LAPATINIB FOR THE TREATMENT OF WOMEN WITH PREVIOUSLY TREATED ADVANCED OR METASTATIC BREAST CANCER

APPEAL AGAINST THE FINAL APPRAISAL DETERMINATION ISSUED BY NICE ON 3 JUNE 2010

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 worse prognosis and a shorter life expectancy than other forms of breast cancer and use of a small molecule inhibitor that blocks several signal pathways may be more effective at preventing tumour growth than use of agents that affect only one receptor and act by different mechanisms to target cancer cells.

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 indicated for the treatment for patients with breast cancer whose tumours over express HER2 (ErbB2)

The initial indication (which is the subject of the current appraisal) was:

- In combination with capecitabine for patients with advanced or metastatic disease with progression following prior therapy, which must have included anthracyclines and taxanes and therapy with trastuzumab in the metastatic setting."

Although not relevant to this appraisal, on 21 June 2010, the indication was extended to include treatment:

- In combination with an aromatase inhibitor for postmenopausal women with hormone receptor positive metastatic disease, not currently intended for chemotherapy. The patients in the registration study were not previously treated with trastuzumab or an aromatase inhibitor.

Lapatinib is supplied in the UK by GlaxoSmithKline UK Ltd ("GSK")

The history of this appraisal is set out below:

February 2007: final Scope was published.

17 April 2007: GSK provided a submission to NICE in accordance with the Single Technology Appraisal ("STA") procedure.

15 June 2007: The Southampton Health Technology Assessments Centre, the Evidence Review Group ("ERG") for this appraisal, prepared its report, which was then issued for consultation.

22 January 2008: First meeting of the Appraisal Committee took place; the appraisal procedure was not then progressed, as a result of delays in the European registration procedure for lapatinib.

3 July 2008: An Appraisal Consultation Document ("ACD") was issued for consultation.

18 September 2008: A second meeting of the Appraisal Committee took place, following which the Appraisal Committee directed further consultation in relation to the preliminary recommendations in the ACD.

19 November 2008: The third meeting of the Appraisal Committee to consider lapatinib took place and a Final Appraisal Determination ("FAD") was prepared and sent to NICE's Guidance 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 Guidance on "End of Life" Treatments.

22 January 2009: The appraisal of lapatinib was considered at a fourth meeting of the Appraisal Committee

4 March 2009: The first FAD was issued.

8 June 2009: The hearing of GSK's appeal to NICE in respect of the FAD.

7 July 2009: The decision of the Appeal Panel was issued; the Panel found in favour of GSK on one point of appeal and a second point of appeal in part: both points related to the application of the new Guidance on End of Life Treatments. The appraisal was therefore returned to the Appraisal Committee.

23 September 2009: The fifth meeting of the Appraisal Committee took place and a second negative ACD was issued on 21 October 2009.

17 November 2009: The sixth meeting of the Appraisal Committee to consider this appraisal took place.

22 December 2009: A draft FAD (assumed to be negative) was sent to the Guidance Executive, who requested that the Appraisal Committee should give further consideration to the appraisal in the context of potential costs savings to the NHS should lapatinib be used in place of trastuzumab containing regimens.

16 February 2010: The seventh meeting of the Appraisal Committee took place.

3 June 2010: The current FAD is issued: this recommends that lapatinib should not be used, within its licensed indications to treat NHS patients.

GlaxoSmithKline therefore notifies its intention to appeal the current Final Appraisal Determination.

The Company requests an oral hearing for the determination of this appeal.

Grounds of Appeal: this appeal is advanced under Ground 1: Procedural Fairness

1. The letter from Professor Home dated 16 February 2010, which seeks to explain the position of the Appraisal Committee, is unclear and does not adequately address the issues raised by the document issued by the Guidance Executive in January 2010.

