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BY E-MAIL

[redacted]
Appeals Committee Chair
National Institute for Health and Clinical Excellence
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24 April 2009

Dear [redacted]

Re: PRELIMINARY SCRUTINY LETTER DATED 8 APRIL 09, RELATING TO 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

Thank you for your consideration of GlaxoSmithKline's Notice of Appeal dated 27 March 09, and for the opportunity for us to comment on your Initial Scrutiny Latter of 8 April 2009.

In acknowledgement of your advice to draw the Appeal Panel's attention to particular documents where they are directly relevant to one of the grounds, we have included references to specific documents in our points below, which are additional to those specifically referenced in our original appeal letter.

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RESPONSE TO PRELIMINARY SCRUTINY LETTER

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.

Initial view:

Valid ground 1 appeal point.

GSK response:

We welcome and accept this conclusion.

We would like to draw the Appeal Panel's attention to the following document/s as further background or support for this point:

GSK's response to the first ACD dated 28 July 2008 (Section 1.1. Market research data on the extent of trastuzumab use).

Addendum to GSK's Response to the ACD: Lapatinib (Tyverb®▼) Patient Access Programme dated 31 July 2008 (Section 3. Blended comparator approach).

GSK's response to the second ACD dated 4 November 2008 (Sections 2.1-2.2, pages 3-5; Section 3, page 7. Blended comparator approach).

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.

Initial view:

Valid ground 1 appeal point.

GSK response:

We acknowledge and accept the initial view that this is a valid ground 1 appeal point. We note your comment on sub-point (4) of our appeal (which asserts 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) and confirm that we will address the issue you raised at the appeal hearing. For the avoidance of doubt, we intended for all four sub-points to be considered as part of a single appeal point, and not as stand alone points.

We would like to draw the Appeal Panel's attention to the following document/s as background or support for this point:

GSK's submission in relation to the advice issued by NICE on appraising end of life treatments dated 21 January 2009 (Section 2)

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.

Initial view:

Valid ground 1 appeal point (limited to Appraisal Committee's interpretation of the 3-month extension to life criterion in the Supplementary Advice on the appraisal of end of life medicines).

Potential Ground 2 appeal points (examples 2-4 provided by GSK).

GSK response:

We welcome your acceptance of the validity of part of our argument under ground 1. However, we would like to point out that the focus of the argument under paragraph (1.3) of our letter is the matter of unfairness in the inflexible approach taken by the Appraisal Committee in applying the criteria set out in the supplementary guidance on the appraisal of end of life medicines. All of sub-points (1-4) made in our appeal relate to and illustrate this single issue of procedural unfairness and should be considered collectively

Whilst we believe that the way in which the evidence has been considered by the Committee raises issues of perversity, the basis for our challenge is the fact that the way in which the Supplementary Advice has been applied in the circumstances of this case has been rigid or otherwise unfair (as demonstrated by sub-points (1-4)). This lack of fairness relates to a general principle, rather than, as suggested in the initial scrutiny letter, the way the evidence has been assessed by the Appraisal Committee; therefore we believe that appeal point 1.3 fails to be determined in its entirety under ground 1.

We would like to draw the Appeal Panel's attention to the following document/s as background or support for this point:

> GSK's submission in relation to the advice issued by NICE on appraising end of life treatments dated 21 January 2009 (Section 2)

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

Initial view:

Potential ground 2 appeal point (limited to sub-point (1) of appeal point 1.4, relating to the Committee's evaluation of the additional evidence provided by GSK).

Invalid ground 1 points (sub-points (2) and (3) provided by GSK, relating to a lack of clarity on why the Appraisal Committee disregarded the additional evidence provided).

GSK response:

Point 1.4 of our appeal letter addresses the fact that the reasons given by the Appraisal Committee for refusing to accept the sub-group of patients who had received fewer than three prior treatments are illogical and therefore the basis upon which use of lapatinib in this sub-group of patients was rejected by the Appraisal Committee is unclear. While we address three reasons given by the Appraisal

Committee for refusing to accept the sub-group of patients, there is only one point of appeal and we do not believe this may properly be divided as suggested in your preliminary determination. The lack of transparency surrounding the Appraisal Committee's rejection of the sub-group is a basic matter of procedural fairness and we believe the point should appropriately be considered under ground 1.

