08 January 2010

NHS
National Institute for
Health and Clinical Excellence

NICE
Midcity Place
71 High Holborn
London
WC1V 6NA

[redacted]

[redacted]

www.nice.org.uk

Dear [redacted],

Re: Single Technology Appraisal – Capecitabine for the treatment of advanced gastric cancer

The Evidence Review Group (ERG), Centre for Reviews and Dissemination and Centre for Health Economics (CRD/CHE) and the technical team at NICE have now had an opportunity to take a look at submission by Roche. 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. As you will only receive the evidence review group report 5 days prior to the Appraisal Committee meeting, you may want to respond to the points raised and provide further discussion from your perspective at this stage.

We request you to provide a written response to this letter to the Institute by **17:00, Friday 22nd January 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 are not already referenced in the main body of your submission and those data are academic/commercial in confidence, 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 Raphael Yugi [redacted] – Technical Lead). Any procedural questions should be addressed to Bijal Joshi – Project Manager [redacted] in the first instance.

Yours sincerely

[redacted]
Associate Director Technology Appraisals
Centre for Health Technology Evaluation

Encl. checklist for in confidence information

Section A: Clinical Effectiveness:

Quality-of Life

A1. In the REAL-2 trial, the submission refers to a single subscale of the questionnaire at baseline and at 12 weeks (page 44). Please provide detailed data for the whole of the EORTC questionnaire at all time points (that is baseline, three months, six months, nine months and 12 months). Please include any measure of variability or uncertainty recorded such as standard deviation, or standard error.

A2. Please provide, if available, any quality-of-life data for ML17032

Safety

A3. Please provide any further relevant information on the safety profile of capecitabine (with the relevant dose). If relevant, please provide safety information from Phase II studies or studies outside gastric cancer

A4. Please clarify the definition of “one dose” as used in the eligibility for safety analyses in both REAL-2 and ML17032. Please clarify, particularly for capecitabine, if this refers to one cycle or a component of a cycle.

A5. Please clarify if there were any further criteria for entry into safety analysis for REAL-2 beyond the one stated in page 37 (that is, “one dose”). Page 48 provides an additional criterion for ML17032 (that is, one post-baseline safety assessment).

A6. Please provide the appropriate numbers (N) for haematological and non-haematological safety outcomes for all arms in table 11. The numbers (N) as currently given appear to be a mixture of the two across all the arms rather than for each arm/outcome. Please confirm that the percentages given for each outcome have been calculated using the appropriate numbers (N). Please clarify why the numbers included in the haematological and non-haematological safety analyses differ; please explain how the numbers were derived

A7. Please provide details for the reasons for treatment delays documented in table 12.

A8. Please provide data on the treatment exposure for ML17032 comparable to that provided for REAL-2 in table 12.

A9. Please clarify why safety outcomes are not listed under secondary outcomes for the ML17032 trial.

A10. Please clarify the criteria for entry into the safety analysis for ML17032. Those listed in page 37 differ from those in page 48.

Individual patient data meta-analysis

A11. Please provide details of the statistical methodology used in the individual patient data meta-analysis.

Current UK practice and treatment pathway

A12. Please provide details of the methods used in the research conducted by First Line Research (summarised in figure 2). Please include, for example, how many hospitals were included, how the information was collected and any other relevant information.

A13. Please include labels for all treatment options in figure 2. One option is currently missing and one is incomplete. Please also provide the actual patient numbers for each regimen per calendar year.

A14. In a statement by one of the clinical experts (Dr Rodney Burnham), reference is made to patients with contraindications to the standard first line regimens ECF, ECX and EOX (for example due to pre-existing peripheral neuropathy, renal impairment or impaired left-ventricular cardiac function). These patients may instead receive a combination of carboplatin and infused 5-FU or capecitabine (Carbo-F or Carbo-X combinations). Please clarify if these regimens were identified in the market research conducted by First line Research.

Chemotherapy cycles

A15. Please provide the mean number of chemotherapy cycles for each trial arm in the REAL-2 trial. Please provide any details of the variability or uncertainty, such as standard deviations.

A16. Please provide an estimate of the average number of chemotherapy cycles for the alternative chemotherapy regimens identified in the submission used in routine clinical practice in the UK. Please state how the average number of cycles might vary.

A17. In table 12 page 51, please provide the number (N) for the median number of cycles in the EOX group in the REAL-2 trial. Please explain what the figures in the brackets for this line represent.

Patient population and efficacy data

A18. For the REAL-2 trial, please provide details of the multivariate analysis by performance status, age and disease that is referred to in page 42.

