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

Tel: 01707 363636
Fax: 01707 363690

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

3rd September 2008

Dear Ms Saile,

RE: Appraisal Consultation Document: Infliximab for the treatment of acute exacerbations of Ulcerative Colitis

Schering-Plough welcomes the opportunity to comment on the appraisal consultation document ("ACD") on infliximab for ulcerative colitis ("UC"). The Appraisal Committee's ("the Committee") preliminary recommendations are that *"Infliximab is recommended as an option for the treatment of acute exacerbations of severely active ulcerative colitis only in patients in whom ciclosporin is contraindicated and in people who do not meet the criterion described above, infliximab should only be used for the treatment of acute exacerbations of severely active ulcerative colitis in the context of clinical trials."*

Schering-Plough is disappointed that the current draft recommendations are overly restrictive and do not offer the most cost effective treatment alternative for patients deemed inappropriate for ciclosporin. The recommendations are not in the best interests of patients with UC, nor are they appropriate in the context of current clinical practice in the UK. Schering-Plough requests that the Committee reconsiders some aspects of its preliminary recommendations in light of our responses to the ACD and the ERG report.

Schering-Plough's response is structured in two separate sections.

1. Response to ACD content
2. Comments on the ERG report.

We anticipate that following a review of our responses along with those of the other consultees, the Committee will establish a guidance that allows infliximab use in sub-groups of acute UC patients deemed inappropriate to receive ciclosporin.

1. Response to ACD content

Choice of comparator

The Appraisal Committee, in its consideration of the evidence, concluded that ciclosporin was the most appropriate comparator for infliximab in acute UC setting (section 4.5). Schering-Plough, however would like to point out that in certain settings as described below, ciclosporin is deemed inappropriate. Where this is the case, another treatment alternative should be considered.

A. In the context of current clinical practice in the UK, ciclosporin is not routinely used in all centres due to concerns about its toxicity and associated mortality. The Committee acknowledged this in the ACD (ACD section 4.5). A market research survey conducted by Schering-Plough also confirmed this view. In a sample of 40 gastroenterologists surveyed in UK, at least 30% do not use ciclosporin and for 60% of clinicians ciclosporin is not the first choice of treatment in this setting. The survey also revealed that 30% of clinicians preferred surgery as a treatment option ahead of ciclosporin (Schering-Plough; data on file). This confirms our view that in the UK clinical practice, ciclosporin is not the only treatment alternative and in such circumstances the appropriate comparator for infliximab is standard care or surgery.

B. The choice of treatment alternative also depends on the clinical history of the UC patient being treated. Our consultation with clinical experts identified the following two treatment algorithms currently used in UK clinical practice to treat UC patients with an acute exacerbation.

   a. Patients with the first presentation of acute UC

      This sub-group comprises patients for whom the acute exacerbation is their first presentation of UC. Such patients are steroid naïve and have not been exposed to immunomodulators (6-MP/Azathioprine). In current practice, a significant proportion of these patients are offered ciclosporin for their acute exacerbation with an aim of preventing surgery and 'bridging' to a long-term immunomodulator. A small proportion of patients in this sub-group are also treated with infliximab even though infliximab is not the preferred option and clinicians prefer to save it for a later stage during treatment.

   b. Chronic UC patients hospitalised with an acute exacerbation

      This sub-group comprises patients diagnosed with chronic UC who are currently receiving corticosteroids and/or immunomodulators for their condition. Such patients, on failure of these therapies, may experience an acute exacerbation of UC. Ciclosporin is not a preferred option as it does not offer a long-term treatment (due to its toxicity) and patients cannot be bridged back to steroids and

immunomodulators which they have already failed. Therefore, the primary treatment options for these patients are infliximab and surgery.

This suggests that both infliximab and ciclosporin play different roles in the treatment pathway for acute UC and are preferred treatment alternatives for two different patient groups. Therefore ciclosporin should not be considered as the only comparator for infliximab, especially in chronic UC patients hospitalised with an acute exacerbation. Surgery may be a more appropriate comparator for infliximab in this setting.

C. The Committee acknowledged the widespread concern among clinicians about the risk of serious infections and the associated mortality with ciclosporin treatment (ACD section 4.5). The literature suggests the risk of mortality to be as high as 3.5% among UC patients treated with ciclosporin (Arts et al; 2004). The majority of studies have also observed serious side effects such as nephrotoxicity, seizures, anaphylaxis and risk of serious infections. Due to such high risks, clinicians may prefer not to use ciclosporin in patients where this is deemed inappropriate. In such circumstances, surgery may be the only treatment option and thus the comparator for infliximab. Although, the Committee expressed doubt about the safety of infliximab in this setting due to insufficient evidence, infliximab has not been associated with mortality or treatment related serious adverse events in acute or chronic UC setting (Jarnerot, 2005; Jakobovits, 2007; ACT I&II)

In summary, Schering-Plough would argue that surgery is often a comparator for infliximab. The current analysis suggests infliximab to be a cost-effective treatment option compared to surgery. Infliximab therefore should be recommended in these settings.

