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27 March 2009

Dear [redacted]

Re: APPEAL BY GLAXOSMITHKLINE LIMITED IN RESPECT OF THE FINAL APPRAISAL DETERMINATION FOR LAPATINIB FOR THE TREATMENT OF WOMEN WITH PREVIOUSLY TREATED ADVANCED OR METASTATIC BREAST CANCER

Following consideration of the Final Appraisal Determination (FAD) issued by NICE in relation to lapatinib (Tyverb▼®) for the treatment of women with previously treated advanced or metastatic breast cancer GlaxoSmithKline (GSK) provides notification to NICE of its intention to appeal. The Company's detailed points of appeal, under NICE's Grounds 1 and 2 are set out below. GSK requests an oral hearing for the determination of its appeal.

This Notice of Appeal does not repeat all of the submissions and information provided by GSK earlier in the appraisal process. We therefore respectfully request the Appeal Panel to consider all of our previous submissions as well as this appeal document, namely the following:

- The original submission by GSK dated 17 April 2007
- An addendum to the original submission by GSK dated 2 May 2008
- GSK's comments on the ERG report dated 28 July 2008
- GSK's response to the first ACD dated 28 July 2008
- Addendum to GSK's Response to the ACD: Lapatinib (Tyverb®▼) Patient Access Programme dated 31 July 2008
- GSK's responses to NICE's clarification letter dated 29 August 2008
- GSK's comments on the ERG report dated 4 November 2008
- GSK's response to the second ACD dated 4 November 2008
- GSK's submission in relation to the advice issued by NICE on appraising end of life treatments dated 21 January 2009

HISTORY OF THE APPRAISAL

Lapatinib (Tyverb) is a dual kinase inhibitor affecting two human epidermal growth factor receptors ErbB1 and ErbB2 (also known as HER1 and HER2). Carcinoma of the breast which over expresses ErbB2 is associated with a poor prognosis and a shorter life expectancy than other tumours and use of an inhibitor that blocks several signal pathways is believed to be more effective at preventing tumour growth than use of agents that affect only one receptor.

Lapatinib is the subject of a conditional marketing authorisation granted to Glaxo Group Ltd by the European Commission under the centralised procedure on 10 June 2008 following a favourable opinion by the CHMP on 24 April 2008. Lapatinib is supplied in the UK by GlaxoSmithKline UK Ltd ("GSK"). Lapatinib, in combination with capecitabine *"is indicated for the treatment of patients with advanced or metastatic breast cancer whose tumours overexpress ErbB2 (HER2). Patients should have progressive disease following prior therapy which must include anthracyclines and taxanes and trastuzumab in the metastatic setting.*"

The final Scope for this appraisal was published in February 2007. GSK provided a submission to NICE in accordance with the Single Technology Appraisal ("STA") procedure on 17 April 2007. The Southampton Health Technology Assessments Centre, the Evidence Review Group ("ERG") for this appraisal, prepared a report on 15 June 2007, however the procedure was delayed as a result of delays in the European registration procedure for lapatinib. Lapatinib was then considered by the Appraisal Committee on 22 January 2008. An Appraisal Consultation Document ("ACD") and the evaluation report were ultimately issued to GSK on 30 June 2008 for consultation. A second meeting of the Appraisal Committee took place on 18 September 2008. Following that meeting the Appraisal Committee required that additional information provided by Consultees, including a Patient Access Programme proposed by GSK, required further consideration. A second ACD and an evaluation report were issued to GSK for consultation on 6 October 2008. The third meeting of the Appraisal Committee took place on 19 November 2008 and a Final Appraisal Determination ("FAD") was prepared and provided to NICE's Evidence Executive prior to being issued to consultees. However, the Guidance Executive concluded that the Appraisal Committee's conclusions should be considered in the light of NICE's final criteria for "End of Life" treatments, which were published on 2 January 2009. The appraisal of lapatinib was, accordingly considered for a fourth time at a meeting of the Appraisal Committee on 22 January 2009 and the FAD ultimately issued to GSK on 26 February 2009.

BACKGROUND INFORMATION

Breast cancer is the most common malignancy among women in the UK, accounting for about 30% of all cancers in women and 17% of all female cancer deaths.

Metastatic breast cancer is, in almost all cases, incurable. The goals of treatment are to prolong survival and time to disease progression, and to maximise quality of life with an acceptable toxicity profile.

Approximately 25-30% of patients with metastatic breast cancer have tumours that over-express ErbB2. ErbB2-positive (ErbB2+) tumours tend to be more aggressive with a more rapid disease progression and reduced survival time.