A19. Please provide further information on the patients involved in the dose escalation phase of the REAL-2 trial documented in Cunningham et al, 2008. Please provide details of the exact treatment received and the outcomes.

A20. Please provide details of the second-line treatment for the 14% of the patients in the REAL-2 trial.

A21. Please provide efficacy data broken down according to the following subgroups from the REAL-2 trial:

- cancer site (gastric, oesophogastric junction and oesophageal)
- performance status
- whether previous treatment was received
- receipt of second-line treatment (14% of patients)

- other prognostic factors eg liver and peritoneal metastases, alkaline phosphatase etc.

A22. For the ML17032 trial, please provide the following:

- independently assessed results for all outcomes in addition to the per-protocol PFS
- Clarification as to why ITT data are reported for mean time to response and median response duration but ORR is reported per protocol. Please provide per protocol and ITT data appropriately
- Clarification whether the p-values are one-sided or two-sided α's
- data broken down by whether previous treatment was received.

Section B: Cost Effectiveness

B1. The meta-analysis suggests statistically significant survival benefits for capecitabine in advanced gastric cancer compared with 5-FU. Please provide details of the expected costs associated with a patients' care during the additional survival period for patients on capecitabine-based therapy.

B2. Please clarify whether the calculations of dose intensity reported for capecitabine in the cost minimisation analysis considered the dispensed amounts or the amounts actually utilised by the patients.

B3. Please state how the mean number of cycles vary between different subgroups of patients, such as by tumour histology, performance status, locally advanced vs metastatic disease. Please provide a sensitivity analysis informed by these data.

B4. Please provide details of the evaluation of adverse events costs referred to in page 100 point 4.

Section C: Search strategy and textual errors

C1. In the QUORUM flow diagram in figure 4, please clarify how the 11 records covering the 4 RCTs are identified from the initial 179 records.

C2. Please include a QUORUM flow diagram for the cost effectiveness review process.

C3. Please clarify the source of the other economic evaluation of capecitabine in gastric cancer conducted in the UK (London Cancer New drugs Group APC/DTC briefing). It is not mentioned in the search process in page 122

C4. Please clarify if there was a search for ongoing studies. This was not mentioned in the search strategy.

C5. Please clarify the following issues identified in the search strategies provided in the submission (appendices 2 and 3):

- In the clinical effectiveness search strategy (lines 52, 53, 56, 57, 84) that relates to the Biosis database, there appears to be an error in the Boolean logic applied. Line 57 combines lines 52 and 53 (xeloda and capecitabine) using the Boolean AND whereas the Boolean OR should have been used. This results in 143 records being identified in line 57 whereas a minimum of 1680 should have been identified.

- In the cost effectiveness Medline search strategy, there appears to be an error in line 14 where all the terms for gastric/stomach cancer have been combined. Line 1 stomach neoplasms.de has not been included in this combination and has not been used at any other point in the strategy. The effect of omitting the one MeSH term for gastric/stomach cancer could be that potential studies were not identified; this may have been compensated for in other lines of the strategy but this cannot be confirmed without reproducing and re-running the search.

C6. In the data extraction of ML17032 (page 37) it is reported that ‘patients were excluded from the per protocol population if they received less than 6

weeks treatment for reasons of PD or death'. Please clarify if this was intended to read 'for reasons **other than** PD or death'.

C7. Page 39 of the submission states that there were 63 centres which were all in the UK. In Cunningham et al. (2008), it is stated that there were 61 centres, 59 of which were in the UK while 2 were in Australia. Please clarify.

C8. In figure 8 (page 42), the title reads 'Kaplan-Meier curves of PFS'. Please clarify if this should be 'Kaplan-Meier curves of **OS**' (as per the caption).

C9. Section 6.5.2 (page 45) reads "Although the authors of the meta-analysis do specify…" please clarify if this was this intended to read "do **not** specify…."

C10. Please confirm that the last paragraph on page 45 should read '5-FU combinations and those treated with **capecitabine** combinations' rather than '5-FU combinations and those treated with 5-FU combinations'.

C11. In table 25 (page 71), 5-FU is given for 21 days in the CF regimen. Please confirm that this should be **5 days.**

C12. In table 39 (page 89), the cost of epirubicin in the ECX regimen is given as £792. The calculations used appear to be £692. Please confirm that this should be £**692.**

Bijal Joshi
Technology Appraisals Project Manager - Committee A
National Institute for Health and Clinical Excellence
MidCity Place | 71 High Holborn | London WC1V 6NA | United Kingdom
Tel: 44 (0)20 7045 2246 | Fax: (0)20 7061 9819