Monday 22nd March 2010

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Dear [redacted]

Re: Single Technology Appraisal – Trastuzumab for advanced gastric cancer

The Evidence Review Group York CRD and the technical team at NICE have now had an opportunity to take a look at submission received on the 1st March 2010 by Roche Products. 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, 7th April 2010**. 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 Joanne Fielding – Technical Lead (joanne.fielding@nice.org.uk) Any procedural questions should be addressed to Lori Farrar – Project Manager lori.farrar@nice.org.uk in the first instance.

Yours sincerely

[redacted]
Centre for Health Technology Evaluation

Encl. checklist for in confidence information

A1. **Priority Question:** Please provide the clinical study report for the ToGA trial.

Survival Modelling

A2. **Priority Question:** Please provide the full set of parameter estimates as well as the variance-covariance matrices in an Excel file for the other survival distributions (both overall survival and progression free survival) considered for the model, e.g. the exponential and Gompertz distributions.

A3. **Priority Question:** Please provide additional cost-effectiveness results assuming these alternative survival distributions.

A4. **Priority Question:** Please clarify whether a proportional hazard model was used to model the progression free survival. Please provide data that justifies the use of a proportional hazard model.

A5. **Priority Question:** The current survival estimates are based on the EMEA approved subgroup. Please provide an Excel file with the equivalent parameter estimates (and variance-covariance matrices) for the full set of survival distributions (overall survival and progression free survival) based on the FAS population.

A6. **Priority Question:** Please justify the use of linear regression rather than other approaches to extrapolating the proportion of patients on treatment out of those in progression free survival.

A7. **Priority Question:** Please provide the full set of parameter estimates as well as the variance-covariance matrices in an Excel file for a parametric fit to the treatment duration of trastuzumab. Please provide the goodness of fit statistics.

Quality of Life

A8. **Priority Question:** Please provide the protocol specifications for the quality of life analysis in the ToGA trial. What was the null hypothesis? Please also provide the results of any statistical analysis of the quality of life data, including any analyses of the EMEA approved subgroup.

A9. **Priority Question:** Please provide the EQ-5D scores from the ToGA trial over time in both tabular and graphical formats, by treatment for the

EMEA approved subgroup and FAS populations. For the tabulated data, please report the mean (and standard error) for each time point.

A10. **Priority Question:** Please provide tabulated data on the number of censored patients and reasons for censoring over time for the EQ-5D data.

A11. **Priority Question:** Please provide additional results from a complete case analysis of the EQ-5D estimates for the patient sample that was measured at all time points. Please report the mean (and SE) for each time point.

A12. **Priority Question:** Please describe the mixed model fitted to the utility data in more detail, including model coefficients and output. Please provide goodness of fit test results for alternative models if any were fitted.

ToGA trial

A13. Baseline Data:

a) Please provide all data on the baseline characteristics of the EMEA approved subgroup of patients comparable to that provided for the FAS population for factors used in the stratification and other prognostic factors.

b) Please provide a breakdown of the CF/CX ratio for each arm of the trial in the EMEA approved subgroup.

c) Please confirm that there was no maximum age for enrolment in the trial.

d) Please provide the number of participating UK centres and the number of patients enrolled from the UK.

A14. Results:

a) Please provide all results data for the EMEA approved subgroup of patients comparable to that provided for the FAS population.

b) Please clarify the definition of the primary analysis; page 55 states that the FAS population is used but page 56 defines the primary analysis as being based on the per protocol population. Where analyses of the per protocol rather than the ITT population are used, please supply the ITT data.

Indirect Comparison

A15. Please clarify the systematic review process for the indirect treatment comparison including the following issues:

i) How were the interventions in the inclusion criteria selected?

ii) What were the treatment regimens “of interest”?

iii) Why was quality of life not considered as an outcome?

A16. Please provide a list of the studies excluded at each stage during the indirect comparison review process (p 79).

A17. Please provide data for all arms of each trial used to illustrate the efficacy of each chemotherapy regimen; this should include numeric and statistical information as well as graphical illustration.

A18. The network diagram supplied (p80) does not appear to reflect the comparisons assessed by the included studies, including ToGA. Were separate analyses of HCF versus CF and HCX versus CX conducted? If so please supply these.