Since the discovery of the validity of ErbB2 as a therapeutic target (Slamon, 2001) there has been an evolution in the management of the care of these patients as the evidence base grows for potentially effective interventions, firstly with the licensing of trastuzumab and most recently with the licensing of lapatinib. For patients with ErbB2+ metastatic breast cancer first-line treatment typically consists of trastuzumab in combination with a taxane, but following further progression there are few treatment options available to patients. Continuous suppression of the ErbB2 receptor is a key factor in improving outcomes for ErbB2+ patients. Indeed, robust market research data has shown that in the absence of other licensed ErbB2-targeted alternatives, approximately 50% of patients who develop progressive disease while being treated with trastuzumab in the metastatic setting continue to receive trastuzumab beyond disease progression, either alone, or more commonly in combination with cytotoxic chemotherapy. This approach is not licensed and is based on limited clinical evidence. The existence of only one randomized controlled trial (RCT) (Von Minckwitz 2009) and a number of non-randomised studies investigating the continuation of trastuzumab in this way suggests, however, that this is a genuine treatment decision which is understandable in light of the lack of alternative options to suppress ErbB2.

Brain metastases are an increasing clinical problem in patients with ErbB2+ breast cancer (Lin 2004), for which there are currently limited treatment options. This condition is associated with substantial morbidity, mortality and increased healthcare costs (Pelletier 2008). Historically, approximately 6-16% of women with metastatic breast cancer developed clinically apparent brain metastases (Lin 2004). However, between 28 and 43% of patients receiving trastuzmab in the metastatic setting have been reported to relapse with brain metastases (Bendell 2003; Lin 2004). This apparent increase may reflect the biology of ErbB2+ tumours and the inability of trastuzumab, a monoclonal antibody, to pass through the blood-brain barrier (Burstein 2005; Lin 2007; Stemmler 2006). Hence, while trastuzumab may effectively control non-central nervous system (CNS) disease, the CNS becomes a ‘sanctuary site’ (Clayton 2004; Lin 2007). In contrast, as a small molecule, lapatinib should be able to cross the blood-brain barrier and preliminary data suggest that it may have some activity in both treating and preventing brain metastases (Cameron 2008; Lin 2008; Van den Abbeele 2006).

The NICE Clinical Guidelines on Advanced Breast Cancer, which were published only one day before the FAD for lapatinib, recommend that trastuzumab should not be continued beyond disease progression if the progression is outside the CNS, but that it should be continued for those in whom the CNS is their only site of progression.

As metastatic breast cancer is incurable, effective treatment options that can delay disease progression or improve the likelihood of survival without negatively impacting quality of life and adding to the toxicity burden associated with treatment 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. The introduction of lapatinib therefore addresses an unmet medical need by providing a rational, specific and evidence-based treatment option for this patient population. It should also be recognised that individual choice is important for the NHS and its users.

In order to improve access to this important new treatment for advanced breast cancer GSK has proposed a patient access programme, the Lapatinib (Tyverb®▼) Patient Access Programme (TPAP). Under the terms of the TPAP all patients will receive free lapatinib up to the first 12 weeks of therapy, and NHS funding is only required for those patients who continue beyond that point after confirmation of the benefits of treatment in the context of their particular disease.

GROUNDS OF APPEAL

1 Ground 1: Procedural Unfairness

1.1 The Appraisal Committee's refusal to base its recommendations on a comparison with trastuzumab (a standard treatment for advanced or metastatic breast cancer) is contrary to NICE's procedures

A standard treatment strategy for NHS patients with advanced or metastatic breast cancer, whose disease progresses following trastuzumab therapy in the metastatic setting, is to continue with such treatment, even though trastuzumab does not have a licence for use following disease progression. In these circumstances, although the Appraisal Committee did accept the analyses of lapatinib in combination with capecitabine compared with trastuzumab regimens, its refusal to base its recommendations on these comparisons is contrary to NICE's procedures.

At paragraph 4.2 of the FAD, the Appraisal Committee notes a range of estimates of continued use of trastuzumab in NHS patients following progression of disease, from 10% to 50%. Evidence from clinical specialists at the first Appraisal Committee meeting, as well as a survey performed by the NCRI Breast Cancer Study Group in response to the second ACD, confirmed that the higher estimates are more appropriate. The evidence from the clinical specialists is supported by the three market research studies where data were provided to NICE by GSK, which consistently found use of trastuzumab, either as monotherapy or in combination with other treatments, in 41-55% of patients following disease progression. On any view therefore trastuzumab therapy constitutes routine NHS practice in patients with advanced or metastatic breast cancer after disease progression in the metastatic setting. Furthermore, following publication of data from a trastuzumab study, GBG-26, the proportion of patients with advanced or metastatic breast cancer who continue to receive trastuzumab following disease progression in the metastatic setting seems likely to increase, irrespective of a recommendation in the (non-binding) Clinical Guideline on Advanced Breast Cancer which states that it should not be continued when progression is outside the central nervous system. .

NICE's Guide to the Methods of Technology Appraisal provides detailed guidance on the criteria which should be used to identify appropriate comparators for the purposes of an appraisal (see eg paragraph 2.2.4). The key factor is stated to be "*routine and best practice in the NHS (including existing NICE guidance) and the natural history of the condition without suitable treatment. There will often be more than one relevant comparator technology because routine practice may vary across the NHS…*" The Guide does not state that comparators are limited to those that are found by the Appraisal Committee to be cost-effective.

