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NHS
National Institute for Health and Clinical Excellence

NICE
Midcity Place
71 High Holborn
London
WC1V 6NA

Tel: 0160 870 3152
Fax: 0207 061 9764

Email: lori.farrar@nice.org.uk

www.nice.org.uk

Dear Yogesh

NICE Single Technology Appraisal – Golimumab for the treatment of psoriatic arthritis

The Evidence Review Group Centre for Review and Dissemination (CRD) and the technical team at NICE have now had an opportunity to take a look at submission received on the 15 June 2010 by Schering-Plough Ltd. 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, Tuesday 13 July 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 Sally Gallaugher – Technical Lead at sally.gallaugher@nice.org.uk. Any procedural questions should be addressed to Lori Farrar – Project Manager at lori.farrar@nice.org.uk in the first instance.

Yours sincerely

pp Frances Sutcliffe
Associate Director – Appraisals
Centre for Health Technology Evaluation

Encl. checklist for in confidence information

Section A: Clarification on effectiveness data

Outcomes

A1. **Priority question**: [P32, Table B3] The details of GO-REVEAL trial specify the modified van der Heijde-Sharp score at 24 weeks as a primary outcome measure. Please provide further summary data for this outcome at 24 weeks and 52 weeks if available or explain what happened to this primary outcome.

A2. **Priority question**: [P46, Table B6] Please provide data on the mean number of prior DMARDs and the proportion of patients with numbers of previous DMARDs for each arm of the GO-REVEAL trial.

A3. **Priority question**: [P68, Table B10] Please provide 95% confidence intervals for the relative risks and mean differences in the result sections of the GO-REVEAL trial. Please also provide the standard deviations for the mean values (e.g. HAQ changes from baseline).

A4. **Priority question**: [P68, Table B10] Please provide tabulated efficacy data of golimumab for the open-label extension at 52 weeks in the GO-REVEAL trial.

A5. **Priority question**: [P69, Table B10] Please provide comprehensive efficacy data (means and standard deviations, mean differences with 95% confidence intervals; event rates, relative risks with 95% confidence intervals) for the treatment arm receiving 100 mg golimumab at 14, 24 and 52 weeks in the GO-REVEAL trial.

A6. **Priority question**: [P90, Table B17] Please provide 95% confidence intervals for the relative risks for adverse events in the GO-REVEAL trial.

A7. **Priority question**: [P90, Table B17] Please provide tabulated adverse event data for the open-label extension at 52 weeks in the GO-REVEAL trial.

A8. **Priority question**: [P96, Section 5.9.3] Please provide further summary data on the adverse events of serious infections and tuberculosis for the GO-REVEAL trial.

A9. **Priority question**: [P166, Section 7.8] The manufacturer's submission (MS) states that golimumab is associated with a lower incidence of injection site reactions compared with other TNF-alpha inhibitors. Please provide summary supporting evidence.

Methods

A10. **Priority question**: Please provide full details of the intention to treat (ITT) method used in the analysis of GO-REVEAL trial at 14 & 24 weeks. Please clarify which method (e.g. last observation carried forward) was used to handle missing data, and whether the approach differed for different outcomes. Please provide full details on the methods used to deal with crossing over data in analyses.

A11. **Priority question**: [P27 & 28, Sections 5.2.1 & 5.2.2] The flow chart in section 5.2.2 describes two searches (efficacy and adverse events). Please clarify whether the study selection criteria described in section 5.2.1 relate to both types of searches. If not, please provide full details on the inclusion/exclusion criteria for the evaluation of adverse events.

A12. **Priority question**: [P28, Figure B1] Study selection flow diagram: Please provide all the references for the studies that are included in the evaluation of efficacy (n=43) and adverse events (n=32).

A13. **Priority question**: [P69, Table B10] Based on Table B10 and Figure B2 (p.60), it appears that the numbers included in the analyses of GO-REVEAL trial do not indicate an intention-to-treat method. Please provide full clarification on how the numbers included in the analyses of GO-REVEAL trial in Table B10 correspond to those reported in Figure B2 (p.60).

