NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

Health Technology Appraisal

Infliximab for acute exacerbations of ulcerative colitis

Response to consultee, commentator and public comments on the Appraisal Consultation Document (ACD)

Definitions:

Consultees – Organisations that accept an invitation to participate in the appraisal including the manufacturer or sponsor of the technology, national professional organisations, national patient organisations, the Department of Health and the Welsh Assembly Government and relevant NHS organisations in England. Consultee organisations are invited to submit evidence and/or statements and respond to consultations. They are also have right to appeal against the Final Appraisal Determination (FAD). Consultee organisations representing patient/carers and professionals can nominate clinical specialists and patient experts to present their personal views to the Appraisal Committee. Where clinical specialists and patient experts make comments on the ACD separately from the organisations that nominated them, these are presented alongside the consultee comments in the tables below.

Commentators – Organisations that engage in the appraisal process but that are not asked to prepare an evidence submission or statement. They are invited to respond to consultations but, unlike consultees, they do not have the right of appeal against the FAD. These organisations include manufacturers of comparator technologies, NHS Quality Improvement Scotland, the relevant National Collaborating Centre (a group commissioned by the Institute to develop clinical guidelines), other related research groups where appropriate (for example, the Medical Research Council and National Cancer Research Institute); other groups (for example, the NHS Confederation, NHS Information Authority and NHS Purchasing and Supplies Agency, and the *British National Formulary*).

Public – Members of the public have the opportunity to comment on the ACD when it is posted on the Institute's web site 5 days after it is sent to consultees and commentators. These comments are usually presented to the appraisal committee in full, but may be summarised by the Institute secretariat – for example when many letters, emails and web site comments are received and recurring themes can be identified.

Comments received from consultees

Consultee	Comment	Response
Royal college of physicians	**Do you consider that all of the relevant evidence has been taken into account?** Yes	Comment noted
Royal college of physicians	**Do you consider that the summaries of clinical and cost effectiveness are reasonable interpretations of the evidence, and that the preliminary views on the resource impact and implications for the NHS are appropriate?** Probably. However the calculations of cost appear to have been done on the basis of 3 infusions of infliximab being given, when the evidence that exists for efficacy of infliximab in this setting relates to a single infusion (5mg/kg) (Jarnerot 2005). This should be redressed.	Guidance relates only to the use of infliximab within its marketing authorisation for an induction course of three doses of infliximab
Royal college of physicians	**Do you consider that the provisional recommendations of the Appraisal Committee are sound and constitute a suitable basis for the preparation of guidance to the NHS?** Yes but the contra-indications to ciclosporin listed in 4.10 should also include a history of epilepsy, other neuropsychiatric disturbance, malignancy, and the patient being in a hospital where there is not immediate access to plasma ciclosporin as well as electrolyte levels including magnesium.	Comment noted. The Committee discussed the issue of contraindications to ciclosporin and noted that those listed in the Summary of Product Characteristics (SPC) related to its use in conditions other than acute exacerbations of ulcerative colitis. The committee therefore concluded that balancing the risks and benefits of ciclosporin would have to be a matter for clinical judgement in individual circumstances. See FAD 4.10
Royal college of physicians	**Are there any equality related issues that need special consideration that are not covered in the ACD?** Only in so far as patients in hospitals unable to assay ciclosporin levels promptly should not be denied infliximab as an alternative to surgery.	See FAD 4.10

