Schering-Plough Ltd
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Dr [redacted]

10th June 2009

Dear [redacted],

RE: Appraisal Consultation Document: Ustekinumab for the treatment of adults with moderate to severe psoriasis

Schering-Plough welcomes the opportunity to comment on the appraisal consultation document ("ACD") on ustekinumab for the treatment of adults with moderate to severe psoriasis.

The Appraisal Committee's ("the Committee") preliminary recommendations are that *"Ustekinumab is recommended as a treatment option for adults with plaque psoriasis when the following criteria are met*

- *The disease is severe, as defined by a total Psoriasis Area Severity Index (PASI) score of 10 or more **and** a Dermatology Life Quality Index (DLQI) score of more than 10.*
- *The psoriasis has not responded to standard systemic therapies, including ciclosporin, methotrexate and PUVA (psoralen and long-wave ultraviolet radiation), or the person is intolerant of or has a contraindication to these treatments.*
- *The manufacturer provides the 90 mg dose (2 x 45 mg vials) for people who weigh more than 100 kg at the same total cost as for a single 45 mg vial."*

Schering-Plough is concerned that the recommendations do not appear to have taken into account the comments made by clinicians and the ERG regarding this appraisal. Additionally, Schering-Plough is concerned that the ACD does not clarify how the recommendations for ustekinumab should be interpreted in the context of anti-TNF guidance. The ACD appears to position a new non anti-TNF treatment alongside existing anti-TNFs without any attempt to guide clinicians in respect of choosing between the different treatment options. Comments are set out below in response to the questions raised by the Institute.

Do you consider that all of the relevant evidence has been taken into account?
Schering-Plough considers that all of the relevant evidence has been presented however the ACD does not appear to reflect the comments made by the ERG and clinicians.

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?
There are a number of issues with respect to interpreting the evidence which have been commented on below.

Clinical effectiveness

Point 4.4, page 16, ACD document
Schering-Plough agrees with the clinical specialists' opinions that since far fewer patients have received ustekinumab compared to anti-TNFs and since there is therefore a lack of long term safety data, ustekinumab should be prescribed more cautiously than comparator therapies. Ustekinumab has only been used in around 2,500 patients compared to an anti-TNF such as infliximab for which there is approximately 1.3 million patient years of experience.

Additionally, Schering-Plough considers that the opinion of the British Association of Dermatologists (BAD) is crucial in contributing to NICE guidance in order to provide the safest care for psoriasis patients in the UK. The BAD guidelines, which we understand are due to be published in August 2009, are likely to differ significantly from the ACD guidance and therefore Schering-Plough is concerned that the overall consensus of clinicians has not been taken into account when producing the guidance for ustekinumab.

The current ACD guidance does not appear adequately to have taken account of the wider context of the psoriasis therapy area in which anti-TNF treatment options are available with well established safety profiles, and where a treatment with an alternative mode of action recommended by the Institute – efalizumab – was withdrawn due to concerns about safety.

Point 4.6, page 17, ACD document
Schering-Plough is concerned that the methods for extracting data for the weight-based subgroup analysis were not explored further. In particular the way in which data was extracted may have resulted in the randomisation of the trial being violated.

Due to the uncertainty in the weight-based dosing subgroup analysis, the use of the data in the mixed treatment comparison results in the efficacy comparisons being uncertain. Schering-Plough believes that this is likely to have an impact on the cost effectiveness results as the clinical effectiveness of ustekinumab compared to the comparitors is made using a mixed treatment comparison which does not compare the same patient populations. All patients in the clinical trials of the comparator therapies are compared to subgroups extracted from the ustekinumab trial, the methods for which are unclear.

Cost effectiveness

Point 4.8, page 18, ADC document
Schering-Plough would like to stress the comments made by the ERG that no formal analysis of the subgroups have been undertaken. The methods used to extract data in order to carry out subgroup analysis of the weight based dosing may not have been explored sufficiently in order to reliably inform the economic model and therefore may not be appropriate for the analysis. This is of particular relevance as the ERG found that the cost effectiveness of ustekinumab was sensitive the choice of patient-level efficacy data.

Although Schering-Plough agrees that the model is robust, due to the uncertainties in the data informing the model, Schering Plough believe it would be premature to issue guidance without the uncertainty in the analysis being addressed further.

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?
Schering-Plough believes that the NICE guidelines should be in line with the British Association of Dermatologists views in order to clarify which treatments clinicians should use.

Are there any equality related issues that need special consideration that are not covered in the ACD?
Schering-Plough has concerns about the uncertainty of the PAS and how this would impact patients over 100kg following a NICE review and the resultant cost implications to the NHS.

Point 8.2, page 23, ACD document
Schering-Plough welcomes the proposed review of all psoriasis treatments however is concerned that there is no date stated for the review. However the discussion in section 8.2 is not clear on how it relates to the existing proposal that NICE communicated to stakeholders on December 22nd 2008, stating that *"the Institute's Guidance Executive has decided to recommend that the reviews of all the guidance should be combined and updated as a multiple technology appraisal. This appraisal should be planned into the work programme as soon as possible. We hope to begin working on this appraisal early next year depending on available resources. We will be in touch again once timelines are set."* Schering-Plough has been working on the assumption that an MTA will commence imminently, however the ACD appears to indicate that a review will not now be considered until towards the end of 2009 at the earliest, presumably with guidance following during 2011. Schering-Plough requests clarification from the Institute regarding this issue.

In summary, Schering-Plough is concerned about the methods used to extract data for the weight based subgroups from the ustekinumab trials and the way in which the subgroups have been compared to whole patient populations in the mixed treatment comparison have informed a robust model. Schering Plough believes the uncertainty in the clinical efficacy of ustekinumab compared to anti-TNFs from the mixed treatment comparison would have fed

into the cost effectiveness evidence. In addition due to the clinicians concerns regarding patient safety, Schering-Plough believes that ustekinumab should be available for patients who are contraindicated to anti-TNFs which would be in line with the consensus with the British Association of Dermatologists.

Sincerely,

[redacted]