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GlaxoSmithKline UK Ltd

8 April 2009

Dear [redacted]

Final Appraisal Determination: Lapatinib for the treatment of women with previously treated advanced or metastatic breast cancer

Thank you for lodging GSK's appeal against the above Final Appraisal Determination.

Introduction

The Institute's appeal procedures provide for an initial scrutiny of points that an appellant wishes to raise, to confirm that they are at least arguably within the permitted grounds of appeal ("valid"). The permitted grounds of appeal are:

- Ground 1: The Institute has failed to act fairly and in accordance with its published procedures as set out in the Institute's Guide to the Technology Appraisal Process.
- Ground 2: The Institute has prepared guidance which is perverse in the light of the evidence submitted.
- Ground 3: The Institute has exceeded its powers.

This letter sets out my initial view of the points of appeal you have raised: principally whether they fall within any of the grounds of appeal, or whether further clarification is required of any point. Only if I am satisfied that your points contain the necessary information and arguably fall within any one of the

grounds will your appeal be referred to the Appeal Panel.

You have the opportunity to comment on this letter in order to elaborate on or clarify any of the points raised before I make my final decision as to whether each appeal point should be referred on to the Appeal Panel.

I can confirm that there will be an oral hearing of GSK's appeal.

I note that in your letter you request that the Appeal Panel consider all of GSK's previous submissions to the appraisal in addition to your grounds of appeal. The Appeal is not a re-appraisal of lapatinib. The Appeal Panel will read particular documents where those documents are directly relevant to one of GSK's grounds of appeal and where they are specifically drawn to its attention. It will not conduct a general review of all documentation provided by GSK to the Appraisal Committee. If there are particular sections of documents that GSK wishes the Appeal Panel to read in support of its grounds of appeal that have not already been highlighted in your detailed grounds of appeal (points 1.1 to 2.4) you should let me know.

Initial View

Ground one: 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.

This is a valid ground 1 appeal point.

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.

This is a valid ground 1 appeal point and the Appeal Panel will hear all the points you raise under this heading. However, I should say that at present your argument outlined at point (4) on page 7 of your appeal letter (that the Appraisal Committee's understanding that it was looking at GSK's supplementary submissions on a discretionary basis affected the weight attached to those submissions) appears weak. I see no reason why, having taken a positive decision to consider the submission, the Appraisal Committee would place less weight on that submission because it considered it had an option not to do so. If you regard that point as a stand alone appeal point then I would not be minded to allow it to proceed.

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.

The argument you raise about the way the Appraisal Committee interpreted what the Supplementary Advice says about extending life by three months is a valid ground 1 appeal point.

The remaining points raised under this heading appear to me to be ground 2 points, relating as they do the evaluation of the evidence in this particular appraisal.

My preliminary view is therefore that these remaining points may proceed to appeal if they are re-categorised as ground 2 points.

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

The argument you raise under point (1) of ground 1.4 about the rejection of the sub-group analysis relates to the weighing up of the evidence in this particular appraisal. My preliminary view is therefore that this is not a valid ground 1 appeal point but is a valid ground 2 appeal point.

The remaining arguments you make under this heading relate to the level of detail provided in the FAD. Under point (2) of ground 1.4 you argue that the Appraisal Committee's objection to the information provided by GSK relating to the sub-group is unclear from the FAD. Under point (3) of ground 1.4 you argue that the reasoning for the Appraisal Committee's conclusion that there was no exploration of the possibility that the differences observed in the subgroup were arrived at by chance is unclear from the FAD.

In the recent case of *R ota Servier Laboratories v National Institute for Health & Clinical Excellence*, in the context of the claim by Servier that the FAD provided insufficient reasons why its sub-group analysis had been rejected by the Appraisal Committee, [redacted] observed at paragraph 176 et seq of his judgment:

"The only question for this court is whether the decision of NICE is intelligibly and adequately reasoned and whether there is an error of reasoning "which robs the decision of logic." Matters of weight are entirely the province of NICE…

In assessing the intelligibility and adequacy of the reasons in the present case I bear in mind, first, that the reasons are addressed to a technically informed reader; and second, as [redacted] *submitted, that the principal purpose and function of a FAD is to give guidance. A FAD needs sufficiently to explain to a technical reader the reasons for the guidance, but it does not need to make a detailed response to every point submitted by consultees. If it did do so it would risk becoming so overburdened by reasoning as not to give clear guidance."*

The FAD therefore does not need to explain the reasoning behind the Appraisal Committee's conclusions on every point raised by consultees. My preliminary view is that there does not appear to be any gap in reasoning that would require the FAD to go into further detail on either of the points you identify.

At present, my view is therefore that points (2) and (3) under ground 1.4 are not valid grounds of appeal.

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

The argument you raise under this heading in fact relates to the Appraisal Committee's conclusion at 4.21 of the FAD that the submission made by GSK on 21 January 2009 could not materially affect the conclusions it had already reached, but could generate a useful hypothesis for future research. Your point is that the research that the Appraisal Committee suggests at 4.21 would be unethical.