A19. The overall survival hazard ratio for EOX in comparison with ECX in the sensitivity analysis quoted in Table 32, page 147, was 0.92. In the REAL II publication, this hazard ratio was the result of comparing the two oxaliplatin groups with the cisplatin groups. It was not the result of comparing EOX with ECX. Please provide the progression free survival and overall survival hazard ratios and confidence intervals for EOX in comparison with ECX or additional support for the current assumption.

A20. Search strategies:

a) Was a search for non-randomised trials conducted? If so please supply details.

b) Please confirm that the search strategy on pages 215-216 (Appendix C2) is that which is referenced on page 77 as section 10.8 in Appendix 3. Please supply the following information relating to this search:

i) Search strategies for the other databases (EMBASE, SciSearch, Cochrane Library).

ii) Confirm which interface was used to conduct the search

iii) Explain lines 15-17 of the strategy: do these relate to database search including other databases?

Current UK Practice

A21. In Table 17, page 113 it is reported that 17.8% of metastatic gastric cancer patients are estimated to be eligible for trastuzumab (IHC2+ FISH+ or IHC3+) and 66% of eligible patients are IHC2+ and require a FISH test. Please provide a summary of factors known to influence the positivity rate in clinical practice and provide any additional supporting evidence on the potential range around these estimates from other sources.

A22. Please provide additional data on the percentage of tests for each of IHC and FISH that needed to be repeated (i.e. test failures due to inadequate tissue sample) in the ToGA study. Please provide any additional data available on the rate of IHC/FISH test failures from other metastatic gastric cancer studies.

A23. Please provide an indication of average delay in routine clinical practice between the time at which a decision is made to test a patient for HER2 status and the availability of IHC and confirmatory FISH results.

A24. Please provide the proportion of patients HER2 eligible for trastuzumab that record an LVEF of 50% or more in the ToGA trial.

A25. Please clarify whether LVEF eligibility would be assessed before or after HER2 eligibility.

A26. Please supply further information on the market research conducted on current treatment practice in the UK; Appendix E6 does not contain sufficient information. In particular please clarify the sources of the data, including patient numbers, provide a clearer version of Figure 5, and confirm which two regimens are at 0%.

Resource Use

A27. Please report the mean number of cycles for each treatment regimen assumed in the model and also the mean (and standard error) number of cycles from the ToGA trial.

A28. Please clarify if the cardiac monitoring frequency numbers are correct in Appendix E1 (page 218) and Excel spreadsheet 'Admin-pharm-mon'. If they are, please explain the derivation. Please justify the lower cardiac monitoring frequency in the trastuzumab arms.

A29. Please provide the sources and/or calculation of the smallest dose/vial quantities given in Excel spreadsheet 'Regimen drug costs' in column K titled 'smallest', and please confirm that they are correct. Is 9000mg the smallest capecitabine quantity?

Costs

A30. Page 139 of the report indicates that the frequency of monitoring varies according to whether the monitoring is during chemotherapy and trastuzumab or during trastuzumab but post-chemotherapy. Please clarify how the model accounts for the different costs of monitoring.

Textual clarifications and additional points

A31. Please clarify test prices on page 142 as the total prices are not the same as in the model (£542.49 vs. £466.67).

A32. Please clarify why the numbers of cycles per month in Appendix E1 and in the Excel spreadsheet 'Admin-pharm-mon' are different to those in Table 17, page 114, and Table 29, page 137, and the Excel spreadsheet 'Dose Table'.

A33. Please clarify why the total admin, pharmacy and monitoring costs in Appendix E1 are different to those in the Excel spreadsheet 'Admin-pharm-mon' (£655 vs. £746, £905 vs. £996, etc.).

A34. Please clarify why the figures in Table 26 (page 134) are different to those in Excel spreadsheet 'Regimen drug costs' (207 vs. 216, 6674 vs. 6689, etc.).

A35. In Figure 16 (page 83) the numbers do not add up – the box on full-text publications sums to 32 instead of 40. Please clarify.

A36. In Figure 6 (page 43) the numbers do not add up (should it be 60 abstracts rather than 57?); please clarify the correct figures for each stage of the review process.