Schering-Plough

1st August 2008

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

Dear

Final Appraisal Determination
Sequential use of adalimumab, etanercept and infliximab for the treatment of rheumatoid arthritis

Appeal Against Final Appraisal Determination

On 11th July 2008, the Institute issued its Final Appraisal Determination (FAD) on sequential use of adalimumab, etanercept and infliximab for the treatment of rheumatoid arthritis. In section 1 of the FAD, the Institute recommends against the sequential use adalimumab, etanercept and infliximab for the treatment of rheumatoid arthritis, except in the context of research.

Schering-Plough is appealing against certain aspects of this guidance. Please treat this letter as the company's appeal in accordance with section 3.3.1 of the Institute's *Guidance for Appellants*.

Grounds of Appeal

The permitted grounds of this appeal are: (1) that the Institute has failed to act fairly and in accordance with its Directions from the Secretary of State and its published procedures as set out in the Institute's *Guide to the Technology Appraisal Process* and *Guide to the Methods of Technology Appraisal*, (2) that the Institute has prepared a FAD that is perverse in the light of the evidence submitted, and (3) that the Institute has exceeded its powers.

Summary

Schering-Plough's appeal has two fundamental bases, both of which the company raised consistently in correspondence with the Institute during the course of this appraisal.

Firstly, the Institute has failed to act in accordance with its published procedures during this appraisal. The Institute argues that its FAD for the sequential use of TNF-α inhibitors is a part of the technology appraisal of rheumatoid arthritis (*i.e.* TA130), but this cannot be the case. The appeal panel required that the Institute reconsider its guidance for TA130 in relation to sequential use. NICE did not do so. Rather, it issued guidance for first use of TNF-α inhibitors under TA130. It then proceeded to develop separate guidance on sequential use. It adopted a

new scoping document for the sequential use appraisal. It commissioned new analyses, including the assessment of new evidence, and added an important additional comparator. The Institute also consulted on an ACD and an assessment report and issued a FAD. In effect, it followed all its procedures for an entirely new technology appraisal with one fundamental omission. It denied stakeholders their fundamental right to submit evidence. Had such submissions been invited, we consider that the Committee would have been presented with a more comprehensive and appropriate evaluation of the evidence and would have reached a different conclusion.

Secondly, Schering-Plough argues that the Institute has prepared a FAD that is perverse in light of the evidence submitted. There is clear evidence that traditional DMARDs are unlikely to be clinically effective when used in patients following the failure of a TNF-α inhibitor. The guidance prepared by the Appraisal Committee assumes that DMARDs are effective in this setting, and relies on inappropriate evidence to inform this assumption.

Detailed appeal points are set out in the remainder of this letter.

Ground 1: The Institute has failed to act fairly and in accordance with its published procedures as set out in the Institute's Guide to the Technology Appraisal Process.

1.1 Failure to invite evidence submissions on the sequential use of TNF-α inhibitors from consultees

Schering-Plough has maintained throughout this appraisal that the process used by the Appraisal Committee in reviewing the products for sequential use is unfair and contrary to the Institute's published procedures. We understand from NICE's response to consultees in this appraisal that the Institute considers the appraisal of anti-TNFs for sequential use in rheumatoid arthritis to form a part of TA130. This is, however, not the case. The Institute chose to conduct a separate appraisal of anti-TNFs in sequential use and, as with any separate appraisal, Schering-Plough, other manufacturers and consultees should have been given the opportunity to submit evidence and models to the Appraisal Committee. Had the Appraisal Committee done so and invited such evidence, Schering-Plough would have been able to demonstrate that the sequential use of infliximab is likely to be a cost-effective use of NHS resources.

In the rheumatoid arthritis appraisal (TA130), the Appeal Panel instructed the Appraisal Committee to reconsider its guidance:

> "The Appeal Panel's decision is that the guidance must be reconsidered by the Appraisal Committee. The Appeal Panel suggests that Appraisal Committee reassess the evidence for the cost effectiveness of a second anti-TNF treatment with an extended sensitivity analysis that considers a wider possible range of effectiveness for standard DMARDs when used after anti-TNF therapy; a wider possible range of doses for infliximab; and a more complete examination of the minimum effectiveness that would be required of a second anti-TNF treatment for it to be marginally cost-effective."[1]

Paragraph 141 of the Appeal Panel decision added that, if the Committee declines to recommend the use of a second anti-TNF, it must explain more fully its reasons for failing to

[1] See Paragraph 140 of the Appeal Panel Decision in TA130.

recommend such treatment if there may be a "reasonable possibility" that the ICERs are within the generally acceptable range for cost-effectiveness. The Committee should also consider explaining more fully why it chose to accept estimates from the BRAM in preference to the estimates from any of the other four models submitted to it.