In the context of this appraisal, therefore, and in view of the evidence that approximately 50% of patients with previously treated advanced or metastatic breast

cancer receive trastuzumab, the Appraisal Committee accepted that it should consider clinical and cost-effectiveness analyses that compared lapatinib with trastuzumab (paragraph 4.3 of the FAD). The Committee agreed that lapatinib was likely to be cost effective when compared with trastuzumab monotherapy (paragraph 4.13 of the FAD). However, based on the ERG's conclusion that regimens containing trastuzumab were not likely to be cost-effective when compared with capecitabine monotherapy, the Appraisal Committee concluded that trastuzumab was not a valid comparator either alone (paragraph 4.14 of the FAD) or as part of a blended comparator (paragraph 4.15 of the FAD).

GSK continues to believe that the blended comparator proposed for the purposes of this STA is most appropriate. The blended comparator was intended to reflect all the main treatment regimens in standard NHS use in this indication, i.e. capecitabine, vinorelbine and trastuzumab combination regimens, and represents a fairer approach than the incremental consideration of lapatinib against each of the alternative treatments, as would be appropriate in a Multiple Technology Appraisal ("MTA"). Which treatments are used in routine NHS practice is a matter of fact and it is not open to the Appraisal Committee, in the context of an STA, to pick and choose from those treatments the therapies it believes should be comparators; guidance issued as a result of such an assessment is not valid.

The strategy followed by the Appraisal Committee in this STA, whereby guidance in relation to a technology is not based on a comparison with one of the principal treatments that is, in fact, used to treat NHS patients - irrespective of whether or not it is cost-effective - cannot be credible. Trastuzumab incontrovertibly represents routine practice and may not be disregarded simply because the Appraisal Committee (which has not formally appraised the cost effectiveness of trastuzumab in this indication) believes such treatment should not occur.

It is of course highly relevant to consider that the effect of the Appraisal Committee's refusal to base guidance on a comparison of lapatinib with trastuzumab-containing regimens, is that certain patients will continue to receive trastuzumab, which has been shown to be less cost-effective than lapatinib in this indication, and will therefore result in a less efficient use of NHS resources. Such use of trastuzumab is unlicensed and therefore protected from appraisal by NICE. As previously stated, in these circumstances it is highly likely that, irrespective of recommendations in the non-binding Clinical Guideline on Advanced Breast Cancer, trastuzumab will continue to be used in the future to treat patients with advanced or metastatic breast cancer, following disease progression in the metastatic setting.

1.2 The procedure for the appraisal of lapatinib should have been modified to reflect the change in approach resulting from the new supplementary advice from NICE in relation to the appraisal of treatments which may extend the life of patients with a short life expectancy.

As a matter of fairness, a consultee must be informed of the procedure to be followed in an appraisal and the criteria that will be applied by the Appraisal Committee in determining whether to issue guidance recommending a particular health technology. While GSK welcomes NICE's recognition that greater flexibility is required when appraising treatments for patients with a short life expectancy, the fact that the procedures for this particular appraisal did not provide for submissions or consultation in the context of the new advice and how it applies to lapatinib is patently unfair.

NICE's supplementary advice to Appraisal Committees on the appraisal of treatments which may extend the life of patients with a short life expectancy ("NICE's Supplementary Advice") identifies particular circumstances in which a more flexible approach should be adopted by the Appraisal Committee, by reference to specific criteria. These are, in summary, that:

- The treatment is indicated for patients with a short life expectancy (normally less than 24 months).
- The treatment offers an extension to life of normally at least 3 months, compared to current NHS treatment.
- No alternative treatment with comparable benefits is available through the NHS.
- The treatment is licensed or indicated for small patient populations.

Where these criteria are satisfied, NICE's Supplementary Advice states that the Appraisal Committee will consider:

- The impact of giving greater weight to QALYs achieved in the later stages of a terminal illness;
- The magnitude of the additional weight that would need to be given to the QALY benefits in this patient group for the cost-effectiveness of the technology to fall within the current threshold range.

NICE's Supplementary Advice was issued by the Institute on 2 January 2009, after the deadline for the submission of comments on the ACD for lapatinib (4 November 2008) and after a meeting of the Appraisal Committee to consider the FAD had taken place (19 November 2008). On 5 January 2009 NICE informed GSK that the Supplementary Advice had been issued and indicated that the Appraisal Committee would consider the recommendations for lapatinib in the context of that advice at its meeting on 22 January 2009.

GSK prepared a further submission directed towards the criteria identified in the Supplementary Advice in the context of the appraisal of lapatinib. In this submission GSK provided a further analysis in a subgroup of patients who had received fewer than three lines of chemotherapy in the metastatic setting, where the gain in survival associated with lapatinib was around seven months (32.2 weeks; p=0.014). GSK provided its submission to NICE on 21 January 2009. This sub-group analysis had been performed for purposes other than the NICE appraisal (to facilitate a more meaningful comparison of cost effectiveness results from lapatinib study EGF100151 and trastuzumab study GBG-26), and had only recently become available. The results are particularly pertinent in light of the new criteria, clearly meeting the requirement for a treatment to offer an extension to life of normally at least 3 months in this important population.

