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Dear Jo Annah,

Re: Single Technology Appraisal –Golimumab for the treatment of rheumatoid arthritis after failure of previous disease-modifying antirheumatic drugs

The Evidence Review Group (School of Health and Related Research [ScHARR]) and the technical team at NICE have now had an opportunity to take a look at submission received on the 2 July 2010 by Schering Plough Ltd (part of MSD). 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, 5 August 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.

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.

Please provide an update on the status of the additional analyses that are being awaited. As previously indicated, the Evidence Review Group (ERG) cannot provide a guarantee that it will be possible to review these extra analyses.

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 Chung
Associate Director – Appraisals
Centre for Health Technology Evaluation

Encl. checklist for in confidence information

Section A: Clarification on effectiveness data

A1. **Priority Question:** The current MS considers golimumab at two points. These are:

- as an alternative to currently available anti-TNFs in second line therapy
- as an alternative to rituximab in third line therapy

In addition to the two comparisons currently considered, please also present comparisons against the additional treatments recommended in the draft guidance of ongoing rheumatoid arthritis appraisals of tocilizumab, and abatacept, adalimumab, etanercept and infliximab after the use of a TNF inhibitor. This would consider golimumab;

- as an alternative to anti-TNF therapy (adalimumab, etanercept, infliximab and abatacept) in patients unable to take the standard third line therapy (rituximab with methotrexate)
- as an alternative to tocilizumab with methotrexate in patients unable to take the standard third line therapy (rituximab with methotrexate)
- as an alternative to current fourth line therapy (tocilizumab with methotrexate)

If the comparisons are not considered appropriate please provide further rationale.

A2. **Priority Question:** Tables 130 and 131, pages 124-126. Please a) clarify the definition of the term 'palliative care' in terms of the treatment pathway and b) describe and justify the selection of evidence to support the modelling of palliative care.

A3. **Priority Question:** Please provide analyses (including use in meta-analyses, mixed treatment comparisons, indirect comparisons and use as comparators in economic analyses as directed above) comparing golimumab with tocilizumab, abatacept and the sequential use of the TNF inhibitors.

A4. **Priority Question:** Page 26. The decision problem lists the outcomes addressed in this assessment. The following outcomes do not appear to have been addressed: Joint damage, mortality, fatigue and radiological progression. Please provide data on these outcomes or state where data are not available. Alternatively please provide justification for the exclusion of these outcomes.

A5. **Priority Question:** Page 28 onwards. ACR70 data are reported in the study publications for the GO-FORWARD, Kay *et al.* (2008) and GO-AFTER trials. Please provide a justification for the omission of this outcome. Please provide full additional analyses (with incorporation into meta-analyses, mixed treatment comparisons, indirect comparisons and economic analysis), incorporating this outcome.

A6. **Priority Question:** We are aware that open label extension data for the included golimumab studies are due to be published in abstract form in quarter 4 2010. Please specify whether data are available currently, and if so please provide.

A7. **Priority Question:** Please state whether any trials of the efficacy and safety of golimumab in combination with methotrexate in patients with RA after failure of previous disease-modifying antirheumatic therapy are ongoing. If so, please provide data where available.

A8. **Priority Question:** Please provide a) full up-to-date adverse events data available subsequent to the reporting of GO-FORWARD, Kay *et al.* (2008) and GO-AFTER for the use of golimumab in patients with rheumatoid arthritis. b) full up-to-date adverse events data relating to the use of golimumab in rheumatoid arthritis.

A9. **Priority Question:** Appendix 7, Page 224 onwards. The number of records from the adverse events searches appear to be very small for the seven interventions searched (i.e. 37 in Medline and 36 in Embase). Please clarify why these numbers are so low.

A10. **Priority Question:** Appendix 8, Page 227. The ERG considers non-randomised controlled trials to be a valid and important source of evidence for the evaluation of adverse events. Please describe any identified non-randomised controlled trial evidence relating to adverse events. If any such evidence was excluded, please justify in full reasons for exclusion.

