.87 (0.014)	◊ 0.94 (0.072)	◊ Assumption: RDI parameters are the same as for capecitabine monotherapy in EGF100151

4. Criteria used in modelling the Lapatinib (Tyverb®▼) Patient Access Programme (LPAP) – and their relevance and generalisability

The economic model used in the estimation of cost effectiveness of the LPAP is essentially identical to that used in our original submission, and uses a survival modelling approach, as described in Section 6.2.6.1 of the original submission. The survival model is based directly on the independently assessed progression-free survival (PFS) data from study EGF100151, whereby patients enter the model at the start of therapy and receive one of the active regimens until they subsequently experience disease progression and/or death.

However, in recognition that study medication was terminated in the trial at the investigators' discretion based on investigator- rather than independently-assessed PFS, as well as the likelihood that patients may not receive the planned amount of medication due to dosage adjustment, skipped doses and/or early discontinuation (i.e. prior to disease progression), adjustments were included in the model to ensure that costs of active treatment are representative. This was achieved by applying relative dose intensities to adjust for these factors, and is fully described in Section 6.2.6.1 of the original submission.

The modelled outputs therefore reflect continuation and discontinuation criteria mandated in the EGF100151 study protocol for determining whether patients should be withdrawn from treatment due to disease progression, unacceptable toxicity or other reasons (e.g., subject refuses further treatment, protocol violation).

The criteria were defined in the protocol as follows:

1. Disease progression - modified RECIST criteria for target lesions (see Appendix 1 for details); and less stringent criteria for non-target lesions (Appendix 2).
2. Unacceptable toxicity – investigator judgement, using a guideline for toxicity and dose modifications provided in the study protocol (Appendix 3), as well as clinical judgement regarding any other toxicity deemed to be unacceptable to the subject.
3. Other reasons – investigator judgement

4.1. Relevance and generalisability of criteria used in modelling the LPAP in clinical practice

Informal advice from UK oncologists regarding the extent of use of the RECIST criteria to determine disease progression in a non-clinical trial setting suggests that these strict criteria are very objective and are not routinely employed in the NHS, e.g., individual lesions are not necessarily documented and tracked. Whilst perhaps desirable, the application of this level of assessment does not reflect current clinical practice, is not necessary to determine disease progression in the clinical setting, nor do breast cancer services have the capacity to support such assessments routinely.

To test the assumption that use of RECIST is not wholly applicable to UK practice, and to explore and validate alternative criteria, we interviewed six UK Consultant Medical Oncologists[1] (one of whom was an EGF100151 investigator) during the

[1] Dr Peter Barret-Lee, Consultant Clinical Oncologist, Velindre Hospital
Dr Stephen Johnston, Consultant Medical Oncologist, Royal Marsden Hospital
Dr David Miles, Consultant Medical Oncologist, Mount Vernon Hospital
Professor Ian Smith, Consultant Medical Oncologist, Royal Marsden Hospital
Dr Mark Verrill, Consultant Medical Oncologist, Newcastle General Hospital

week commencing 25 August 2008; the discussion guide and questionnaire used is included in Appendix 4. Feedback from respondents is summarised in Appendix 5. The interviews confirmed the assumption that the strict clinical trial criteria are not reflective of current practice, and that alternative criteria are required that are workable in routine clinical practice, in the context of the LPAP. See Section 4.2 for a discussion of alternative criteria.

Regarding the applicability of the assessment schedule in study EGF100151 to real life: Safety and efficacy assessments were performed every 6 weeks for the first 24 weeks, then every 12 weeks and at the end of treatment. Haematology and clinical chemistry assessments were conducted on all subjects every 3 weeks and at the end of treatment. This schedule is broadly reflective of UK clinical practice, where on the whole patients undergo 3-weekly clinical reviews in line with treatments cycles, with more detailed assessments, including radiological assessment, on a less frequent basis (see summary of oncologist feedback later in this document). Therefore it is unlikely that the distribution of patients through the model will be significantly different from that observed in clinical practice.

4.2. Suggested criteria for the Lapatinib (Tyverb®▼) Patient Access Programme (LPAP)

To address the implementation issues that would be associated with applying clinical trial criteria, GSK has developed continuation and discontinuation criteria for the LPAP which are clinically practical and meaningful, and which we believe would be reasonably reflective of the trial criteria in terms categorisation of patients as having progressed or not. These criteria were validated with UK oncologists in the interviews described above, and the feedback is summarised in Appendix 5. The suggested criteria were amended to reflect this feedback, and are listed below:

Continuation criteria

- Patients are deriving clinical benefit and are able to tolerate the treatment.