At the meeting on 22 January 2009, the Appraisal Committee considered its recommendations for lapatinib in the context of NICE's Supplementary Advice, but concluded that the gain in overall survival of approximately 1.9 months associated with lapatinib plus capecitabine as compared with capecitabine monotherapy, did not satisfy the criteria listed in NICE's Supplementary Advice, which was not, therefore, applicable (paragraph 4.19 of the FAD). The Appraisal Committee did consider the further submission provided by GSK the previous day, but stated that the new subgroup analysis "*could not materially affect the conclusion that lapatinib should only be used in the context of clinical trials*" (paragraph 4.21 of the FAD).

In the circumstances described above, GSK believes that the failure to revise the procedure and timelines for this appraisal to incorporate NICE's Supplementary Advice into the process was unfair for the following reasons:

1. While the introduction of NICE's Supplementary Advice at the end of the appraisal of lapatinib modified the procedure and approach of the Appraisal Committee, NICE did not invite further submissions directed towards the application of the criteria listed in the Supplementary Advice. Additionally, no changes were made to the process to involve consultees in the consideration of whether the Supplemental Advice should apply to lapatinib. This omission by NICE unfairly deprived GSK and other consultees from proper participation in this important aspect of the appraisal.

2. If NICE's Supplementary Advice had been issued before the commencement of the appraisal of lapatinib, GSK would have been able to prepare its initial submission in the context of the specific criteria. Therefore, in circumstances where NICE's Supplementary Advice was issued only towards the end of the appraisal of lapatinib, GSK should have been permitted an appropriate amount of time in which to prepare appropriate arguments in the context of lapatinib and to submit these formally to NICE before the Supplementary Advice was considered by the Appraisal Committee. While GSK attempted to prepare an appropriate submission after becoming aware of the final details of NICE's Supplementary Advice in early January 2009, there was insufficient time for the work GSK would have wished to carry out before the Appraisal Committee met on 22 January 2009.

3. While GSK made every effort to prepare a submission directed towards NICE's Supplementary Advice expeditiously, it was not possible to provide this to the Institute before 21 January 2009, less than one day before the Appraisal Committee met to consider this appraisal. This meant that members of the Appraisal Committee were not provided with GSK's further submission in advance of the meeting and had no opportunity to consider this adequately, if at all, before reaching their conclusions regarding lapatinib.

4. Furthermore, as explained above, a fair procedure requires that consultees are informed of the approach to be followed by the Appraisal Committee and given the opportunity to make appropriate submissions in the context of that procedure. Where the criteria to be taken into account by the Appraisal Committee are modified during the course of an appraisal, consultees must be given an appropriate opportunity to make submissions in relation to the modified criteria and these must be taken into account by the Appraisal Committee. Therefore the incorrect assumption by the Appraisal Committee that it had no obligation, but merely a discretion, to consider GSK's further submission would inevitably have influenced the Committee's consideration of GSK's further submission and the weight attached by the Committee to the subgroup analysis presented in it.

For the avoidance of doubt, the fact that consultees were not given adequate opportunity to make submissions in relation to NICE's Supplementary Advice may not be corrected through the appeal procedure. The potential grounds for appeal are limited by NICE's procedures and do not include a challenge based on a difference of scientific opinion, as would be possible through a consultation process, unless this reaches the perversity threshold. In these circumstances we believe that the fact that NICE's Supplementary Advice clearly has application to lapatinib means that this

appraisal must be returned to the Appraisal Committee for consideration following effective consultation with consultees.

1.3 The Appraisal Committee's application of NICE's Supplementary Advice in relation to the appraisal of treatments which may extend the life of patients with a short life expectancy was overly restrictive and unfair.

GSK believes that the way in which NICE's Supplementary Advice was applied by the Appraisal Committee, in the context of its consideration of lapatinib at paragraphs 4.19 - 4.21 of the FAD, was unfair.

In particular the criteria listed in NICE's Supplementary Advice include a requirement that the treatment should offer "*an extension to life, normally of at least an additional 3 months, compared with current NHS treatment*". The way in which this criterion was interpreted by the Appraisal Committee in the appraisal of lapatinib was highly restrictive; the Appraisal Committee concluded, at paragraph 4.19 of the FAD that the trial data for lapatinib offered an overall survival advantage of 1.9 months compared with capecitabine alone, which did not reach conventional levels of statistical significance and that, accordingly, the size of the possible benefit was not in keeping with NICE's Supplementary Advice. The Appraisal Committee therefore seemingly considered that no further consideration of the Supplementary Advice was required in the context of the appraisal of lapatinib. This was unfair for the following reasons:

1. An inflexible application of the requirement that a treatment should extend life by at least three months is inconsistent with NICE's procedures: the Supplementary Advice provided only that this should "normally" be the case.

