[redacted]
Health Economics and Strategic Pricing Director

15th July 2011

NOTICE OF APPEAL

[redacted]
Chair, Appeal Committee
National Institute for Health and Clinical Excellence
MidCity Place
71 High Holborn
London WC1V 6NA

RE: FINAL APPRAISAL DETERMINATION FOR LAPATINIB AND TRASTUZUMAB IN COMBINATON WITH AN AROMATASE INHIBITOR FOR THE FIRST-LINE TREATMENT OF METASTATIC HORMONE RECEPTOR POSITIVE BREAST CANCER WHICH OVER-EXPRESSES HER2

Dear [redacted],

Roche Products Ltd would like to appeal against the Final Appraisal Determination for the above mentioned technology appraisal on the following grounds:

Ground one: The Institute has failed to act fairly

Ground two: The Institute has formulated guidance which cannot reasonably be justified in the light of the evidence submitted

If you require any further information or clarification then please do not hesitate to contact us.

Yours Sincerely,

[redacted]
Health Economics and Strategic Pricing Director

LAPATINIB AND TRASTUZUMAB IN COMBINATON WITH AN AROMATASE INHIBITOR FOR THE FIRST-LINE TREATMENT OF METASTATIC HORMONE RECEPTOR POSITIVE BREAST CANCER WHICH OVER-EXPRESSES HER2

NOTICE OF APPEAL

BACKGROUND

Roche Products Limited ("Roche") is responsible for the sale and marketing of trastuzumab (Herceptin) in the UK. The indications for use of trastuzumab include utilisation in combination with an aromatase inhibitor for the treatment of postmenopausal patients with hormone-receptor positive metastatic breast cancer, not previously treated with trastuzumab; this is the therapy considered in this appraisal.

HISTORY OF THE APPRAISAL

2008: referral to NICE and commencement of multiple technology appraisal process.

17 November 2009: Draft Scope issued.

24 February 2010: Final Scope issued.

7 June 2010: Submissions by consultees, including Roche.

17 November 2010: Appraisal Committee meet to develop ACD.

15 December 2010: ACD issued.

16 February 2011: Appraisal Committee meet to develop FAD

18 May 2011: Appraisal Committee meet again to finalise FAD.

1 July 2011: FAD issued.

GROUNDS OF APPEAL

Roche's grounds of appeal in relation to the FAD for trastuzumab in combination with an aromatase inhibitor for the treatment of HR+/HER2+ mBC are presented below.

Ground 1: The Institute has failed to act fairly

1.1 The Appraisal Committee's conclusions in relation to (a) the life expectancy of people eligible for trastuzumab in combination with an aromatase inhibitor for first line treatment of metastatic hormone receptor positive breast cancer that over expresses HER2 and (b) the survival gain associated with trastuzumab therapy, are not stated and it is unclear whether the Committee concluded that these criteria for the 'End of Life' advice were met.

a) Life expectancy of less than 24 months

In Section 4.3.17 of the FAD, the first 'End of Life' criterion (a life expectancy that is normally less than 24 months) is considered. The Committee first states that "people with HER2+ status have a worse prognosis" and "would be expected to have a life expectancy of less than 24 months". It then refers to the fact that, in the ITT analysis of the TAnDEM trial, the overall survival of the control population exceeded 24 months.

While Roche believes that the control population from the TAnDEM ITT analysis cannot be relied upon to reach any conclusions regarding the life expectancy of patients with metastatic hormone receptor positive breast cancer that over expresses HER2, unless the results are adjusted to take account of patient's receiving trastuzumab in the control arm(see appeal point 2.2) the fact that the Committee has seemingly not reached a conclusion regarding the life expectancy of patients eligible for trastuzumab treatment within this appraisal is unfair and has prejudiced Roche in its ability to fully engage with the appraisal process in the context of the application of the end of life criteria.

b) A three month survival gain

In Section 4.3.18 of the FAD, the second 'End of Life' criterion (overall survival gain greater than 3 months) is discussed. While the Committee refer to the overall survival data from the TAnDEM trial and note that the ITT analysis suggested an overall survival gain of 4.6 months associated with trastuzumab therapy, which was increased to 6.5 months after adjustment for cross over, they then comment on the fact that these results were not statistically significant and that the data for progression free survival suggested a gain of less than three months.