A11. **Priority Question:** Page 86. Please clarify how 'serious adverse events' have been defined in this assessment.

A12. **Priority Question:** Please provide a full breakdown of the number and types of serious adverse events reported by treatment arm for the following golimumab trials: GO-FORWARD (including for published 52 week data [Keystone *et al.,* 2010]), Kay *et al.* (2008), GO-AFTER.

A13. **Priority Question:** Page 89. Please clarify how 'serious infections' have been defined in this assessment.

A14. **Priority Question:** Please provide a full breakdown of the number and types of a) infections and b) serious infections reported by treatment arm for the following golimumab trials: GO-FORWARD (including for published 52 week data (Keystone *et al.,* 2010)), Kay *et al.* (2008), GO-AFTER.

A15. **Priority Question:** Table 126, Page 114. Please a) define the malignancies referred to in this table, b) state whether these malignancies occurred in patients with other significant co-morbidities (eg. asthma) (as referred to the European Medicines Agency assessment report for Simponi), and c) provide any supporting up-to-date data on the occurrence of malignancies in patients receiving golimumab. Please also a) define the malignancies referred to in the published 52 week data (Keystone *et al.,* 2010) and b) state whether these malignancies occurred in patients with other significant co-morbidities (eg. asthma, as above).

A16. **Priority Question:** Please provide a full breakdown of all adverse events reported by treatment arm in the Kay *et al.* (2008) trial.

A17. **Priority Question:** Page 86 onwards. Please provide all available information on numbers of and causes of death by treatment arm for the following golimumab trials: GO-FORWARD (including for published 52 week data [Keystone *et al.,* 2010]), Kay *et al.* (2008), GO-AFTER.

A18. **Priority Question:** Please provide all available information on the impact of golimumab on liver enzyme levels and liver function.

A19. **Priority Question:** Page 86 onwards. Please present all available data on the impact of steroid use on adverse events among patients receiving golimumab (as referred to the European Medicines Agency assessment report for Simponi).

A20. **Priority Question:** Page 86 onwards. Please provide any available information on the management of and outcomes in patients for whom golimumab has been discontinued due to the development of infection.

A21. **Priority Question:** Table 14, Table 15, Table 176. Please provide trial identifier codes for included and excluded golimumab trials

A22. Section 2.7, page 23. The submission states that no significant adverse reactions of these treatments are known. The clinical advisors to the ERG group do not agree with this statement, on the basis that a range of significant adverse events, including serious infections, are known. Please comment.

A23. Page 14 and subsequently throughout document. The executive summary states that robust clinical and safety evidence is presented in the form of '2 large RCTs'; however 3 randomised controlled trials are described (GO-FORWARD, Kay *et al.* (2008), GO-AFTER) in the submission. Please clarify and correct this point.

A24. Page 28 onwards. Please confirm whether any searches were undertaken for any ongoing trials in research registers or databases (e.g. metaRegister of Controlled Trials, Health Technology Assessment Database)?

A25. Appendices relating to all search strategies, page 221 onwards. Please state the coverage dates for searches in PubMED and EMBASE.

A26. Please clarify why the searches for adverse events data were carried out in a different platform (Ovid) compared to the efficacy searches.

A27. Appendices relating to search strategies, page 221 onwards. Please state the coverage date for searches in Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R).

A28. Appendices relating to search strategies, page 221 onwards. Please provide the search strategy used for the Cochrane Library.

A29. Appendices relating to search strategies, page 221 onwards. Please clarify whether the below terms were used in the adverse events searches. If not, please justify their omission:

Rituxan

Tocilizumab or Atlizumab or Actemra or Roactemra

A30. Appendices relating to search strategies, page 221 onwards. Please clarify the use of statement 35 in the EMBASE search strategy (adverse events searches).