Clinical benefit will be determined by the patient's oncologist during routine clinical follow-up, based on imaging and clinical assessments and/or other investigations. Clinical benefit may be characterised by the reduction in size or disappearance of existing lesions (whether measurable or not), stable disease and/or improvement of other response criteria including symptomatic improvement.

Discontinuation criteria

- No clinical benefit derived at the time of the first planned, comprehensive assessment.
- Patient experiences disease progression following an initial response, or following a period of stable disease.
- Patient is unable to tolerate the combination treatment despite appropriate dose modifications

Clinical progression will be assessed by the patient's oncologist, based on (i) the increase in size of existing lesions or appearance of new lesions [whether measurable or not] and/or (ii) symptomatic deterioration.

4.3. Suitability of LPAP criteria to deliver cost effective use of lapatinib in the NHS

[Anonymous], Consultant Medical Oncologist, England

Feedback from the oncologists interviewed was very supportive of the criteria developed for the LPAP, in terms of practicability and pragmatism, being both clear and representative of routine clinical practice.

One consideration on the part of the NHS might be that application of such pragmatic continuation/discontinuation criteria and the less formal assessment schedule implemented in everyday clinical practice may result in patients being treated with lapatinib plus capecitabine for a longer period of time than they would have been in the clinical trial, thus having a negative impact on the cost effectiveness of lapatinib and the LPAP. Although the criteria are less precise than those used in EGF100151, this a common issue when clinical trial evidence is used to inform the relative cost effectiveness of an intervention. It may be a reasonable assumption that that they provide a pragmatic and implementable way of reflecting the criteria used in the clinical trial, and in modelling the LPAP.

4.4. Potential use of LPAP criteria in NICE recommendations

In response to the question of how we envisage the criteria might be used in NICE recommendations, and in light of criteria detailed in existing NICE guidance, we believe that those suggested for the LPAP are similarly suitable for such use.

We suggest that the LPAP and associated continuation/discontinuation criteria could be summarised in any guidance, and that the type of wording might include:

- The acquisition cost of lapatinib for up to a maximum of the first 12 weeks is met by the manufacturer;
- Treatment with lapatinib in combination with capecitabine should be continued at any point only if patients are judged by their oncologist, during routine clinical follow-up, to be deriving clinical benefit and are able to tolerate the treatment.
- Treatment should be discontinued if no clinical benefit or response is derived at the time of the first planned, comprehensive assessment, if the patient experiences disease progression following an initial response or after an initial period of stable disease, or if the patient is unable to tolerate the combination treatment despite appropriate dose modifications.
- Clinical benefit and clinical progression should be assessed by the patient's oncologist, based on imaging and clinical assessments and/or other investigations.
- Clinical benefit may be characterised by the reduction in size or disappearance of existing lesions (whether measurable or not), stable disease, and/or improvement of other response criteria including symptoms.
- Clinical progression may be based on (i) the increase in size of existing lesions or appearance of new lesions, whether measurable or not, and/or (ii) symptomatic deterioration.

I hope this is helpful and provides the information required. Please do not hesitate to contact me if you or the Decision Support Unit have any further questions.

Yours sincerely

[redacted]
Health Outcomes
GlaxoSmithKline UK Ltd
email: [redacted]

Appendix 1

Definition, documentation and evaluation of target lesions used in the determination of disease progression in study EGF100151 (modified RECIST criteria)

Measurable disease was defined by the presence of at least 1 measurable lesion. If the measurable disease was restricted to a solitary lesion, its neoplastic nature was confirmed by cytology/histology. Palpable lesions that are not measurable by radiologic or photographic evaluations may not be utilised as the only measurable lesion.

The same diagnostic method was used throughout the study to evaluate a lesion. A measurable lesion was defined as a lesion that could be accurately measured in at least 1 dimension (longest diameter, LD) of:

- 15mm with conventional techniques (medical photograph [skin or oral lesion], palpation, plain X-ray, computerized tomography (CT), or magnetic resonance imaging –MRI); or
- ≥ 10mm with spiral CT scan.

