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

GlaxoSmithKline (4 November 2008)

Thank you for the opportunity to respond to the second Appraisal Consultation Document for lapatinib. The key issues that GlaxoSmithKline wish to raise are listed below, and discussed in more detail in Sections 1-4.

Key issues

- This draft guidance effectively denies access to a proven treatment which is licensed and cost effective within the context of the proposed Lapatinib Patient Access Programme, for patients with a particularly aggressive form of advanced breast cancer, and for whom there are few treatment options available.
- Rejecting lapatinib on the basis that the key comparator is itself cost-ineffective is inconsistent with current methodological guidelines. Indeed this approach is at variance with previous guidance issued by NICE which has approved an intervention on the basis of comparison with a cost ineffective comparator.
- The current draft guidance *de facto* endorses the continued cost-ineffective and inequitable use of trastuzumab regimens, which are not licensed in this indication, and which are likely to continue to be used increasingly in routine clinical practice.
- It is unclear how current practice could be changed though the proposed guidance, given that a recommendation regarding the discontinuation of comparators is outside the scope, and trastuzumab regimens will not themselves be appraised without a licence in this indication.
- Rejecting trastuzumab as a comparator on the basis of a draft clinical guideline which may be subject to challenge and change through the consultation process, and which is ultimately not subject to mandatory implementation, is not sound.
- The Appraisal Committee has given undue weight to 'worst case' assumptions which does not reflect the balance of evidence.
- The recommendations of the Committee do not appear to have taken account of the acknowledgement in the NICE methods guides that consideration of the cost effectiveness of a technology should not be the sole basis for decision-making.
- The value of additional time without progression at this stage of a person's life is not fully represented in the cost/QALY estimates, and clearly does not include any impact on their value to others such as dependents.
- Within NICE's current threshold there is very little spare capacity to justify cost effectiveness, and this may disadvantage patients whose management is, by definition, difficult and expensive; a higher cost effectiveness threshold should be considered in these circumstances.

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

The current ACD presents the data clearly, and broadly reflects the relevant evidence. However, we are concerned that evidence supporting the level of continued use of trastuzumab beyond progression, as well as new market research advising on the most appropriate estimates of intravenous medication wastage and three weekly trastuzumab use, have not been comprehensively taken into account:

1.1. Evidence for trastuzumab use in current clinical practice

The Committee notes inconsistency in the market research provided to support the level of trastuzumab use beyond progression in clinical practice (Section 4.2), quoting a range of 10% to 50% of patients receiving this treatment. Whilst the Committee accepted that the higher estimates were likely to be the more appropriate (as suggested by the recent, independently collected IMS data submitted in our response to the first ACD, and confirmed by NICE-nominated clinical specialists), the ACD continues to use the 12% figure in sensitivity analyses. This figure was proposed by the manufacturer of trastuzumab, but was rejected as an unrealistic estimate by the specialists at the 18 September 08 Appraisal Committee meeting; it has also been highlighted that there is no information on the methodology used to derive it. Furthermore, the Royal College of Physicians in their feedback on the first ACD[1] confirmed that the standard of care is changing as data emerges to support the strategy of continued ErbB2 suppression, and that trastuzumab is frequently and increasingly used beyond progression in many centres throughout the UK.

Further interrogation of the independently collected IMS dataset, which was considered by clinical experts at the Appraisal Committee meeting as the more robust data source, confirms that trastuzumab has been consistently used over several years in the majority of patients whose disease has progressed after receiving trastuzumab (Table 1).

Table 1. Trastuzumab use beyond progression – IMS market research data

Dates	Total number of metastatic patients in the IMS database at each time point	Database sample as a proportion of the total MBC population (N=15,100) †	Number of patients whose disease has progressed following trastuzumab	Proportion of patients receiving trastuzumab beyond progression
January 2004 to September 2006*	1,410	9.3%	24	45%
2006 and 2007**	2,815	18.6%	98	55%
January to March 2008	3,311	21.9%	71	53%
April to June 2008	3,231	21.4%	53	55%

† IMS data
* Included in original submission, April 07
** Included in response to 1st ACD July 2008; includes Jan 04 to Sept 06 data

In continuing to employ the lowest estimate of trastuzumab use beyond progression we believe that the DSU/Committee has failed to take into account fully the evidence from clinical experts, the lack of methodological detail in how the lower estimate was

obtained, and the comprehensive reports of market research (including methodology) provided by GSK.

