Schering-Plough Ltd
Shire Park, Welwyn Garden City
Hertfordshire, AL7 1TW

Tel: 01707 363636
Fax: 01707 363690

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National Institute for Health and Clinical Excellence
MidCity Place, 71 High Holborn
London WC1V 6NA

[redacted]

RE: Etanercept, Infliximab and Adalimumab for the Treatment of Psoriatic Arthritis: a Systematic Review and Economic Evaluation – Comments on the Technology Assessment Report (TAR)

Schering-Plough welcomes the opportunity to comment on this report and its content. Following a thorough review of the TAR, this letter sets out Schering-Plough's comments – a summary of what we perceive to be the significant findings for infliximab followed by critical issues relating to The CRD/CHE Technology Assessment Group (TAG) analysis.

Schering-Plough is pleased to notice that the TAG has been able to incorporate the benefit of TNF-α inhibitors on psoriatic component of the disease in their analysis. This evidence was not available to the Committee in the previous appraisal and Schering-Plough believes it will further help in demonstrating the value of TNF-α inhibitors in PsA.

1 Significant findings for infliximab

1.1 Superior efficacy to other TNF-α inhibitors

The TAG compared TNF-α inhibitors on several different efficacy parameters including Psoriatic Arthritis Response Criteria (PsARC), American College of Rheumatology improvement criteria (ACR), Health Assessment Questionnaire (HAQ) and Psoriasis Area Severity Index score (PASI). The comparative analysis found infliximab to be the most effective TNF-α inhibitor and infliximab to have the highest probabilities of response across all outcomes.

1.2 Treatment of choice for patients with significant psoriasis

The TAG concludes that among PsA patients with moderate to severe psoriasis, if the response is defined as PsARC or PASI 75 then infliximab has the highest probability of being cost effective at a threshold of £30,000 per QALY. If a higher threshold of PsARC and PASI response is used then infliximab has the highest probability of being cost effective at both £20,000 per QALY and £30,000 per QALY thresholds.

1.3 Treatment of choice for patients requiring inpatient treatment

The TAG also concludes that for uncontrolled moderate to severe psoriasis patients requiring inpatient treatment infliximab is likely to be the most cost effective strategy at a threshold of £20,000 per QALY.

Schering-Plough thus requests the Committee to consider these significant benefits offered by infliximab for PsA patients with moderate to severe psoriasis whilst drafting their recommendations.

2 Key Issues

2.1 Incorrect calculations of drug acquisition and administration costs used in the model

In the analysis and the accompanying report, TAG have used incorrect calculations of drug acquisition costs for all the TNF-α inhibitors and estimated higher costs for infliximab administration. Adjusting these costs leads to infliximab ongoing treatment being more economical compared to etanercept and adalimumab for all patients weighing less than 60kg and will have significant impact on the resulting Incremental Cost Effectiveness Ratios (ICERs).

2.2 No consideration of vial optimisation

Vial optimisation with infliximab has implications on the cost-effectiveness argument currently being appraised. In conjunction with point 1.1, this may significantly reduce the drug acquisition and administration cost of infliximab thereby affecting final ICERs. The TAG did not consider vial optimisation in their analysis. Schering-Plough believes that vial optimisation is a widespread practice in the UK, acknowledged by NICE (Technology Appraisal 133) and should therefore be considered as part of evidence presented to the Committee.

Schering-Plough thus recommends the following:

- Correction of drug acquisition costs for TNF-α inhibitors and administration cost for infliximab.
- Incorporation of vial optimisation when calculating the cost of infliximab.

3 Detailed response on limitations identified in the TAR

3.1 Incorrect calculations of drug acquisition and administration costs used in the model

In the analysis TAG interchangeably refers cycle length to be 12 weeks or 3 months especially beyond the 3rd cycle (24+ weeks). The model code assumes a cycle length of ¼ year (= 3 months) and the estimated resource use displayed in Table 10.13.1 also seems to assume a cycle length of 3 months. However, the first two cycles (0-12 weeks and 12-24 weeks) seems to suggest a cycle length of 12 weeks.

Assuming first two cycles of 12 weeks and the subsequent ongoing cycle length of 3 months, the doses estimated for TNF-α inhibitors are incorrect. The 3rd cycle onwards (24+ weeks), the TAG estimated 24 doses for etanercept and 6 doses for adalimumab. The correct doses are 26 for etanercept and 6.5 for adalimumab every 3 months. In contrast, the dose for infliximab has been incorrectly estimated in the 2nd cycle (12-24 weeks). On a maintenance treatment, the dose of infliximab is every 8 weeks which amounts to 1.5 per 12 week cycle. This has been incorrectly represented as 2 doses in the 2nd cycle of 12-24 weeks.