Following the appeal panel decision, however, NICE did not reconsider its guidance as required but wrote to consultees informing them that it had decided to "split" the FAD and issue two separate guidance documents.[2] In its letter, the Institute noted that the reason for the split was so that guidance could be issued to the NHS as quickly as possible regarding the first use of anti-TNFs. In response, Schering-Plough wrote to NICE on 1 November 2007 expressing our concerns that splitting the guidance in this way was a significant departure from the agreed scope. We have not yet received a reply. However, we note that there is no obvious reason to expedite separate guidance on first use anti-TNFs as current guidance on infliximab and etanercept was still extant and the recommendations were effectively unchanged. The only difference was that adalimumab was included in the TA130 appraisal.

Further, the Institute's sequential use analyses included a new dataset of patients from the US National Databank for Rheumatic Diseases. It also broadened the scope of the appraisal without any consultation with stakeholders by including rituximab as a comparator.

Since the Appraisal Committee has issued guidance for TA130 and commenced the development of separate guidance, rather than reconsidering its guidance in accordance with the Appeal Panel's suggestions, NICE cannot argue that the sequential use of anti-TNFs remained part of TA130. By publishing the guidance as it existed, splitting the appraisal, commissioning analyses based on new data and departing from the agreed scope, we consider that the only fair way to assess the products would be to allow the submission of evidence from stakeholders, as it would with any separate appraisal.

Indeed, NICE itself has indicated that it is conducting a separate appraisal for sequential use. In addition to publishing a new final scope entitled "Rheumatoid arthritis - adalimumab, etanercept and infliximab (sequential use): final scope",[3] the issuance of an ACD and evaluation report, NICE has created a separate webpage for the appraisal.[4] Furthermore, the FAD itself states at paragraph 1: "This guidance should be read **in conjunction with** 'Adalimumab, etanercept and infliximab for the treatment of rheumatoid arthritis' (NICE technology appraisal guidance 130)." (Emphasis added).

In previous cases where NICE has "split" appraisals, or where there are serious concerns over the reliability of a particular model, the Appraisal Committee has invited further submissions from the manufacturer. For example, in the NICE appraisal of infliximab for ulcerative colitis, the appraisal was split into an appraisal for the chronic and acute forms of the condition. In that instance, Schering-Plough was invited to submit further evidence for acute ulcerative colitis.

NICE has attempted to distance itself from this precedent by stating that the need to seek evidence from manufacturers in a single technology appraisal is different from that in a multiple technology appraisals because, in the latter, it argues that there is an independent source of

---

[2] Letter from NICE to Consultees/Commentators dated 19 October 2007.

[3] See http://www.nice.org.uk/guidance/index.jsp?action=download&o=40341, last accessed 23 July 2008.

[4] See http://www.nice.org.uk/guidance/index.jsp?action=byID&o=11902, last accessed 23 July 2008. Please note that the website refers to the first and second appraisal meetings suggesting that this is a distinct appraisal.

evidence (the Assessment Group) and so the need to ask manufacturers for evidence was not the same. We completely disagree with this analysis as it would effectively "second guess" any evidence submitted, or considered significant, by a manufacturer, which is contrary to the fundamental principles of fair procedure and the rules of natural justice. We also believe that such an approach is inconsistent with previous decisions by the Institute to invite submissions from manufacturers in multiple technology appraisals at various stages of the appraisal process.[5]

NICE's own procedures, including the Guide to Technology Appraisal ("GTA"), the Guide to the Methods of Technology Appraisal ("GMTA") and the Guide for Contributing to a Technology Appraisal ("GCTA"), indicate that manufacturers of a technology will be invited to participate in the appraisal by commentating and writing a submission.[6] To dispense with this step is unfair.

The Institute will no doubt argue that Schering-Plough was given the opportunity to submit evidence on sequential use during the TA130 appraisal. We would point out, however, that submissions for that appraisal were requested in 2005, some three years ago. Since then the evidence base has developed significantly and it would unfairly prejudice infliximab if Schering-Plough were not given the opportunity to submit fresh evidence and modelling to the Committee. Even if we were required to stick only to evidence available in 2005, we should have been entitled to present this in a way that responded directly to the question posed in the later sequential use scope. For instance, at the time when submissions were invited for TA130, the management strategies without anti-TNFs included various combinations of non-steroidal anti-inflammatory drugs (NSAIDs), analgesics, corticosteroids and DMARDs. Any submissions by the consultees were made on that basis.