We therefore believe that £63,034/QALY (Section 4.14 of the ACD) is an unrealistic and misleading representation of the cost effectiveness of lapatinib in combination with capecitabine, in the context of the Lapatinib Patient Access Programme (LPAP), and that the more relevant range would be a maximum of £26,993 per QALY gained (at the lower estimate of 49% use) and as low as £16,387 if a figure of 56% is used. In addition, given the publication of the GBG-26 study (von Minckwitz et al)[2] and the resulting evidence of the clinical validity of this treatment approach, the unlicensed use of trastuzumab regimens in this indication may actually increase further. In these circumstances the Lapatinib Patient Access Programme would provide an even more cost effective use of NHS resources than those presented above.

1.2. Consideration of evidence underlying assumptions on trastuzumab wastage and administration

In the original ACD, concerns were raised as to the appropriate assumptions for the extent of wastage for intravenous therapies, the extent to which trastuzumab is given three-weekly, and that the cost effectiveness estimates were sensitive to these assumptions. As a result GSK undertook a survey of 24 oncology pharmacists from 17 cancer networks to understand the most appropriate assumptions to be used in the analysis. The mean results from this research were the basis of the assumptions used within the revised cost effectiveness analysis, and were presented along with the methodology used in our response to the ACD. The results of this research are not referred to in the ACD and clinical opinion is used to justify the consideration that the estimates for the costs of trastuzumab treatment may still be over estimated. We accept that our research shows that in some centres this would be the case. However as means were used, the results of the research also demonstrate that in some centres these figures were likely to be underestimates. We believe that in reaching its conclusions the Committee should also give consideration of the impact of these alternative assumptions that would result in improved cost effectiveness for lapatinib.

1.3. Lack of consideration of the Lapatinib Patient Access Programme (LPAP)

Very minimal consideration appears to have been given to the Lapatinib Patient Access Programme *per se*. We would like to reinforce that the programme has been designed to be consistent with current clinical practice and NHS financial flows to aid implementation in the NHS. It also allows all eligible patients to receive up to the first 12 weeks of treatment free meaning that in general terms the NHS does not pay for those patients who do least well on lapatinib. The programme also allows equitable access for all patients to lapatinib whereas currently, although widespread, the use of trastuzumab beyond progression is variable.

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?

As acknowledged in our previous comments on the first ACD, we consider the interpretation of the pivotal clinical trial EGF100151 is reasonable, as well as the interpretation of the cost effectiveness of lapatinib plus capecitabine versus single-agent chemotherapies.

However, we have significant concerns about the interpretation of the cost effectiveness evidence versus trastuzumab-containing regimens submitted by GSK.

Whilst we agree with the Committee's conclusion that the standard of treatment could include capecitabine, vinorelbine, and trastuzumab-containing regimens (Section 4.2), we are very concerned about the Committee's consideration of trastuzumab regimens within the appraisal. Our concerns are several-fold, and are discussed below:

2.1. Definition of standard treatment for patients whose disease progresses after receiving trastuzumab in the metastatic setting

We welcome the Committee's acceptance that trastuzumab regimens are included in the range of treatments given in usual clinical practice in this patient population, and acknowledge that this practice is variable despite its ubiquity. In our response to the first ACD we specifically addressed the issue of variability in standard clinical practice by including the costs and effects of the different options in a single 'usual practice' comparator arm (the 'blended' analysis). To define the average levels of different interventions used in usual clinical practice, we interrogated IMS patient note level data, commissioned and collected independently of GSK, and this was backed up with physician-based market research commissioned to answer this question. The results have since been endorsed by the clinical community, not least at the September 2008 Appraisal Committee meeting.