Consultee	Comment	Response
Royal college of physicians	**Other comments on the ACD:** **Para 3.3:** As we pointed out at the meeting in July, the placebo failure rate in the Lichtiger 1994 paper on ciclosporin in refractory acute severe UC has been presented inaccurately. In fact, 9/9 patients (100%) given placebo failed to respond, 5 then being rescued with open-label ciclosporin. It is inappropriate therefore to use in this context a 44% surgery rate for the placebo patients, since all would have had surgery had some not been rescued with ciclosporin. **Para 3.4:** For the same reason, we think the figure of 0.67 for the probability of a patient having colectomy in the first 3 months is too low: almost all patients failing to respond to iv steroids given placebo need surgery (eg 100% in Lichtiger paper (see above), 66% in Jarnerot paper). **Para 4.6:** Adjust line 2 to make clear that that this statement applies to 'intravenous steroid-refractory' acute severe UC. **Para 4.8:** We believe that the existing evidence supports use of only 1 infusion (not 3) of infliximab in refractory acute severe UC (Jarnerot 2005).	Comments noted and points have been addressed in the FAD 4.5, 4.6 See preamble to the guidance – the committee considered the licensed regimen
Royal College of nursing	The Royal College of Nursing welcomes the opportunity to review the Appraisal Consultation Document (ACD) of the technology appraisal of Infliximab for acute exacerbations of ulcerative colitis. The ACD is comprehensive and the relevant evidence appears to have been taken into consideration. We consider that the provisional recommendations constitute suitable basis for preparation of guidance to the NHS. We would welcome guidance to the NHS on the use of this health technology.	Comment noted
Schering-Plough Ltd	Schering-Plough is disappointed that the current draft recommendations are overly restrictive and do not offer the most cost effective treatment alternative for patients deemed inappropriate for ciclosporin. The recommendations are not in the best interests of patients with UC, nor are they appropriate in the context of current clinical practice in the UK. Schering-Plough requests that the Committee reconsiders some aspects of its preliminary recommendations in light of our responses to the ACD and the ERG report. We anticipate that following a review of our responses along with those of the other consultees, the Committee will establish a guidance that allows infliximab use in sub-groups of acute UC patients deemed inappropriate to receive ciclosporin.	Infliximab is recommended where ciclosporin is clinically contraindicated.

Consultee	Comment	Response
Schering-Plough Ltd	*Choice of comparator* The Appraisal Committee, in its consideration of the evidence, concluded that ciclosporin was the most appropriate comparator for infliximab in acute UC setting (section 4.5). Schering-Plough, however would like to point out that in certain settings as described below, ciclosporin is deemed inappropriate. Where this is the case, another treatment alternative should be considered. A. In the context of current clinical practice in the UK, ciclosporin is not routinely used in all centres due to concerns about its toxicity and associated mortality. The Committee acknowledged this in the ACD (ACD section 4.5). A market research survey conducted by Schering-Plough also confirmed this view. In a sample of 40 gastroenterologists surveyed in UK, at least 30% do not use ciclosporin and for 60% of clinicians ciclosporin is not the first choice of treatment in this setting. The survey also revealed that 30% of clinicians preferred surgery as a treatment option ahead of ciclosporin (Schering-Plough; data on file). This confirms our view that in the UK clinical practice, ciclosporin is not the only treatment alternative and in such circumstances the appropriate comparator for infliximab is standard care or surgery.	As per the scope the appropriate comparators to infliximab are: ciclosporin, surgery, standard clinical management

