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Dear [redacted]

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 third appraisal consultation document ("ACD3"), published on 19th November 2009, which sets out the appraisal committee's (the "Committee") recommendations on infliximab and adalimumab for the treatment of Crohn's Disease ("CD").

Schering-Plough welcomes the Committee's decision to allow eligible CD patients equal access to infliximab and adalimumab treatment within their licensed indications, and firmly supports this stance, believing it to be in the best interests of patients and clinicians.

Nonetheless, we still consider some sections of ACD3 perverse in the light of available evidence and urge the Committee to reconsider the following three points:

1. The guidance to reflect the range of plausible treatment costs with infliximab and adalimumab
2. The guidance to acknowledge the broader evidence base and superior long term outcomes profile of infliximab compared to adalimumab; and
3. The guidance to exclude an obligatory treatment discontinuation rule as it is not based on robust evidence.

Schering-Plough has outlined these concerns in detail in the following letter.

Response to ACD content

1. 1 Incorrect representation of infliximab treatment cost in the ACD3

Schering-Plough welcomes the Committee's acknowledgement of the uncertainty surrounding infliximab treatment costs and its comparison with adalimumab treatment costs, arising out of variations in patient body weight, administrations costs, vial sharing practices and local discounting agreements (section 4.3.11).

The uncertainty regarding treatment costs is further augmented due to the higher induction dose used in clinical practice for adalimumab[i,ii] and variable dose escalations required for both agents, albeit more frequently for adalimumab compared to infliximab (45.8%[iii] vs 30%[iv]). Current clinical evidence also suggests that the majority of patients receiving infliximab dose escalations are subsequently able to de-escalate back to 5mg/kg[v]. No such dose reduction evidence exists for adalimumab. Lastly, further real-world evidence suggest dose frequency escalation with adalimumab in the range of 30% to 65.4%.[vi,vii]

Based on the available evidence, a range of plausible induction and maintenance costs estimated by varying some of the above parameters, is displayed in table 1 below.

Table 1 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

In light of the uncertainty regarding the treatment costs, Schering-Plough urges the Committee to acknowledge this in the guidance by presenting a range of plausible administrations costs (TAG 134; Section 4.11, page 14) and a range of plausible treatment costs such as £2,717-£3,556 for induction and £8,828-£14,828 for maintenance for infliximab and £1,546-£2,618 for induction and 9,295-£15,337 for maintenance for adalimumab (sections 3.6 and 3.10 respectively).

1.2 Interpretation of cost-effectiveness evidence

The Committee has taken a pragmatic decision to recommend equal access to CD patients for infliximab and adalimumab even though the supporting evidence is inconsistent and incomplete. Schering-Plough welcomes this decision in the context of providing equal access to eligible CD patients. Schering-Plough however, would like to reiterate its position on evidence generation and interpretation phase.

The models submitted by the manufacturers, the model developed by the assessment group ("AG") and the economic analysis by an independent group (Bodger et al.)[viii] used different structural and parametric assumptions. These models have never been never fully reconciled even though it was deemed essential by the Decision Support Unit ("DSU") to produce robust Incremental Cost Effectiveness Ratios ("ICERs") [DSU report 1 and DSU report 2]. In the absence of full reconciliation, ICERs presented to the Committee from several different analyses are not comparable with each other.

In addition, 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 TNF-α inhibitors. The infliximab ICERs thus obtained are conservative and should not directly be compared with adalimumab ICERs in these analyses.

2 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. Schering-Plough believes that this assumption 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 TNF-α inhibitors in general. Infliximab has demonstrated significant in outcomes such as mucosal healing. 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.[ix] Recent evidence has identified mucosal healing as the only clinical endpoint linked to long term remission. Importantly, Infliximab is the only biologic to achieve this clinical endpoint prospectively. Finally, Infliximab also has a broader indication covering fistulising and paediatric CD patients compared to adalimumab.

Schering-Plough accepts the Committee's pragmatic decision to allow access to CD patients for both TNF-α inhibitors in the absence of any head to head analysis as this is in the best interests of patient and their providers. However, Schering-Plough would strongly urge the Committee to ensure that the above uncertainties are reflected in the final guidance.

3 Treatment discontinuation strategy

Section 1.3 of ACD2 recommended treatment discontinuation from primary responders 12 months after the start of the treatment unless they show *"clear evidence of ongoing active disease"*. In response, Schering-Plough argued that this recommendation was unsupportable, as it was not based upon the best evidence that is currently available, was likely to lead to significant patient morbidity, and as such was not in the best interests of patients.