While therefore, 1.4 represents one point of appeal, relating to the procedural fairness of the appraisal of lapatinib, we respond to the particular matters raised in your initial scrutiny letter as follows:

- With respect to your preliminary view that sub-point (1) of appeal point 1.4 should be considered under ground 2, we agree that the issue raised in our appeal letter may suggest perversity by the Appraisal Committee; however this cannot be confirmed before the reasoning of the Committee has been clarified.
- You suggest that sub-points (2) and (3) relate to the level of detail provided in the FAD and rely on the decision of the Court in R ota Servier Laboratories v NICE to support a view that there is no requirement for the Appraisal Committee to provide further detail in the FAD in relation to these issues. However the thrust of GSK's appeal at 1.4 is that, in this respect, the FAD is not "intelligibly and adequately reasoned" and that there appear to be errors of reasoning which rob the decision of logic. We therefore believe that this point of appeal (including sub-points (2) and (3)) falls clearly within the scope of those which, according to the decision of the Court in Servier, form a proper basis for challenge.

Significantly, while the reasons given by the Appraisal Committee do not appear to be logical, it seems that the Committee may have also based their decision to reject the sub-group on an incorrect assumption that further data in relation to the use of lapatinib in these patients could be generated from future research. Section 6.2.11 of the June 2008 Guide to the Methods of Technology Appraisal states that when evidence of effectiveness is either absent or weak, certain factors should be considered in recommending use only in the context of research, including recommendations that the research is realistic, planned or ongoing, and that there is a real prospect that it will inform future NICE guidance.

It is important to note, as pointed out in point 1.5 of GSK's appeal letter of 27 March 2009, that for ethical and practical reasons it is highly unlikely that meaningful research will be feasible to test the hypothesis in question, i.e. 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.

Therefore we argue that since the subgroup data provided by GSK is likely to be the only such evidence on which to make a recommendation in this important subgroup of patients, the reasons for the Committee's rejection of the evidence should be made absolutely clear to all stakeholders in this appraisal. The reasons are not clear in the FAD, and there has been no opportunity for further exploration of the concerns raised by the Committee through a comprehensive submission and consultation process. Therefore we believe that the process is unfair, and that all three sub-points should be considered under ground 1.

We would like to draw the Appeal Panel's attention to the following document/s as background or support for this point:

> GSK's submission in relation to the advice issued by NICE on appraising end of life treatments dated 21 January 2009 (Section 2)

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.

Initial view:

Invalid ground 1 appeal point.

GSK response:

We note the point made in your initial view, that the reference to further research involving lapatinib at 4.21 of the FAD is a general comment. However, we are concerned that that the point that we were making may not have been fully understood.

Our point relates specifically to the Committee's rejection of the additional data submitted on 21 January 2009 without full consideration of use of lapatinib in these patients; we believe this rejection was unfair.

In particular, the Appraisal Committee has seemingly failed to recognise that the data submitted to NICE are likely to be the only evidence available to support the use of lapatinib in this patient group. The reference by the Committee at paragraph 4.21 to the possibility of future research simply supports that view.

We also question the assertion in the initial view that the Committee does not appear to say or imply that the research should be in the form of a clinical study with a comparator (e.g., capecitabine) that is less effective than other interventions which are currently licensed (e.g., trastuzumab). It is unclear to us as to what other form of research could possibly be used to inform this element of the decision problem. The only ethical and feasible study design would be one in which the comparator included an ErbB2-targeted therapy, e.g. trastuzumab plus capecitabine, which would not answer the question of whether the lapatinib (or indeed trastuzumab) combination is effective and cost effective versus a single agent regimen. Since the Committee has rejected trastuzumab regimens as comparators on the basis that they are unlikely to be cost effective against single agent chemotherapy, this alternative clinical trial design is clearly inappropriate. Therefore we believe that the Committee's conclusions do imply this form of research in the absence of other possibilities, and as stated in our appeal it would be unethical to design a clinical trial with such a comparator which is established to be less effective. This adds further weight to our point that the Committee has dismissed the data without fully appreciating the implications.

In this context we believe that the dismissal of the additional evidence is unfair, and we believe this point should be reconsidered for appeal under ground 1.

We would like to draw the Appeal Panel's attention to the following document/s as background or support for this point:

> GSK's submission in relation to the advice issued by NICE on appraising end of life treatments dated 21 January 2009 (Section 2)

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

Initial view:

Invalid ground 1 appeal point.

GSK response:

The initial view concludes that this point of appeal is not admissible on the basis that the Appraisal Committee is not required to record all the matters that were taken into account in the FAD and that it is a matter for the Committee to decide what weight to attach to evidence. Reliance is placed upon the decisions of the Court in Servier and in R ota Fraser and Short v NICE .

However, the clinical need of patients is central to this appraisal and is a factor which the Appraisal Committee is expressly required to take into account as a result of Directions issued by the Secretary of State and reflected in NICE's Guide to the Technology Appraisal Process. The clinical need of patients is therefore in a wholly distinct category from the evidence considered in Servier and which was the subject of the application for judicial review by Fraser and Short on the grounds of irrationality.

