# National Institute for Health and Clinical Excellence

# Centre for Health Technology Evaluation

## Pro-forma Response

## Executable Model

## Psoriatic Arthritis - etanercept, infliximab & adalimumab

The economic model enclosed and its contents are confidential and are protected by intellectual property rights, which are owned by the **Centre for Reviews and Dissemination/Centre for Health Economics, University of York**. It has been sent to you for information only. It cannot be used for any other purpose than to inform your understanding of the appraisal. Accordingly, neither the model nor its contents should be divulged to anyone other than those individuals within your organisation who need to see to them to enable you to prepare your response. Those to whom you do show the documents must be advised they are bound by the terms of the Confidentiality Acknowledgement and Undertaking Form that has already been signed and returned to the Institute by your organisation.

You may not make copies of the file and you must delete the file from your records when the appraisal process, and any possible appeal, are complete. You must confirm to us in writing that you have done so. You may not publish it in whole or part, or use it to inform the development of other economic models.

**The model must not be re-run for purposes other that the testing of its reliability**.

Please set out your comments on reliability in writing providing separate justification, with supporting information, for each specific comment made. Where you have made an alteration to the model details of how this alteration was implemented in the model (e.g. in terms of programme code) must be given in sufficient detail to enable your changes to be replicated from the information provided. Please use the attached pro-forma to present your response.

Please prepare your response carefully. Responses which contain errors or are internally inconsistent (for example where we are unable to replicate the results claimed by implementing the changes said to have been made to the model) will be rejected without further consideration.

Results from amended versions of the model will only be accepted if their purpose is to test robustness and reliability of the economic model. Results calculated purely for the purpose of using alternative inputs will not be accepted.

No electronic versions of the economic model will be accepted with your response.

Responses should be provided in tabular format as suggested below (please add further tables if necessary).

**December 2009**

## Issue 1 Mixed Treatment Comparison Inputs provided to different levels of precision

| Description of problem | Description of proposed amendment | Result of amended model or expected impact on the result (if applicable) |
|---|---|---|
| The HAQ changes for etanercept are provided to 3 decimal places, to 2 decimal places for infliximab, and to 1 decimal place for adalimumab.<br><br>In order to assess the impact of rounding to different decimal places, Abbott have re-run the MTC with the HAQ changes rounded to 2 decimal places for each drug.<br><br>A comparison of the results shows that this issue has a large impact on the mean HAQ improvements for both adalimumab responders and non-responders, with an increase of 0.0506, and 0.0573 respectively. | Since the results of the MTC are so sensitive to the number of decimal places reported for the change in HAQ, Abbott has provided these data to 4 decimal places in Appendix 1 of our response to the Assessment Group report.<br><br>Abbott suggests that the Assessment Group request the data to this level of detail from the other manufacturers and uses these data to re-run the MTC and the cost-effectiveness analysis. | Since Abbott does not have access to the response rates from the etanercept and infliximab clinical trials to this level of accuracy, we were unable to determine the exact impact this change will have on the cost-effectiveness results.<br><br>However, given that the differences in the change in HAQ between treatments is a key driver of the results, the improvement in HAQ observed when more precise data is used for adalimumab will result in an increase in QALYs for adalimumab thus changing the cost-effectiveness results. |

## Issue 2 The meta analysis used to inform the changes in HAQ for each treatment fails to adjust for differences in baseline HAQ scores

| Description of problem | Description of proposed amendment | Result of amended model or expected impact on the result (if applicable) |
|---|---|---|
| Since a patient's baseline outcome is likely to be strongly correlated with their change in outcome over the follow-up period, the concept of baseline adjustment with respect to the analysis of outcome measures is well understood in the clinical trial literature and the health economic literature. In the trials of PsA included in the MTC, it is clear there are differences in baseline HAQ.<br><br>Data from both the ADEPT and M02-570 trials indicate that there is a clear relationship between baseline HAQ and HAQ change<br><br>A failure to adjust for baseline HAQ when considering HAQ change in the MTC will therefore bias the results of the analysis. | In order to assess the impact of baseline HAQ on the change in HAQ, Abbott adapted the MTC code as outlined in our response to the Assessment Group report.<br><br>After adjusting for baseline HAQ, the mean HAQ improvement increases for both adalimumab responders and non-responders.<br><br>Abbott requests that the Assessment Group re-run the analyses using more precise input values for each of the anti-TNF therapies (see issue 1 above), and adjusting for baseline HAQ as it appears that these changes will have a significant impact on the results. | The baseline HAQ level used in the base case analysis is higher than was observed in the adalimumab trials, but lower than the baseline HAQ in either the etanercept or infliximab trials.<br><br>It is therefore expected that in contrast to the impact on the mean HAQ improvement for adalimumab, adjusting for baseline HAQ would result in a decrease in the mean HAQ improvement for etanercept and infliximab.<br><br>Abbott therefore expect that this analysis will result in increased QALYs for adalimumab and worse QALYs for infliximab and etanercept. |

