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5th October 2009

Dear Bijal,

RE: Appraisal Consultation Document: Infliximab (review) and adalimumab for the treatment of Crohn's disease (including a review of technology appraisal guidance 40)

Schering-Plough welcomes the opportunity to comment on the second appraisal consultation document ("ACD2") which sets out the Appraisal Committee's ("the Committee") recommendations on infliximab and adalimumab for the treatment of Crohn's Disease ("CD").

Schering-Plough considers the current recommendations for severe active luminal CD patients perverse in the light of available evidence and procedurally unfair.

Schering-Plough would urge the Committee to address the following points in their interpretation of the evidence.

1. Inappropriate interpretation of cost effectiveness evidence due to
    a. incorrect estimation of infliximab and adalimumab treatment costs
    b. inappropriate assumption of therapeutic equivalence between TNFα inhibitors
2. Treatment withdrawal strategy despite lack of robust evidence
3. Selective consideration of new evidence

Schering-Plough believes that severe active luminal CD patients should have equal access to both the TNFα inhibitors, infliximab and adalimumab.

Schering-Plough has outlined these concerns in detail in the response that follows. We expect that following a review of our response along with those of the other consultees and commentators, the Committee will establish a recommendation that allows CD patients fair and

equal access to both TNFα inhibitors, infliximab and adalimumab, and will reconsider its stance on the treatment withdrawal strategy.

Response to ACD content

Interpretation of cost effectiveness evidence

The Committee recommends adalimumab ahead of infliximab based on consideration of cost-effectiveness estimates across the evidence available. However, the supporting evidence considered by the Committee is inconsistent and at best partial.

- The models submitted by the manufacturers and the model developed by the assessment group ("AG") used different structural and parametric assumptions. The Schering-Plough model and the AG model, the only two models where reconciliation was attempted, did not account for partial responders unlike the Abbott model. The infliximab ICERs from Schering-Plough model thus are highly conservative and should not directly be compared with adalimumab ICERs in the Abbott model.
- The DSU attempted to reconcile the Schering-Plough model and the AG model due the similarity in the model structures and then used parameter estimates presented in Abbott submission to generate ICERs for adalimumab. However, DSU clearly acknowledge the discrepancies between the three models and in their report conclude that the process of reconciliation is incomplete. DSU believe that a full reconciliation, which is essential to produce robust ICERs, would ultimately require both structural, as well as individual parameter values, to be fully considered and amended where appropriate.
- An independent analysis by Bodger and others[1] compared adalimumab and infliximab maintenance treatment in CD and concluded that adalimumab maintenance treatment is more cost effective compared to infliximab maintenance treatment. However, the results must be interpreted with caution since the authors used the same Silverstein cohort deemed inappropriate for this appraisal and assigned differential mortality risks (higher for infliximab) to the two TNFα inhibitors based on an infliximab registry with no equivalent data being considered for adalimumab. The authors in fact concluded that "Apparent differences between rival biological agents must be interpreted cautiously as head-to-head trial data are not available."[2]

Hence, even though multiple cost effectiveness analyses are available, none of them compare infliximab directly with adalimumab and all of them have significant limitations leading to more conservative ICERs for infliximab than adalimumab. The cost effectiveness estimates for infliximab are further hampered by use of incorrect infliximab costs and inappropriate assumption of therapeutic equivalence between the two TNFα inhibitors in the AG, Abbott and Bodger analysis.

[1] Bodger et al. Alimentary Pharmacol Ther 2009; 30:265-74
[2] Bodger et al. Gut 2008; 57:A48

Incorrect estimation of infliximab treatment cost

Throughout this appraisal the treatment cost of infliximab has been incorrectly estimated. This leads to the erroneous conclusion that adalimumab is a less costly treatment option thus resulting in a perverse decision of it being more cost effective than infliximab.