GSK's 'usual practice' comparator approach has been rejected by the DSU and Appraisal Committee in favour of an alternative methodology which, in effect, assumes that the lapatinib regimen would replace only the least costly intervention used in clinical practice, and more costly interventions would cease to be used. This is unrealistic in the context of a Single Technology Appraisal (STA), does not reflect the realistic opportunity cost to the NHS of comparisons with current practice, and is discussed further below. We assert that the blended comparator is a more accurate reflection of average standard practice that would be displaced by the introduction of lapatinib in combination with capecitabine.

We would also like to respond to Section 4.3 of the ACD, which states that the Committee was mindful that allowing unlicensed comparators to be considered (2008 methodological guidance)[3] was intended 'to reflect the inclusion of technologies used routinely on the basis of clinical experience for many years and for which a licence had not therefore been requested'. This caveat is not explicitly stated in the methodological guidance, and appears to be a post hoc interpretation of the guidance. We therefore believe this should not be a factor for the Committee to consider. Both the 2008[3] and 2004[4] methods guides are very clear that both routine and best practice should be considered, that there will often be more than one relevant comparator technology because routine practice may vary across the NHS, and because best alternative care may differ from routine NHS practice.

In conclusion the most reliable data sources suggest that the use of trastuzumab beyond progression is the most commonly used treatment strategy in these patients and therefore should be considered as a valid comparator for this appraisal.

2.2. Consideration by the DSU of all treatment options in a single incremental analysis

We argue that our approach to the economic analysis, using a composite comparator representing standard practice in England and Wales, addresses the STA decision problem more appropriately than the consideration of all options in a single incremental analysis comparing each successive treatment from the least costly to the most. The STA decision problem, by definition, focuses on the evaluation of the economic impact of introducing a single intervention into clinical practice; the

interventions that it will displace are not being appraised *per se*, and as such, any conclusions drawn on their cost effectiveness are unlikely to be implementable. The incremental approach adopted by the DSU and considered by the Committee is more suitable for an MTA, where several options are being assessed alongside each other to determine which should, and should not, be used on the NHS.

The single incremental analysis employed by the DSU is only one of several methodologies that might be used to evaluate the cost effectiveness of an intervention, and is not explicitly recommended in the methods guide. In considering the interpretation of the evidence provided, GSK's approach is consistent with the 2004 methodological guidance[4] (Section 1.4.1) which states that technologies can be considered cost effective if their health benefits are greater than their opportunity cost in terms of the health benefits associated with *programmes* that may be displaced to fund the new technology. In this case the programme that would be displaced by introducing lapatinib would consist of combination trastuzumab regimens (predominantly), as well as single-agent capecitabine. As discussed in our original submission, patients who receive trastuzumab beyond progression are those in whom the drug still appears to be having an effect, although we recognise that other factors such as local policy may also impact. Therefore whilst there is no evidence to confirm whether these interventions would be replaced at differential rates, there may be an increased clinical rationale for replacing trastuzumab, particularly when lapatinib is given as part of the proposed Lapatinib Patient Access Programme, as this would result in direct cost savings to the NHS. This would only serve to increase the relevance of trastuzumab-containing regimens within the comparator base, and to improve the relative cost effectiveness of lapatinib in combination with capecitabine versus usual practice.

Furthermore, to insist that the comparator itself must be cost effective is inconsistent with the methodological guidelines,[3,4] which explicitly state that consideration should be given to routine and best practice in the NHS, that there will often be more than one relevant comparator because of variability in routine practice, and because routine practice may differ from best alternative care. The guidance does not state that in order to be considered, routine practice should be cost effective *per se*, and this is reflected in the current guidance for imatinib in chronic myeloid leukaemia[5] where an Appraisal Committee has approved an intervention on the basis of its cost effectiveness versus a cost-ineffective comparator. Indeed, the previous ACD, which acknowledged the cost effectiveness of lapatinib plus capecitabine versus trastuzumab-containing regimens in the base case, did not raise the lack of cost effectiveness of trastuzumab regimens *per se* as an issue, which implies that this is not a standard decision criterion for the Committee.