A31. Please clarify why the cost-effectiveness searches were carried out in a different platform (OVID) compared to the efficacy searches.

A32. Appendices relating to search strategies, page 221 onwards. Please clarify whether the following terms were used in the cost-effectiveness searches. If not, please justify their omission:

Simponi

Abatacept or Orencia

Certolizumab or Cimzia

Rituximab or Mabthera or Rituxan

Tocilizumab or Atlizumab or Actemra or Roactemra

A33. Please provide a full study description of the Kay *et al.* (2008) study.

A34. Page 107 onwards. Please state whether the analyses from the GO-AFTER study are presented in original form or in re-analysed form following the exclusion of patients from a single trial site in the efficacy analyses (as referred to in the European Medicines Agency document entitled: 'Simponi: procedural steps taken and scientific information after the authorisation').

A35. Page 100 onwards. Please a) clarify in full the handling of data from patients who received rescue therapy in golimumab trials and b) describe in full how these data were handled when deriving estimates for the economic model.

A36. Page 59 onwards. Please provide raw and meta-analysed data (with full heterogeneity estimates) for the etanercept analyses with the exclusion of the TEMPO study.

A37. Page 95 onwards. Please describe in full the number of and reasons for golimumab discontinuations due to adverse events.

A38. Page 107. Please clarify how upper respiratory tract infection, cough, nasopharyngitis and infections differ in terms of classification.

A39. Table 120, Page 107. Please clarify what the term adverse events and the numbers (placebo n=90, golimumab 50mg n=65) relate to in this table.

A40. Table 126, Page 114. Please clarify how upper respiratory tract infection, nasopharyngitis, cough, sinusitis and infections differ in terms of classification.

A41. Page 77 onwards. Please complete the labelling of tables to accompany the mixed treatment comparison and indirect comparison sections and confirm whether relative risk data are presented.

A42. Table 12, page 29. Not all outcomes listed in the decision problem are included in this table. Please provide justification for their omission.

A43. Page 31. Please note that the top box of the QUOROM flowchart appears to be incomplete. Please amend as appropriate.

A44. Please note that Section 2.8 (as referred to in the NICE specification) is absent in the submission document. Therefore, please identify the main resource use to the NHS associated with the technology being appraised. Describe the location of care, staff usage, administration costs, monitoring and tests. Provide details of data sources used to inform resource estimates and values.

A45. Table 66, page 87. The table heading states that these data relate to adalimumab. Please check and confirm whether this should read certolizumab.

A46. Table 166. This appears to be an accidental repeat of Table 164. Please clarify.

A47. Page 168. The value of 42% of existing and newly diagnosed patients being eligible for biologics was considered to be rather high. Please a) justify the choice of this value and b) describe the applicability of this value to the UK setting.

A48. Section 8.2.7, page 190. The description of the data abstraction strategy states that outcomes listed in Table 175 were sought. However, this table does not include all outcomes specified in the decision problem (and only lists measures of treatment efficacy: ACR responses, mean DAS or DAS28, number of patients achieving low DAS (<3.2), or DAS remission (<2.6), HAQ-D1; and measures of safety of safety and tolerability: adverse events, treatment discontinuations). Please clarify whether all outcomes specified in the decision problem were included in the systematic review and if any were omitted please justify their omission.

Indirect / mixed treatment comparison

A49. Section 5.6. The TNF inhibitor-experienced data is analysed in an indirect comparison using the Bucher method. Please clarify why a network mixed treatment comparison approach was not used (as in the DMARD-experienced population) and please provide a network mixed treatment comparison for this population.

A50. Page 82. I^2 Statistics are not provided in the mixed treatment comparison output. Please provide these values, and provide a comment on the estimate of heterogeneity.

