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BY EMAIL

Dr Maggie Helliwell
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The National Institute for Health and Clinical Excellence
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15th July 2010

Dear Dr Helliwell

Appeal against the Final Appraisal Determination for lapatinib for the treatment of women with previously treated advanced or metastatic breast cancer

We refer to your letter dated 1 July 2010 setting out your preliminary views as to the admissibility of our appeal against the above FAD. We now provide our further comments in advance of your final decision on the admissibility of the points of appeal we have advanced. These comments are stated beneath the particular appeal points to which they relate

1. **The letter from Professor Home dated 16 February 2010 is unclear and does not adequately address the issues raised by the Guidance Executive**

As a general matter while you recognise that the correspondence between Professor Home and NICE's Guidance Executive may raise evidence of issues which are the subject of appeal, you express the view that GSK would not have standing to challenge any failure by the Appraisal Committee to act as directed by the Guidance Executive. We do not agree: any directions issued by the Guidance Executive provide clarification of NICE's written procedures and GSK has a legitimate expectation that the Appraisal Committee will follow such directions in carrying out its functions.

> 1(a) The final paragraph of Professor Home's letter suggests that the Appraisal Committee has misunderstood the treatment pathway for use of lapatinib.
>
> Our appeal letter refers to the sentence of Professor Home's letter where he states that the Appraisal 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*".

As you say in your letter of 1 July, we agree that the reference to "*a drug used out of licensed indication*" is to trastuzumab. However, Professor Home's belief that trastuzumab is not licensed for therapy prior to lapatinib is incorrect. Lapatinib is intended to be used for women who have progressed on trastuzumab, prescribed within the terms of its marketing authorisation and, to that extent, the Appraisal Committee has misunderstood the treatment pathway for lapatinib.

1(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.

Your decision is noted.

1(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

The letter from Professor Home expands upon the reasoning of the Committee provided at paragraph 4.16 of the FAD and provides information regarding the Appraisal Committee's consideration of use of lapatinib in women who have progressive disease on trastuzumab, limited to the central nervous system.

NICE's Clinical Guideline on Breast Cancer recommends continued use of trastuzumab in these patients on the basis that they are viewed as continuing to derive benefit from ErbB2 suppression. However for some patients, trastuzumab may be a less suitable treatment - as a result, for example, of unwanted effects or difficulties with venous access. It is GSK's position that, in these patients, lapatinib therapy should be considered as an alternative treatment option - not, as Professor Home states, only as a replacement for trastuzumab.

Both Professor Home's letter and paragraph 4.16 of the FAD make clear that the Appraisal Committee considered only whether lapatinib should be considered as a replacement for trastuzumab in patients with progressive disease limited to the CNS. They did not consider whether it should be recommended as a treatment option in patients who would otherwise have been recommended to continue with trastuzumab, but for whom an alternative such as lapatinib is considered more suitable. This omission is unfair.

2. **The effect of the direction from the Guidance Executive was that the committee should have considered the cost effectiveness of lapatinib vs trastuzumab in the context of the lapatinib patient access scheme**

Point 2 of GSK's appeal relates to the fact that, in considering the cost effectiveness of lapatinib, compared with trastuzumab regimens, the Appraisal Committee has failed to take into account a comparison which incorporates the patient access scheme for lapatinib. There is no mention of this comparison in section 4 of the FAD and paragraph 4.26, which specifically responds to the document of January 2010 from the Guidance Executive, disregards the patient access scheme, referring only to "*small differences in costs…*" between lapatinib and trastuzumab and relying on

statements by the DSU relating to analyses in Section 3.1.8 of their 7th September 2008 report, which did not take account of the scheme. In reaching its conclusions regarding lapatinib, the Committee has not therefore considered a comparison reflecting the basis upon which the medicine would be supplied to the NHS.

