NICE National Institute for Health and Care Excellence

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Single Technology Appraisal (STA)

Ramucirumab for treating metastatic gastric cancer or gastro-oesophageal junction adenocarcinoma after chemotherapy [ID741]

Dear [redacted]

The Evidence Review Group, Kleijnen Systematic Reviews, and the technical team at NICE have now had an opportunity to take a look at the submission received on the 15th May 2015 by Eli Lilly and Company Limited. 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 **5pm** on **Thursday 25 June 2015**. 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.

Please do not 'embed' documents (i.e. PDFs, spreadsheets) within your response as this may result in your information being displaced or unreadable. Any supporting documents should be emailed to us separately as attachments or sent on a CD.

If you have any further queries on the technical issues raised in this letter then please contact Chris Chesters, Technical Lead (chris.chesters@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

Frances Sutcliffe
Associate Director – Appraisals
Centre for Health Technology Evaluation

Encl. checklist for in confidence information

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Section A: Clarification on effectiveness data

A1. **Priority request:** Please provide the full clinical study reports for the RAINBOW and REGARD studies. We received clinical study reports for REGARD and RAINBOW, but these are short versions (each less than 200 pages).

A2. Please provide the number of UK patients for each arm in the two trials: RAINBOW and REGARD.

A3. Please provide the number of participants from the subgroup 'Region 1' by individual country (separate for each European country, Israel, Australia, USA and New Zealand) and for each arm.

A4. Please indicate whether there were differences in overall dose modification between patients with gastric cancer and gastric oesophageal junction cancer.

A5. Please indicate the number and proportion of patients recruited for each arm that received anthracycline in the two trials: RAINBOW and REGARD.

A6. Neuropathy (peripheral sensory, neuropathy peripheral, polyneuropathy, peripheral motor neuropathy, neuralgia, hypoesthesia, paraesthesia) as an adverse event occurred at a higher rate in the intervention group compared to the comparator.

Please indicate the proportion of neuropathy cases (adverse events) that were irreversible in both RAINBOW and REGARD, by treatment group.

A7. The population chosen for the monotherapy analysis is people for whom further cytotoxic chemotherapy is not appropriate. The marketing authorisation population for the monotherapy indication is those for whom treatment in combination with paclitaxel is not appropriate. However, the inclusion/exclusion criteria of the REGARD trial suggests that people who would be suitable for further cytotoxic chemotherapy or for whom treatment with paclitaxel is appropriate, would still have been eligible to join the trial. Please confirm if this was the case.

Priority request: Please provide numbers of patients in each arm and separate data of overall survival and progression-free survival from the REGARD trial for patients for whom treatment in combination with paclitaxel is not appropriate.

A8. Please provide the number of responders of the EQ-5D index scores of Table 21 of the company submission.

A9. **Priority request**: Please provide the additional mean survival of ramucirumab in combination with paclitaxel compared with <u>all</u> comparators in the NICE scope (similar to the comparisons provided in tables 51 [versus BSC] and 52 [versus docetaxel]).

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Network meta-analysis

A10. **Priority request**: Please provide a full list of the 18 trials included and the corresponding 22 publications mentioned in Figure 24 (page 109 of the company submission). Please explain how this relates to Figure 25 (page 111 of the company submission) and Appendix 6. (Figure 25 includes 21 trials and Table 3 of Appendix 6 lists 18 trials, but does not include the RAINBOW trial, Qin 2014, Nishikawa 2014, Satah 2014 and Cohen 2014; Table 3 does include Kim 2011 and Kim 2012, but these are not in Figure 25.)

Please provide data extraction tables (as in Appendix 6) for studies used in the network meta-analysis, such as RAINBOW.

References and/or PDFs for Sym 2013, Qin 2014, Nishikawa 2014, Satah 2014 and Cohen 2014 seem to be missing. Please provide these, and any other missing publications.

The numbers in the appendix do not seem to correspond with the references in the folder 'Appendices Refs'. Please provide all PDFs for the references in the appendices.

A11. Please clarify the meaning of the 'm' in mFOLFIRI on page 110 of the company submission, as leucovorin (folinic acid) is already in the FOLFIRI regimen.

A12. Please explain why (m)FOLFIRI was not included in any of the evidence networks for combination therapy. According to Figure 25 this is possible using Sym 2013, but Sym 2013 is not included in Fig 26 (overall survival), Fig 27 (progression-free survival) or Fig 28 (adverse events).

A13. **Priority request**: For table 44 (overall survival), table 46 (progression-free survival) and table 48 (adverse events), please add results for comparisons with irinotecan and FOLFIRI. These are relevant comparators as per the final scope issued by NICE and the data are available. Please do the same for the network meta-analyses analyses in Appendix 6.