All measurable lesions, up to a maximum of 5 lesions per organ and 10 lesions in total, were identified as target lesions, and were recorded and measured at baseline. A sum of the LDs for all target lesions was calculated and reported as the baseline sum LD. The baseline sum LD was used as a reference by which to characterise the objective tumour response.

Definitions for assessments of response for target lesion(s) were:

- Complete Response (CR) – disappearance of all target lesions;
- Partial Response (PR) – at least a 30% decrease in the sum of the LD of the target lesions, compared to the baseline sum LD;
- Stable Disease (SD) – neither sufficient shrinkage to qualify for a PR nor sufficient increase to qualify for progressive disease (PD), compared to the smallest sum LD since the treatment started.
- Progressive Disease – at least a 20% increase in the sum of the LD of target lesions, compared to the smallest sum LD recorded since the treatment started, or the appearance of 1 or more new lesions; and
- Not Evaluable (NE) – any subject who cannot be classified by 1 of the 4 preceding definitions.

Appendix 2

Definition and evaluation of non-target lesions used in the determination of disease progression in study EGF100151

Definitions of the criteria used to determine the objective tumour response for non-target lesions were as follows:

- Complete Response – the disappearance of all non-target lesions.
- Incomplete Response – the persistence of 1 or more non-target lesion(s).
- Progressive Disease – the appearance of 1 or more new lesions and/or unequivocal progression of existing non-target lesions.

Although a clear progression of “non-target’ lesions only is exceptional, in such circumstances, the opinion of the treating physician should prevail, and the progression status should be confirmed later by the independent radiologic reviewer.

Appendix 3

Extract from EGF100151 study protocol - guideline for toxicity and dose modifications

Table 3 Toxicity and Dose Modification (Any exceptions must be discussed with the medical monitor)

Toxicity NIC-CTCAE Grade	During Course of Therapy	GW572016 Dose Change	Capecitabine Dose Change
Grade 1	Maintain dose	No change	No change
Specific Events of Grade 2/3			
Hematology –ANCs <1.0 × 10^9/L Platelet count is <75.0 × 10^9/L Hemoglobin is <9.0 g/dL (after transfusion if needed Chemistry- Bilirubin is ≥2 times ULN (unless Bilirubin was higher at study entry and has not yet fallen below 2X ULN) Serum Creatinine-≥1.5 mg/dL Calculated Creatinine Clearance ≤ 40mL/mins	GW572016 - Interrupt treatment until resolved to grade 0-1, up to 14 days. Capecitabine- Interrupt treatment until resolved to grade 0-1, up to 14 days If Toxicity does not resolve consult GSK Medical Monitor, to determine if it is in the best interest of the patient to continue in the study.	1st appearance Resume 100% 2nd appearance Resume 100% or dose reduce to 1000 mg/day. 3rd appearance-Resume 100% or dose reduce to 1000 mg/day	1st appearance -Resume at 100% or Resume at 75% (rounded to nearest 150 mg) as clinically indicated 2nd appearance Resume at 75% (rounded to nearest 150 mg) 3rd appearance-Resume at 50% of starting dose rounded to nearest 150 mg) 4th appearance-Discontinue permanently
Grade 2-Any other event			
For Toxicity of Cardiac Ejection Fraction, refer to Section 6.2.3.2 for dose interruption and modification schedule	GW572016 -Maintain dose. Capecitabine-Interrupt treatment until resolved to grade 0-1, up to 14 days.	1st appearance-Maintain dose-No change 2nd appearance- Maintain dose No change 3rd appearance – Resume 100% or dose reduce to 1000 mg/day 4th appearance – Resume with a dose reduce to 1000 mg/day	1st appearance -Resume at 100% or Resume at 75% (rounded to nearest 150 mg) as clinically indicated 2nd appearance Resume at 75% (rounded to nearest 150 mg) 3rd appearance-Resume at 50% of starting dose rounded to nearest 150 mg) 4th appearance-Discontinue permanently

Table 3 Continued Toxicity and Dose Modification (Any exceptions must be discussed with the medical monitor.)