2. In addition, an inflexible approach also fails to take into account the very variable life expectancies that may be encompassed within a category of patients who have less than 24 months to live. By way of example, where a patient has only three months to live, a doubling of that life expectancy arguably represents a greater treatment benefit than an extension of life of three months in a patient who, in the absence of treatment, could expect only 23 months of life. The median survival in the capecitabine monotherapy arm of the pivotal lapatinib trial in this indication was 15 months. The fact that an extension of life of approximately two months from 15 months (the position in the lapatinib trial) is proportionate to an extension of life of three months from 24 months (as provided in NICE's Supplementary Advice) has not seemingly been considered by the Appraisal Committee at all. In fact, where patients who have received fewer than three chemotherapy regimens are considered, as submitted for consideration by the Appraisal Committee on 21 January 2009, a lapatinib containing regimen produces a median survival advantage of 32.2 weeks, over twice the three month period specified by NICE in its Supplementary Advice.

3. The criticism by the Appraisal Committee that the survival advantage associated with lapatinib in the pivotal trial in this indication did not reach conventional levels of statistical significance (paragraph 4.19 of the FAD), failed to take account of the fact that recruitment to the trial was halted early as a result of the superior results associated with lapatinib treatment. The Committee noted, at paragraph 3.2 of the FAD, that enrolment to study EGF100151 was discontinued in view of the emerging data showing increased time to disease progression (the primary endpoint) associated with lapatinib therapy. It was deemed unethical to continue the study in light of this positive benefit seen with the use of lapatinib. Accordingly, the study may have been underpowered to

detect certain secondary endpoints (such as overall survival) and subject to confounding as a result of cross over from the capecitabine arm of the study (paragraph 3.4 of the FAD). Paradoxically, therefore, it is by virtue of lapatinib's proven superior efficacy that it has not been possible to demonstrate a statistically significant improvement in overall survival. It is clearly unfair that the most effective treatments, with the best early trial results, are less likely to satisfy NICE's criteria for more flexible consideration by the Appraisal Committee.

4. NICE's Supplementary Advice does not consider the additional costs associated with prolonging life in patients who will live only a short time - excluding the costs of the technology under consideration - and this has not been taken into account by the Appraisal Committee in the context of this appraisal. Almost invariably, a patient with a short life expectancy will require additional health and/ or social services support in terms of nursing care, medical consultations, hospital costs and the costs of medicines that alleviate symptoms - before the costs of health technologies directed towards the disease under consideration are considered. Therefore the survival benefits associated with lapatinib treatment affect the assessment of cost-effectiveness - before any costs associated with the drug itself are considered. Even if lapatinib is provided at zero cost the cost utility ratio in comparison to capecitabine alone is still £11,000/QALY - i.e. employing NICE's methodology, the very benefits associated with use of lapatinib, mean that it appears less cost effective than a comparator.

For the above reasons, the application of the Supplementary Advice to the appraisal of lapatinib has failed adequately to take into account the benefits of treatment, and the rigid application of the requirement for a three month survival benefit is inconsistent with NICE's Supplementary Advice and unfair in the context of the life expectancy of patients with the disease under consideration.

1.4 The Appraisal Committee's rejection of the subgroup of patients who had received fewer than three prior treatment regimens lacks transparency.

In January 2009 GSK submitted an analysis showing the cost-effectiveness of lapatinib in the subgroup of patients who had received fewer than three previous chemotherapy regimens. The results were very favourable; such patients had a median increase in survival of some seven months (32.2 weeks) as compared with patients who received capecitabine monotherapy. It is self evident that these substantial clinical benefits translate into improved cost-effectiveness. The incremental cost effectiveness ratio (ICER) for lapatinib regimens compared with capecitabine monotherapy was reduced from over £90,000/QALY gained (the base case analysis) to around £55,000/QALY ([redacted]). It is likely that this ICER would be considerably reduced if lapatinib were administered under the terms of the Lapatinib (Tyverb®▼) Patient Access Programme (TPAP).

At paragraph 4.21 of the FAD, the Appraisal Committee states that it considered GSK's submission proposing use of lapatinib in patients who had received fewer than three prior treatment regimens. The Appraisal Committee concluded "*the data analyses could, at this stage, generate a useful hypothesis for future research, but it could not materially affect the conclusion that lapatinib should only be used in the context of clinical trials*".

However, the reasons given by the Appraisal Committee for reaching this conclusion are unclear and do not properly reflect the data provided by GSK.

1. One of the reasons identified by the Committee for rejecting the subgroup proposed by GSK was the small number of patients involved. This simply reflects the fact that the majority of patients in the registration study had received multiple lines of prior treatments, and the fact that the study was halted before full patient recruitment was achieved. However, the Appraisal Committee does not appear to have taken into consideration the fact that the results from this subgroup were highly statistically significant, despite the fact that relatively small numbers of patients were involved.