In conclusion, we believe that the methodology that GSK employed provided a suitable interpretation of the cost effectiveness evidence for lapatinib in combination with capecitabine in comparison with the programmes of care likely to be displaced by its introduction.

2.3. Interpretation of market research data, and its impact on cost effectiveness estimates

We are concerned that by including an estimate of 12% for trastuzumab beyond progression in a sensitivity analysis exploring the impact of varying the proportion of patients receiving trastuzumab, the DSU has given this estimate undue credence. No methodological detail for the market research has been provided, and as acknowledged by the Committee in Section 4.2 of the ACD the clinical specialist advisors considered the higher estimates (49%-56%) to be more appropriate. As mentioned in Section 1, IMS data shows that over the past three years trastuzumab

has been used consistently in over half of patients whose disease has progressed after receiving trastuzumab (Table 1).

We strongly believe that the IMS is the most reliable data source for the following reasons: IMS Oncology Analyzer uses a representative panel of hospitals; these hospitals are geographically varied and a minimum of 70% of all major cancer centres is included. IMS data is longitudinal enabling full patient history to be obtained since diagnosis, and is collected and analysed independently of the manufacturer. As a result end users of the data have no part in selecting participants, or in data collection or collation. The IMS and data set therefore represents a robust picture of prescribing behaviour from an independent source.

We therefore believe that the sensitivity analysis including the range 49% to 56% is more representative of the likely proportion, and that at the lower level of 49% lapatinib in combination with capecitabine in the context of the Lapatinib Patient Access Programme still represents a cost effective use of resources, at around £27,000/QALY.

In addition, the interpretation of the evidence with respect to assumptions on the wastage and administration of trastuzumab do not fully consider the impact on cost effectiveness. As discussed above, the assumptions in our analysis were mean estimates derived from market research data from 17 cancer networks. The DSU sensitivity analysis only considered conservative scenarios regarding wastage and three-weekly trastuzumab, resulting in a lower acquisition cost for trastuzumab. The data demonstrate that there are also UK centres where wastage is higher, and 3-weekly trastuzumab administration is lower, and we believe that the implications of these alternative scenarios should also be considered to provide a balanced reflection on the likely cost effectiveness of the lapatinib regimen.

2.4. Interpretation of the relative clinical effectiveness of lapatinib and trastuzumab regimens

We agree that there is uncertainty in the relative clinical effectiveness of lapatinib- and trastuzumab-containing regimens in this setting, due to a lack of head-to-head data, and the consequent need to use alternative methods of estimating relative effectiveness. However since the original ACD randomised trial evidence on the effectiveness of trastuzumab beyond progression has been published and allows a significantly more robust estimation of this than was previously possible.

The primary analysis of lapatinib- versus trastuzumab-containing regimens presented in our response to the first ACD was based on hazard ratios derived from the results of study GBG-26, and suggested that trastuzumab regimens are marginally less effective than lapatinib in combination with capecitabine. The DSU critique of the methodology used to derive the relative hazard ratios is addressed in our response to the Evaluation Report, and we maintain robustly that our methodology was appropriate given the data available.

A secondary analysis was conducted using an updated pooled estimate of mostly non-comparative studies, and was included in our ACD response for completeness, as this was the method used in the original submission. Indeed, as acknowledged by the DSU in the Evaluation Report, the primary result is supported by this secondary result.

In these circumstances we support our position that the best estimate of relative effectiveness is that from the indirect analysis based on hazard ratios from study GBG-26, particularly as the results are supported by the alternative secondary analysis.

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 acknowledge that, compared with single agent chemotherapies, lapatinib in combination with capecitabine is unlikely to be cost effective within NICE's current decision making framework, even in the context of the proposed Lapatinib Patient Access Programme. However, as indicated above, we have major concerns with the Committee's decision not to consider the overall cost effectiveness of lapatinib in relation to a composite comparator consisting of the major treatments used in current clinical practice, including trastuzumab regimens.

