

10 December 2010

NHS
**National Institute for
Health and Clinical Excellence**

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Dear [REDACTED],

Re: Single Technology Appraisal – Abatacept for the treatment of rheumatoid arthritis after the failure of conventional disease-modifying anti-rheumatic drugs

The Evidence Review Group, the School of Health & Related Research Sheffield and the technical team at NICE have now had an opportunity to take a look at submission received on the 19 November by Bristol-Myers Squibb. 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, 7 January 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 Scott Goulden – Technical Lead (scott.goulden@nice.org.uk) Any procedural questions should be addressed to Jeremy Powell – Project Manager (jeremy.powell@nice.org.uk) in the first instance.

Yours sincerely

Elisabeth George
Associate Director – Appraisals
Centre for Health Technology Evaluation

Encl. checklist for in confidence information

Section A: Clarification on effectiveness data

Literature searches

- A1. **Priority question:** Please clarify why only two studies of infliximab were included in the network of studies (Figure B25) when a recent systematic review of infliximab plus methotrexate vs methotrexate alone (Zintzaras et al Clinical Therapeutics 2008;30(11):1939-1955) included 12 studies. What criteria were used to select the studies included in the submission? Furthermore, please detail the criteria used to select the trials for the remaining interventions within the network meta analysis.
- A2. Page 26: Please confirm whether any searches were undertaken for any ongoing trials in research registers or databases (for example, metaRegister of Controlled Trials, Health Technology Assessment Database)?
- A3. Pages 67-68: In section 5.2.1, the electronic literature searches were said to have identified a total of three clinical trials and two long-term extension studies. However, the QUOROM diagram also indicates that two relevant 'clinical study reports' were also identified. Please provide details of these reports.

Population

- A4. Page 33: In section 2.2, it is estimated that 346,357 adults have RA; this figure appears to apply to the UK. However, in Table C 1 it appears to relate only to England and Wales. Please provide clarification on this point.
- A5. Page 33: It is estimated in the submission that 10% of the total rheumatoid population has a DAS28 of ≥ 5.1 , and 30% has a DAS28 of ≥ 3.2 . It is also reported that 10% of the estimated eligible population receive an IV administered biologic agent. Please provide clarification of the source of these figures.

Comparators

- A6. **Priority question:** Please clarify why a treatment sequence was used that did not include a second biologic agent or rituximab.
- A7. **Priority question:** Please explain if the inclusion of trials on rituximab and tocilizumab would help to complete the network meta analysis, and if so please include these trials.

Clinical evidence

- A8. **Priority question:** Please clarify the relationship assumed in the model between an increase in the dosage of infliximab and efficacy. Please confirm whether the efficacy has been taken from RCTs in which the dose of infliximab remained constant?
- A9. **Priority question:** Please provide the rationale for why the distribution for 'time on treatment' for patients whose disease responds to treatment is assumed equal for all biologics (p252), whereas the differential effects on HAQ change from baseline and in serious adverse events are not assumed equal for all biologics

- A10. **Priority question:** Please confirm whether weight-based dosing is assumed for infliximab.
- A11. **Priority question:** Please confirm whether there are any statistically significant differences between abatacept and infliximab observed within the ATTEST trial.
- A12. Page 26 and 70: Please provide trial identifier codes for the AIM, ATTEST, Kremer Phase 2b and ATTAIN trials
- A13. Page 42: In section 2.8, please provide details of the location of care, staff usage, administration costs, monitoring and tests associated with the use of abatacept.
- A14. Pages 60/85: Table A2 states that the outcomes addressed in the submission were those specified by NICE in the scope, namely disease activity; physical function; joint damage; pain; mortality; fatigue; extra-articular manifestations of disease; adverse effects of treatment; health related quality of life. However, on pages 85-86, the outcomes discussed in considering the decision problem appear to exclude the following: pain (except inasmuch as it is included in the ACR 20/50/70 responses), mortality, and extra-articular manifestations of disease. Please provide data on these outcomes or state where data are not available. Alternatively, please provide justification for the exclusion of those outcomes.
- A15. Page 76: Please clarify why the primary objective of the AIM study was ACR20 at 6 months but HAQ at one year.
- A16. Page 79: Please clarify why, in the Kremer Phase 2b study, ACR20 was assessed only at 6 months, while ACR50 and ACR70 were assessed at 6 months and 1 year. If ACR20 data are available at 1 year, please provide them.
- A17. Page 95: Please provide a clinical rationale for the various subgroup analyses undertaken on data from the AIM and ATTEST trials.
- A18. Please provide the results from the placebo arms of the non-abatacept trials used in the network meta-analysis, with a particular focus on the infliximab trials that may be used for an indirect comparison.
- A19. Page 100: Please clarify why, in relation to all three trials, the text of the submission states that 'it is not clear if allocation was adequately concealed' but Table B10 indicates that concealment of treatment allocation was adequate.
- A20. Pages 105 – 115: Please indicate the number of patients included in Figures B7, B10, B13, B16, and B19.
- A21. Page 120: The text describes the number of missed infusions in the ATTEST trial. Please confirm that the mean is 0.2 and the median is 0 rather than vice versa.
- A22. Page 128: Table B 19 Please clarify the meaning of NR in this table? Please comment on why point estimates and 95% confidence intervals not provided, whereas p-values are given?