To conclude, Schering-Plough has a legitimate expectation that it would be invited to make submissions on sequential use of anti-TNFs given that the Institute is developing separate guidance and its precedents for inviting further submissions at different stages of the appraisal process, the time-lag from submissions in the TA130 appraisal and the departure from its scope. Despite our reservations in this regard throughout the appraisal process, NICE has failed to request further submissions on sequential use or to respond to the points that we have raised in correspondence. This is clearly unfair.

---

[5] In the NICE appraisal of beta interferons and glatiramer for multiple sclerosis, the Appraisal Committee invited further submissions from consultees given the unreliability of the model used in that appraisal. See http://www.nice.org.uk/guidance/index.jsp?action=download&o=32263, last accessed 23 July 2008. Further, in the appraisal of acetylcholinesterase inhibitors for Alzheimer's disease, the Institute invited further submissions from the manufacturers after the ACD1 stage and further submissions prior to issuing the FAD. See http://www.nice.org.uk/guidance/index.jsp?action=download&o=32263, last accessed 23 July 2008.

[6] See paragraph 4.2 of the GMTA, which states: "Submissions **are** invited from manufacturers and sponsors of the technology or technology being appraised." (Emphasis added).

See paragraph 4.4.2.1 of the GTA, which states: "When the appraisal begins, all consultees are invited to make submissions to the Institute." See also paragraph 4.4.1.4 of the GTA, which states: "The Assessment Group prepares and Assessment Report - a review of the clinical and cost-effectiveness of the technology or technologies based on a systematic review of the literature **and** a review of manufacturer and sponsor submissions to the Institute." (Emphasis added).

See page 15 of the GCTA, which states: "If you are the manufacturer of sponsor of a technology that is the subject of the appraisal, you **will** be invited by NICE to participate as a consultee. **This will involve both commenting on the various documents produced and writing a submission**." (Emphasis added).

1.2 Failure to provide consultees with a fully executable version of the model

Schering-Plough has also been denied the opportunity to check, and comment on, the reliability of the models used by the Assessment Group because the company has not been given access to an executable file the source code for the model was not disclosed. This unfairly prejudices infliximab. Schering-Plough requested the source code for the model during TA130 but, contrary to the Court of Appeal's judgment in the *Eisai* case, was provided only with an executable file.

As you know, the model used by the Assessment Group is central to the Appraisal Committee's determination of a drug's cost-effectiveness and in particular to the cost per QALY and whether it comes within the threshold of acceptable cost. The NICE's GMTA states in paragraph 5.1 that "[t]he estimates of clinical and cost effectiveness are, individually, key inputs into the decision-making of the Appraisal Committee" and that "they are interdependent because comprehensive, transparent and reproducible synthesis of all relevant evidence on health effects is needed for high-quality cost-effectiveness analysis". It is through the model that the synthesis is achieved.

The robustness or reliability of the model is therefore a key question. For the thorough testing of reliability, there can be no doubt that the source code is required, especially if a manufacturer wants to carry out a sensitivity analysis. We were of course aware of the assumptions that were being applied to the Assessment Group's model and were given an opportunity to comment on them, however, in our view, this does not address the point that we were limited in what we could do to check and comment on the reliability of the model itself because we received a read-only version.

Ground 2: The Institute has Prepared a FAD that is Perverse in the Light of the Evidence Submitted

2.1 Reliance on Placebo-Arm of the ATTAIN Trial to Demonstrate Effectiveness of DMARDS and on an unreliable and unauthorised cost-effectiveness model is perverse

Schering-Plough considers that the Appraisal Committee's 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 a TNF-α inhibitor is perverse as this interpretation has no factual basis and is, in our view, likely to underestimate the incremental effect of anti-TNF inhibitors.

Following a review of the evidence by the Institute's Decision Support Unit (DSU), response to DMARDs in the additional economic analyses presented to the Committee was modelled using two alternative sources of evidence – firstly, effectiveness estimates provided in the original assessment report for TA130 and secondly estimates based on the treatment effect observed in the methotrexate plus placebo arm of the ATTAIN trial. However, as noted by the Committee in section 4.3.13 of the FAD, the values from the original assessment report reflected DMARD effectiveness in early RA and may overestimate effectiveness following failure of a first TNF-α inhibitor. Therefore, estimates of effectiveness drawn from the ATTAIN trial were considered more appropriate and informed the Committee's judgements on the cost-effectiveness of a second TNF-α inhibitor compared to a DMARD.

