Schering-Plough Ltd
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National Institute for Health and Clinical Excellence
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7th October 2008

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 appraisal consultation document ("ACD") which sets out the Appraisal Committee's ("the Committee") recommendations on infliximab and adalimumab for the treatment of Crohn's Disease ("CD").

Schering-Plough believes that the Committee's has taken a pragmatic approach while drafting its recommendations based on the limited evidence available in the Assessment Report. However, while the recommendations provide access to treatment with TNF-α inhibitors for CD patients, they fall short of offering optimal treatment and appear to be at odds with current clinical practice in the UK. Schering-Plough therefore urges the Committee to reconsider some aspects of its preliminary recommendations in light of our response to the ACD.

We hope that following a review of our response along with those of the other consultees, the Committee will establish wider recommendations that allow appropriate access to treatment for CD patients.

Response to ACD content

The Committee's perverse decision is based on an inappropriate consideration of the evidence

The Committee appears to have based its recommendations largely on the evidence as presented by the Assessment Group ("AG") in its Technology Assessment Report 2 ("TAR2") as well as the response to consultees' comments on TAR2. Schering-Plough believes this to be problematic and unsatisfactory in several important regards. A number of the concerns that we raised in our responses to the TAR have still not been addressed. Our primary concern relates to the modelling approach which is based on the Silverstein cohort, a significantly less symptomatic patient group in comparison to the standard care treatment arms of pivotal trials for TNF-α inhibitors.

Although Schering-Plough agrees with the AG that the Silverstein cohort is the most accurate representation of the clinical population of CD, we do not agree that the Silverstein cohort most accurately represents those patients eligible to receive TNF-α inhibitors and those studied in clinical trials of TNF-α inhibitors. This view has been confirmed by the panel of gastroenterologists advising Schering-Plough in relation to this appraisal. Schering-Plough believes that economic analysis based on patients in the clinical trials of TNF-α inhibitors along with some of the other amendments suggested below would have led to a different recommendation in favour of scheduled maintenance treatment with TNF-α inhibitors for certain patients.

The critical role of infliximab scheduled maintenance treatment in specific subgroup of patients

Based on the analysis presented by the AG, Schering-Plough acknowledges that infliximab maintenance treatment may not represent a cost effective treatment option compared to episodic treatment with a TNF-α inhibitor in all eligible CD patients. However, Schering-Plough believes that certain patient groups, those more likely to suffer from the severe relapsing form of CD, continue to have considerable unmet needs, and standard care or episodic treatment may not be the most appropriate or cost-effective therapeutic option. These groups will derive significant benefit from scheduled maintenance treatment and should be offered such treatment. Such patient cohorts have been identified in the literature and below are few examples of patients in need of scheduled maintenance treatment

- Patients with a requirement for steroid treatment at the time of diagnosis[1]
- Patient below 40 years of age at the time of diagnosis[1]
- Presence of perianal disease at the time of diagnosis
- Patients with biological markers predictive of relapse such as[2]
    - C-reactive protein > 20 mg/L

[1] Beaugerie L et al. Predictors of Crohn's Disease *Gatroenterology* 2006: 130(3):650-6
[2] Consigny Y et al. A simple biological score for predicting low risk of short-term relapse in Crohn's disease. *Inflamm Bowel Dis.* 2006 Jul;12(7):551-7.

- Erythrocyte sedimentation rate > 15 mm

Schering-Plough therefore urges the Committee to carefully consider recommending scheduled maintenance treatment with infliximab in those patients most likely to suffer relapse.

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

The ACD recommends that if all other considerations are equal the choice of drug between adalimumab and infliximab should be based on the lowest acquisition and delivery cost (section 1.3). This implicitly assumes therapeutic equivalence between adalimumab and infliximab in general and for episodic treatment in particular.

The AG chose not to conduct any formal comparison between the two TNF-α inhibitors under consideration. Heterogeneity between the trials was cited as the primary reason for this approach. In the absence of any formal comparison, the Committee's recommendation, which assumes therapeutic equivalence between infliximab and adalimumab, is perverse.

Schering-Plough supports the Committee's recommendation that the choice of drug should be determined by the healthcare professional in consultation with the patient and should take into account preferences regarding delivery of the drug, potential side effects and contraindications. Following this, Schering-Plough however would like the Committee to reconsider recommending the cheapest alternative and allow healthcare professionals and patients to choose the most appropriate alternative for them.

Incorrect representation of infliximab treatment cost

In the description of the technologies, the ACD presents a drug acquisition cost of £1,678, which assumes 4 vials of infliximab per infusion, per patient.

Drug acquisition cost: - This has been estimated assuming 4 vials of infliximab per infusion. However, Schering-Plough would like to point out that in actual clinical practice not all patients need four vials and the mean number of vials used depends upon the distribution of CD patients in different weight categories. In response to the ACD, Schering-Plough requested patient level information from one of the most widely quoted cohorts of CD patients in UK (Jewell, 2005; Information obtained through personal communication). The weight distribution and hence the number of vials required per infusion of infliximab are shown below.

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This indicates that the mean acquisition cost of infliximab is £1,469 per infusion.

Drug administration cost: - In the description of the technologies, the ACD presents a drug administration cost of £258 per infusion.

Schering-Plough would like to point out that the estimated cost of an infliximab infusion is £99.25 per infusion. This is based on a day case in an IBD ward costing £397, during which time there can be as many as 4 infusions (2 hours/infusion). This is well within the range of plausible administration costs for infliximab accepted by the Committee in a previous appraisal of infliximab in psoriasis (TAG 134; Section 4.11, page 14).

In conclusion, following these two cost amendments, the total cost of infliximab maintenance treatment is estimated to be £10,191 per year, assuming no vial sharing occurs. Schering-Plough would therefore like the Committee to reconsider the estimated drug acquisition and administration cost and, amend the references for infliximab treatment cost appropriately.

Appropriate recommendations for fistulising and paediatric patients

The committee recommended episodic treatment for fistulising patients and scheduled maintenance treatment for paediatric CD patients. In fistulising disease, this was based on the assumption of at least equivalent benefit to that in luminal CD whereas in paediatric CD it was based on lower drug acquisition and potential benefit of continued treatment on growth and quality of life. In light of the paucity of evidence, this seemed to be a reasonable approach. Schering-Plough agrees that these recommendations are in the best interest of the patients and would like to the Committee to take a similar approach in adult luminal CD patients.

In light of our comments above, Schering-Plough would like the Committee to reconsider its guidance and allows unrestricted access of scheduled maintenance treatment with TNF-α inhibitors to subgroups of CD patients at risk of future relapse.

Sincerely,

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