The comment made at 4.21 is a very general one. It says simply that *"The Committee considered 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."* Even assuming for present purposes that it would be unethical to conduct a trial in which patients were not offered treatment with lapatinib, the Committee does not appear to say or imply that the research should be in such a form.

My preliminary view is therefore that this is not a valid ground 1 appeal point.

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

I have set out in relation to ground 1.4 above the comments made by [redacted] in the *Servier* case and the fact that the FAD is designed to be used as guidance, not a comprehensive record of all of the deliberations of the Appraisal Committee. Given this, the fact that the FAD does not make a direct reference to the Secretary of State's direction that NICE take account of *"the degree of clinical need of the patients with the disease of condition under consideration"* is not sufficient to establish or suggest that the needs of patients were not taken into account.

In relation to your argument that no adequate weight was given to this consideration I note the judgment of [redacted] in the case of *Douglas Fraser and Kevin Short vs the National Institute for Health and Clinical Excellence*. In his judgment [redacted] stated (at paragraph 64), when considering a challenge to the weight NICE had given to evidence:

"On the clearest and highest authority it was for the GDG [ie, NICE] *to decide what weight to attach to evidence, and it cannot be said that the decision to make the recommendations on the basis of what was available to the GDG was irrational. Decisions of fact are for those entrusted to make those decisions."*

He added at paragraph 47(iii)

There is an important distinction to be drawn between the question of whether something is a material consideration and the weight which should be given. The latter is a matter for the decision maker, subject to questions of Wednesbury *irrationality; and, providing the decision-maker has taken* [it] *into account,* ***the fact that it has given it no weight is not a ground for review****,* Emphasis supplied

I regard the same principle as applying to the appeal panel. Therefore, it seems to me that the argument you make about the weight placed on the evidence is not a valid ground of appeal.

My preliminary view is that none of the arguments you make under this heading is a valid ground 1 point.

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

For the reasons set out above, the fact that the FAD does not refer to a particular direction of the Secretary of State is not sufficient grounds for arguing that that direction has not been complied with. It is for the Appraisal Committee to decide how much weight to give the evidence and unless there are grounds for arguing that the Committee acted perversely (and my preliminary view is that such grounds have not been made out) there is no valid ground of appeal.

My preliminary view is that none of the arguments you make under this heading is a valid ground 1 point.

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

This recommendation appears in section 6 of the FAD entitled *"Recommendations for further research".* It is not a recommendation for treatment (which are set out in paragraph 1 of the FAD).

My preliminary view is that this is not a valid ground 1 point.

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 produce which is

unlicensed for this indication and less cost-effective than lapatinib.

This is a valid ground 2 point.

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.

Under this heading you make two points.

The first is that the Appraisal Committee did not recommend lapatinib for patients with brain metastases because there were insufficient data, but the GDG did make recommendations for trastuzumab for such patients, even though the data to support the use of trastuzumab were more limited than that for lapatinib. The implication is that this inconsistency means that the FAD is perverse.

Lapatinib and trastuzumab are different treatments with a different evidence base to inform considerations about their use. Also, there appears to be a good reason why disease progression in the CNS would not indicate that treatment with trastuzumab should be discontinued, and hat reason does not, on the facts set out in your letter, apply to lapatinib.. In this situation it is not inconsistent for different conclusions to be drawn from the different evidence bases. As outlined above, it is for the decision-maker – the GDG and the Appraisal Committee respectively – to decide on the weight to be given to the evidence.

For these reasons, my preliminary view is that this is not a valid ground 2 point.

The second is that while the Appraisal Committee was aware of the NICE guideline on Advanced Breast Cancer, which recommends trastuzumb should be discontinued where there is disease progression outside the central nervous system (CNS), this does not appear to have been taken into account by the Appraisal Committee when determining that trastuzumab was not an appropriate comparator for lapatinib in any circumstances.

Your point here appears to be that because the Appraisal Committee's reasoning is not in complete agreement with the recommendations set out in the Guideline, the FAD is perverse. Inconsistency between the conclusions reached by the GDG and those reached by the Appraisal Committee is not in itself sufficient to establish perversity, as reasonable decision makers may differ.

Therefore, my preliminary view is that this is not a valid ground 2 point.

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

This is a valid ground 2 point.

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.

This is a valid ground 2 point.

Conclusion

As I am minded to rule that at least some of your appeal points are valid, I will pass your appeal to the Appeal Panel for consideration.

I note your comments on the appropriate steps to be take should the Appeal Panel uphold any of your grounds. These will be considered by the Appeal Panel if your appeal is successful.

If you wish to make any further comment on the points that I have indicated that I do not, at this preliminary stage, view as valid or that I have suggested be re-categorised, please provide to me this within ten working days from the date of this letter (Friday 24 April 2009). I will then reach a final decision on the validity of those points.

Yours sincerely

[redacted]

Appeals Committee Chair
National Institute for Health and Clinical Excellence