Crucially, the ATTAIN trial was not designed to assess the effectiveness of traditional DMARDs in patients who had already failed a TNF-α inhibitor. In fact, as is noted by the DSU in its report

on the effectiveness of non-biologic DMARDS after anti TNF α inhibitor failure, all patients had to have been taking oral DMARDs or anakinra for at least 3 months (and a stable dose for 1 month) prior to enrolment in the study:

> "Alternative evidence from trials of abatacept and rituximab are consistent in terms of the degree of HAQ improvement in the placebo arms of these two trials. However, since patients started DMARD therapy 3 months prior to the baseline measures in the trials, the observed improvement is not equivalent to the initial effect of treatment required in the cost effectiveness model."

However, despite this clear statement, effectiveness estimates from the ATTAIN study were used to model cost-effectiveness and to support the Committee's recommendations.

Schering-Plough commented on the inappropriateness of using the placebo effect from the ATTAIN trial to represent the effectiveness of DMARDs in prior TNF-α failures in its letter of 20th May 2008, responding to the ACD for sequential use. In response to Schering-Plough's comments the Institute responded:

> "People in the ATTAIN study were on stable doses of DMARDs prior to randomisation to either placebo or abatacept. Therefore the effect of a conventional DMARD would not be captured in this study." [7]

This is a restatement of the point originally made by the DSU. In section 4.3.14 of the FAD, the Committee acknowledges that data from the ATTAIN study could reflect an effect of placebo, however it further argues that it was not persuaded the placebo data had substantially overestimated the effect of conventional DMARDs. This statement is made despite clear evidence to the contrary being available to the Committee.

Data from the British Rheumatology Outcomes Study Group, brought to the Institute's attention during consultation on the ACD, indicates that HAQ scores in patients treated with DMARD therapy progressively worsen.[8] The Committee acknowledges this evidence in section 4.3.8 of the FAD, noting that it did not provide clinical effectiveness estimates for individual DMARDs and could not therefore be used in the economic modelling. It also noted that the population studied was not patients with established RA who had already failed a TNF-α inhibitor.

Neither of these arguments is convincing. Firstly the lack of data regarding specific DMARDs in the BROSG study cannot be put forward as a rationale for ignoring this evidence as this would surely rule out the use of the ATTAIN trial placebo arm. Secondly, the fact that patients in the BROSG study are at an earlier stage of the disease surely reinforces the relevance of this evidence to the sequential use setting – in other words, if HAQ scores progressively and consistently worsen in an earlier RA population treated with traditional DMARDs, it is unlikely that a later RA population (who had already failed treatment with a TNF-α inhibitor) would show a better response to DMARDs.

---

[7] Response to consultee, commentator and public comments on the ACD and comments from website consultation 21st July 2008 http://www.nice.org.uk/guidance/index.jsp?action=download&o=41285

[8] Abbott's response to the Appraisal Consultation Document for sequential use of TNF inhibitors in Rheumatoid Arthritis, 20th May 2008 paragraph 1.1.
http://www.nice.org.uk/nicemedia/pdf/FADTNFSequentialAbbottComments.pdf

Further, data from the BSRBR[9] found that patients who stopped anti-TNF therapy and did not go onto another biologic had no change in their HAQ over one year. The Committee acknowledge this evidence in section 4.3.7 of the FAD but argued that a proportion of patients had a response, and that the evidence was consistent with the possibility that conventional DMARDs could have a positive effect by preventing further HAQ score deterioration. This evidence clearly does not support an assumption that, on average, patients receiving traditional DMARDs following failure of a first TNF-α inhibitor achieve a response as observed in the ATTAIN study. Nonetheless, the Committee argues that the evidence reviewed does not support an assumption of no positive effect of DMARDs. Schering-Plough strongly disputes this conclusion and argues that there is good evidence to support a conservative assumption of no effect for a DMARD in patients following failure of a first TNF-α inhibitor.

Given the inappropriate reliance on a placebo-effect to represent the effect of DMARDs in patients who have previously failed a TNF-α inhibitor, the contradictory statements by NICE in this regard, the rejection of important evidence without justification and the lack of any factual basis, Schering-Plough believes the FAD is perverse. The Appraisal Committee should at the very least have requested evidence and modelling from the manufacturers and consultees as it did in TA130, where it was supplied with four models on sequential use. Again, the passage of time from submissions on this point in TA130 to the present day should require the Appraisal Committee to invite further modelling on this point.