A14. Please provide a full list of eligibility criteria for indirect comparisons. Table 42 lists some criteria, but according to Figure 24 (page 109 of the company submission), language and year of publication were also exclusion criteria.

Please explain why language and year of publication were exclusion criteria and please provide a list of references of records excluded because of language and year of publication.

A15. **Priority request**: Please provide full Winbugs codes and the corresponding data used in all network meta-analyses.

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Section B: Clarification on cost-effectiveness data

B1. **Priority request**: Please provide the cost-effectiveness analyses (including all relevant input values and outcomes) for the additional comparators in the scope issued by NICE but not in the model: ramucirumab in combination with paclitaxel compared with irinotecan and compared with FOFIRI (in the same way as has been provided for the comparisons with docetaxel and BSC).

B2. Please clarify if the hazard ratio=1.00 arrow in figure 42, (page 160 of the company submission) between best supportive care and irinotecan should instead have been drawn between ramucirumab and irinotecan. In its current position the figure implies that the indirect comparison of best supportive care compared with ramucirumab is also 1, which is not in line with the hazard ratio observed in the REGARD trial.

B3. Please provide a rationale for using adjusted baseline EQ-5D utility scores for clinically meaningful events (i.e., adverse events and tumour response) instead of using the treatment arm specific utility values (Table 21) derived at different time points (including response rate and adverse events).

B4. Please explain why studies which may have provided inputs for the cost estimates in the model were excluded from the literature search (Figure 29, page 136 of the company submission). Alternatively, please clarify if these 5 excluded studies were included in the literature search on page 185 of the company submission.

B5. Please provide a rationale to explain why the adverse events odds ratios from the indirect treatment comparison or network meta-analyses were not used in the model.

B6. Please provide a sensitivity analysis in which patients remain on treatment whilst they are in the pre-progression health state (i.e. time on treatment = progression-free survival).

B7. Please clarify whether data relating to the duration of hospitalisations due to adverse events were collected in the RAINBOW and REGARD trials.

B8. In the model, treatment-specific hospitalisation probabilities have been estimated that are used in both the post-progression and progression-free health states. This means that the probability of hospitalisation in the post-progression health state after ramucirumab in combination with paclitaxel is different to the probability of hospitalisation after paclitaxel (or another comparator) as indicated in Table 108 of the company submission. However, it is also assumed that the treatment after progression in both arms do not differ much (the majority of patients receive palliative care and only a small proportion receive active 3rd line treatment). Please explore the effect of this assumption in sensitivity analysis,

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using an alternative scenario with the post progression rate equal for all treatments, based on the individual patient level data.

B9. Please clarify whether the Healthcare Resource Groups provided in table 115 of the company submission include hospitalisations for adverse events. If so, please clarify if hospitalisations are double counted in the model, as they are also estimated through the individual patient level data from the pivotal trials. According to the CSR of REGARD "The most common reason for hospitalization was AEs, accounting for 80 (33.9%) patients in the ramucirumab arm and 44 (38.3%) patients in the placebo arm".

B10. **Priority request**: Please provide more details on the clinical expert consultation mentioned in Chapter 5 of the company submission (for example for follow-up costs on page 187). How many experts were consulted, what was their area of expertise, which questions were asked and if applicable, what was the range of their responses?

B11. Please explain if there is potential double counting by including both terminal costs separately and the admission days as obtained from the trial data during the post-progression phase.

B12. In the treatment pattern study, were the inclusion or exclusion criteria for selecting BSC components discussed with clinical experts? (Table 85 of the company submission).

B13. Please provide an overlay of Kaplan Meier curves for progression-free survival (figures 33 and 43) and time on treatment (figures 53 and 55), separately for the ramucirumab in combination with paclitaxel, placebo in combination with paclitaxel, and the ramucirumab in combination with best supportive care arms.

B14. Figure 55 shows clear steps in the Kaplan Meier curve, just as with the progression-free survival Kaplan Meier curve (figure 43). Please clarify if the fitted parametric curve in figure 55 was based on interval-censoring or not. If not, please provide justification.

B15. On page 240 of the company submission the results are presented for region adjusted overall survival, progression-free survival and time on treatment. Two incremental cost effectiveness ratios (ICERs) are presented, one for the log-logistic distribution and one for the Weibull distribution. Please clarify if these distributions were used for overall survival, progression-free survival and time on treatment.