A14. **Priority question**: [P97] The MS states that 'in the RCT considered, golimumab has been administered for a period of 24 weeks before the non-responders switched to a higher dose'. However, based on the CONSORT flow chart for the GO-REVEAL trial (p.60), it appears that non-responders switched to a higher dose at week 16. Therefore please confirm whether the time for those non-responders switching to a higher dose was at week 16.

Mixed Treatment Comparison

A15. [P83, Section 5.7.5] Figure B9 and Table B15 imply that the analysis assumes that the change in HAQ and change in PASI are independent. The ERG would like further data to support this assumption. Please provide 2x2 tables for each treatment showing the number of patients with psoriasis at baseline who achieved PsARC response with and without achieving PASI 75 response, for golimumab and for placebo, in the GO-REVEAL trial.

A16. [P83, Section 5.7.5] For the reasons mentioned in the above point (A15), please also conduct a statistical test to show that the differences in mean PASI change are the same in PsARC responders and non responders.

A17. [P84, Section 5.7.5] The MS used the last randomised endpoint before week 24 to measure the change in HAQ and PASI. The ERG would like to check if this assumption is important. Please re-estimate the meta-analysis using data from the time point closest to 3 months.

A18. **Priority question**: [P86, Section 5.7.6] Results of Winbugs analyses are shown as absolute probabilities or changes from baseline for each drug for each outcome. It is difficult to use this table to assess a) Heterogeneity of relative treatment effects between the trials for each outcome b) Whether the pooled relative effects calculated by the analysis are in fact consistent with the original data from the RCTs. Given the complexity of the Winbugs code, the ERG would like to check that assumptions about priors or the structure of the analyses are not dominating the data. Please present relative treatment effects for each drug compared with placebo, for each outcome. To make comparison with trial results straightforward, relative risks or weighted mean differences (95% CIs) would be best.

Quality Assessment

A19. [P66, Section 5.4.3] There is insufficient information to allow for proper evaluation on the quality assessment of the GO-REVEAL trial in the submission. Please provide details of information relating to the randomisation method (e.g. centralised randomisation), concealment of allocation, and blinding (of patients, investigators and assessors).

A20. [P66, Section 5.4.3] For the reasons mentioned in the above point (A19), please provide details of the number of drop-outs in the different arms in the GO-REVEAL trial, to give evidence to support the MS statement that there were unexpected imbalances in drop-outs between groups for the GO-REVEAL trial.

Searches

A21. **Priority question**: [P170, Section 9.2] Appendix 2: Search strategy for section 5.1 (Identification of studies): The Cochrane Library (specifically CENTRAL) is listed as a resource searched, but there is no search strategy. Please clarify if this database has been searched and provide details of the search strategy if appropriate.

Section B: Clarification on cost-effectiveness data

B1. [P112, Section 6.2.2] Description of first cycle is missing in Figure B10. Please correct this figure.

B2. **Priority question**: [P113, Section 6.2.3] The MS states that Kyle 2005 recommends treatment with biologics for at least 6 months before the continuation decision. The ERG understands that the Kyle 2005 guideline recommends a continuation decision at 12 weeks / 3 months. Could the MS explain further which part of the guideline recommends a decision at 6 months, e.g. provide an exact quotation from the guideline to support this.

B3. **Priority question**: [P113, Section 6.2.3] The model appears to allow a treatment continuation decision at either 3 or 6 months. The base case should be 3 months. Please clarify that the base case is 6 months and that all sensitivity analyses are relative to this. In the scenario where a decision is made at 6 months, please clarify the data sources and results of the meta-analysis for PsARC responses and HAQ changes at this time. Please conduct sensitivity analyses to a 3month assessment.

B4. **Priority question**: [P118, Section 6.2.7] The sheet “Therapy costs” in the model refers to Golimumab 50mg or 100mg every 4 weeks. A 4-weekly cycle would not correspond to the number of doses given of Golimumab in the 1st and 2nd cycles (2.8 doses). Please confirm that the dose of Golimumab is 50mg every calendar month.