Section B: Clarification on cost-effectiveness data

B1. **Priority Question:** Tables 130 and 131. In the DMARD experienced population, patients whose disease does not respond adequately to golimumab or a TNF inhibitor progress to leflunomide. However, as modelled in the TNF inhibitor experienced population, patients in UK clinical practice will progress to rituximab therapy. Please can you amend the DMARD experienced model to include rituximab at the appropriate position as determined by NICE appraisal TA126.

B2. **Priority Question:** Table 137. Please can you provide more detail on the Kristensen *et al* (2006) study used to estimate the long-term discontinuation rates and justify this choice of evidence. Please can you clarify how the estimate of 20 years (mean) is derived for methotrexate from the Edwards *et al* (2005) study. Please provide the calculation method and worked formula.

B3. **Priority Question:** Section 6. ACR70 response rates are not incorporated into the cost effectiveness analysis, and therefore underestimate the benefits of all treatments. Please incorporate ACR70 into your analysis, or justify your reasoning for not doing so.

B4. **Priority Question:** Page 128, Table 145, and Table 168. Please can you clarify the dosing regimen provided for rituximab, (whether it is re-administered every 6 (as referred to on page 126) or every 9 months (as referred to in table 145)) and the justification for this regimen. The submission refers to a number of international surveys to determine the frequency between rituximab infusions, please can you provide further justification with specific reference to UK clinical practice.

B5. **Priority Question:** Page 137. Please justify the selection of a 0.09 HAQ progression rate on palliative care, 0.045 on DMARDs, and 0 on TNF inhibitors. Please provide full details of any published evidence to support these rates.

B6. **Priority Question:** The HAQ progression rate for rituximab is not provided. However the model suggests that the assumed rate is that of conventional DMARDs rather than the TNF inhibitors. Please clarify the assumed HAQ progression rate for patients on rituximab therapy and provide further justification for its use. Please provide a sensitivity analysis using a value equal to the assumed HAQ progression rate for patients on any TNF inhibitor therapy.

B7. **Priority Question:** Section 6.5. Please clarify why a systematic search for resource used was not conducted. Please justify the choice of evidence used to model resource use.

B8. **Priority Question:** Table 146. Please provide further justification for the administration and infusion costs for infliximab, rituximab . Please compare to values accepted by appraisal committees when appraising these therapies previously and where these differ, please conduct a sensitivity analysis.

B9. Please can you confirm there are no other differences between the two submitted Excel files other than the patient population group selected/treatment sequence modelled?

B10. Sections 6.4.6, 6.4.7. A search for HRQoL data has not been conducted; instead a search for functions that map HAQ to HRQoL has been conducted. Please summarise the SF-36 data in the golimumab trials, and please provide a full justification for choosing to use a HAQ to utility mapping function to estimate utilities in the model.

B11. Page 152. Please justify the dosage used in the model of methotrexate as 7.5mg per week.

B12. Table 1. Please clarify that the model operates using a 24 week/6 month cycle length. The golimumab key features table (Table 1) suggests that response should be assessed at 12 weeks. Please could you clarify when assessment(s) take place and when a patient will be considered a non-responder. If it is more appropriate, then please adjust the model cycle length to incorporate a 12 week period.

B13. Section 6.3. Please could you clarify how the results of the mixed treatment comparison have been incorporated in the economic analysis, and why the CODA samples from the MTC using WinBUGS have not been used to maintain the correlation between parameters within the PSA. Please amend the model to incorporate the CODA samples.

B14. The economic model incorporate 2006 Reference Costs and 2008 Unit Costs. Please can you amend the model with the most up-to-date Reference and Unit Costs?

B15. Section 6.6. Please clarify how many PSA simulations are run. The model suggests 2000 runs and so please can you confirm how this number was estimated, and if appropriate increase the number of simulations and show stability in the mean results.

B16. Page 144. Please clarify how patients who receive rescue therapy are handled when estimating mean HAQ by health state from the golimumab trials.

B17. Table 142. Table 142 appears to be mislabelled as some rows have same health state but different data. Please correct or explain as appropriate.