The interpretation of the guidance

The ACD recommends the use of infliximab for the treatment of acute exacerbations of severely active ulcerative colitis only for patients in whom ciclosporin is contraindicated or for all UC patients with an acute exacerbation in the context of a clinical trial. In practical terms therefore, the guidance neither allows clinicians to consider use of infliximab in patients deemed unsuitable for ciclosporin (will only allow in patients contraindicated), nor does it allow patients or clinicians to choose infliximab ahead of ciclosporin. Schering-Plough believes that the guidance fails to address two key aspects of acute UC treatment outlined below.

- In our view, the wording of the recommendation implies that clinicians should consider the use of infliximab in a treatment pathway that formally includes ciclosporin. Although, we accept the inclusion of ciclosporin in the scope as one of the appropriate comparators based on current clinical practice, we would like to stress that the Institute's remit does not extend to the recommendation (explicitly or otherwise) of technologies outside their licensed indications.

- The current guidance also fails to recommend a course of treatment for patients previously treated with ciclosporin. The recommendation assumes that such patients in their next presentation would undergo surgery. However, a proportion of such patients may be unsuitable for surgery or may choose not to undergo surgery. In this sub-group, infliximab may be the best choice of treatment. Although no randomised trial evidence currently exists in this patient group, infliximab has been used in this cohort (Jakobovits, 2007; Kohn, 2007). For such patients wanting to avoid surgery infliximab is likely to be the most appropriate cost-effective treatment option.

2. Response to the ERG / Evaluation Report

Errors & concerns identified by ERG in the modelling exercise

1. *"On the basis of these results (base case; S-P submission), it is clear that the move from standard care to ciclosporin is highly cost-effective given that it is associated with lower costs and higher QALYs. Thus, the policy question then to be addressed is the subsequent move from ciclosporin to infliximab, and so the only appropriate comparator for infliximab is ciclosporin. It would be a mistake to consider either standard care or surgery as comparators for infliximab."(ERG report; Section 5.1, page 24)*

Based on the base case results presented in the Schering-Plough submission, ERG has taken a hierarchical approach to rule out the comparison between infliximab and surgery/standard care. Although this is a common approach in health economic decision analysis, it is applicable only if all the comparators are relevant in the treatment setting. In this appraisal, current UK clinical practice would suggest that ciclosporin is not routinely used in centres across the UK and therefore is not an appropriate comparator in all settings as explained above. In settings where ciclosporin is not used or preferred, surgery or standard care should be considered as a comparator.

2. *Additional work undertaken by ERG*

The ERG revised their cost-effectiveness estimates based on the errors identified in the Schering-Plough submission. However, the base case results presented by the ERG also include some serious errors. The ERG claim to have changed the resource use associated with ciclosporin and the costs associated with oral ciclosporin and azathioprine. It is however unclear how the total QALYs change by changing the costs associated with the treatments (Table 6.3.3.1 to Table 7). Schering-Plough believes that there is an error in the additional analysis undertaken by ERG which may undermine the credibility of any further analysis undertaken by the ERG in general.

In the additional analysis ERG also presented an analysis excluding the D'Haens trial. Although Schering-Plough believes this trial should have been included in the evidence synthesis, the ERG did not address the uncertainty around the 12 month efficacy estimates of

ciclosporin. In the short-term analysis (0-3 months), the ERG considered only the Lichtiger trial to derive a relative treatment effect for ciclosporin. The Lichtiger trial did not have 12 month follow-up colectomy data and the ERG assumed a 0.18 colectomy rate (apparently based on our original submission) for ciclosporin during 4-12 months. The Schering-Plough submission sourced this 0.18 colectomy rate from the D'Haens trial, thus its inclusion in the ERG's new analysis seems inappropriate. In the absence of any point estimates for the 4-12 month colectomy rate, we can at best assume that it lies somewhere between 0.143 (Placebo; 4-12 months) and 0.48 (Ciclosporin; 0-3 months); this uncertainty should have been addressed via a sensitivity analysis.

Schering-Plough conducted further analyses after rectifying the errors identified by the ERG. The resultant ICERs for infliximab versus ciclosporin were in the range of £9,323 (pp=0.48) to £52,080 (pp=0.143). No trial data exists up to 12 months for ciclosporin. However, clinical opinion has suggested that the predictive probability of colectomy is likely to be higher than the assumed value of 0.18 and therefore the resultant ICER is likely to be significantly lower than £48,367 reported in ERG report.

3. *"The ERG obtained clinical opinion suggesting that the colectomy rate estimated for ciclosporin was 'completely inconsistent with the current evidence and with clinical experience.' Consequently, the ERG considered the assertion that infliximab has greater benefit than ciclosporin based on the indirect comparison to be unfounded." (Evaluation report; page 13)*

The primary purpose of the indirect comparison in this appraisal was to synthesise a composite efficacy estimate based on the published trial evidence. However, ERG has selected to ignore the trial evidence and adjust their efficacy estimates based on the expert opinion. Such an approach is inconsistent with the Institute's own published guidelines and especially inappropriate given the availability of published trial data.

In light of our response above, Schering-Plough would like the Appraisal Committee to reconsider its guidance and recommend infliximab in patients deemed inappropriate to receive ciclosporin.

Sincerely,

[redacted]