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Dear Natalie,

Re: Sequential use of adalimumab, etanercept and infliximab for the treatment of rheumatoid arthritis – Appraisal Consultation Document

Schering-Plough welcomes the opportunity to comment on the Appraisal Consultation Document for the appraisal of the sequential use of adalimumab, etanercept and infliximab for the treatment of rheumatoid arthritis. We concur with the Appraisal Committee's view that TNF-α inhibitors are clinically effective when used sequentially. Indeed there is good evidence from the British Society for Rheumatology Biologics Registry (BSRBR) that a similar proportion of patients achieve a good response to their first and second TNF-α inhibitors. However, Schering-Plough has a number of serious concerns regarding the Appraisal Committee's interpretation of evidence as set out in the ACD as well as the overall manner in which evidence has been incorporated within this appraisal.

Our response is set out in the main body of this letter, under the headings requested by the Institute for consultee feedback.

In summary, Schering-Plough would like to make the following broad comments on the ACD:

1) The recommendations of the Committee are based on an inappropriately restrictive analysis and interpretation of the evidence. In Schering-Plough's view, this has resulted from the failure of the Institute to approach this separate appraisal of the sequential use of anti-TNFs in accordance with its published procedures. This departure from the usual process was not justified to consultees and is, in Schering-Plough's view, highly unsatisfactory.

2) The recommendations set out in the ACD reflect the Committee's view that TNFα inhibitors are unlikely to be a cost-effective use of NHS resources for patients who have previously failed treatment with a TNFα inhibitor and DMARDs. Schering-Plough believes that this view is, in large part, based on an evaluation of the clinical effectiveness of DMARDs that overestimates the effectiveness of DMARDs and so is likely to underestimate the incremental effectiveness associated with TNF-α inhibitors.
3) The Committee argues that estimates of cost-effectiveness for infliximab taking account of vial optimisation (no vial wastage) are not appropriate for the purposes of its decisions. Since the Appraisal Committee was instructed to consider an appropriate range of doses for infliximab and to take account of vial wastage following the Appeal against the FAD for TA130, it is surely perverse to ignore ICERs that take account of vial optimisation.

Schering-Plough's detailed response is set out below:

i) <u>Do you consider that all of the relevant evidence has been taken into account?</u>

A separate appraisal for the sequential use of TNF inhibitors

Further to our comments in response to the additional analyses that were circulated to consultees earlier this year, Schering-Plough would like to reiterate its continuing concerns regarding 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 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 surprising that additional evidence (aside from consultee comments) is only being submitted by the Assessment Group and the Decision Support Unit.

This restrictive approach to the separate appraisal of sequential use is contrary to the Institute's procedures and this has put Schering-Plough and other consultees at a major disadvantage. The ACD indicates that this appraisal of the sequential use of TNF-α inhibitors is an individual appraisal

[conducted pursuant to Directions from the Secretary of State]. Under such circumstances, the Institute's own procedures allow stakeholders the opportunity to make submissions.

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 TNF-α 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 formal consultee evidence submissions.

Vial wastage

In section 4.3.11 of the ACD, the Committee notes that it was:

> *"mindful that the analyses of the cost effectiveness of infliximab assumed no sharing of vial contents between people and that if it was possible to minimise vial wastage then the cost effectiveness would be improved. The Committee considered that it could not be assumed that there would be no vial wastage and that the original estimates of cost effectiveness that assumed that infliximab vials were not shared were appropriate."*

The Committee had been specifically asked to consider a wider range of doses for infliximab by the Institute, following the Appeal against the original FAD for the Appraisal of TNF inhibitors for rheumatoid arthritis. The Institutes request that this matter be investigated properly confirms its relevance and importance to the Committee's deliberations. When taking account of vial wastage, using an average patient weight of 70kgs and an average dose of 210mgs per infusion, the Assessment Group estimates the ICER for infliximab to be in the range 22-33k/QALY.