1. *Drug acquisition and administration costs*

   In the description of the technologies, the ACD2 presents a drug acquisition cost of £1,678, which assumes 4 vials of infliximab per infusion, per patient and an administration cost of £258 per infusion. In reality, the comparative costs observed for infliximab and adalimumab based on their licensed dose for patient weights of 60kg and 80kg are presented in the table below.

Table 1 Annual drug and administration costs for adalimumab and infliximab

Drug	**Induction costs**†			**Yearly maintenance costs**‡		
	Drug acquisition	Admin	Total costs	Drug acquisition	Admin	Total costs
Adalimumab	£1,073	£473§	£1,546	£9,295	-	**£9,295**
Infliximab (60kg = 3 vials)	£2,518	£199	£2,717	£8,183	£645	**£8,828**
Infliximab (80kg = 4 vials)	£3,357	£199	£3,556	£10,910	£645	£11,555

†Assumes one 80mg and one 40mg dose (160mg & 80 mg) for adalimumab and 2 infusions for infliximab
‡Assumes twenty-six 40mg injections for adalimumab (with dose escalation) and 6.5 infusions for infliximab
§Assumes £171.67 for one outpatient visit in gastroenterology and eight hours of nursing time (4 hours/injection at £37.64/hour) to teach patients self-injections. [NHS reference costs 2006 inflated using PSSRU]

These data clearly show that the true cost of infliximab induction and maintenance treatment per year in a typical 60kg patient is lower than the corresponding adalimumab costs at the licensed dose. The majority of patients with moderate-to-severe CD eligible to receive biologics in the UK weigh less than 60kg as evident from one of the most widely quoted cohorts of CD patients in the UK (Jewell, 2005; Information obtained through personal communication). The weight distribution observed in this cohort has been displayed below.

Table 2 Patient weight distribution in luminal Crohn's disease

NICE routinely emphasizes its mandate to take account the most efficient use of NHS resources and hence should consider recommending the least costly alternative, which it has previously done in an infliximab appraisal in RA (TAG 130). In light of data presented above, which was also presented to the Committee in our response to ACD and DSU report, the current recommendations to use adalimumab in severe active luminal CD are not only perverse but also inconsistent with the previous recommendations (TAG 130).

2. *Dose escalation in real-life clinical practice*

Widespread feedback received from UK gastroenterologists suggests that a majority of clinicians use the higher induction dose (160/80 mg) for adalimumab, and indeed, recent open label trials have used this higher induction dose (EXTEND; CLASSIC-I).[3,4] Therefore, the true costs of adalimumab in UK clinical practice is higher than that presented above.

Patients receiving adalimumab maintenance therapy often require dose frequency escalation. Although the same data are not available for both studies, in CLASSIC II, of patients completing 56 weeks of therapy, 45.8% required escalation to a dose of 40mg weekly; of these, only 42% were in remission at 56 weeks[5]. In contrast, in ACCENT I, 30% of patients required an infliximab dose escalation to 10mg/kg, with 89.3% regaining response[6]. The obvious conclusion is that in addition to patients receiving adalimumab requiring more frequent dose escalations in comparison to patients receiving infliximab, 58% of those escalated doses of adalimumab were be wasted, due to a failure to respond.

A further crucial aspect, from an economic standpoint, is that evidence suggests that the majority of patients receiving infliximab dose escalations are subsequently able to de-escalate back to 5mg/kg[7]. No such dose reduction evidence exists for adalimumab.

Lastly, further real-world evidence exists regarding dose frequency escalation with adalimumab. Data published by Ho *et al* and Karmiris *et al* report dose escalation rates from 30% to 65.4%.[8,9] While these cohorts are heterogeneous, in the absence of other real-world data for patients receiving adalimumab, these data must cast further doubt on the treatment patterns and costs ascribed to adalimumab within ACD2.