   Following a meeting of the Appraisal Committee on 17 November 2009, a draft FAD was prepared and sent to NICE's Guidance Executive prior to publication. While GSK has not seen this document we understand that it reflected the wording of the previous ACD and recommended that lapatinib should not be used for the treatment of breast cancer within the terms of its marketing authorisation. This determination followed the Appraisal Committee's refusal to base guidance on a comparison of lapatinib plus capecitabine with trastuzumab, which showed lapatinib is likely to be highly cost effective, particularly when made available within the context of a patient access programme (Tyverb Patient Access Programme, TPAP). The Committee's decision relied on a comparison of trastuzumab with capecitabine, which the Committee did not consider to be cost effective, even though the Committee accepted that trastuzumab, although unlicensed in this indication, is widely used in the NHS.

   Following receipt of the draft FAD, the Guidance Executive issued a document in January 2010 providing directions to the Appraisal Committee as to how it should approach the appraisal of lapatinib "*in circumstances where there is a prima facie case for considering that a new technology might help the NHS make better use of resources than current standard practice [i.e. trastuzumab]*". So far as GSK is aware, this step by the Guidance Executive is unprecedented and reflects the controversial nature of this appraisal and the approach of the Appraisal Committee in this case, which are matters of high public interest.

   The Appraisal Committee responded to the document issued by the Guidance Executive through a letter from the acting chairman, Professor Home, dated 16 February 2010. However that letter, which provides information regarding the consideration of lapatinib by the Appraisal Committee in the context of the Guidance Executive's document, is unclear and has failed adequately to respond to important issues raised by the Guidance Executive. These deficiencies and the approach of the Appraisal Committee constitute a lack of fairness in the procedure followed in this appraisal.

   GSK's particular concerns in relation to the letter from Professor Home, which provides further explanation for the conclusions set out in the FAD, are set out below:

   (a) The final paragraph of Professor Home's letter suggests that the Appraisal Committee has misunderstood the treatment pathway for use of lapatinib.

   The final paragraph of the letter from Professor Home indicates that the Committee was concerned regarding the "*broader effects*" of a decision to recommend lapatinib "*in women progressing on a drug used out of licensed indication and against NICE guidelines*".

   While GSK has explained on several occasions the licensed indication for lapatinib, the statement by Professor Home indicates that this has still not been correctly understood by the Appraisal Committee. Lapatinib, in combination with capecitabine, is indicated for the treatment of advanced or metastatic breast cancer whose tumours overexpress ErbB2 (HER2). Patients should have progressive disease following prior therapy, which

must include anthracyclines, taxanes and trastuzumab (each used within the terms of their respective marketing authorisations) in the metastatic setting. Professor Home is therefore incorrect in his view that a decision to recommend lapatinib would involve any use of a medicine outside its licensed indications.

In these circumstances, Professor Home's reference to the "*broader effects"* of a decision to recommend lapatinib is unclear and, in the absence of further explanation, GSK is unable to respond to it.

For completeness, this appraisal does involve consideration of lapatinib compared with current standard NHS treatment, which includes trastuzumab, used outside the terms of its current marketing authorisation. While NICE does not generally issue guidance in respect of unlicensed medicines or unlicensed indications, its procedures envisage that recommendations may be based on comparisons with such products, where these unlicensed medicines or unlicensed indications can be shown to represent standard treatment within the NHS (paragraph 2.2.4 of NICE's Guide to the Methods of Technology Appraisal). The Appraisal Committee has accepted that this is the position with trastuzumab in the context of this appraisal. The implications of a recommendation for lapatinib would therefore be to replace use of a medicine used outside the terms of its marketing authorisation with one that is licensed. GSK believes such a situation could not be objectionable to the Committee.

While Professor Home states that Committee members did not take the "broader effects" of a decision to recommend lapatinib into account in reaching their overall conclusion, in circumstances where such matters are stated in his letter in response to the document issued by the Guidance Executive, there is a strong inference that the Appraisal Committee's misunderstanding of the treatment path for and regulatory status of lapatinib, has inappropriately influenced its decision.