Schering-Plough argues that it must be perverse for the Institute to address the issue consistent with the directions of the Appeal Panel, and subsequently to rule the results inappropriate. In the guidance for TA130, the Institute recognises that a number of issues are important in the choice of TNF inhibitor for rheumatoid arthritis. Section 1.7 the Institute recommends that:

> *"Treatment should normally be initiated with the least expensive drug (taking into account administration costs, required dose and product price per dose). This may need to be varied in individual cases due to differences in the mode of administration and treatment schedules."*

This guidance recognises the importance of required dose and implies that this should be a central consideration in the decision to prescribe. It is also clear that there are a number of parameters that will vary considerably across patients and that this in turn will affect estimates of cost-effectiveness. In the current ACD for the sequential use of TNF-α inhibitors, the Committee argues that it cannot assume infliximab vials will be used efficiently and on this basis it does not accept the revised ICERs as appropriate. Schering-Plough agrees that the optimally efficient use of vials cannot be assumed uniformly across the NHS, but argues that since vial wastage is such a crucial consideration affecting estimates of cost-effectiveness, ICERs for infliximab assuming no vial wastage must inform the Committee's recommendations.

Therefore it is not possible to conclude that all relevant evidence has been taken into account.

ii) Do you consider that the summaries of clinical and cost effectiveness are reasonable interpretations of the evidence and that the preliminary views on the resource impact and implications for the NHS are appropriate?

Schering-Plough does not believe that the summaries of clinical and cost-effectiveness are reasonable interpretations on the evidence. We believe that the Committee's interpretation of the evidence is unsound in two main regards.

Estimation of treatment effects for the economic evaluation of sequential use of TNF inhibitors

For the evaluation of TNF-α inhibitors against both conventional DMARDs and rituximab, ICERs ranging from £31,000–919,000/QALY are presented in the ACD (section 4.2.5). These are based on a number of sources for estimates of the effectiveness of anti-TNFs and DMARDs.

Table 1 Scenarios for estimating the cost-effectiveness of TNF-α inhibitors as sequential treatment in RA

	Clinical Effectiveness (HAQ reduction) source:		**ICER vs rituximab**	**ICER vs DMARD**
	TNF-α inhibitors	*Conventional DMARDs*		
1	British Society for Rheumatology Biologics Registry	Chen et al. 2006[i] (TA130 values)	£255,000 to £919,000	£136,000 to £164,000
2	ReACT (Bombardieri et al. 2007[ii])	Chen et al. 2006[i] (TA130 values)	£56,000 to £138,000	£56,000 to £94,500
3	British Society for	ATTAIN (Genovese et	£56,400 to	£44,500 to

	Rheumatology Biologics Registry	al. 2005[iii])	£74,800	£47,500
4	ReACT (Bombardieri et al. 2007[ii])	ATTAIN (Genovese et al. 2005[iii])	£32,200 to £50,500	£31,000 to £38,700

Schering-Plough believes that the ReACT trial provides the most relevant estimates for the effects of TNF-α inhibitors. The ReACT trial included a washout period in which patients did not receive TNFα inhibitor treatment for 2 months before enrolment., This trial design allows for an accurate estimate of the incremental treatment effect of TNF-α inhibitors over DMARDs since there is no carry-over of the effect of the preceding TNFα inhibitor. This is in contrast to the BSRBR study where measurement of the incremental effect treatment effect of a second TNFα inhibitor compared to a DMARD is problematic as described in some detail in the report by Mark Lunt ("Effect of a second course of anti-TNF therapy on HAQ following lack of response to the first course").

We also believe that it is most important to model the effectiveness of DMARDs, as a comparator to sequential TNF-α treatment, using data from a late RA patient population. Scenarios 3 and 4 use evidence from the ATTAIN trial and this appears to be more appropriate than scenarios 1 and 2 which rely on early RA evidence as reported in TA130 (Chen et al. 2006). Using early RA data for DMARDs in the sequential TNF-α setting is likely to overestimate their effectiveness. .