Unfortunately, ACD3 is now even more stringent, stating that treatment may only continue until *"treatment failure (including the need for surgery), or until 12 months after the start of treatment, whichever is shorter."* Patients who relapse are subsequently allowed further treatment, following the development of symptoms. As previously discussed, due to the chronic progressive nature of active CD, any patient who suffers a relapse of their disease will suffer irreversible damage to their bowel, as a result.

The successful withdrawal of treatment is a current area of active investigation, and as such knowledge is constantly evolving. There are three pieces of evidence which we believe have bearing on this issue:

1. The prospective STORI study[x] (as discussed in our response to ACD2) has recruited 115 patients who are receiving infliximab. All were in remission for at least one year and off steroids for at least 6 months, prior to discontinuation of infliximab. During the first 12 months, 45 patients (39%) had relapsed. Various predictors of relapse were identified.
2. At the GASTRO 2009 conference, Armuzzi *et al*[xi] presented a retrospective study of patients who had discontinued infliximab treatment following a "sustained clinical benefit" from infliximab for at least 12 months prior to discontinuation. 69 patients discontinued infliximab electively following prolonged steroid-free remission; of these, 30 (44%) relapsed within a median follow-up of 13 months. Mucosal healing was found to be a predictor of sustained clinical benefit following discontinuation (HR 2.7, 95% CI 1.3-6,6; p=0.009).

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The available evidence suggests a 12-month relapse rate, post-discontinuation, in the region of 39-44%, in patients who have been in stable steroid-free remission for 6-12 months prior to discontinuation. This is a critical point, as the strategy suggested in ACD3, involving an obligatory blanket discontinuation following 12 months of treatment irrespective of disease status, presence of remission, or known risk factors for relapse, will result in a *significantly* higher relapse rate than those reported.

In conclusion, there is no current evidence which supports the treatment discontinuation strategy suggested in ACD3, and indeed, several pieces of evidence suggest that current best practice differs significantly from this approach. It is highly likely that this approach would be directly harmful to patients. As such, based on the evidence available, and with the interests of patients in mind, Schering-Plough strongly recommends that the Committee should remove the treatment discontinuation strategy, as it stands, from any future recommendations.

Summary

Schering-Plough acknowledges the paucity of head to head evidence between infliximab and adalimumab presented to the Committee upon which to make recommendations. However, in the context of the Committee recommending the least expensive drug to be used, Schering-Plough would urge the Committee to accurately represent the plausible ranges of treatment costs for both TNF-α inhibitors in the final guidance. Schering-Plough would also urge the Committee to acknowledge the broader evidence base available for infliximab, its stronger heritage and its established efficacy and safety profile including superior real-world outcomes in the final guidance. Finally, Schering-Plough would request the Committee to reconsider its position on the treatment discontinuation rule and to exclude it from the final guidance in absence of any strong supporting evidence.

In summary, Schering-Plough would urge the Committee to consider its comments along with those of other consultees and commentators to ensure that the pragmatic approach that has been adopted throughout this last phase of the process allows for refinements to the points above to best reflect the latest evidence and so provide optimal care for patients within the resources of the NHS.

Yours sincerely,

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[i] Rutgeerts et al. Gastroenterology 2009; 136-5, Suppl 1:A-116 (DDW 2009, Abstract 751e)
[ii] Hanauer et al. Gastroenterology 2006; 130:323-33.
[iii] Sandborn et al. Gut 2007;56;1232-1239
[iv] Rutgeerts et al. Gastroenterology 2004;126:402–413
[v] Schnitzler et al. Gut 2009; 58:492-500
[vi] Ho et al. Alimentary Pharmacol & Ther 2009; Mar 1;29(5):527-34.
[vii] Karmiris et al. Gastroenterology 2009, Aug 5 [Epub ahead of print]
[viii] Bodger et al. Alimentary Pharmacol Ther 2009; 30:265-74
[ix] Rutgeerts et al. (2006); Schnitzler et al. (2008b); Baert et al. (2008); Frøslie et al. (2007)
[x] Louis et al. Gastroenterology 2009; 136 Suppl 1:A-146
[xi] Armuzzi et al. Gut 2009; 58(Suppl II) A466 (abstract P1803)
[xii] Data on File, Schering-Plough – personal communication