## Issue 3 Probabilistic Sensitivity Analysis does not appropriately reflect the uncertainty in the results

| Description of problem | Description of proposed amendment | Result of amended model or expected impact on the result (if applicable) |
|---|---|---|
| The base case analysis indicates that the cost-effectiveness of adalimumab and etanercept versus palliative care are very | Although the exact cause of this issue is not clear, sensitivity analysis 22 suggests that this apparent lack of uncertainty is driven to a large extent by the HAQ change by PsARC | Abbott anticipates that if the PSA was adapted to incorporate all of the uncertainty around the model inputs, the probability of |

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| similar, with ICERs of £17,274 and £15,990 respectively.<br><br>Furthermore, the results of the mixed treatment comparison indicate that there is significant overlap in the credible intervals for response – in particular for ACR and PsARC response rates.<br><br>It is therefore surprising that the probabilistic sensitivity analysis shows that there is very little uncertainty in which is the most cost-effective of these two treatments (p=0.524 for etanercept and p=0.044 for adalimumab). | responder/non-responder. In this analysis, it is assumed that HAQ change depends only on PsARC response rate, and does not differ between treatments, which clinical opinion suggests is an equally plausible assumption.<br><br>Under this assumption, the probability that adalimumab is the most cost-effective treatment at a threshold of £20,000/QALY increases to 0.198 while the probability that etanercept is the most cost-effective treatment falls to 0.400.<br><br>Abbott therefore propose that the PSA should be amended to ensure that the uncertainty around the differences in the change in HAQ by PsARC responder/non-responder is fully incorporated. | adalimumab being the most cost-effective treatment would be similar to that for etanercept. |

## Issue 4 Infliximab drug and administration costs are underestimated in the model

<table>
<tr><th>Description of problem</th><th>Description of proposed amendment</th><th>Result of amended model or expected impact on the result (if applicable)</th></tr>
<tr>
<td>The Assessment Group assumes an average patient weight of 70kg based on the average weight of the UK population. However, analysis of the clinical trial data indicates that the average weight of PsA patients is 87kg.<br><br>Since infliximab has a weight-based dosing schedule, patients weighing over 80kg would require one additional vial than patients weighing 70kg which will increase the costs associated with infliximab.<br><br>Furthermore, the Assessment Group assume a ½ day in-patient hospital cost for each infusion of infliximab at a cost of £144 per infusion. However, since an infliximab infusion is more likely to be a day case rather than an in-patient procedure, this would be a more appropriate cost to use. The NHS reference</td>
<td>Abbott proposes that the following drug costs should be applied for infliximab:<br><br>
<table>
<tr><th></th><th>Vials per dose</th><th>Doses</th><th>Cost per vial</th><th>Total cost</th></tr>
<tr><td>0-12 weeks</td><td></td><td></td><td></td><td></td></tr>
<tr><td>Infliximab (87kg patient)</td><td>5</td><td>3</td><td>£419.62</td><td>£6,294.30</td></tr>
<tr><td>12-24 weeks</td><td></td><td></td><td></td><td></td></tr>
<tr><td>Infliximab (87kg patient)</td><td>5</td><td>2</td><td>£419.62</td><td>£4,196.20</td></tr>
<tr><td>24 weeks +</td><td></td><td></td><td></td><td></td></tr>
<tr><td>Infliximab (87kg patient)</td><td>5</td><td>1.625</td><td>£419.62</td><td>£3,409.41</td></tr>
</table>
<br>Abbott also proposes that a cost of £462 per administration should be used.</td>
<td>Increasing the drug and administration costs for infliximab will increase their ICER and reduce the probability that they are cost-effective.</td>
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| costs (2007/08) indicate that the cost would therefore be £462. | | |

(please cut and paste further tables as necessary)