2. The Committee also stated that little information was provided on how the subgroup was identified. As indicated in our submission of 21 January 2009, the subgroup had been identified for purposes other than this appraisal, as being a better match for those recruited to the GBG-26 study (trastuzumab) in terms of their previous exposure to chemotherapy regimens in the metastatic setting. This was done in order to facilitate a more meaningful comparison of cost effectiveness results from both studies. Regarding the patients involved, the fact that the patients proposed by GSK had received fewer than three prior treatment regimens is readily ascertained. In these circumstances, the objection of the Appraisal Committee is unclear. Furthermore, these concerns could have been addressed if the timing and process had allowed for a comprehensive submission.

3. Finally, the Appraisal Committee states that there was no exploration of the possibility that the differences in efficacy observed for this subgroup could have occurred by chance. However, this sub group analysis included statistical testing, and the results were provided to NICE. The resultant p values and confidence intervals indicate a high degree of statistical significance, and again the Appraisal Committee's reasons for disregarding these results are unclear. Again, further exploration of this matter would have been possible if the timing and process had allowed for a comprehensive submission.

Overall therefore GSK believes that the Appraisal Committee should provide greater reasoning to explain its rejection of use of lapatinib in the subgroup of patients who had received fewer than three prior treatment regimens. In the absence of such reasoning, GSK is prejudiced in its ability to understand the conclusions reached by the Committee.

1.5 The failure to consider fully the additional evidence provided by GSK in response to the publication of supplementary advice from NICE regarding the appraisal of end of life treatments is unfair.

In section 4.21 the FAD acknowledges the provision by GSK of the additional subgroup analysis, and states that the Committee reviewed the document to assess whether the data presented would materially affect the conclusions already reached. The Committee concluded that "*the data analysis could, at this stage, generate a useful hypothesis for future research but it could not materially affect the conclusion that lapatinib should only be used in the context of clinical trials.* "

Due to the evolution of care for patients with ErbB2+ breast cancer, the gold standard comparators in studies of a population whose disease has progressed

following trastuzumab used in the metastatic setting are now ErbB2-targeted therapies. Nowadays it would be unethical to design a clinical study with a comparator (e.g., capecitabine) that is less effective than other interventions which are currently licensed (e.g., trastuzumab). Even if this were possible it is very unlikely that patients would agree to participate in such studies unless the use of trastuzumab in clinical practice in this population had been completely ablated by the implementation of the NICE clinical guideline, which given its non-binding status is very unlikely.

Therefore it is highly unlikely that meaningful research will be feasible to test the hypothesis that: *lapatinib in combination with capecitabine in patients who have received fewer than three prior chemotherapies in the metastatic setting gives a significant and substantial survival advantage over single agent capecitabine*. We assert that the scope for further research to inform the decision problem in this appraisal is extremely limited, and that bearing in mind the extent of the benefit demonstrated in this subgroup the Committee should therefore place more weight on the existing evidence in an important group of patients with a high level of clinical need.

In the context of the lack of feasibility of further research we believe that the Committee's refusal to consider fully through a submission and consultation process is unrealistic and unfair. The failure of the Appraisal Committee to recommend that lapatinib be returned to ACD within the process in order to enable a full submission of the evidence by GSK, and a full review by NICE/ERG is unfair.

1.6 The Appraisal Committee has placed inadequate weight on the medical need of patients with the disease under consideration.

In formulating its recommendations, the Appraisal Committee is required to have regard to factors listed in Directions issued by the Secretary of State for Health. These factors include "the degree of clinical need of the patients with the disease or condition under consideration".

Patients eligible for treatments with lapatinib have a very high unmet medical need. They will have advanced or metastatic breast cancer which has progressed despite previous treatments with at least three agents (an anthracycline and a taxane and trastuzumab). In addition, all women eligible for treatment have breast cancers which over express the ErB2 (HER2) receptor and therefore have a worse prognosis and an increased prospect of relapse, as compared with the general breast cancer population.

These women have few treatment options and there is no accepted standard of care. Lapatinib is the only therapy specifically licensed in this indication. The average overall survival in patients randomised to the control arm of the main trial of lapatinib was only 15 months and, in circumstances where many of these patients will be relatively young, an extension of a few months may be highly meaningful.

However, despite the clear medical needs of the patients under consideration, there is no indication in the FAD for lapatinib that the Appraisal Committee placed adequate or any weight upon the Secretary of State's Direction in this regard or if they did, how such matters were taken into account in formulating the draft guidance in the FAD.

1.7 The Appraisal Committee has failed adequately to consider the effect of its recommendations on innovation in the NHS

The Directions issued to NICE by the Secretary of State, also require the Appraisal Committee to take into account "the potential long term benefits to the NHS of innovation". However GSK believes this requirement has not been given adequate weight by the Committee in the context of its appraisal of lapatinib.

Lapatinib represents an innovative approach to cancer treatment, directed towards specific features of the particular tumour. Such a directed approach aims to produce focused anti-neoplastic activity with reduced potential for toxicity, with very substantial benefits for patients. This is in marked contrast to traditional anti-cancer chemotherapies which exert non-specific anti-neoplastic effects.