Toxicity NIC-CTCAE Grade	During Course of Therapy	GW572016 Dose Change	Capecitabine Dose Change
Grade 3			
For Toxicity of Cardiac Ejection Fraction and interstitial pneumonitis, refer to Section 6.2.3.2 for dose interruption and modification schedule	Both treatments- Interrupt until resolves to grade 0-1, up to 14 days.	Any appearance-Resume 100% or Reduce dose to 1000 mg permitted in consultation with GSK Medical Monitor.	1st appearance-Resume 75% of starting dose (rounded to nearest 150 mg) 2nd appearance- Resume 50% of starting dose (rounded to nearest 150 mg) 3rd appearance- Discontinue study treatment permanently
Grade 4			
1st appearance For Toxicity of Cardiac Ejection Fraction and interstitial pneumonitis, refer to Section 6.2.3.2 for dose interruption and modification schedule	Both treatments- Interrupt until resolves to grade 0-1.	Consult with GSK monitor to determine if in the best interest of the patient to continue at a dose reduction.	Consult GSK medical monitor to determine if it is in the best interest of the patient to continue at a dose level lower than the original capecitabine dose

Appendix 4

Discussion guide and questionnaire used to validate assumptions and continuation/discontinuation criteria for use in the Lapatinib (Tyverb®▼) Patient Access Programme

Validating Continuation and Stopping Criteria: Lapatinib Patient Access Programme (1)

SUGGESTED CRITERIA

Patient eligibility

- NHS patients that fall within the initial licensed indication for lapatinib plus capecitabine, that is:
    - Patients with ErbB2+ metastatic breast cancer
    - Prior therapy with an anthracycline and a taxane
    - Prior therapy with trastuzumab in the metastatic setting
    - Co-prescription with capecitabine

Continuation criteria

- Patients will be eligible to continue treatment with lapatinib and capecitabine if they are deriving clinical benefit and are able to tolerate the treatment.

- Clinical benefit will be determined by the patient's oncologist during routine clinical follow-up, based on clinical and imaging assessments and/or other investigations.

- Clinical benefit may be characterised by:
    - the reduction in size or disappearance of existing lesions (whether measurable or not)
    - stable disease and/or improvement of other response criteria including symptom improvement

Discontinuation criteria

- Patients should discontinue treatment with lapatinib and capecitabine:

1. If there is no clinical response to the treatment at the first planned assessment point
2. If the patient experiences disease progression following an initial response
3. If they are unable to tolerate the combination treatment despite appropriate dose modifications

- Clinical progression will be assessed by the patient's oncologist, who will make a judgement concerning the status of the disease and the degree of clinical benefit currently derived based on:
    - the increase in size of existing lesions or appearance of new lesions (whether measurable or not)
    - symptomatic deterioration

Validating Continuation and Stopping Criteria: Lapatinib Patient Access Programme (2)

DISCUSSION GUIDE/QUESTIONNAIRE

Introduction

- Explain the situation and the objectives of the consultation and establish any conflict of interest (e.g. that respondent is not formally involved in NICE review).

- Obtain (verbal) agreement on confidentiality, highlight sensitive nature of terms of programme offered by GSK.

- Establish whether the respondent is willing to be named as an expert consulted by GSK in this regard and, potentially, to be quoted in GSK's response to questions from NICE.

- Review the criteria proposed by GSK.

Questions:

1. GSK has assumed that very objective criteria used in clinical trials (such as RECIST) are not employed in everyday clinical practice – is this a reasonable assumption?

2. Focusing on the **continuation criteria**, how well do the proposed criteria match with existing clinical practice?

3. What changes, if any, would you propose to the **continuation criteria** to ensure that they are clearly understood within the oncology community and match existing clinical practice as closely as possible?

4. Focusing on the **stopping criteria**, how well do the proposed criteria match with existing clinical practice?

5. What changes, if any, would you propose to the **stopping criteria** to ensure that they are clearly understood within the oncology community and match existing clinical practice as closely as possible?

6. GSK has proposed to fund the initial cost of lapatinib up to a maximum of 12 weeks per patient. Payers may therefore be interested to ensure that only those patients deriving clinical benefit at week 12 continue with therapy. Bearing this in mind, please comment on the implications of assessing clinical response at week 12 and how this might be managed in practice.