Overall we believe that, of the four scenarios presented in the ACD, Scenario 4 is the most relevant to the clinical population for sequential TNF-α treatment..

The cost-effectiveness of a second TNF-α inhibitor compared to conventional DMARDs in scenario 4 is estimated in the range 31-39k/QALY. The ICER for infliximab falls to 22k/QALY if vial wastage is minimised. Under scenario 4, the cost-effectiveness of a second TNF-α inhibitor compared to rituximab is estimated to be in the range 32-55k/QALY.

Within scenario 4, the range of ICERs reported is based on a range of HAQ reduction observed in the ReACT study from 0.33 to 0.51;

- The lowest estimate for HAQ reduction (0.33) is derived from a small sample of 63 patients
- HAQ reduction estimates in the remaining treatment groups (accounting for 595 patients) in the REACT study were 0.51, 0.52, 0.46, 0.55, 0.54.
- The overall mean estimate for HAQ reduction (n=899) was 0.48.

Of the range of ICERs suggested by the Institute, the expected ICER will be towards the lower end of the reported range (£31k/QALY) and certainly not as high as the estimates, as shown in the table above, that are reported elsewhere in the ACD.

Treatment effect for DMARD after TNF

Whilst we argue that scenario 4 appears to be the most clinically relevant, it appears to underestimate the incremental treatment effect of a second TNF-α inhibitor as the effects of DMARDs, in patients who have already failed multiple DMARDs, are overestimated.

Response to DMARDs in the economic model presented to the Committee has been assumed to be the same as the response seen in the methotrexate plus placebo arm of the ATTAIN trial. Importantly however, many patients are likely to receive DMARDs such as MTX alongside their anti-TNFs (e.g. 69% in ReACT study). The estimated effect of 2nd line anti-TNF treatment from the ReACT trial is already net of the effect of any background DMARDs such as MTX given alongside an anti-TNF, as patients received baseline DMARDS during the baseline period.

To illustrate this issue further with respect to the ACD: in the Institute's analysis, the response to a DMARD that might be given instead of or after a 2nd line anti-TNF is taken as the response seen in the MTX+Placebo arm of the ATTAIN trial. If the placebo effect seen in the ATTAIN trial was due to MTX, the use of MTX is already accounted for in the estimate from ReACT analysis. It is not clear that this response can be attributed to other, unnamed DMARDs that might be used instead of TNF-α inhibitors. If the response is due a placebo effect, it is not clear that this effect could be attributed to other DMARDs.

Overall, Schering-Plough argues that reliance on the treatment effect observed in the placebo arm of the ATTAIN trial to represent the effect of DMARDs in patients who have previously failed DMARDs is inappropriate and is likely to underestimate the incremental effect of TNF-α inhibitors.

iii) Do you consider that the provisional recommendations of the Appraisal Committee are sound and constitute a suitable basis for the preparation of guidance to the NHS?

Further to the comments set out above, Schering-Plough does not consider the provisional recommendations of the Appraisal Committee to be sound.

iv) Are there any equality related issues that may need special consideration?

Schering-Plough is not aware of any particular equity related issues that require special consideration.

[i] Chen YF, Jobanputra P, Batron P et al. A systematic review of the effectiveness of adlimumab, etanercept and infliximab for the treatment of rheumatoid arthritis in adults and an economic evaluation of their cost-effectiveness. Health Technology Assessment. 2006;10 (42).
[ii] Bombardieri S, Ruiz AA, Fardellone P et al. Research in Active Rheumatoid Arthritis (ReACT) Study Group. Effectiveness of adalimumab for rheumatoid arthritis in patients with a history of TNF-antagonist therapy in clinical practice. Rheumatology (Oxford). 2007;46(7):1191-9.
[iii] Genovese M, Becker J-C, Schiff M et al. Abatacept for rheumatoid arthritis refractory to tumor necrosis factor α inhibition. NEJM 2005;353:1114-23.