Again, while Roche believes that the consideration of this issue as set out in the FAD is flawed (appeal point 2.3), the fact that the Committee appears to have reached no conclusion as to whether trastuzumab offers this minimum gain of 3 months additional life, is unfair and has limited Roche in its ability to participate in this appraisal.

Remedy:

Roche requests that the Appraisal Committee should provide reasoned conclusions in relation to trastuzumab's eligibility for consideration under all three criteria required for the application of the 'End of Life' guidance including criterion one (short life expectancy) and two (overall survival benefit), allowing appropriate opportunity for consultation by stakeholders on these matters.

1.2 <u>The lack of guidance issued by the Institute in relation to the calculation of small patient populations for the purposes of the End of Life advice is unfair</u>

Given the variation in interpretation and application of the EoL 'small population' criterion displayed across appraisals (as demonstrated in our appeal in NICE TA227 and again in this appraisal) the lack of any guidance by NICE as to how appraisal committees should calculate the size of patient populations for which a product is indicated results in procedural unfairness.

In the context of this appraisal, guidance is required to assist appraisal committees in estimating populations for technologies in which indications 'overlap', as they do with trastuzumab. Furthermore it is plainly necessary, as a matter of fairness for NICE to determine the proper approach to be followed in considering patients who may be theoretically eligible for treatment in accordance with the marketing authorisation for a product, but who are in fact clinically ineligible as a result of co-morbidities. NICE has stated that the reason for the small patient population limitation on the End of Life advice is that higher ICERs may be acceptable where a company is limited in its ability to recoup development costs by the small number of patients eligible for therapy. If that is the case, then clearly it is the actual number of patients who may receive treatment who should be considered and the theoretical number within the authorisation is irrelevant.

If guidance on the proper approach to the End of Life advice is not issued, NICE risks patient access to the relevant technologies being determined by 'Committee Lottery' rather than the consistent, objective application of the evidence to a known decision rule. This is unfair.

Remedy:

Roche requests that NICE issues guidance on the proper approach to calculation of a "small patient population" for the purposes of End of Life advice, consistent with the recommendation of the Appeal Panel in TA227, and that the Appraisal Committee reconsiders this appraisal in the context of that guidance.

Ground 2: The Institute has formulated guidance which cannot be reasonably justified in light of the evidence submitted

2.1 The Appraisal Committee's addition of a further 2,000 patients to the 7,000 population figure estimated by Roche for trastuzumab equates to double counting of patients. These calculations suggest that nearly twice as many mBC patients are potentially eligible for trastuzumab as there are HER2+ mBC patients in the UK. This cannot be reasonably justified in light of the evidence presented and is not a sound a suitable basis for the issuance of guidance to the NHS.

In sections 4.3.16 - 4.3.19 of the FAD the Committee consider trastuzumab's eligibility for consideration under NICE's supplementary 'End of Life' guidance. The third criterion, the requirement that the product is indicated for a small patient population, was considered in section 4.3.18 and the Committee concluded that "the potential cumulative patient population covered by the trastuzumab licence would be more than 7,000 and possibly up to 9,100 people and that therefore trastuzumab did not fulfil the small population criterion". This is later relied upon to conclude that:

'... or trastuzumab plus an aromatase inhibitor do not fulfil all of the criteria for special consideration under the supplementary advice from NICE'

FAD Section 4.3.19

Roche believes that the calculations by the Appraisal Committee in relation to the size of the patient population eligible for treatment with trastuzumab in accordance with its marketing authorisation, are incorrect and that accordingly the conclusions of the Committee in this respect are unreasonable in the context of the available evidence.

In 2007 there were approximately 2,500 patients with HER2+ mBC in England and Wales (see appendix 1). Of these trastuzumab is indicated for 94.5% of patients but not indicated for the remaining 5.5% due to the presence of cardiac co-morbidities (i.e. angina or MI, Genactis Breast Cancer Patient Record Survey: Q4 2007). In our submission, we therefore estimated that trastuzumab was potentially indicated for a total of just under 2,500 mBC patients per annum. This figure comprises the maximum number of mBC patients for whom trastuzumab is potentially indicated in accordance with its marketing authorisation, irrespective of whether such patients will also receive chemotherapy or an aromatase inhibitor.

