From: [redacted] [redacted]
Sent: 27 February 2008 17:35
To: Natalie Bemrose
Cc: Carole Longson; [redacted]
Subject: TNF inhibitors for seqeuntial treatment of Rhuematoid Arthritis - Schering-Plough comments on additional analyses

Importance: High

Attachments: S-P comments on the RA sequential analyses.DOC

Dear Natalie,

Please find attached a letter containing Schering-Plough's response to the additional analyses conducted by the Decision Support Unit and the Assessment Group.

I would also like to draw particular attention to our comments regarding the process for this additional analysis and the subsequent appraisal of TNF inhibitors in the sequential treatment of rheumatoid arthritis. It is Schering-Plough's view that given the broadening of the scope of this separate appraisal and given the fact that the appraisal was formally split towards the end of 2007, the failure of the Institute to invite further evidence submissions from consultees with regard to the sequential use of TNF inhibitors has placed Schering-Plough at a disadvantage in this appraisal. This is obviously a matter of considerable disappointment and we would welcome comment from the Institute.

I would be grateful if you could acknowledge receipt of this email and our letter.

Kind regards,

[redacted]

[redacted]

[redacted]

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27th February 2006

Natalie Bemrose,
Technology Appraisal Project Manager
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MidCity Place
71 High Holborn
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Dear Natalie,

RE: ADALIMUMAB, ETANERCEPT AND INFLIXIMAB FOR THE TREATMENT OF RHEUMATOID ARTHRITIS - ADDITIONAL ANALYSIS REGARDING THE SEQUENTIAL USE OF TNF INHIBITORS.

Schering-Plough welcomes the opportunity to comment on the additional analyses commissioned by NICE following its decision to split the appraisal of TNFα inhibitors in rheumatoid arthritis. Our comments are set out below in relation to the three separate sets of analyses as follows:

1. The Effectiveness Of Non Biologic DMARDS After Anti TNFα Inhibitor Failure
   (produced by the Decision Support Unit)

2. The Sequential Use Of TNFα Inhibitors
   (produced by the Decision Support Unit)

3. Further cost-effectiveness analysis of sequential TNFα inhibitors for rheumatoid arthritis patients
   (written by Dr Pelham Barton)

Aside from our comments on the technical content of these reports, Schering-Plough would also like to comment on procedural aspects of this appraisal. In the Institute's written request for consultee comments on the additional analyses we are asked to note that these reports are only one component of the evidence that the Appraisal Committee will use to inform their recommendations to the Institute. Other components are reported to include the assessment report, the comments received during this consultation, submissions received from consultees and the views and experience of clinical specialists and patient experts. Importantly however,

consultees have not been given an opportunity to submit further evidence in relation to the specific issue under consideration in this separate appraisal – i.e. sequential use. Given the separation of the original appraisal into two parts – first use and sequential use, and given the broadening of the scope of this appraisal to include consideration of rituximab as a comparator, it is disappointing that additional evidence (aside from consultee comments) is only being submitted by the Assessment Group and the Decision Support Unit. It is our view that this restrictive approach to the separate appraisal of sequential use has put Schering-Plough and other consultees at a disadvantage. It is also apparent that other ongoing appraisals, albeit within the Single Technology Appraisal process, allow further evidence submission by consultees subsequent to the splitting of an appraisal – e.g. infliximab for ulcerative colitis. It is not clear why the Institute decided to limit the provision of further evidence within the appraisal of TNFα inhibitors for sequential treatment of rheumatoid arthritis, indeed there was to our knowledge no consultation outside the Institute on this matter. However, Schering-Plough believes that the separate appraisal of sequential use should have allowed for additional consultee evidence submissions.

Notwithstanding Schering-Plough's disappointment with the process for this separate appraisal of the sequential use of TNFα inhibitors, our comments on the technical aspects of the additional analyses are set out below.

1) The effectiveness of non biologic DMARDS after anti TNF-a inhibitor failure

Schering-Plough is satisfied that the additional analyses of non biologic DMARDs after TNFα inhibitors have been conducted appropriately and in line with the specification set out by the Institute. With reference to the findings of this additional research, we note in particular that:

- No direct evidence of the effectiveness of non biologic DMARDS was found
- Whilst the British Society for Rheumatology Biologics Registry (BSRBR) evidence appears to suggest that response rates for non biologics may only be slightly reduced post TNF treatment, the analysis does not consider patients that specifically failed a TNFα inhibitor
- Abatacept and rituximab clinical trial data may provide an estimate of the lower bound of effectiveness as the initial response to DMARDS was not recorded. This estimate was used for the "New" values in the cost-effectiveness analysis.