B16. Table 146 of the company submission shows that the median observed progression-free survival was 4.40, 95% confidence intervals (CI) of 4.24 and 5.32, and the median modelled progression-free survival was 4.14, which is outside the 95% CI of the randomised controlled trial. Please clarify why no

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further adjustments have been made to the model to reduce the difference between observed and modelled results.

B17. On page 242 of the company submission Table 147 presents results of the comparison of model results and clinical data for median overall survival. Please provide the same results for progression-free survival.

B18. Please clarify if unit costs from previous years have been adjusted to 2015 prices.

B19. Please provide similar progression-free survival Kaplan-Meier curves as presented in figures 6 and figure 7 on page 60 of Appendix 9 for the ramucirumab in combination with paclitaxel arm, and for each of these please also provide the Cox-Snell residual plots.

B20. Appendix 9: Please clarify if the Cox-Snell residual plot in figure 8 (page 61) matches figure 6 or figure 7.

B21. Excel model: on the worksheet 'trace' a column 'progressing' is defined. The formula shows that the percentage of patients progressing in each cycle is estimated by the %PF in cycle t-1 minus %PF in cycle t. This seems to imply that all patients leaving the progression-free survival state go to post-progression survival, and that there are no deaths. This is not clear from figure 21 (page 140 of the company submission). Should the arrow between the pre-progression health state and the death state be deleted in figure 21?

B22. Excel model: on the worksheet 'trace', half cycle correction is applied for the one-off type cost component "Third-line" (Column AO), but not applied for other one-off type cost components: "Terminal" (Column AP) or "Consultation (PPS)" (Column AQ). Please can you explain if there is a rationale behind this?

B23. **Priority request**: For ramucirumab in combination with paclitaxel compared with docetaxel, progression-free survival is informed by an assumed hazard ratio of 1,this is despite there being a hazard ratio from Roy 2013 estimated (as with overall survival) using methods of Parmar 1998 i.e. 1.26 (0.94,1.68). Please provide a justification for this and re-run the analysis using the estimated value?

B24. On page 147 of the company submission, it is stated that: *"The choice of dosing regimen for the economic model was based on the clinical trials of DOC included in the NMA [REFS 2, 110]. In these studies, DOC was administered at a dose of 75mg/m2 every 3 weeks. Treatment is assumed to be continued until disease progression, unacceptable toxicity or for a maximum of 6 cycles due to toxicity concerns as per the COUGAR II study [REF2]. This was a UK-only study and its dosing regimen for DOC was confirmed to be reflective of clinical practice in England."*

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In the Excel model (combination therapy), in the base case (when Developer!G69=1), docetaxel is administered to all patients (progressed /non-progressed) for the first 9.2 weeks. Please explain the difference in the time on treatment modelling calculations for docetaxel treatment in the combination therapy Excel model compared to how it is reported in the company submission? Please also explain the scenarios in the Excel model (Sheet "Developer", Cell G69)?

B25. On page 160, it is stated that: *"The objective of assigning HR=1 for RAM, IRI and DOC was to constrain the hazards of progression to be equivalent, (i.e. no uncertainty) so standard errors of 0.01 were assigned."*

In the Excel model (combination therapy), in the base case it seems that standard error=0 values are used (for best supportive care, please see sheet "HR", Cells V13 and W13) in contrast to standard error=0.01 (95% CrI 1.89, 7.14) that was mentioned in the sentence above in the company submission. Please explain this discrepancy.

Furthermore, please confirm that the following assumptions in the options for sheet "User", Cell J29 are correct:

- Base case standard error=0
- Scenario 1 standard error=0.287
- Scenario 2 standard error=0.01

Also, in the company submission in table 65, the progression-free survival hazard ratio estimates (plus 95% CI) for paclitaxel cannot be found, even though they seem to be used in the Excel model on sheet HR, Cells U9, V9 and W9. Please document the progression-free survival hazard ratio estimates for paclitaxel.

Section C: Literature searches

C1. Please clarify the date on which the clinical effectiveness searches took place. Section 4.1 states 2nd December 2014 but the search strategies provided in Appendix 2 indicate the searches may have taken place in February 2015.

C2. Please clarify the number of records identified through database searching. The results from the search strategy in Appendix 2 (45 records) do not match those detailed in the PRISMA flow diagram in figure 5, page 46 of the company submission (55 records).

C3. Please clarify the date span for the Embase search detailed in Table 26, page 73 of Appendix 10: it is given as 1980-2012 but searched on 25th September 2013.

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C4. Please clarify whether the date for the search for studies included in the evidence network is correct. Appendix 6 dates the search as December 2013, yet several papers were published in 2014 (for example, Qin 2014, Nishikawa 2014, Satah 2014 and Cohen 2014, Wilke 2014).