For completeness, we should say that our estimate that approximately 50 patients per annum would be eligible for trastuzumab in combination with an aromatase inhibitor was provided to give context to this appraisal. In view of the requirement to cumulate the patient populations eligible for the various indications for which trastuzumab is licensed, it is wholly irrelevant for the purposes of end of life criteria whether 50 patients would be eligible for trastuzumab in combination with an aromatase inhibitor, as estimated by Roche, or whether the figure is higher than this, as assessed by the Appraisal Committee. With the exception of patients with cardiac co-morbidities, all other patients with HER2+ mBC will be eligible for trastuzumab in combination with chemotherapy.

In Section 4.3.18 of the FAD the Appraisal Committee have referred to uncertainty over the number of patients eligible to receive trastuzumab in combination with an aromatase inhibitor,

but instead of appreciating that the more patients who receive the trastuzumab/ aromatase inhibitor regime, the fewer will be eligible for trastuzumab in combination with chemotherapy, they have simply added a further 2,000 mBC patients to the figure estimated by Roche. The addition of these 2,000 patients brings the Appraisal Committee's estimate to the number of HER2+ mBC patients potentially eligible for trastuzumab to 4,500 per annum. This is patently unreasonable in light of the fact that there are only 2,500 HER2+ mBC patients in total in England and Wales per annum.

We explicitly raised this issue in response to consultation on the ACD (Section 1.3.2 of Roche's response) but either it has not been considered by the Appraisal Committee or, if it has been considered, the Committee's reasons for disregarding our response have not been stated.

If the double-counting by the Appraisal Committee is corrected, this results in a conclusion that the total patient population eligible for trastuzumab is approximately 7,000, consistent with figures approved in other appraisals as satisfying the small patient population criterion for the purposes of the "End of Life" guidance.

Remedy:

Roche requests that the Appraisal Committee should reconsider trastuzumab's eligibility for consideration under the EoL guidance (criterion 3) in light of the fact that its population is 7,000 rather than 9,000 patients.

2.2 The Appraisal Committee's statement regarding the overall survival of patients who received aromatase therapy monotherapy in the TAnDEM trial failed to allow for patient cross over

At paragraph 4.3.16 of the FAD, the Appraisal Committee states that survival in the aromatase inhibitor monotherapy arm of the TAnDEM trial exceeded 24 months. The basis for this conclusion is not reported within the FAD. The only figure from TAnDEM which exceeded 24 months was that for the centrally confirmed group (28.6 months survival) which was not adjusted for patient cross over (paragraph 4.1.9 of the FAD). It should first be clarified that the centrally confirmed group is a subset of the TAnDEM ITT population where the ITT control arm had 23.9 months survival. The centrally confirmed group does not reflect UK clinical practice as hormone receptor status is not normally centrally confirmed in England or Wales. If an adjustment to reflect patient cross over is incorporated, overall survival in the aromatase inhibitor monotherapy ITT group is found to be 21.98 months (paragraph 4.1.10 of the FAD).

In these circumstances, the statement at paragraph 4.3.16 is not reasonable in light of the available evidence.

Remedy:

Roche requests that the Appraisal Committee should reconsider its statement in relation to the overall survival of patients who receive aromatase inhibitor monotherapy, in the context of patient cross overs in the TAnDEM trial.

2.3 The Appraisal Committee's statements regarding the overall survival benefit associated with trastuzumab therapy are unreasonable in light of the totality of the data presented

Section 4.3.17 of the FAD questions the magnitude of the survival benefit associated with trastuzumab as a result of the fact that the data lack statistical significance. This lack of statistical significance can largely be attributed to the fact that, like many other trials for end of life treatments, the TAnDEM trial was not powered to show statistically significant difference in overall survival. However, all the figures presented to the Appraisal Committee did suggest a greater than 3 month gain in overall survival:

Analysis	**Overall survival gain**	**Reference**
TAnDEM ITT analysis (ignoring 70% cross-over)	4.6 months gain (median)	Kaufmann et al. 2009
TAnDEM post-hoc censoring analysis	11.3 months (median)	Kaufmann et al. 2009
Roche cross-over method (RPSFT – medians from adjusted OS curves)	6.5 months (median)	Roche submission
Roche cross-over method in economic model (undiscounted)	12.4 months (mean)	Roche submission
Liverpool cross-over method in economic model (undiscounted)	8.4 months (mean)	LRiG Assessment Report – economic model

Against this background a conclusion that the overall survival benefit associated with trastuzumab may be less than 3 months is wholly unreasonable and inconsistent with the approach followed in other appraisals of end of life treatments (e.g. pazopanib for renal cell carcinoma TA215).

