National Institute for Health and Clinical Excellence

NICE
1a City Tower
Piccadilly Plaza
Manchester
M1 4BD

Tel: 0161 870 3152
Fax: 020 761 9764

Email: lori.farrar@nice.org.uk

www.nice.org.uk

Dear [redacted]

Re: Single Technology Appraisal – Tocilizumab for the treatment of systemic juvenile idiopathic arthritis

The Evidence Review Group Kleijnen Systematic Reviews Ltd and the technical team at NICE have now had an opportunity to take a look at submission received on the 5 April 2011 by Roche Pharmaceuticals. 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, Tuesday 17 May 2011**. 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 Alfred Sackeyfio – Technical Lead Alfred.sackeyfio@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]

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Centre for Health Technology Evaluation

Encl. checklist for in confidence information

Section A: Clarification on effectiveness data

Requests for additional data

A1 **Priority question:** Please provide full clinical study reports for the TENDER study, as well as MRA316JP, MRA317JP and MRA324JP.

A2 **Priority question:** Please describe which proportion of participants in each trial (especially TENDER) were MTX non-responders; and provide separate data for these participants only (including AEs).

A3 **Priority question:** Please provide similar tables as table 23, page 106 MS, for all other relevant outcomes mentioned in the NICE scope (including AEs), with data separately reported for children and young people 2 years and older who used MTX and those who did not.

Treated with and without methotrexate

A4 **Priority question:** Looking at the response for placebo without MTX (45%) versus the response for placebo with MTX (15%) (see table 23, page 106 MS), it looks like MTX is harmful in these patients; is this interpretation correct?

A5 **Priority question:** Please provide a list of patient characteristics and relevant outcomes (including AEs) mentioned in the NICE scope at baseline for children and young people 2 years and older with MTX and without MTX.

A6 **Priority question:** The indirect comparisons described in section 5.7 are for population 2 as described in the NICE scope: "Children and young people 2 years and older with systemic JIA which has not responded adequately to prior NSAID(s), systemic corticosteroids and methotrexate." However, the data from the TENDER trial used in the analyses (table 36, page 141 MS) are for the combined population of children (with and without MTX), irrespective of MTX response. Please provide the relevant data (including AEs) from the TENDER trial for children and young people 2 years and older who have not responded adequately to prior NSAID(s), systemic corticosteroids and methotrexate – i.e. not just children and young people 2 years and older who did not use MTX, but children and young people 2 years and older who did not respond adequately to MTX.

Additional clarifications on clinical effectiveness

A7 Please provide references for the 6 excluded citations that did not report ACR outcomes and the 4 non-English citations, plus any duplicates relating to these (see Figure 11, page 115 MS).

A8 For the 6 excluded citations that did not report ACR outcomes, were any other relevant outcomes (see NICE scope) reported?

Literature searches

A9 For section 9.2.3 'Date span of search' please provide the issue numbers for the searches of CDSR and CENTRAL, as part of the Cochrane Library search. For example, CDSR Issue 1:2011.

A10 Please can you can you clarify why the comparators were not included in the search strategy of the outcomes but were included in the search for adverse events.

A11 Please provide the search terms for the ACR & EULAR searches. Please provide URLS for the ACR & EULAR conference abstracts searched in section 9.2.4.

A12 Please provide details of the searching undertaken to perform the rapid review described on page 116. Please provide full search strategies, details of databases, database providers, search date and date span.

A13 For the date span of searches for indirect and MTC searches in section 9.2.3, please provide the issues numbers for the Cochrane Library search.

A14 Please provide the full search strategy, including issue number and all terms searched, for the Cochrane Library searches for the indirect and MTC searches in section 9.4.4.

A15 Please provide the issues numbers for the Cochrane Library search for the date span of adverse events searches in section 9.8.3.

A16 Please provide URLS for the ACR & EULAR conference abstracts searched for the search strategies for the adverse event searches in section 9.8.4.

<u>Section B: Clarification on cost-effectiveness data</u>

Model structure

B1 **Priority question:** Please could you redo the cost effectiveness analyses by restructuring the model in health states defined by CHAQ values and use response to treatment to define transition probabilities. The current economic model does not adhere to conventions in Markov modelling. In a Markov model the health states defined should comprise the full range of conditions that are relevant to a patient population, and the states should be mutually exclusive. In the submission, the health states defined reflect a *change* in a patients' condition (change in CHAQ based on ACR response) instead of the absolute condition of the patient. Change in a patients' condition should be included in a Markov model as a health state transition and not as a health state as such. The consequence of using a change in a patients' condition as a health state is that the Markov states are heterogeneous and not mutually exclusive regarding a patients' condition, depending on the disease variation of the cohort at the start of the model. In fact a patient uniquely defined by absolute CHAQ can be situated in any of the ACR-response defined health states. Besides this, the ultimate objective of the model is to report cost-effectiveness in terms of efficiency of interventions expressed in QALYs. As reported, the utility values are not directly linked to the ACR-response (and thus health states) but indirectly via a CHAQ value. Therefore absolute CHAQ is a more accurate parameter to distinguish health states, but absolute ACR score may also be considered. Another way to address this problem would be to use the current model and redo the analysis including a patient level simulation. This will make it possible to define the cost and utility value of a health state depending on the starting CHAQ-value and change in CHAQ in relation to ACR-response.