2.2 Failure to Consider Sub-Group of Patients with Seronegative Disease

The Appraisal Committee failed to take proper account of the fact that patients with rheumatoid arthritis who are seronegative for rheumatoid factor do not respond as well to rituximab compared with those patients with rheumatoid arthritis who are seropositive. The number of patients in this sub-group is not insignificant and represents approximately 28 per cent of patients with rheumatoid arthritis and this sub-group of patients should have been taken into account in the modelling as rheumatoid factor is important in predicting response to rituximab.[10] We understand, for example, that the study by Hyrich K *et al.*, suggests that seronegative RA may be more cost-effectively treated by a second anti-TNF than by rituximab.

The failure by the Committee to consider fully this important cohort of patients is perverse. NICE claims at section 4.3.20 of the FAD to have reviewed the estimates of clinical and cost-effectiveness of patients in this sub-group, however the assumptions are inappropriate and unreliable (*e.g.* placebo response data, rituximab dosing schedule) and based on an unauthorised and unreliable model. We note that the Assessment Group that developed the economic model relied upon by the Committee to develop its recommendations does not endorse the cost-effectiveness estimates for sequential use.[11]

If the Committee had invited submissions from manufacturers and consultees on this point, then this sub-group of patients could have been properly factored into a model. The failure to do so is perverse.

---

[9] Hyrich K et al, Effect of switching to a second anti-TNF therapy on HAQ response in rheumatoid arthritis patients with lack of response to their first anti-TNF therapy: results form the BSRBR. Ann Rheum Dis 2007;66(suppl II):173

[10] ARMA Response to Sequential Use of Anti-TNF ACD 20th May 2008, page 2. http://www.nice.org.uk/nicemedia/pdf/FADTNFSequentialARMAcomments.pdf

[11] Barton P. Further cost-effectiveness analysis of sequential TNF inhibitors for rheumatoid arthritis patients (WMHTAC). 29th April 2008, paragraph 1 http://www.nice.org.uk/guidance/index.jsp?action=download&o=40512

Ground 3: The Institute has Exceeded its Powers

3.1 Change to the final scope for appraisal (TA130) and no consultation on revised scope

Schering-Plough considers that NICE has exceeded its powers by departing from the scope of the appraisal of anti-TNFs for sequential use by including rituximab as a comparator. The final scope used for the sequential use appraisal was approved by the Institute without formal consultation as per normal procedures.

That scope states clearly that the comparators used shall be management strategies with or without anti-TNFs and other anti-TNFs. At the time when submissions were invited for TA130, the management strategies without anti-TNFs included various combinations of non-steroidal anti-inflammatory drugs (NSAIDs), analgesics, corticosteroids and DMARDs. Any submissions by the consultees were made on that basis.

However, since NICE made the decision to develop separate guidance, it published guidance on rituximab and sought to include rituximab as a comparator in the sequential use appraisal. In our view, the inclusion of rituximab is clearly outside the scope of the appraisal and therefore NICE has acted outside its remit. At the very least, NICE should have consulted on the inclusion of rituximab in the sequential use scope document and given consultees the opportunity to submit fresh evidence and models that took account of this new variable. Our comments as to procedural fairness apply equally here.

We consider therefore that NICE has departed from its remit by including a comparator that was not expressly provided for in the scope. NICE has exceeded its powers in this regard.

Concluding remarks

Schering-Plough argues that NICE has acted unfairly in 'splitting' its appraisal of the sequential use of TNF-α inhibitors for rheumatoid arthritis and conducting a separate appraisal with a revised scope but not inviting evidence submissions from consultees. This is unfair on Schering-Plough, clinicians and on those patients suffering from this crippling disease who will be left with no effective treatment.

We also argue that the Committee has prepared a FAD that is perverse in light of the evidence submitted. DMARDs are unlikely to be clinically effective when used after the failure of a TNF-α inhibitor and there is good evidence to support this view. The Institute's guidance is perverse in light of this evidence. The guidance as it stands, requiring that patients are treated with traditional DMARDs following the failure of a TNF-α inhibitor, would necessitate the use of ineffective treatments and the wasteful use of vital NHS resources.

Schering-Plough reserves the right to add to and/or elaborate upon these submissions in its oral presentation to the Appeal Panel. It also reserves the right to put additional material/arguments before the Panel in the light of any further information which it may receive.

Actions Required

Schering-Plough

Schering-Plough requests that the Appraisal Committee amends the recommendation contained in the current FAD for the cogent reasons set out in this letter. In particular, Schering-Plough requests the opportunity to submit formal evidence to this appraisal of the sequential use of TNF-α inhibitors in rheumatoid arthritis and a reassessment of the evidence with regard to traditional DMARDs in patients who have already received treatment with a TNF-α inhibitor.

I look forward to hearing from you in due course.

Yours sincerely,

Schering-Plough Ltd.