<u>(b) The basis for the Committee's belief that it would be difficult to ensure the implementation of any recommendation that lapatinib should replace trastuzumab in a defined population of women progressing on the drug is not stated.</u>

Professor Home's letter states that the Committee noted that it would be difficult to ensure the implementation of any recommendation that lapatinib should replace trastuzumab in a defined population of women progressing on the drug. However the basis for this conclusion, which appears at odds with the multiple recommendations issued by NICE for use of health technologies in defined patient populations, in other appraisals is unexplained and GSK has been given no opportunity to respond to the Committee's concerns.

There is no statement in the FAD reflecting the concerns set out in Professor Home's letter and no indication as to how the Committee sought to consider potential implementation of a positive recommendation for lapatinib. While GSK is aware of the statements at paragraph 4.26 of the FAD suggesting that the Committee considered that a positive recommendation for lapatinib might displace capecitabine and vinorelbine monotherapy regimens as well as regimens containing trastuzumab, in circumstances where the Committee's concerns regarding implementation have not been articulated by the Committee, GSK has been given no opportunity to respond to them.

(c) The Committee appears only to have considered replacing trastuzumab with lapatinib containing regimens in patients with brain metastases, rather than offering lapatinib as a treatment option for women for whom trastuzumab is considered unsuitable

Professor Home refers to the situation of patients treated with trastuzumab, who develop disease progression limited to the CNS and notes that NICE's Clinical Guideline No 81 recommends continuation of trastuzumab in such patients, which he states is on the basis that there is the possibility of continuing efficacy outside the brain. He said it was felt to be inappropriate to suggest replacing trastuzumab "*with a drug of limited evidence both in the individual and in clinical trials*" which, he states, are due to report in 2012 .

However his letter indicates that, while the Committee concluded that it should not recommend lapatinib in place of trastuzumab in such patients, it did not consider whether lapatinib should be recommended as a treatment option, even in circumstances where trastuzumab might be considered by the treating doctor to be unsuitable for an individual patient.

Finally, Professor Home's letter refers to clinical trials of lapatinib, which he states, are due to report in 2012. This is misleading. While clinical trials investigating the efficacy of lapatinib in patients with both early and advanced breast cancer in the prevention of brain metastases are due to report from 2012, these will not provide evidence in relation to the outcome of interest in this appraisal, namely the efficacy of lapatinib in treating patients with metastatic disease in the brain. A trial to investigate use of lapatinib in patients with brain metastases is currently under consideration, at development stage; however even if this trial proceeds, results will not be available until 2013 at the earliest.

2. The effect of the direction from the Guidance Executive in January 2010, was to require the Appraisal Committee to consider the cost effectiveness of lapatinib compared with trastuzumab, in the context of the patient access scheme for lapatinib (the Tyverb Patient Access Programme (TPAP)).

The direction from the Guidance Executive in January 2010, informed the Appraisal Committee that "*there may be circumstances in which an intervention might represent an improvement in the effectiveness with which NHS funds are being used, even though those funds themselves, may not necessarily represent the most effect use of resources*". The Guidance Executive also stated, that the option of a new technology "*should be explored and only rejected where the wider interests of the NHS and the patients who rely on it for their care would clearly be damaged*".

The Committee's consideration of the cost effectiveness of lapatinib compared with trastuzumab containing regimens is set out at paragraphs 4.12, 4.15, 4.25 and 4.26 of the FAD. The Appraisal Committee appeared to have concerns about the relative treatment effects of lapatinib compared with trastuzumab regimens and about the assumptions included in the assessments of cost effectiveness, which might make the cost benefits associated with lapatinib, smaller than originally calculated by GSK. However any consideration of the balance of the evidence, supports a conclusion that lapatinib is at least as effective as trastuzumab regimens in this indication and the inclusion of the TPAP, proposed by GSK and approved by the Department of Health, addresses any remaining uncertainty by substantially increasing the likelihood that lapatinib regimens will be cost effective even if unfavourable assumptions form the basis for the calculations.