The TAG assumed an administration cost of £144 per infusion in their calculations. Schering-Plough would also like to point out that an infusion cost of £124 per infusion is the upper limit of £65.02-£124 range of plausible administration costs for infliximab accepted by the Committee in a recent appraisal of infliximab in psoriasis (TAG 134; Section 4.11, page 14) and should therefore be used in the calculations of ICERs.

Schering-Plough has reproduced Table 10.13.3 with the above changes in blue text in the parenthesis.

Table 10.13.3: Costs used in the York model

0-12 weeks	*Drugs*	*Administration*	*Monitoring*	*Total*
Etanercept	2145.12	116.00	55.43	2316.55
Adalimumab	2145.00	116.00	55.43	2316.43
Infliximab (4 vials)	5035.44	432.00 (372.00)	55.43	5522.87 (5462.87)
Infliximab (3 vials)	3776.58	432.00 (372.00)	55.43	4264.01 (4204.01)
12-24 weeks	*Drugs*	*Administration*	*Monitoring*	*Total*
Etanercept	2145.12	116.00	3.71	2264.83

Adalimumab	2145.00	116.00	3.71	2264.71
Infliximab (4 vials)	3356.96 (2517.72)	288.00 (201.50)	3.71	3648.67 (2722.93)
Infliximab (3 vials)	2517.72 (1888.29)	288.00 (201.50)	3.71	2809.43 (2093.50)
24 weeks +	*Drugs*	*Administration*	*Monitoring*	*Total*
Etanercept	2145.12 (2323.88)	58.00	3.71	2206.83 (2385.59)
Adalimumab	2145.00 (2323.75)	58.00	3.71	2206.71 (2385.46)
Infliximab (4 vials)	2727.53	234.00 (201.50)	3.71	2965.24 (2932.74)
Infliximab (3 vials)	2045.65	234.00 (201.50)	3.71	2283.36 (2250.86)

As displayed above, the 12 week onwards treatment costs for a 60kg patient on infliximab are lower than the treatment costs for etanercept and adalimumab. The treatment costs for an average 80kg patient are slightly higher but could become comparable with vial optimisation. Schering-Plough therefore urges the TAG to re-estimate the ICERs with these appropriate costs which may have significant impact on the final recommendations.

3.2 No consideration of vial optimisation for infliximab

Vial optimization with infliximab has significant implications on the resulting ICERs. The TAG did not consider vial optimization in their analysis, even as part of sensitivity analysis. A recent survey of rheumatology centres across England and Wales suggested that 31 out of 89 centres (34.8%) covering 63% of rheumatology patients undertake vial optimisation and a minimum of 50% of drug wastage is avoided in centres that undertake vial optimisation.

Vial optimisation has also been considered in other appraisals. In a previous appraisal for an asthma medication, omalizumab, the Committee has considered vial optimisation while issuing their guidance (Technology Appraisal 133)[1]. Paragraph 4.12 of TA 133 states:

> "The Committee considered the basis for estimating omalizumab drug costs in the manufacturer's model. It noted that this had been done on a per-mg basis (assuming no wastage and reuse of unused vial portions) and that in scenarios in which omalizumab drug costs were estimated on a per-vial basis, the ICERs for omalizumab were higher. It was mindful that vial sharing might not be feasible in primary care settings. However, the Committee heard from patient experts and clinical specialists that vial wastage could be

avoided reasonably easily in regional specialist centres where larger numbers of patients are treated. The Committee therefore concluded that the ICERs for omalizumab in comparison with standard therapy may be lower when omalizumab is administered in a dedicated session in a specialist day care setting where vial wastage can be minimised."

As infliximab is administered within specialist centres, it may be reasonably assumed that vial optimisation may be applicable. Indeed, the ongoing NICE appraisal of infliximab for the treatment of Crohn's disease recently released an Appraisal Consultation Document which stated that local vial sharing arrangements should be taken into account in the consideration of which treatment should be administered[2].

Schering-Plough therefore strongly urges that the TAG considers vial optimisation in their analysis prior to presenting this evidence to the Committee. Schering-Plough believes that both the changes suggested above will further improve the ICER for infliximab in comparison with other TNF-α inhibitors.

In summary, Schering-Plough urges the Committee to consider infliximab's superior efficacy on all outcomes and its significant benefit to PsA patients with moderate to severe psoriasis whilst recommending the TNF-α treatment. Schering-Plough also requests TAG to rectify the drug costs in the model and re-analyses the evidence incorporating vial optimisation.

Once again, we are grateful for the opportunity to comment on the TAR and look forward to continued dialogue with NICE regarding the issues raised in this response.

Sincerely,

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Schering-Plough

[1] NICE Final Appraisal Determination (TA 133), Omalizumab for severe persistent allergic asthma, August 2007, available at http://www.nice.org.uk/nicemedia/pdf/FADOmalizumabAsthma.pdf.

[2] NICE. Crohn's Disease: Infliximab and adalimumab. Appraisal Committee Document. Section 4.3.11. Available from: http://www.nice.org.uk/guidance/index.jsp?action=folder&o=46233