In these circumstances, the failure by the Appraisal Committee to recommend use of lapatinib on the basis of a view that patients should continue to receive treatment with conventional, older forms of chemotherapy - despite the fact that ErbB2-targeted treatments are now recognised as the gold standard of care for such patients internationally - will inevitably stifle innovation within the UK to the detriment of patient care within the NHS.

This situation does not appear to have been recognised or taken into account by the Committee in reaching its conclusions.

1.8 The Appraisal Committee has issued recommendations in relation to trastuzumab, which are beyond its remit for this appraisal

The Remit given to NICE by the Department of Health and the Welsh Assembly Government for this appraisal was "To appraise the clinical and cost-effectiveness of lapatinib plus capecitabine within its licensed indications for advanced, metastatic or recurrent breast cancer". This Remit is reflected in the final Scope for the appraisal dated February 2007. Neither the Remit nor the Scope permit NICE to issue recommendations in respect of technologies other than lapatinib. However, at paragraph 6.2 of the FAD the Appraisal Committee "recommended that a study of the clinical and cost-effectiveness of trastuzumab continued following progression of disease should be carried out."

Paragraph 6.2 of the FAD falls outside the Remit and Scope for this appraisal and the recommendation on research involving trastuzumab therefore constitutes a breach of NICE's procedures.

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2 Ground 2: Perversity

2.1 The refusal of the Appraisal Committee to make recommendations based on a comparison with trastuzumab has the effect of promoting use of a product which is unlicensed for this indication and less cost-effective than lapatinib

Lapatinib is authorised for the treatment of all patients with advanced or metastatic breast cancer, following treatment with an anthracycline and a taxane and following progression of disease after treatment with trastuzumab, irrespective of the site of progression. Furthermore, lapatinib is highly cost-effective when compared with trastuzumab (paragraph 4.13 of the FAD) or with a blended comparator representing the range of treatment currently used in this indication in the NHS. Despite these results, NICE declined to base recommendations on use of lapatinib on a comparison with trastuzumab in circumstances where it did not consider trastuzumab to be cost-effective.

This creates a situation which is perverse:

- Patients will be denied access to treatment with lapatinib, the only product with a specific licence in this indication, and will instead continue to receive trastuzumab, which has no licence for use in these patients.
- The data presented by GSK has shown that, trastuzumab represents routine NHS treatment for approximately 50% of women with advanced or metastatic breast cancer following disease progression. While the Clinical Guideline on Advanced Breast Cancer states it should be discontinued after progression of disease, unless progression is limited to the CNS, the Guideline is non-binding and in view of the emerging data that trastuzumab is more effective than capecitabine, usage may actually increase.
- NICE has accepted that lapatinib is likely to be cost effective compared with trastuzumab - and that position is further strengthened by the fact that lapatinib is being offered under the terms of the TPAP, which means it is effectively considerably cheaper than trastuzumab, and would deliver savings to the NHS in those patients who would otherwise be continued on trastuzumab.
- There is evidence to suggest that lapatinib may have beneficial effects in the prevention and treatment of brain metastases (Cameron 2008; Lin 2008; Van den Abbeele 2006), in contrast to trastuzumab. This is because it is a small molecule and therefore likely to cross the blood brain barrier.

Therefore the fact that the Appraisal Committee has declined to base its recommendations on a comparison with trastuzumab means that use of trastuzumab will increase, even though it is unlicensed in this setting, likely to be less effective in patients with brain metastases and less cost-effective overall than lapatinib. This outcome is perverse.

2.2 The approach of the Appraisal Committee to the use of lapatinib in patients who have central nervous system metastases is inconsistent with that followed in the Clinical Guideline on breast cancer in relation to trastuzumab and creates a situation that is arbitrary and therefore perverse.

While the Appraisal Committee was aware of NICE's Clinical Guideline on Advanced Breast Cancer (NICE Clinical Guideline AT1) which recommends that trastuzumab

should be discontinued where there is disease progression outside the central nervous system, but not if disease progression is limited to the central nervous system (paragraph 4.4 of the FAD), this was not, seemingly, taken into account by the Appraisal Committee when determining that trastuzumab was not an appropriate comparator for lapatinib in any circumstances.

The approaches taken by the Appraisal Committee and the Guideline Development Group therefore present two inconsistencies:

1. The Appraisal Committee concluded that there were insufficient data to allow them to consider a recommendation for lapatinib limited to patients with brain metastases. In contrast, the Guideline Development Group felt able to issue a positive recommendation for use of trastuzumab in such patients, even though the data to support use in this patient population is substantially more limited than that available for lapatinib. As mentioned in the background section, as a small molecule lapatinib should be able to cross the blood-brain barrier, and preliminary data suggest that it may have some activity in both treating and preventing brain metastases (Cameron 2008; Lin 2008; Van den Abbeele 2006). Conversely, by virtue of its lack of activity in the brain, trastuzumab does not actively address the issue of brain metastases in these patients. Furthermore, there is good evidence to suggest that control of non-CNS disease by lapatinib is comparable to that afforded by trastuzumab (Gomez 2008, Vogel 2002).