Consultee	Comment	Response
Schering-Plough Ltd	*Choice of comparator* B. The choice of treatment alternative also depends on the clinical history of the UC patient being treated. Our consultation with clinical experts identified the following two treatment algorithms currently used in UK clinical practice to treat UC patients with an acute exacerbation. a. Patients with the first presentation of acute UC This sub-group comprises patients for whom the acute exacerbation is their first presentation of UC. Such patients are steroid naïve and have not been exposed to immunomodulators (6-MP/Azathioprine). In current practice, a significant proportion of these patients are offered ciclosporin for their acute exacerbation with an aim of preventing surgery and 'bridging' to a long-term immunomodulator. A small proportion of patients in this sub-group are also treated with infliximab even though infliximab is not the preferred option and clinicians prefer to save it for a later stage during treatment. b. Chronic UC patients hospitalised with an acute exacerbation This sub-group comprises patients diagnosed with chronic UC who are currently receiving corticosteroids and/or immunomodulators for their condition. Such patients, on failure of these therapies, may experience an acute exacerbation of UC. Ciclosporin is not a preferred option as it does not offer a long-term treatment (due to its toxicity) and patients cannot be bridged back to steroids and immunomodulators which they have already failed. Therefore, the primary treatment options for these patients are infliximab and surgery. This suggests that both infliximab and ciclosporin play different roles in the treatment pathway for acute UC and are preferred treatment alternatives for two different patient groups. Therefore ciclosporin should not be considered as the only comparator for infliximab, especially in chronic UC patients hospitalised with an acute exacerbation. Surgery may be a more appropriate comparator for infliximab in this setting.	The committee heard from the clinical experts that either ciclosporin or infliximab may be considered for people with chronic UC admitted with an acute exacerbation while receiving maintenance treatment with an aminosalicylate if intravenous corticosteroids are not effective within a short time. Patients admitted for an exacerbation developing during long term maintenance with azathioprine or other immunomodulators would usually be offered prompt surgery, although there may be the option switching from a thiopurine to methotrexate..Where where prompt surgery is contraindicated or refused, then there may be some preference for infliximab over ciclosporin, but the issue is not clear cut.

Consultee	Comment	Response
Schering-Plough Ltd	*Choice of comparator* C. The Committee acknowledged the widespread concern among clinicians about the risk of serious infections and the associated mortality with ciclosporin treatment (ACD section 4.5). The literature suggests the risk of mortality to be as high as 3.5% among UC patients treated with ciclosporin (Arts et al; 2004). The majority of studies have also observed serious side effects such as nephrotoxicity, seizures, anaphylaxis and risk of serious infections. Due to such high risks, clinicians may prefer not to use ciclosporin in patients where this is deemed inappropriate. In such circumstances, surgery may be the only treatment option and thus the comparator for infliximab. Although, the Committee expressed doubt about the safety of infliximab in this setting due to insufficient evidence, infliximab has not been associated with mortality or treatment related serious adverse events in acute or chronic UC setting (Jarnerot, 2005; Jakobovits, 2007; ACT I&II) In summary, Schering-Plough would argue that surgery is often a comparator for infliximab. The current analysis suggests infliximab to be a cost-effective treatment option compared to surgery. Infliximab therefore should be recommended in these settings.	Infliximab is recommended where ciclosporin is clinically contraindicated. The issues surrounding the interpretation of this are discussed in FAD section 4.10

Consultee	Comment	Response
Schering-Plough Ltd	*The interpretation of the guidance* The ACD recommends the use of infliximab for the treatment of acute exacerbations of severely active ulcerative colitis only for patients in whom ciclosporin is contraindicated or for all UC patients with an acute exacerbation in the context of a clinical trial. In practical terms therefore, the guidance neither allows clinicians to consider use of infliximab in patients deemed unsuitable for ciclosporin (will only allow in patients contraindicated), nor does it allow patients or clinicians to choose infliximab ahead of ciclosporin. Schering-Plough believes that the guidance fails to address two key aspects of acute UC treatment outlined below. • In our view, the wording of the recommendation implies that clinicians should consider the use of infliximab in a treatment pathway that formally includes ciclosporin. Although, we accept the inclusion of ciclosporin in the scope as one of the appropriate comparators based on current clinical practice, we would like to stress that the Institute's remit does not extend to the recommendation (explicitly or otherwise) of technologies outside their licensed indications. • The current guidance also fails to recommend a course of treatment for patients previously treated with ciclosporin. The recommendation assumes that such patients in their next presentation would undergo surgery. However, a proportion of such patients may be unsuitable for surgery or may choose not to undergo surgery. In this sub-group, infliximab may be the best choice of treatment. Although no randomised trial evidence currently exists in this patient group, infliximab has been used in this cohort (Jakobovits, 2007; Kohn, 2007). For such patients wanting to avoid surgery infliximab is likely to be the most appropriate cost-effective treatment option.	The FAD recommends infliximab where ciclosporin is clinically contraindicated. The issues surrounding the interpretation of this are discussed in FAD section 4.10.