B5. **Priority question**: [P118, Section 6.2.7] The model assumes 50mg per month. The RCT showed that a proportion of patients increased dose to 100mg at 13 weeks to achieve or maintain response. Please provide evidence about what the mean or distribution of dosage would be in the long term in clinical practice. Please conduct a sensitivity analysis with the relevant proportion of the cohort on this higher dose with corresponding costs.

B6. [P122, Section 6.3.6] Table B 21 shows the baseline PASI is 9.9. Is this the mean in all patients or only those with psoriasis?

B7. [P122, Section 6.3.6] Does the data used to determine PsARC responder PASI change (only applied to those with >3% BSA) include patients with <3% BSA?

B8. **Priority question**: [P123, Section 6.3.6] An additional 4 hours of staff nurse time for administration of golimumab, adalimumab and etanercept has been added to the 1st cycle costs. This is in addition to the outpatient visit taken from reference costs. Please provide the justification for the inclusion of this additional cost and comment on the possibility of double counting the cost for training patients to self-administer.

B9. [P125, Section 6.3.7] The MS states that PASI would return to baseline and follow natural history thereafter following withdrawal from biologic. Please clarify if the 'natural history' of PASI is 'no change from baseline'?

B10. [P126, Section 6.3.7] The MS states the mean relative change in PASI in patients achieving PASI 25 and no higher improvement was 38.2%. Does this refer to patients who achieved between 25% and 49% improvement in PASI?

B11. [P130, Section 6.4.3] Table B22 shows the Gray algorithm for HRQOL includes PASI- squared and HAQ squared terms. These do not seem to be significant or have much impact on QOL in Table B24. Please exclude these terms from the regression and present the revised coefficients, the QOL equation. Please conduct a sensitivity analysis with the decision model using the revised Gray algorithm.

B12. [P132, Section 6.4.3] Table B25 indicates a non-zero PASI term for HRQOL, although this is for a group who has no psoriasis. Please provide justification for using a non-zero value for those without measurable psoriasis.

B13. [P143, Section 6.5.6] Please confirm the costs as a function of HAQ and PASI are for one year.

B14. **Priority question**: [P143, Section 6.5.6] Please provide further detail of the cost per PASI data and analysis. Please provide (CIC if necessary):

- The data for each specialist
- The summary of the data by question
- The unit costs used in the analysis of the data (i.e. for inpatient, outpatient, phototherapy, drugs)
- The method of analysis (e.g. simple mean / OLS)
- A measure of variance

B15. **Priority question**: [P151, Section 6.7.7] Table B33 shows the sensitivity analyses as ICERs versus palliative care. Please include another column in Table B33 showing the incremental ICER of golimumab versus the next best alternative for each scenario, or indicate if extendedly dominated

B16. **Priority question**: [P151, Section 6.7.7] The results of the sensitivity analyses are deterministic. Please provide the probability that golimumab is the most cost-effective at 20,000 and 30,000 per QALY for each sensitivity analysis, relative to all the other strategies (not just palliative care).

B17. [P151, Section 6.7.7] The analysis has assumed vial sharing. Please provide a sensitivity analysis assuming that vial sharing is not permitted.

B18. **Priority question**: [P152, Section 6.7.7] NICEs position in the previous MTA of biologics for PsA was that all the biologics have similar effectiveness in terms of PASI, HAQ and PsARC response. Please carry out an additional sensitivity analysis reflecting NICEs position with regard to biologics for PsA in the previous MTA.

B19. **Priority question**: [P153, Section 6.7.8] The cost effectiveness acceptability curves are shown for each biologic relative to palliative care. Please provide a figure showing the probability that each is the most cost effective compared with all the other strategies.

B20. **Priority question**: [P207, Section 9.14] There are no measures of variance. Please show the standard errors in the table for mean HAQ changes from baseline.

B21. **Priority question**: [Model] When selecting the York_MTA option for QOL values, this returns an error on the New QOL sheet. Please provide a corrected version of the model.

Section C: Textual clarifications and additional points

C1. In the version of the MS with the filename "GLM in PsA - NICE STA - Final_CIC marked", it appears that the responses in the appendices 12 and 13 have been completed but in the version named "GLM in PsA - NICE STA - Final", they have not. Please clarify whether these are the only differences between the two versions of the MS (aside from CIC marking).