[3] Rutgeerts et al. Gastroenterology 2009; 136-5, Suppl 1:A-116 (DDW 2009, Abstract 751e)
[4] Hanauer et al. Gastroenterology 2006; 130:323-33.
[5] Sandborn et al. Gut 2007;56;1232-1239
[6] Rutgeerts et al. Gastroenterology 2004;126:402–413
[7] Schnitzler et al. Gut 2009; 58:492-500
[8] Ho et al. Alimentary Pharmacol & Ther 2009; Mar 1;29(5):527-34.
[9] Karmiris et al. Gastroenterology 2009, Aug 5 [Epub ahead of print]

Table 3 Annual drug and administration costs for adalimumab and infliximab, with real-world dosing

Drug	Induction costs			Yearly maintenance costs‡		
	Drug acquisition	Admin	Total costs	Drug acquisition	Admin	Total costs
Adalimumab (80/40 induction) with licensed dose	£1,073	£473§	£1,546	£9,295	-	£9,295
Adalimumab (160/80 induction) with licensed maintenance	£2,145	£473§	£2,618	£9,295	-	£9,295
Adalimumab (160/80 induction) with escalated maintenance dose (range: 30-65%)††	£2,145	£473§	£2,618	£12,084-£15,337	-	£12,084-£15,337
Infliximab (60kg patient) with licensed maintenance	£2,518	£199	£2,717	£8,183)	£645	£8,828
Infliximab (80kg patient) with licensed maintenance	£3,357	£199	£3,556	£10,910	£645	£11,555
Infliximab (60kg-80kg) with escalated maintenance dose (30%)†††	£2,518-£3,357	£199	£2,717-£3,556	£10,638-£14,183	£645	£11,282-£14,828

‡Assumes twenty-six 40mg injections for adalimumab and 6.5 infusions for infliximab
§Assumes £171.67 for one outpatient visit in gastroenterology and eight hours of nursing time (4 hours/injection at £37.64/hour) to teach patients self-injections. [NHS reference costs 2006 inflated using PSSRU]
††Assumes 30-65% of patients receiving adalimumab every week, with the remainder receiving every other week
††† Assumes 30% of patients receiving infliximab at a dose of 10mg/kg, with the remainder receiving 5mg.kg

Thus the true cost of infliximab induction and maintenance treatment per year is lower than corresponding adalimumab costs while taking into account the dose frequency escalation observed in clinical practice.

3. *Vial optimisation*

It is important to note that the above analysis does not take into account the practice of vial optimisation which is highly prevalent in the UK but has been consistently ignored by the Committee in this appraisal. Critically this omission is inconsistent with the omalizumab appraisal (TAG 133, 4.12) as quoted below

"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 delivered in specialist centres in the UK, vial optimisation is a very reasonable inclusion; when incorporated, the cost savings due to vial optimisation will make infliximab even more cost effective.

Recommendations based on inappropriate conclusion of therapeutic equivalence between the TNF-α inhibitors

The Committee's present recommendations are based on the assumption of therapeutic equivalence between infliximab and adalimumab. This is unsupportable and perverse, because:

1. There is no head-to-head trial data available to support this assumption.
2. No formal efficacy comparison has been made between infliximab and adalimumab in any of these analyses. Schering-Plough emphasised this point in our previous responses to the ACD and the DSU report, yet the committee has not acknowledged or remedied this obvious weakness.
3. The available evidence clearly differentiates both the products, and TNFα inhibitors in general. There are markers of efficacy which suggest greater efficacy of infliximab, in comparison to adalimumab.

Some TNFα inhibitors have failed to achieve an indication in CD in the UK (etanercept, certolizumab and CDP571) and in general seem to have different molecular structure leading to differing clinical effects.

Amongst TNFα inhibitors with CD indications, such differences have also been recognised by EMEA in its product summaries (displayed in Appendix A). One such important difference is that infliximab can be administered without the co-administration of corticosteroids, which is not the case for adalimumab.