Both the 2004 and 2008 guides to the methods of technology appraisal[3,4] state that standard decision rules should be followed in combining costs and QALYs, and these should reflect any situation where dominance or extended dominance exists. However, the methods guides also highlight the importance of constructing an analytical framework so that estimates of clinical and cost effectiveness can be made *that are relevant to the clinical decision-making context*. We strongly believe that an incremental analysis is not a valid methodology for determining whether introducing a single intervention, which will displace a range of alternatives used in current practice, is a cost effective use of NHS resources (as in STA).

The 'blended' comparator described in our submission represents current clinical practice, and is more reflective of the opportunity cost of interventions that would be displaced by lapatinib and capecitabine. Relying on single-agent chemotherapy as the principal comparator therefore fails to account for the cost savings that would accrue from the displacement of trastuzumab-containing regimens which are likely to continue to be used in current clinical practice. It is also dependent on a complete change in current practice which, given the widespread use of trastuzumab in this setting, and the recent data that supports its clinical validity, is unlikely to be achievable in practice.

In their deliberations the Committee was mindful of the draft clinical guideline currently under consultation,[6] which provisionally recommends that people who are receiving treatment with trastuzumab should not continue trastuzumab at the time of disease progression outside the central nervous system. Clearly this guideline is still subject to consultation and therefore should not form the basis of what constitutes current clinical practice. Also, whilst this recommendation suggests that continuation with trastuzumab should not be part of standard practice in the future, the implementation of this aspect of the guideline would be challenging in light of the acceptance by the clinical community of the importance of continued ErbB2 suppression despite progression. This was indicated in the Royal College of Physician feedback on the first ACD, which highlighted the changing standard of care with the emergence of new data for ErbB2-suppressing agents such as lapatinib and trastuzumab. It is also interesting to note that the draft guideline does, by implication, allow those patients that have progressed only in the brain to continue to receive trastuzumab. Therefore in effect trastuzumab would, at least, constitute standard of care in this patient group. The current proposals if implemented would result in allowing the unlicensed use of trastuzumab to continue at a higher cost to the NHS whilst denying the same use of an alternative product within its product licence.

In rejecting GSK's approach to the decision problem (the blended comparator analysis), we believe that the provisional recommendations are not sound, and that they will *de facto* result in less efficient use of NHS resources, through the continued use of an intervention that is more expensive than the predominant alternative, especially when the Lapatinib Patient Access Programme is applied.

We would also like to point out that the recommendations of the Committee do not appear to have taken account of the acknowledgement in the methods guides that consideration of the cost effectiveness of a technology should not be the sole basis for decision-making.[3,4] The Committee's decision appears to be based purely on health economic grounds, some of which we believe are not relevant in the current decision making context.

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

In GSK's original submission, we presented an argument that lapatinib plus capecitabine presents a cost effective alternative to trastuzumab-containing regimens in the subset of patients that is more likely to receive such treatment. This subgroup included patients with progression at an isolated site, patients with few metastases in the soft tissues or bone and patients who experience a previous good response to trastuzumab. However, acknowledging the equity issues associated with trying to identify such a sub-group, and in a sincere attempt to provide equitable access to lapatinib for all eligible patients, GSK offered a patient access programme (LPAP) which demonstrated cost effectiveness of £16,384/QALY, which:

- accounts for the key uncertainties in our original analysis, as highlighted by the Evidence Review Group;
- includes more recent and robust evidence of the effectiveness of both lapatinib and trastuzumab regimens;
- accounts for the current variability in trastuzumab use beyond progression in England and Wales by using an average 'standard practice' comparator.