In summary there does not appear to be any high quality evidence on which to base the effectiveness of DMARDS following TNF treatment. At best it seems their effectiveness may be slightly reduced but this is clearly subject to considerable uncertainty.

2) The sequential use of TNFα inhibitors

Schering-Plough notes that the evidence base for HAQ change on a second TNFα inhibitor is currently limited.

We note that:

- Evidence that a good response can be achieved but the probability of response is lower than that of first TNF.
- For adalimumab there is some evidence that the probability of response differs with previous TNF with a better outcome switching from infliximab compared with etanercept.

Schering-Plough believes that this research has been conducted thoroughly and has identified all relevant studies. In particular we note that a large study (Bomardieri, 899 patients) was identified as the best source of HAQ change data for second use of TNFs used for options B and C in the cost-effectiveness analysis.

3) Further cost-effectiveness analysis of sequential TNF inhibitors for rheumatoid arthritis patients

This section considers the cost-effectiveness analysis undertaken by WMHTAC using the BRAM model. The report presents 4 separate analyses, considering different research questions and we have set out our comments on these separately.

Part 1. Second TNF inhibitor compared to conventional DMARDs

- The ICERs are all above £30,000/QALY ranging from £31,000 with new data to £164,000 using old DMARD effectiveness data.
- There is some variability in the costs and QALYs presented in the appendix demonstrating that results are dependant on the first TNF used. Infliximab and Adalimumab give similar results for option A with Infliximab having lower ICERs for option B and C when the effectiveness of adalimumab is lower than that of infliximab.
- The ICERS for etanercept are higher and this would seem to be driven by the lower cessation rates between 6 and 24 weeks and hence longer mean duration on treatment compared with the other TNFs.

Note - In the first table in the appendix the results for the base conventional (DMARD) cost and QALYs has been incorrectly entered, the Etan-Infl comparison data has been entered in error.

Part 2. Cost effectiveness of using second TNF compared with rituximab.

- The results in this section differ to those published in the earlier NICE guidance for rituximab. The earlier guidance suggested that rituximab had increased costs and better outcomes leading to a positive ICER. The new results are the opposite of this with lower costs and worse outcomes.
- No comparison with the previous evidence base for rituximab considered by NICE is provided in this report. However some discussion regarding the reasons for the difference would be useful. Our interpretation would be that because the ACR20 response rate of 51% is used as the rate of short term 'quitters', this leads to a lower mean time on treatment and hence lower costs and outcomes when compared with TNFs.
- Overall, the ICERs compared to rituximab using the updated evidence base (new values) range from £32,000/QALY (infliximab following adalimumab) to £75,000/QALY (adalimumab following etanercept).

Part 3. Effect of alternative infliximab dosing assumptions.

Schering-Plough notes the results of these additional analyses, in particular the results incorporating the efficient use of infliximab with vial optimisation. Based on a 70kg patient, and a dose of 2.1 vials per infusion, ICERs for infliximab using the revised evidence base (new values) are estimated in the range £22,000-33,000/QALY.

- The analysis in this section does not adequately address the questions posed by the appeal panel.
- For the alternative dosing scenarios (sections 3.2-3.3), the assumptions used by the AG have been applied to all patients receiving infliximab as the second TNF with the obvious result of higher costs and higher ICERs. The alternative dosing should only have been applied to a proportion of patients who did not respond on the initial dose.
- Furthermore patients moved to a different dose would have an improved outcome which is also not considered in the analysis.
- The analysis could also be modeled as infliximab as first TNF then alterative dosing modeled as second TNF in comparison with other TNFs and DMARDs. The scenario of infliximab as a second TNF then alternative doses modeled versus conventional DMRDS could also be considered.
- In addition alternative dosing scenarios could have been modeled in conjunction with rituximab (part 2) and minimum effectiveness (part 4).

Part 4. Minimum effectiveness of a TNF to be cost-effective

- The effectiveness values used for the new analysis option B and C (0.27) are close to the 0.3 need to be marginally cost-effective at £30K. At a threshold of £20k the effectiveness required (57-60%) is a little higher than that used for the first TNF (53%)

Schering-Plough is grateful for the opportunity to review and comment on the additional analyses conducted by the DSU and Assessment Group and looks forward to continued dialogue with regard to this appraisal.

Sincerely,

[redacted]
Schering-Plough