The Committee also referred to the evidence for progression-free survival gain and commented that this appeared convincing, and could be taken as a surrogate measure for overall survival. Whilst it is possible in some situations that PFS may be required as aa surrogate for OS, this is not necessarily appropriate when mature randomised control trial OS data are available. Furthermore the Committee focused on the median PFS gain of 2.4 months rather than the mean PFS gain of 8.6 months (undiscounted mean PFS gain from the TAnDEM Kaplan-Meier PFS curves).

Remedy:

Roche requests that the Appraisal Committee should reconsider the survival benefit associated with trastuzumab therapy in light of the fact that all overall survival estimates provide figures above 3 months and because if PFS is used as a surrogate for OS, it should be clarified that the average PFS gain was 8.6 months.

2.4 The conclusion by the Appraisal Committee that estimates of progression free survival for the aromatase inhibitor monotherapy in the TAnDEM trial were likely to be too low disregards the fact that the patient population in TAnDEM was different from that in EGF30008

At paragraphs 4.3.4 and 4.3.12 of the FAD, the Appraisal Committee expresses the view that the data from EGF30008 were more likely to represent progression-free survival of patients receiving aromatase inhibitor monotherapy in clinical practice than the data from TAnDEM. The Committee's reasons (paragraph 4.3.4 of the FAD) were:

- Clinical specialists indicated that the progression free survival seen in the aromatase inhibitor monotherapy group in EGF30008, was what they would expect to see in clinical practice.
- Very low numbers of patients could be the cause of sustained gain in survival between the groups in TAnDEM. However this would not account for the lower progression free survival in the comparator group in TAnDEM as compared with EGF30008.
- A protocol amendment to allow people in the aromatase inhibitor monotherapy group in TAnDEM to receive trastuzumab may have added uncertainty to the validity of the data from the aromatase inhibitor monotherapy group in this trial, particularly if fitter people left the group earlier than they otherwise might. However, the protocol amendment only permitted use of trastuzumab in patients in the aromatase inhibitor monotherapy group whose disease had progressed. Such cross over could not therefore affect the results for progression-free survival.

The second and third reasons given by the Appraisal Committee for its conclusion that the progression-free survival seen in the comparator group in TAnDEM was likely to be an underestimate do not therefore support this conclusion.

With respect to the first reason given by the Committee, the progression-free survival seen in any group of patients will depend on the baseline characteristics of that group. While the Appraisal Committee has recognised that the patient population in TAnDEM was different from that in EGF30008, precluding comparison of the trials (paragraph 4.3.5 of the FAD), it has not seemingly taken such differences into account when considering whether the data for progression-free survival in the comparator group in TAnDEM are reliable. This is unreasonable. As stated by the Assessment Group, an important difference between the two studies was the exclusion criteria; EGF30008 excluded patients in which their disease was considered by the investigator to be rapidly progressing or life threatening and this difference could account for the inconsistent results between the two aromatase inhibitor monotherapy groups. The fact that the patient population in TAnDEM had more advanced disease is supported by the fact that both groups had shorter progression-free survival than patients in EGF30008.

Roche accepts that comparison of TAnDEM and EGF30008 is problematic. However it is wrong to use EGF30008 as a reason to question the comparator data from TAnDEM in circumstances where the trial populations are different.

Remedy:

Roche requests that the Appraisal Committee should reconsider the data from TAnDEM based on the features of that trial population.

REQUEST FOR ORAL HEARING

Roche requests an oral hearing for the determination of this appeal.

APPENDIX 1

Metastatic Breast Cancer algorithm presented in original Roche submission (page 336):