The decision not to recommend lapatinib for use on the NHS under the terms of the proposed programme raises several issues concerning the equitable access to treatment in England and Wales:

a. There is a clear signal from the clinical community that the unlicensed use of trastuzumab beyond progression will continue to increase in light of the results of the GBG-26 study. Rejecting lapatinib under the terms of the proposed access programme on the basis that its cost effectiveness is dependent on the inclusion of a comparator that is itself cost-ineffective, will be a *de facto* endorsement of the continued cost-ineffective and inequitable use of trastuzumab in this setting, thereby perpetuating the current inequity associated with treatment of these patients, and contributing to the decline in cancer outcomes in England and Wales;

b. The guidance for imatinib in chronic myeloid leukaemia[5] suggests that this approach is inconsistent with a decision in similar circumstances (i.e. regarding a cost ineffective comparator), which ultimately will lead to inequality between different populations;

c. As metastatic breast cancer is incurable, effective treatment options that can delay progression or improve the likelihood of survival without negatively impacting quality of life and adding to the toxicity burden are greatly needed in this patient group. In particular, given that ErbB2-targeted therapy is a crucial component of treatment for patients with ErbB2 positive disease, there is a clear need for alternative ErbB2-targeted therapies. Lapatinib plus capecitabine is a treatment option that has been specifically evaluated and licensed for use when disease has progressed after trastuzumab treatment in the metastatic setting. It is increasingly apparent that proving cost effectiveness of new interventions in late-stage cancer is difficult within the NICE reference case. The background costs of

managing these patients is significant and the cost effectiveness estimates are impacted by costs associated with the prolonged survival results in lapatinib patients: even if the lapatinib is provided at zero cost the cost utility ratio in comparison to capecitabine alone is still £11,000/QALY. This means that within NICE's current threshold there is very little spare capacity to justify cost effectiveness, and this may disadvantage patients whose management is, by definition, difficult and expensive.

d. For these relatively young women the additional time without disease progression afforded by lapatinib can be disproportionately valuable. Whilst the average increase in survival may be limited to months, data from the Lapatinib Extended Access Programme (LEAP, protocol EGF103659)[7] suggest that the benefit to individual patients can be greater than this. The LEAP study, in which patients received lapatinib plus capecitabine according to the licensed indication, and follow-up is still ongoing, found that while the median duration of treatment to date is 24 weeks, the maximum duration to date has been 104 weeks, indicating that some patients are gaining an additional two years of life without their disease progressing. The value of this additional time without progression at this stage of a person's life is not fully represented in the cost/QALY estimates, and clearly does not include any impact on their value to others such as dependents. Recent research would also suggest that the UK public would apply greater priority to diseases with greater severity and hence that in these patients a higher threshold or 'QALY weighting' should be considered.[8]

e. The draft clinical guideline under consultation[6] highlights a group of patients where the strategy of continuation of ErbB2 suppression with either trastuzumab or lapatinb would be the rational treatment approach (those with progression only in the brain). This reflects what the majority of clinicians would currently do in routine clinical practice; additional local therapies would then be employed to treat the intra-cranial disease. Lapatinib has demonstrated activity in treating established brain metastates[9,10,11] hence there is a strong rationale to consider use of lapatinib in this group of patients with solely intra-cranial disease progression where continued ErbB2 suppression, including trastuzumab, is the standard of care. The current ACD, in rejecting trastuzumab as a comparator on the basis of its cost-ineffectiveness, therefore denies the consideration of lapatinib in the treatment of this important patient group.

f. Principle 11 of NICE's Social Value Judgments (NICE 2005)[12] states that whilst not promoting the use of interventions that are clinically and/or cost-effective, it is recognised that individual choice is important for the NHS and its users. As an all-oral combination lapatinib plus capecitabine may be preferred over IV therapy by patients because of quality of life benefits. Wider societal benefits may be possible through the effects on carers of reduced burden of hospital attendance and/or time required for medication administration. We believe that the ACD recommendations do not reflect the spirit of these social values.

In conclusion, we believe that the decision to reject lapatinib in combination with capecitabine, in the context of the Lapatinib Patient Access Programme, means that patients for whom there are few options available will be denied access to a proven treatment which is licensed, cost effective overall, and cost saving when compared with the intervention most commonly used in clinical practice. If current practice continues, this will inevitably lead to further inequality in access to medicines for these patients across England and Wales.

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