B2 **Priority question:** Based on Fig 13, page 216 MS, it seems that transitions between ACR-response categories is impossible. Please redesign this figure so it reflects all possible health states and all possible transitions between health states

Treatment strategies

B3 **Priority question:** In the submission MTX is considered not to have impact in terms of treatment response (p 211: it can be assumed that they have inadequate response). Please provide evidence that MTX treatment is inadequate in these patients. Otherwise, this combination treatment should be regarded as a separate strategy, thus in the first population (failure on NSAIDS and corticosteroids) the option tocilizumab/MTX should be included as a separate strategy. Please provide a comprehensive cost-effectiveness analysis comparing MTX alone vs. Tocilizumab alone vs. MTX/Tocilizumab combination treatment and describe the uncertainty of the cost-effectiveness results in cost-effectiveness acceptability curves.

B4 **Priority question:** Please provide observed standard deviations and confidence intervals for the data in tables 74 and 75, pages 213 and 215 of MS.

B5 **Priority question:** Please provide evidence that treatment efficacy is constant regarding the life expectancy of patients. If not, please provide sensitivity analyses using loss of treatment efficacy.

B6 **Priority question:** On page 227 of MS and in figure 14, a constant risk of withdrawal from biologicals is assumed. Please provide full details on other models considered, especially goodness-of-fit statistics. Also, please provide the SEs for the parameter estimates.

B7 **Priority question:** As previous question but for mortality risk (figure 15): please provide full details on other models considered, especially goodness-of-fit statistics. Also, please provide the SEs for the parameter estimates.

B8 **Priority question:** In table 87, page 236 of MS a summary of variable values is presented, with the distributions used in the PSA. The text in the table for the various transition probabilities is unclear 'assume N=alpha of the one parameter Gamma distribution for each ACR category'. This seems to suggest that the true N is used in deriving random draws from the Dirichlet distribution. However, in the electronic model, N=100 is assumed for all treatments and all transitions. Please change the model input to reflect the true N on which the transition probabilities are based, and provide the PSA outcomes.

B9 **Priority question:** For table 87, page 236 of MS, please provide more details on the confidence interval used for withdrawal and mortality risk. Please discuss if for example the standard errors of the regression parameters have been used to assess the amount of uncertainty around the point estimate.

B10 **Priority question:** In the main analyses adjustments based on Prince 2009 are performed. Please add a sensitivity analysis using not only a variation of the Prince adjustment but use the raw Prince data as mentioned in Table 83.

B11 **Priority question:** Both internal and external model validation are lacking. If possible please verify model outcomes with real life data (external validity), for instance using the trial data on follow up CHAQ-score. If the pivotal trials collected utility data, please validate the model against these data as well. Besides this, show the internal validity of the model for instance by performing extreme values analyses.

Additional clarifications on cost effectiveness

B12 Please justify why in section 6.1.1 papers not in English were excluded. Please provide a reference list of those papers excluded.

B13 Please confirm that in table 74, page 213 MS, ACR-response refers to the 12 week follow up measurement of patients.

B14 Please confirm that the probabilities mentioned in tables 80 and 82, pages 229 and 234 MS, refer to ACR response as determined after 12 weeks of treatment.

B15 Please explain what the word 'sampling' refers to in table 87, page 236 MS, related to utility values.

B16 The costs associated with the heath states show a very large difference between patients without response and patients with response. While the difference between ACR90 and ACR30 is only 171.44, the difference between ACR30 and no response is 3094.91. Please justify these differences, considering that the only source of information was expert opinion.

B17 Related to the previous question please justify the remark in table 97, index 21, that the current assumptions about cost of inpatient stay are conservative.

B18 Please provide a new PSA with larger margins around the duration of hospitalisation and the percentage of patients requiring hospitalisation.

Literature searches

B19 For section 6.1.1 please clarify whether the required database, EconLIT, was searched.

B20 For section 9.10.2 please provide the date HEED was searched.

B21 According to page 202 of the MS, HEED was searched to identify cost-effectiveness evaluations. Please provide the full search strategy, date searched and date span for the HEED search.

B22 Please provide the full search strategy for the NHS EED search.

B23 Section 6.4.5 states that the cost-effectiveness searches details in 6.1.1 were also used to retrieve HRQL references. Please explain why the search strategies described in 6.1.1 and 9.10 do not include terms such as 'HRQOL' or HRQL instruments such as EuroQOL, EQ5D or SF36.