Furthermore, while the Committee expresses concerns regarding uncertainty in relation to the ICER for lapatinib compared with trastuzumab containing regimens, clearly the implications of any uncertainty are reduced where the calculated ICER value is lower - as it is where the lapatinib patient access scheme is taken into consideration. (In these cases the effect of uncertainty with respect to particular inputs in the economic assessment is highly unlikely to push the ICER into a range that is not considered cost effective by NICE.) Therefore by failing to consider a comparison based on lapatinib supplied within the patient access scheme, the Appraisal Committee has not adequately considered the implications of uncertainty surrounding the ICER which are limited in this context.

In circumstances where the direction from the Guidance Executive dated January 2010, required the Appraisal Committee fully to explore the option of use of a new technology, the fact that the Appraisal Committee has not considered a comparison of lapatinib supplied under the patent access scheme, with trastuzumab regimens, is unfair and represents a deficiency in the procedure followed in this appraisal.

For completeness, we have referred, in our appeal letter, to the analysis provided in our submission of July 2008 (Appendix 3) which compared the cost effectiveness of lapatinib, supplied under the patient access scheme, with trastuzumab containing regimens. There was no opportunity, following the letter from the Guidance Executive, for GSK to make a further submission to NICE in relation to the Guidance Executive's directions.

3. No explanation is given for the 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.

In your letter of 1 July 2010, you say that implementation is a matter to be taken into account when formulating guidance and suggest that the Appraisal Committee is entitled to refuse to recommend a technology where it has identified a difficulty in substituting a new medicine for a current standard treatment, because the criteria for use of the current standard treatment are matters of opinion.

The letter of January 2010 from the Guidance Executive specifically required the Appraisal Committee to explore the option of a new technology and only reject usage where the wider interests of the NHS and the patients who rely on it for their care would clearly be damaged. The Appraisal Committee has accepted that use of lapatinib regimens in place of current standard treatment with trastuzumab is likely to be a cost effective use of resources. Therefore the obligation of the Appraisal Committee to explore the use of lapatinib containing regimens, in place of those containing trastuzumab is not satisfied by a simple assertion that implementation of guidance would be difficult. There is no indication in the FAD as to the consideration, if any, given by the Appraisal Committee to this issue and whether any possibilities for implementation were discussed. If any discussions took place regarding possible options for implementation, GSK would wish to learn the basis upon which they were rejected and, if no options were in fact considered, that omission would represent a procedural deficiency in this appraisal.

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 and 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.**

Your decision that this point of appeal should be considered at an appeal hearing is noted.

For completeness, and in response to your query that the Appraisal Committee may already have assessed such cost savings, in the context of their consideration of the blended comparator proposed by GSK, we do not believe this is the case. The blended comparator was proposed by GSK to represent the real life costs associated with the introduction of lapatinib containing regimens in the context of the economic modelling. This approach was rejected by the Appraisal Committee who preferred an incremental cost effectiveness analysis. The issue raised at point 4 of our appeal is however the extent to which the additional costs associated with the use of lapatinib, in patients who would otherwise be prescribed capecitabine or vinorelbine monotherapy, would be outweighed by the cost savings resulting from the replacement of trastuzumab with lapatinib regimens under the patient access scheme.

In circumstances where GSK's appeal arises from an omission by the Appraisal Committee, we continue to believe that this point should be advanced under Ground 1.

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 relies upon a statement by GSK which it interprets as suggesting that any uncertainty in relation to the results of a comparison of the effectiveness of lapatinib with trastuzumab, may favour lapatinib. In point 5 of our appeal, we explain how the statement from GSK has been misinterpreted and why the view expressed by the Appraisal Committee is not one that is supported by the balance of the available data. While clinical trial populations may frequently differ from those seen in clinical practice, the conclusions of the Committee extend beyond such matters, in a way that we believe is not consistent with the available data.

We do not believe it is fair for substantive determination of this issue to take place at the initial scrutiny stage, rather than proceeding to proper consideration at an appeal hearing. We therefore reiterate our request for the point to proceed.

We are grateful to you for considering these further submissions clarifying our appeal letter and we look forward to hearing from you with respect to your final decision on the admissibility of our appeal.

Yours sincerely

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