2. The Guideline Development Group concluded that trastuzumab should be recommended for use in patients who have experienced disease progression limited to the central nervous system, whereas the Appraisal Committee concluded that trastuzumab is never an appropriate comparator for lapatinib.

The result of the inconsistent approaches followed by the Guideline Development Group and the Appraisal Committee is that patients with advanced or metastatic breast cancer who have experienced disease progression on trastuzumab, limited to the central nervous system, will continue to receive treatment with trastuzumab, which is unlicensed in this indication and in circumstances where there is little in the way of data demonstrating benefit. Patients will be denied treatment with lapatinib, which is licensed for use in such patients, and where the emerging data suggest some benefit. In addition, it will mean that patients will receive a treatment which is less cost effective, particularly if the TPAP is taken into account.

These inconsistencies create a situation that is arbitrary and therefore perverse.

2.3 The Appraisal Committee's refusal to consider the use of lapatinib in patients with brain metastases was based on an error and is therefore perverse

At paragraph 4.5 of the FAD, the Appraisal Committee sets out its reasons for declining to consider use of lapatinib in patients who have brain metastases. The FAD states:

"*However, the Committee noted that the evidence to support this in terms of clinical effectiveness was still limited and that the manufacturer was specifically requested by the EMEA to further investigate this potentially important effect of lapatinib. The manufacturer will conduct a phase III randomised, controlled clinical study to evaluate the incidence of brain metastases as the site of relapse with a lapatinib-*

containing therapy compared with an appropriate trastuzumab-containing therapy….."

As recognised in the FAD, the additional research requested by the EMEA, relates to the potentially favourable effects of lapatinib in preventing brain metastases. The EMEA did not request research to investigate the effects of the product in treating patients who had developed brain metastases. Therefore the statement by the Appraisal Committee, that the EMEA had "specifically requested" GSK to investigate the effects of lapatinib in patients with brain metastases is incorrect, and the fact that this error was relied upon by the Committee in deciding not to consider use of lapatinib in such patients means that such decision is flawed and therefore perverse.

2.4 The Appraisal Committee's recommendation that trials should be conducted to compare lapatinib in sub groups of patients that included all appropriate treatment comparisons is unethical and therefore perverse.

At paragraph 4.17 of the FAD, the Appraisal Committee expressed the view "*that trials to establish the effectiveness of lapatinib in such sub groups of patients that included all appropriate treatment comparisons should be considered*". However, in circumstances where recruitment to the pivotal clinical trial comparing lapatinib with capecitabine monotherapy was halted early as a result of the superior efficacy of the lapatinib regime demonstrated in preliminary analyses of the data, it would clearly be unethical to carry out a randomised controlled trial of the type proposed by the Appraisal Committee involving products such as capecitabine.

Furthermore, in view of the fact that lapatinib in combination with capecitabine is now accepted as the standard of care both in the regulatory context and clinical care internationally, the only trials that would be ethical are those that compare lapatinib with new treatments that allow for continued ErbB2 suppression, and are potentially more efficacious. By way of example, two large randomised phase III studies including over 1,500 patients are currently ongoing in this population, and lapatinib in combination with capecitabine is the standard arm for comparison with either neratinib or trastuzumab DM-1.

In circumstances where randomised controlled trials comparing lapatinib with the treatments viewed by the Committee as appropriate comparators (capecitabine or vinorelbine monotherapy), would be unethical, the evidence currently available should be considered with more weight, and the Committee's recommendations are perverse.

REQUESTED ACTION OF THE APPEAL PANEL

In the above circumstances, the Appeal Panel is respectfully requested to return this appraisal to the Appraisal Committee for further consideration with the following directions:

1. The Appraisal Committee should reconsider the guidance for lapatinib in the context of NICE's Supplementary Advice after allowing consultees an adequate opportunity to make appropriate submissions. This should include a full exploration of the additional data for the sub group of patients who have

received fewer than three prior chemotherapies, the preliminary results of which were submitted on 21 January 2009.

2. The guidance should be reissued in the form of a further ACD to allow for consultation following the submissions by consultees.
3. The Appraisal Committee should make recommendations based on a comparison of lapatinib with current routine NHS practice, including trastuzumab.
4. The Appraisal Committee should reconsider the guidance for lapatinib in patients whose disease has progressed only in the brain, in the context of the clinical guideline recommendation for trastuzumab.
5. The reasoning for the Appraisal Committee's conclusions (including those in relation to the subgroup of patients who have received fewer than three previous chemotherapy regimens) should be clearly stated in the new ACD.
6. The recommendations of the Appraisal Committee should be limited to the Remit and Scope for this appraisal.

Please let me know if you have any questions concerning this appeal.

Yours Sincerely

[redacted]

GlaxoSmithKline UK

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