In these circumstances it is unfair that the Committee has failed, in reaching its conclusions with respect to the cost effectiveness of lapatinib containing regimens, to consider a comparison between use of lapatinib supplied under the TPAP, with trastuzumab regimens - even though it has compared supply of lapatinib under the TPAP with capecitabine and vinorelbine monotherapy and with the blended comparator proposed by GSK. GSK believes that the Appraisal Committee is required to consider use of lapatinib in the context in which the company has agreed to make the product available (namely under the TPAP). In this context it is relevant, for the Appeal Panel to be aware that GSK provided NICE with details of a calculation of the cost effectiveness of lapatinib supplied under the TPAP, compared with trastuzumab containing regimens in its submission of July 2008 (Appendix 3 of submission). This calculation suggests that lapatinib consistently dominates trastuzumab (i.e. it is both less costly and marginally more effective). GSK calculated that the likelihood of lapatinib plus capecitabine being cost effective in the £5,000-£20,000/QALY range is over 85% when compared with trastuzumab-containing regimens (trastuzumab plus capecitabine, or vinorelbine). These results reflect the fact that the cost of lapatinib plus capecitabine, in the context of the access scheme, is considerably lower than the cost of the trastuzumab combination regimens (lifetime acquisition costs of £11,114 versus: £13,150 for trastuzumab plus capecitabine, and £14,029 for trastuzumab plus vinorelbine). These results, should address any remaining concerns that might be held by the Committee in relation to uncertainty.

Finally, we believe that, in failing to take into account the results of a cost effectiveness comparison between lapatinib (supplied under the TPAP) and trastuzumab, the Appraisal Committee has not adequately complied with the direction from the Guidance Executive to consider the "circumstances in which an intervention might represent an improvement in the effectiveness in which NHS funds are being used, even though those NHS funds themselves may not necessarily represent the most cost effective use of resources".

3. <u>No explanation is provided in respect of NICE's concern that a positive recommendation for lapatinib would mean potentially displacing capecitabine and vinorelbine monotherapies and this appears to represent a matter of implementation of guidance rather than clinical effectiveness and cost effectiveness.</u>

   At paragraph 4.26 of the FAD, the Appraisal Committee appears to base its decision not to recommend lapatinib at least in part upon a concern "*that a positive recommendation for lapatinib would mean potentially displacing not only trastuzumab regimens but also capecitabine and vinorelbine monotherapies, against which lapatinib was shown not to be cost effective*". The basis for this concern is not explained in the FAD and appears to reflect a matter of implementation, rather than any assessment of clinical effectiveness or cost effectiveness of lapatinib.

   In expressing a view that a positive recommendation for lapatinib would displace capecitabine and vinorelbine, the Appraisal Committee does not explain the basis for this concern, whether it has relied upon any evidence to this effect or simply believes that, if doctors are given the option of prescribing lapatinib regimens for their patients they will prefer to do this, rather than to prescribe vinorelbine or capecitabine monotherapy. In these circumstances, it is difficult for GSK to understand NICE's concerns and to respond to them. In particular, it is unclear why the Appraisal Committee concluded that a recommendation for lapatinib, as a treatment option in patients who would otherwise be prescribed trastuzumab containing regimens (i.e. those who, in the opinion of the prescribing doctor, are likely to receive benefit from further ErbB2-targeted treatment) would not be acceptable.

Furthermore, in circumstances where, as accepted by the Committee, substantial numbers of patients are continuing to receive trastuzumab therapy beyond progression, and the replacement of this treatment with lapatinib, in the context of the TPAP, would represent a more efficient use of NHS resources, we believe the Appraisal Committee is required to give proper consideration to how guidance to the NHS could be worded, in order to achieve this outcome. There is no indication that such an exercise has been conducted by the Committee.