The Appraisal Committee has a legal obligation to take into account the clinical need of patients with the disease under consideration. In many cases, the Appraisal Committee refers to the clinical circumstances of patients with the relevant medical condition in the FAD and expressly considers their need for new treatments to become available. The fact that this FAD, in contrast to others, does not give any recognition to the very high clinical need of patients with advanced or metastatic breast cancer raises an inference that the Secretary of State's directions were not taken into account adequately or at all. Such an omission would constitute a serious procedural flaw in this appraisal and should be permitted to be considered at an appeal hearing.

We would like to draw the Appeal Panel's attention to the following document/s as background or support for this point:

> The original submission by GSK dated 17 April 2007 (Section 4.1, page 17: Prognosis; Section 4.5, page 21, Issues relating to current clinical practice; brain metastases)
>
> GSK's response to the second ACD dated 4 November 2008 (Section 4c, page 8: Consideration of unmet medical need; Section 4e, page 9: brain metastases).

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

Initial view:

Invalid ground 1 appeal point.

GSK response:

NICE's Guide to the Technology Appraisal Process provides explicitly that the Appraisal Committee will consider the implications of its recommendations in the context of encouraging innovation in the NHS. Furthermore, the Guide to the Methods of Technology Appraisal provides at paragraph 6.2.23, that:

"Above a most plausible ICER of £20,000 per QALY gained, judgments about the acceptability of the technology as an acceptable use of NHS resources will specifically take account of the following factors:

> *The innovative nature of the technology specifically if the innovation adds demonstrable and distinctive benefits of a substantial nature which may not have been adequately captured in the QALY measure."*

Lapatinib clearly provides such a technology. It is indicated for use in patients with advanced or metastatic breast cancer for whom there is no accepted licensed therapy and few treatment options. There is evidence to suggest that lapatinib demonstrates activity in the prevention and treatment of brain metastases (Cameron 2008; Lin 2008; Van den Abbeele 2006). Moreover, as an oral treatment that does not require hospital or healthcare professional visits for administration, it represents an important development in the management of patients with malignant disease. The very substantial advantages associated with such a therapy have not been adequately taken into account when assessing the cost effectiveness of use of lapatinib in this appraisal as they were not fully captured in current utility estimates. In these circumstances we believe the fact that there is no indication that the Appraisal Committee considered the effects of their recommendations on innovation in the NHS, constitutes a valid appeal point which should proceed to a hearing.

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

Initial view:

Invalid ground 1 appeal point.

GSK response:

We acknowledge that recommendations under section 6 of the FAD are not normally subject to appeal because this section does not relate to recommendations on treatment. However, we would like to point out that matters raised in sections of the FAD other than 1-4 may have a real impact on the interests of consultees and potentially be subject to judicial review and should, accordingly, be capable of being raised at appeal.

We understand that this is not a point for appeal that NICE will allow to proceed according to the current process, although we do not agree that this is appropriate. In the context of this appraisal we would ask you please to draw our submission to the attention of the Guidance Executive for consideration before the guidance on use of lapatinib is finalised. We will also raise the issue of whether the content of the FAD - beyond paragraph 1, should be capable of challenge, through future consultations on the NICE appeal process.

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

Initial view:

Valid ground 2 appeal point.

GSK response:

We welcome and accept this conclusion.

GSK's submission in relation to the advice issued by NICE on appraising end of life treatments dated 21 January 2009 (Section 2)

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.

Initial view:

Invalid ground 2 appeal points.

GSK response:

We strongly believe that this item should be reconsidered for validity under ground 2. Our reasoning is provided below.

The two items of inconsistency raised in GSK's appeal point 2.2 are intended to illustrate why the recommendations of the Appraisal Committee are perverse, rather than being different points of appeal *per se*. We would like to clarify that whilst we accept that lapatinib and trastuzumab are different treatments with a different evidence base to inform considerations about their use the different conclusions drawn by the GDG and the Appraisal Committee from the evidence have led to a perverse situation.

- While the fact that different decisions have been issued by different bodies is not sufficient to establish that the decision of either is perverse, the fact that NICE has produced two inconsistent decisions based on the same evidence and issued almost simultaneously, without any explanation for such differences, raises an inference of arbitrariness and therefore perversity. Furthermore the relationship between determinations of an Appraisal Committee and a GDG raises an important point of principle, which should not be dismissed without proper consideration at a hearing.
- In the context of the appraisal of lapatinib, the inconsistency raises a particularly perverse outcome. The result of the Clinical Guideline is that trastuzumab is recommended for use in patients who have disease progression on such therapy, limited to the CNS. However, despite this recommendation by the GDG (which now constitutes recommended best practice in the NHS) the Appraisal Committee has declined to consider

trastuzumab as an appropriate comparator for lapatinib in the assessment of cost-effectiveness during the appraisal in this population.