A surrogate marker of efficacy whose importance is now widely acknowledged amongst gastroenterologists is mucosal healing.[10] Healing a previously ulcerated bowel mucosa indicates an excellent response to treatment, and in assocation with other markers, can indicate disease remission has been achieved. Mucosal healing has various associated benefits, the most pertinent of which is a proven significant reduction of hospitalisations and surgeries – major cost drivers in CD.[11] While further study is required, therapies that result in mucosal healing offer the ultimate possibility of changing the natural course of Crohn's disease, with potential benefits for both patients and payors.[12]

In the SONIC trial, 30-44% of patients treated with infliximab achieved complete mucosal healing at week 26.[13] In contrast, adalimumab did not achieve significance in its primary endpoint of mucosal healing at 12 weeks in the ITT analysis of EXTEND trial, and achieved

[10] Rutgeerts et al. Gut 2007;56;453-455
[11] Rutgeerts et al. (2006); Schnitzler et al. (2008b); Baert et al. (2008); Frøslie et al. (2007)
[12] Vermeire et al. Aliment Pharmacol Ther 2006;25, 3–12
[13] Colombel et al. (2009)

only 24.2% mucosal healing at week 52. Furthermore, compelling real-world data exist regarding the efficacy of infliximab in inducing mucosal healing. In a cohort of 214 patients reported by Schnitzler *et al*, 67.8% of responders achieved mucosal healing.[14]

Schering-Plough also notes that mucosal healing, as a treatment aim, was included in the final scope for this appraisal, as published in April 2007. Despite this signal of the committee's acknowledgement of the importance of mucosal healing, it has not been considered further. This is highly unfortunate, as beyond its evident importance in clinical practice and its direct association to drivers of cost, mucosal healing could be reasonably used to compare, and differentiate between, infliximab and adalimumab, thereby avoiding the committee's unsupportable and perverse assumption of therapeutic equivalence of the two agents.

Treatment withdrawal strategy despite lack of evidence

Section 1.3 of ACD2 recommends treatment withdrawal from primary responders 12 months after the start of the treatment unless they show *"clear evidence of ongoing active disease"*.

The Committee appears to have based this recommendation on evidence presented by the clinical experts at the committee meeting held on 20th August 2009. Schering-Plough understands that this evidence was restricted to a single study only published in abstract form[15], which assesses the impact of withdrawing infliximab treatment among patients in remission.

Basing the existing recommendation on this study is unsupportable because:

1. The study only considers patients receiving infliximab, and no data exist for adalimumab treatment withdrawal. It therefore provides no evidence regarding discontinuation of adalimumab treatment whatsoever, and it would be perverse for the committee to base a recommendation for withdrawal of adalimumab on this study.
2. In addition to having received infliximab for 12 months, the patients in the study had all been in "stable steroid-free remission" for at least 6 months. This degree of stable remission prior to treatment withdrawal is likely to be vital to patients' chances of maintaining remission post-withdrawal. This requirement has not been incorporated within the recommendations, and as a result, upon implementation of this approach, it is probable that a higher proportion of patients will suffer relapse than observed in the study.
3. A number of risk factors (current smoking, previous steroid treatment, lower haemoglobin, higher CDAI, higher CDEIS, higher USCRP and higher faecal calprotectin) and four subgroups of patients (those with CDEIS ≥2, USCRP ≥5 mg/l, haemoglobin ≤14.5g/dl, and infliximab trough levels ≥2microg/ml) associated with a higher probability of disease relapse post treatment discontinuation were discovered. However, the recommendation states only that *"clear evidence of ongoing active disease, as determined by clinical symptoms and investigation, including endoscopy if necessary"* should be considered when making a discontinuation decision – thereby ignoring potentially valuable evidence from the study.

[14] D'Haens et al. (2008); Rutgeerts et al. (2006); Schnitzler et al. (2008a)

[15] Infliximab Discontinuation in Crohn's Disease Patients in Stable Remission On Combined Therapy with Immunosuppressors: A Prospective Ongoing Cohort Study. Edouard Louis et al, abstract 961, DDW 2009

4. This study is only published in preliminary abstract form, and is still ongoing. As a result, the full impact of this approach to treatment withdrawal is, as yet, unavailable. It would be prudent to await the final study publication to allow full consideration of the evidence, prior to utilising it as the basis for such a recommendation.