A23. Page 140: Tables B25, B26 B27, B28, B29 and B30: The power of the test for heterogeneity between trials is low, particularly with a limited number of trials. Please present a random effects meta-analysis allowing for uncertainty in the true value of the between-study standard deviation.

Please also clarify how missing standard errors were taken into account in meta-analyses of continuous outcome measures.

A24. Page 193: Table B57 describes the sustained ACR50 and ACR70 response over time. Please provide a statistical comparison of sustained response between abatacept and infliximab

A25. Page 199: Provide statistical evaluation and p-values for adverse events and discontinuation rate

A26. Page 200: Please confirm that the percentage urinary tract infection in the placebo arm of the AIM trial should be 5.0%.

Section B: Clarification on mixed treatment comparison

A27. Page 170: Sections 5.7.6.1, 5.7.6.3, 5.7.6.5 and 5.7.6.7: Please present results compared to placebo, and present estimates of the between study standard deviation together with their 95% credible intervals. Please also clarify what measures were taken to explain the heterogeneity between trials (that is, to reduce the between-study standard deviation through methods such as meta-regression)

A28. Page 170: Sections 5.7.6.2, 5.7.6.4, 5.7.6.6 and 5.7.6.8: It is assumed that “adjusted mean HAQ CFB” means the presentation of absolute mean change from baseline. The estimate of the abatacept change from baseline is based on the average of the population means from each trial. Although baselines are typically assumed to be fixed when estimating treatment effects, baselines will vary across trials. Please provide a rationale for not modelling the abatacept change from baseline using a random effects model

A29. Page 172: Section 5.7.7: The estimates of the residual deviance are incorrect in the case of the models for continuous data because they assume that the standard errors of the means are known and equal to the sample standard errors. Please present total residual deviances for each model and discuss any large individual deviance values for treatment arms.

A30. Page 173: Section 5.7.8: Whilst a random effects meta-analysis quantifies the degree of heterogeneity between trials, the resulting posterior distribution in the presence of uncertainty means that the treatment effect varies with trial. Please clarify what measures were taken to evaluate differences between trials.

A31. Page 174: Section 5.7.9: Please clarify how the abatacept response rates were estimated from the MTC given that abatacept was the baseline treatment used in the meta-analysis.

A32. Page 332: Section 9.4.8: The models for continuous data (Code 1 and 2) appear to be incorrect, as they assume that the within study standard error is known and equal to the sample standard error. Please could you amend the analysis to allow for uncertainty in the between study standard deviation. The

models should include the data to allow for checking of the analysis. Please also clarify how any missing standard errors to be accounted for in the analyses of continuous data e.g. Kramer, Table B20, Page 129.

Section C: Clarification on health economic model

- A33. **Priority question:** Please present the cost-effectiveness results incrementally (with the identification of interventions that are dominated or extendedly dominated).
- A34. **Priority question:** Please confirm whether the CODA (the convergence diagnostic and output) from the WinBugs output was used in the modelling, or whether the data were transformed into independent normal distributions. A proper representation of uncertainty should be based on the results of the MTC and will use samples from the joint posterior distribution, thereby preserving the unknown underlying distribution and correlation between treatments.
- A35. **Priority question:** Please clarify the rationale for assuming that serious adverse events are not associated with a cost implication.
- A36. **Priority question:** Please tabulate the proportion (and associated confidence intervals) of patients likely to respond to each treatment at 6 months.
- A37. **Priority question:** The Cost Effectiveness Acceptability Curve (CEAC) should detail the probability of each intervention being cost effective, and therefore the summation of the individual probabilities should equal 100%. Please provide a correct CEAC that considers the interventions simultaneously
- A38. Page 236: The results from the Vera Llonch study appear internally inconsistent in that an incremental cost of £68k and an incremental QALY of 1.1 does not appear to produce an ICER of £43k. Please check and clarify.
- A39. Page 251: Table B75: Please provide a rationale for using results of a fixed effects model for the analysis of serious adverse events (SAEs).
- A40. Page 251: Please provide confidence intervals for the long-term HAQ progressions reported in Table B75.
- A41. Page 260: Please clarify if in the citation of the Hurst et al utility equation the final term should be relates to HAQ squared rather than to HAQ alone.
- A42. Page 263: Please confirm that the utility derived from the HAQ score is based on the individual patient's HAQ score rather than placing the HAQ within a band (e.g. 1.25-1.50) and using the midpoint from that HAQ range. If the latter, please justify why the loss in accuracy was necessary.
- A43. Page 276: Table B84 describes the parameters in the probabilistic sensitivity analyses:
- Please confirm that there should be no value in the placebo and MTX row as this is the metric with which the other treatments are compared.

- Please provide a justification for the uncertainty associated with patients who fail on treatment, treatment duration, discontinue due to SAEs and have dose increases, and in the utility parameters.
- Please clarify assumptions made about the correlation between parameters and revise the analysis if correlation is currently assumed to be zero. An analysis based on a normal distribution should model the intercept, slope and slope2 as being multivariate normally distributed.
- Please clarify what 'assumed 20%CrL' and 'assumed 20%' refer to.

A44. Page 281: Please confirm if the admin costs for certolizumab should be £30?

A45. Page 283: Table B88. Please confirm if the last column should be labelled the cost effectiveness of abatacept compared with the intervention.

A46. Page 299: Table C3. Please confirm whether the value for infliximab in scenario 2 should be 9,321?