Therefore we request that the point of appeal is considered in its entirety, and that the general point that these inconsistencies create a situation that is arbitrary and therefore perverse is considered as the primary point of appeal.

We are also concerned that the initial view seems to be based on a view on the merits of the appeal point *('….there appears to be a good reason why disease progression in the CNS would not indicate that treatment with trastuzumab should be discontinued, and that reason does not, on the facts set out in your letter, apply to lapatinib*')., which appears to go beyond the purpose of the initial scrutiny, which is to assess admissibility of appeal points. On any view the matters we have raised represent an arguable point of appeal, formulated within one of NICE's permitted grounds, which should be allowed to proceed to a proper hearing.

The points below are intended to provide further clarification on the reasoning behind our claim that the situation created with this guidance is perverse, and therefore warrants hearing under ground 2.

- The 2008 Guide to the Methods of Technology Appraisal states that in the selection of comparators, consideration should be given specifically to routine and best practice in the NHS, including existing NICE guidance. Trastuzumab is recommended in patients with progression in the brain in the NICE clinical guideline, and is considered as best practice in these circumstances, in the absence of any alternative treatment. This is also reflected in the extent of trastuzumab use after progression currently within the NHS (>50% of patients).
- There is good evidence that control of non-CNS disease by lapatinib is comparable to that afforded by trastuzumab (Gomez 2008, Vogel 2002), and unlike trastuzumab, lapatinib may actually demonstrate activity in the prevention and treatment of brain metastases (Cameron 2008; Lin 2008; Van den Abbeele 2006). There is nothing in the evidence base for lapatinib to suggest that it is less suitable than trastuzumab in patients with CNS progression.
- Trastuzumab is a treatment consideration in these circumstances (disease progression restricted to the CNS) only by virtue of the fact that patients are already receiving it, and there is an assumption that its continuation will still enable control of non-CNS disease.
- Whilst the clinical decision to continue trastuzumab if it is having an effect on non-CNS disease, rather than to initiate a new treatment, may be a valid one, there will be circumstances in which its continuation is not considered appropriate or desirable, e.g. difficult venous access, patient choice, etc.
- Therefore a failure to consider trastuzumab as a comparator in patients with brain metastases means that patients will be denied the opportunity for an alternative, licensed treatment which may be more suitable (and less costly to the NHS) in their particular circumstances, which is perverse.

Discounting trastuzumab as a comparator, and consequently discounting an evaluation of lapatinib compared with trastuzumab in this setting, is contrary to the methods guide, and leads to perverse guidance.

We would like to draw the Appeal Panel's attention to the following document/s as background or support for this point:

GSK's response to the second ACD dated 4 November 2008 (Section 4c, page 8: Consideration of unmet medical need; Section 4e, page 9: brain metastases).

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

Initial view:

Valid ground 2 appeal point.

GSK response:

We welcome and accept this conclusion

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.

Initial view:

Valid ground 2 appeal point.

GSK response:

We welcome and accept this conclusion.

Once again, thank you for the opportunity to respond to your initial scrutiny of the appeal. Please let me know if you have any questions concerning this response.

Yours Sincerely

[redacted]

GlaxoSmithKline UK

References

Cameron D, Casey M, Press M, et al. A phase III randomized comparison of lapatinib plus capecitabine versus capecitabine alone in women with advanced breast cancer that has progressed on trastuzumab: updated efficacy and biomarker analyses. Breast Cancer Res Treat 2008; 112:533–543

CG81 Advanced breast cancer: NICE guideline
http://www.nice.org.uk/nicemedia/pdf/CG81NICEGuideline.pdf
Accessed March 2009

Gomez HL, Doval DC, Chavez MA et al. Efficacy and safety of lapatinib as first-line therapy for ErbB2-amplified locally advanced or metastatic breast cancer. JCO Jun 20 2008: 2999-3005

Lin NU, Carey LA, Liu MC et al. Phase II trial of lapatinib for brain metastases in patients with human epidermal growth factor receptor 2-positive breast cancer. J Clin Oncol 2008; 26(12): 1993-1999

Van den Abbeele AD, Lin NU, Yap JT, Urban T, de Vries DJ, Barnes AS et al. Evaluation of response to lapatinib in patients with HER2-positive metastatic breast cancer using FDG-PET. San Antonio Breast Cancer Symposium 2006, Abs. 1089. [CTEP6969]

Vogel CL, Cobleigh MA, Tripathy D et al. Efficacy and safety of trastuzumab as a single agent in first-line treatment of HER2 overexpressing metastatic breast cancer. *J Clin Oncol* 2002; 26 (34): 5544