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NICE

Dear [redacted]

Multiple Technology Appraisal (MTA)

Infliximab, adalimumab and golimumab for treating moderately to severely active ulcerative colitis after the failure of conventional therapy (including a review of TA140 and TA262) [ID695]

The BSG thanks you for the opportunity to comment on the model used to assess the cost effectiveness of anti-TNFs for patients with ulcerative colitis. Members of the IBD Committee have reviewed the model and discussed its findings. The template you sent has been used to present many of our concerns.

We have tested the model using the programme provided.

You will be aware that we are commenting as clinical experts rather than as health economists. The Committee is thoroughly familiar with the literature on anti-TNFs for ulcerative colitis and, perhaps more importantly, we are all practising clinicians who work with the nuances of managing real patients and the range of issues and problems that they present. We have major concerns with the model:

1. The cost of conventional treatment, in the model, is very conservative. Most patients take considerably higher doses of mesalazine than those mentioned. We acknowledge that low dose mesalazine is likely to be used for maintenance in each group but will be discontinued after surgery. Please note though, patients may have several relapses per year: we cannot see how the model has considered this. The model uses the cheapest mesalazline preparation but take no account of the range of products available: the model should be based on market share and higher doses used. Patients taking immunomodulators have frequent trips to clinics for blood monitoring (typically 2-monthly). Patients taking repeated courses of steroids are likely to have DEXA scans and those with bone loss will be prescribed bisphosphonates.

2. The modelling of response and maintenance therapy with anti-TNFs is opaque to us.

The remissions rates quoted are similar to those in the key papers, but not exactly the same. We do not know why or how it has been adjusted. The transition for induction to maintenance appears to be based on the outcome of induction therapy, but the rate of patients actually going forward is not clear: we assume it includes both the responders and those in remission; this is a huge assumption. If patients are not satisfied with the ‘response’ or if we/NICE insist on complete remission, then the models will be completely different.

Patients lose response at any time. Those in remission may deteriorate to ‘response’ or non-response: the definitions of which are far from clear when applied to the ongoing maintenance of patients. The modellers should look at the survival curves from the trials and decide when patients fail and not assume they continue to the end

of the year. It is not certain that these non-responders will 1) switch to another anti-TNF, 2) accept surgery, 3) struggle on with conventional therapy.

There is no data on which to base the models after the first year. Assessment and stopping rules have been neither discussed nor defined.

3. The cost of surgery is grossly underestimated: most patients in the UK will undergo a colectomy with an ileostomy in the first instance. Only that first step has been costed in the model. Using the programme to test the model we were able to demonstrate that have a second or third operation will increase the cost of surgery and reduce, in the relative terms, the costs of anti-TNFs.

A proportion of patients will keep their ileostomy in the medium to long term: the cost of this is £3000 per year. For younger patients who keep their stoma for life, the cost of 50 years of stoma care is £150000. Patients may keep their ileostomy for a range of reasons notably issues around fertility/impotence in men and fecundity in women. Older patients may refuse further surgery to avoid hospital admissions. Patients with stomas require lifelong stoma care, loperamide and risk hospitalisation because of stoma related problems.

However, the model could not be adjusted to account for cost of managing a stoma. Our estimated costs of stoma care is £3000 per year, but CCGs estimate the cost to be as high as £5000 per year.

Many patients will undergo second and third operations to create an ileoanal pouch. For these patients, the cost of surgery itself is thus 2 or 3 times that used in the model. They too will require stoma care while awaiting surgery.

Ileoanal pouch surgery is a risk for substantially reduced fecundity: young women may require fertility treatment after pouch surgery.

The model assumes pouchitis is infrequent and only occurs soon after surgery. This is in correct. 10% of patients have pouchitis that require recurrent or maintenanece medication. OF these patients half will ultimate give up their pouch and revert to an ileostomy, with its associated costs and problems.

Due consideration needs to be given to the proportion of patients in each of these groups and the associated costs.

4. The care of teenagers with UC, who have received anti-TNFs by paediatricians, but who later become adults with UC is not addressed. Consideration needs to be given to the particular issues of managing those aged 16-18 years that had refractory UC, that come into remission with anti-TNF agents.

5. Sensitivity analysis. In our hands, the greatest change in the incremental cost per QALY were changes in the QOL in various disease states. “The model is however very sensitive to assumptions regarding the relative utilities of remission, response, active UC and postsurgery.” (p 243). We think this data is some of the weakest in the model. Of the sources cited, one was only an abstract (Woehl et al) and although there were 180 patients, only 10 had pouches and 19 ileostomies. Basing assumptions on such a small dataset is hard to defend. When we used the model small changes in these assumptions significantly changed the costs.

Finally, we are confused by the conclusions that appear contradictory:

> *Based on the NMA for clinical response and remission, in the induction phase, all treatments were associated with statistically significant beneficial effects relative to placebo, with the greatest effect being associated with infliximab. For patients classified as responders at the end of the induction phase, treatment effects were not statistically significant, although the greatest effect at 8-32 weeks was associated with golimumab 100mg. At 32-52 weeks, only infliximab and golimumab 50mg were associated with beneficial effects on clinical response. For patients classified as being in remission at the end of the induction phase, all treatments except for adalimumab were associated with beneficial treatment effects relative to placebo with the greatest effect being associated with golimumab 50mg and 100mg, although the effects were not statistically significant at 8-32 weeks.*
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> *At 32-52 weeks, all treatments except golimumab 50mg were associated with beneficial treatment effects relative to placebo, with the greatest effect being associated with adalimumab (the only treatment with statistically significant effect). Adalimumab was associated with the highest probability of staying in remission, and the smallest probability of moving from remission to response and from remission to no response.*

We would urge the model to be re-considered. We have made specific suggestions using the template you provided.

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