16 May 2011

NHS
National Institute for Health and Clinical Excellence

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Dear [redacted],

Re: Single Technology Appraisal – Fulvestrant for the treatment of locally advanced or metastatic breast cancer

The Evidence Review Group (Liverpool Reviews and Implementation Group) and the technical team at NICE have now had an opportunity to take a look at submission received on the 15 April 2011 by AstraZeneca. In general terms they felt that it is well presented and clear. However, the ERG and the NICE technical team would like further clarification relating to the clinical and cost effectiveness data.

Both the ERG and the technical team at NICE will be addressing these issues in their reports.

We request you to provide a written response to this letter to the Institute by **17:00, 31 May 2011**. Two versions of this written response should be submitted; one with academic/commercial in confidence information clearly marked and one from which this information is removed.

Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise, and all information submitted under 'academic in confidence' in yellow.

If you present data that is not already referenced in the main body of your submission and that data is seen to be academic/commercial in confidence information, please complete the attached checklist for in confidence information.

If you have any further queries on the technical issues raised in this letter then please contact Sally Doss – Technical Lead (sally.doss@nice.org.uk) Any procedural questions should be addressed to Kate Moore – Project Manager (kate.moore@nice.org.uk) in the first instance.

Yours sincerely

Helen Knight
Associate Director – Appraisals
Centre for Health Technology Evaluation

Encl. checklist for in confidence information

Detailed below are points of clarification on the submission. All points have priority status – there are no non-priority points for this appraisal.

SECTION A - Clarifications of the CONFIRM data:

A1. Please provide a version of the Clinical Study Report (CSR), including working links and appendices, and a copy of the protocol and statistical analysis plan for the CONFIRM trial.

A2. Neither the average length of follow-up nor the duration of treatment appears to be reported in the manufacturer's submission (MS), it is simply stated that patients were treated until progression. Please provide the information on the length of follow-up and duration of treatment for each study arm and the overall trial population (mean, median, minimum and maximum).

A3. If available for each study arm and the overall trial population, for previous adjuvant therapy and previous advanced disease therapy, please provide the proportion of patients who received previous endocrine therapy with an anti-oestrogen (AO) only, aromatase inhibitor (AI) only and both an AO and AI (as in the 'Adjuvant therapy' and 'Advanced disease therapy' rows in table B6 on p47 of the submission).

A4. If available, for each study arm and the overall trial population, for previous adjuvant therapy and previous advanced disease therapy, please provide the baseline characteristics (as in Table B6 of the MS) and the findings for overall survival (OS), time to progression (TTP) and overall response rate (ORR) for patients who received previous endocrine therapy with an AO only, AI only and both an AO and AI.

A5. It is noted from section 1.6 of the MS that more mature survival data are expected. Please provide these data if they are now available.

A6. No data regarding post-progression treatments given to patients in the CONFIRM trial appear to have been provided. Please provide information on the post-progression treatments given to patients in both arms of the trial and the number of patients who received each treatment.

SECTION B - Clarifications of the indirect comparisons data:

Please provide sufficient information with regard to the conduct of the network analyses and provide all relevant data so the ERG would have the capability to re-run these analyses. In addition, please provide further clarification on the following:

B1. It appears on first reading of the MS that the extra trials included in the scenario analyses are those that were excluded from the base case due to ER status (p78 of the MS). However, from an examination of the Appendices, it appears only three of these were included in the scenario analyses (Kaufmann 2000, Dombernowsky 1998 and Gershanovich 1998) while a fourth (Rose 2003) was excluded. An additional trial not referred to elsewhere in the MS (EFFECT) is also included in the scenario analyses. Please provide further information with regard to the inclusion and exclusion of trials for the scenario analyses and also why EFFECT was originally excluded.

B2. Currently the assessment of proportional hazards for TTP is based only on data from the CONFIRM trial but a parametric model is fitted to all trials. Please

provide justification for fitting the same parametric model function to all other trials in the network analysis.

B3. Currently the findings for TTP are presented in a rather complex manner (Tables B35 and B36 on page 117 of the MS) and have not been interpreted or summarised in the text. Please provide a clinical interpretation for the results of the network analysis of TTP, for example, how the findings for each treatment in Table B36 may relate to fulvestrant 250mg or, ideally, fulvestrant 500mg (see also clarification request B7) in terms of their relative effect on TTP.

B4. For all the trials included in the network analyses, please provide the numbers of events and numbers at risk for each time point as extracted from the Kaplan Meier curves, for both OS and TTP, and any directly presented estimates of logHR and SE(logHR) where available from trial reports.

B5. In table B38 on page 123 of the MS, the following is listed as a limitation of the CONFIRM trial: “The position of the median quartile for TTP in the CONFIRM trial does not represent the scale of the significant difference seen in AUC on the Kaplan-Meier curves as represented by the 0.8 hazard ratio”. Please clarify what is meant by this.

B6. The CONFIRM trial includes patients who have received prior treatment with an AI as well as those that have been pre-treated with an AO, whilst the other trials in the network analysis include only patients that have been pre-treated with an AO. Please provide evidence that these two populations are sufficiently similar so that it can be confidently assumed that the effect estimated in the CONFIRM trial is generalisable to the patients in the other trials.

B7. Please rerun the network analyses (both OS and TTP) with fulvestrant 500mg as the baseline comparator since they currently compare all treatments to fulvestrant 250mg. Please also provide the probabilities that each treatment is the best.

SECTION C - Clarifications of the economic data

C1. Please provide Product-limit survival tables (e.g. using SAS LIFETEST procedure or equivalent) from analysis of CONFIRM trial data for the following outputs:

a) Time to progression (TTP)

b) Overall survival (OS)

c) Post-progression survival (PPS)

d) Time on treatment (TOTx)

by treatment arm (Fulvestrant 500mg vs. Fulvestrant 250mg)

and

by whether or not patients were previously treated at any time with an AI

(i.e. 4 outputs x 2 treatment arms x 2 prior use of AIs = 16 K-M analyses)

In each case please provide a table of results showing for each event time:

- Time of event from baseline (days)
- Product-limit estimate of survival proportion
- Standard error of survival proportion
- Number of patients failed
- Number of patients remaining at risk

SECTION D - Clarifications of the number of patients eligible to receive fulvestrant

D1. In section 7 of the MS, the manufacturer provides estimates for patients eligible for fulvestrant from 2011 up to 2015. Please clarify whether it is assumed if any of the patients may have also received an AI as well as an AO.

D2. According to section 7.1 of the MS, a total of 2,209 patients are potentially eligible for fulvestrant 500mg, out of a population of 11,603 patients, i.e. around a fifth of all patients. In section 7.3, the MS states that the market share for fulvestrant is anticipated to be 1.0% in 2011 (22 patients), rising to 8.5% in 2015 (193 patients). Please clarify why the market share is anticipated to rise to 8.5%.

SECTION E – References

E1. Please provide in electronic format, copies of all documents cited in the references, in particular those that are not available in the public domain.