In summary, after a median follow-up of 12 months post-discontinuation, 39% of patients in this study had relapsed. Due to the chronic progressive nature of active CD, these patients will all have suffered some degree of irreversible damage as a result. Considering point 2, it is likely that the relapse rate will be notably higher in reality, if the recommendation in ACD2 is applied in its current form. Considering point 3, by choosing to make no reference to important prognostic factors and implying that endoscopic evaluation is optional at best, this recommendation does not in fact reflect valuable evidence provided by the study.

Future studies investigating treatment cessation within a subgroup of patients identified as having a low risk of relapse (considering the safeguards and risk factors discussed above, and perhaps others) might allow a similar recommendation that will not risk harm to large numbers of patients; unfortunately, at this point, the studies and the evidence necessary to support this approach simply do not exist.

Importantly, Schering-Plough notes that DSU were commissioned to conduct further analysis on treatment discontinuations. DSU did not address this in their report (DSU Report 2, 10th June 2009) and stated a lack of evidence as the rationale for excluding this analysis from their report, during the Committee meeting. Despite this advice, the committee still included a treatment withdrawal strategy prominently in the recommendations. In the absence of a cost-effectiveness analysis incorporating the chosen treatment withdrawal strategy, it is inappropriate for the Committee to draw conclusions from the existing model, while this recommendation remains in place.

Selective consideration of new evidence

The Committee asked DSU to consider new evidence in order to facilitate the reconciliation efforts. DSU included new evidence related to relapse rates and an independent cost effectiveness study in their further analysis. Schering-Plough however was not given the opportunity to present additional evidence related to the decision problem and within the scope of this appraisal, at that stage. Schering-Plough believes this to have significant impact on the Committees recommendation and considers this to be procedurally unfair.

Procedural aspects

The DSU's attempt to reconcile the various models is procedurally flawed as it did not complete a full reconciliation as requested by NICE.[16] The report was based on inappropriate evidence (as outlined above) and continued to assume therapeutic equivalence between adalimumab and infliximab without any robust evidence to support this assumption.

[16]DSU Project specification form; February 2009

Making national recommendations based on the DSU's incompletely reconciled version of the model is therefore perverse and any reasonable appraisal committee faced with the same facts (and widespread criticism of the model), would have requested further analysis from the DSU or a fresh model from a different Assessment Group taking into account the latest evidence.

These points above are particularly important given the preferential positioning of adalimumab for luminal CD. The preferential approach appears to be inconsistent with previous anti-TNF appraisals that refer to selecting the "least expensive drug" (e.g., see TA130) and the well-established basis for determining therapeutic effectiveness and making comparative analyses (*i.e.*, based on robust scientific evidence). As such, the preferential positioning lacks any evidential basis and is perverse.

Schering-Plough would urge the Committee to reconsider its guidance and allow unrestricted access of scheduled maintenance treatment with infliximab to eligible CD patients.

Sincerely,

[redacted]

Appendix A: SPC Comparison

The information below directly compares the Summary of Product Characteristics (SPC) from sections 4.1 and 5.1 for infliximab and adalimumab.

	Infliximab[17]	Adalimumab[18]
Severe active CD	√	√
Fistulising CD	√	X
Paediatric CD	√	X
Ulcerative colitis	√	X
Used for maintenance	√	√
Dose increase allowed	√	√
Evidence of mucosal healing	√	X
Allows steroid sparing	√	√
Reduces hospitalisation compared to placebo	√	X
Reduces surgery compared to placebo	√	X
Improves quality of life	√	√

[17] Infliximab SPC 27 July 09
[18] Adalimumab SPC July 09