Appendix 5

Summary of feedback from interviews with 6 UK oncologists during week commencing 25 August 2008

Specific questions	Summary response/s
1. GSK has assumed that very objective criteria used in clinical trials (such as RECIST) are not employed in everyday clinical practice – is this a reasonable assumption?	Very objective criteria such as RECIST are not routinely employed in everyday clinical practice. For example, individual lesions are not routinely documented and tracked as per RECIST. Clinicians use a number of clinical and investigational parameters to assess the risk-benefit of continuation/discontinuation of treatment. The suggested assessment criteria are in line with standard UK clinical practice, but are not as strict as RECIST Whilst many clinicians may wish to use RECIST criteria, they recognise that on a day to day basis this is not practical as radiology departments do not have the capacity to make assessments in this way.
2. Focusing on the continuation criteria, how well do the proposed criteria match with existing clinical practice?	The continuation criteria seem reasonable and in line with current practice. It is important however to recognise that patients with stable disease would continue on treatment. The proposal was pragmatic and reflective of UK practice; current practice in the majority of centres would be to make a decision regarding continuation by start of cycle 3 (i.e. after 6 weeks of therapy). Continued evidence of clinical benefit as assessed by the oncologist would be clearly understood by everyone treating breast cancer patients. If the patient felt better and scan was worse would stop, objective criteria would override subjective criteria if they are not going in the same direction.
3. What changes, if any, would you propose to the continuation criteria to ensure that they are clearly understood within the oncology community and match existing clinical practice as closely as possible?	In the presence of clear progression of disease outside the brain clinicians would not normally continue with lapatinib and capecitabine even if symptoms remain well controlled. If the disease remains well controlled but progression is at one site (brain/painful bone metastasis/pleural effusion) that is amenable to an alternative treatment (such as radiotherapy) patients should continue in these circumstances.

	[GSK COMMENT: GSK has not included these additions in its proposed continuation criteria as they are not reflective of the EGF100151 clinical trial design]
4. Focusing on the stopping criteria, how well do the proposed criteria match with existing clinical practice?	The stopping criteria match well with clinical practice. Essentially stopping treatment would be based on a worsening of the disease at any point. The stopping criteria are fine. A lack of continued clinical benefit would suggest stopping treatment.
5. What changes, if any, would you propose to the stopping criteria to ensure that they are clearly understood within the oncology community and match existing clinical practice as closely as possible?	Important to clearly identify that a lack of response in a patient with stable disease would not be grounds for stopping treatment. However, if the disease progressed following a period of stable disease then this would be grounds for discontinuation. Could add in 'no symptomatic improvement' as a consideration. Not brain metastases unless accompanied by other lesions. Patients should stop treatment if stable disease with symptoms or progressive disease
6. GSK has proposed to fund the initial cost of lapatinib up to a maximum of 12 weeks per patient. Payers may therefore be interested to ensure that only those patients deriving clinical benefit at week 12 continue with therapy. Bearing this in mind, please comment on the implications of assessing clinical response at week 12 and how this might be managed in practice.	Patients are seen every cycle of treatment (3 weekly). Arrangements are made for scans to be carried out either around week 5 or week 8 so that an assessment of response to treatment can be conducted and a decision on further treatment made at the week 6 or week 9 appointment. A clinical assessment is made at each visit although a radiological assessment is made less frequently as appropriate to the individual patient. Patients with stable disease may be re-assessed at week 6 and week 12. It is likely that a number of patients would discontinue lapatinib treatment after 3 cycles (week 9) when they are assessed and the scans have been carried out. Patients will be seen routinely at week 12 so a routine clinical assessment would be carried out. If a patient is responding then they would be kept on treatment but would not necessarily be re-evaluated every visit if there were no clinical grounds or symptomatic changes that would warrant it. Therefore, it does not appear that the proposed criteria would change any normal clinical practice. Although the assessment of response will take place before this 12 week cut-off the time taken before the patient next attends

	clinic and treatment is stopped might mean the patient is still on treatment until up to 12 weeks. Routine after 3 cycles (trials 2 cycles). Always see a practitioner every cycle for toxicity/tolerability assessment. Must plan ahead with our scans to ensure they fall at the correct time. In clinical practice, imaging is undertaken every 2-3 months (more commonly 3 months, very few at 6 weeks). Personally would do more often than every 3 months in those with rapidly progressing disease. HER2 -positive tend to progress more quickly when not responding. You could expect a patient to be assessed by a doctor at each visit (tolerability and toxicity). Scheme could dictate continue only beyond week 12 if clinical benefit has been proven and he feels this is easily manageable with pre-planned booking of scans.