The issue of concern to the Committee appears to be one of implementation, rather than clinical effectiveness and cost effectiveness. While GSK accepts that guidance must be clear, whether compliance may be enforced is a matter for PCTs and NHS Trusts, rather than for NICE. It is not a matter for the Institute to refuse to issue guidance based on an efficient comparison, simply because it believes that doctors will not comply with its recommendations.

4. Even if the Appraisal Committee is correct that, should lapatinib be recommended as a treatment option, then some patients who would otherwise have been treated with capecitabine or vinorelbine monotherapy, will receive treatment with regimens including lapatinib, the Committee is required to consider whether the extent of change to lapatinib regimens, would outweigh cost savings to the NHS associated with replacement of trastuzumab containing regimens.

   While it is GSK's position that clear guidance could be given to the NHS that lapatinib was simply to be a treatment option only in cases where trastuzumab would otherwise have been prescribed, even if that is not possible, the Appraisal Committee has not considered the amount of treatment with capecitabine or vinorelbine monotherapy that would need to be displaced by lapatinib regimens, to outweigh the cost savings to the NHS achieved through replacement of trastuzumab regimens with lapatinib, supplied in accordance with the TPAP. The Committee's failure to undertake this exercise means that it has not followed the direction from the Guidance Executive that a product should only be rejected where the wider interests of the NHS and the patients who rely on it for their care would clearly be damaged.

   The concerns now raised by the Appraisal Committee had not previously been made known to GSK or the company would have sought to alleviate some of the Committee's concerns. Should this appeal succeed and this appraisal be returned to the Appraisal Committee, GSK will seek to clarify the Committee's concerns and to work with NICE to investigate this issue.

5. The conclusion by the Appraisal Committee that patients receiving trastuzumab in the context of the clinical trial programme may have been different from those treated with trastuzumab in clinical practice, is not based on reliable evidence

   At paragraph 4.25 of the FAD, the Appraisal Committee states that the patients who participated in the trials of trastuzumab after progression of disease were not necessarily the same as those patients treated with trastuzumab after disease progression in clinical practice. This conclusion is based on a statement from GSK suggesting that patients most likely to receive trastuzumab after disease progression in clinical practice are those in whom the product appears to be having some continuing benefit, whereas the Committee said that the patients who received treatment in the clinical trials were not selected on that basis.

This statement by the Appraisal Committee reflects the inevitable difficulty extrapolating from the clinical trial situation to clinical practice. In this case however any lack of generalisability from the clinical trial data will not affect the relative effectiveness of trastuzumab and lapatinib containing regimes. The GBG 26 clinical trial included patients who were receiving trastuzumab as first or second line biologic therapy - and in circumstances where patients receiving first line treatment would be expected to have a more favourable prognosis than patients receiving therapy second line, it is reasonable to assume that the population of patients receiving trastuzumab beyond progression in clinical practice may generally have a worse prognosis than those participating in the GBG 26 trial. The registrational trial for lapatinib enrolled patients who had a median of 3 previous trastuzumab containing regimens and the estimates which have been given for the efficacy of lapatinib are conservative.

Therefore in forming a view that the data from the clinical trial programme for trastuzumab are in some way less extrapolable to patients treated in clinical practice and that any differences may in some way favour lapatinib in any comparison, the Appraisal Committee has misunderstood the data.

Requested action following this appeal

In the above circumstances GSK respectfully requests the Appeal Panel to return this appraisal to the Appraisal Committee with directions to reconsider the use of lapatinib, specifically in the context of a cost effectiveness comparison between lapatinib (supplied in accordance with the patient access scheme) and trastuzumab regimens. Furthermore, that if the Appraisal Committee finds that lapatinib is cost saving compared with trastuzumab in the context of similar clinical effectiveness, it should issue appropriate guidance to the NHS recommending use of lapatinib in patients who would otherwise be prescribed trastuzumab.