Consultee	Comment	Response
Schering-Plough Ltd	Errors & concerns identified by ERG in the modelling exercise 1. *"On the basis of these results (base case; S-P submission), it is clear that the move from standard care to ciclosporin is highly cost-effective given that it is associated with lower costs and higher QALYs. Thus, the policy question then to be addressed is the subsequent move from ciclosporin to infliximab, and so the only appropriate comparator for infliximab is ciclosporin. It would be a mistake to consider either standard care or surgery as comparators for infliximab."(ERG report; Section 5.1, page 24)* Based on the base case results presented in the Schering-Plough submission, ERG has taken a hierarchical approach to rule out the comparison between infliximab and surgery/standard care. Although this is a common approach in health economic decision analysis, it is applicable only if all the comparators are relevant in the treatment setting. In this appraisal, current UK clinical practice would suggest that ciclosporin is not routinely used in centres across the UK and therefore is not an appropriate comparator in all settings as explained above. In settings where ciclosporin is not used or preferred, surgery or standard care should be considered as a comparator.	As per the scope the appropriate comparators to infliximab are: ciclosporin, surgery, standard clinical management
Schering-Plough Ltd	2. *Additional work undertaken by ERG* The ERG revised their cost-effectiveness estimates based on the errors identified in the Schering-Plough submission. However, the base case results presented by the ERG also include some serious errors. The ERG claim to have changed the resource use associated with ciclosporin and the costs associated with oral ciclosporin and azathioprine. It is however unclear how the total QALYs change by changing the costs associated with the treatments (Table 6.3.3.1 to Table 7). Schering-Plough believes that there is an error in the additional analysis undertaken by ERG which may undermine the credibility of any further analysis undertaken by the ERG in general.	The revisions made by the ERG were based on data provided by the manufacturer in its second clarification letter to NICE rather than the model originally submitted.

Consultee	Comment	Response
Schering-Plough Ltd	In the additional analysis ERG also presented an analysis excluding the D'Haens trial. Although Schering-Plough believes this trial should have been included in the evidence synthesis, the ERG did not address the uncertainty around the 12 month efficacy estimates of ciclosporin. In the short-term analysis (0-3 months), the ERG considered only the Lichtiger trial to derive a relative treatment effect for ciclosporin. The Lichtiger trial did not have 12 month follow-up colectomy data and the ERG assumed a 0.18 colectomy rate (apparently based on our original submission) for ciclosporin during 4-12 months. The Schering-Plough submission sourced this 0.18 colectomy rate from the D'Haens trial, thus its inclusion in the ERG's new analysis seems inappropriate. In the absence of any point estimates for the 4-12 month colectomy rate, we can at best assume that it lies somewhere between 0.143 (Placebo; 4-12 months) and 0.48 (Ciclosporin; 0-3 months); this uncertainty should have been addressed via a sensitivity analysis.	The committee were aware that there was no alternative estimate for the 4-12 month colectomy rate with ciclosporin. The committee discussed the range of alternative estimates presented by the manufacturer (see FAD 4.7)
Schering-Plough Ltd	Schering-Plough conducted further analyses after rectifying the errors identified by the ERG. The resultant ICERs for infliximab versus ciclosporin were in the range of £9,323 (pp=0.48) to £52,080 (pp=0.143). No trial data exists up to 12 months for ciclosporin. However, clinical opinion has suggested that the predictive probability of colectomy is likely to be higher than the assumed value of 0.18 and therefore the resultant ICER is likely to be significantly lower than £48,367 reported in ERG report.	See FAD 4.7.
Schering-Plough Ltd	3. *"The ERG obtained clinical opinion suggesting that the colectomy rate estimated for ciclosporin was 'completely inconsistent with the current evidence and with clinical experience.' Consequently, the ERG considered the assertion that infliximab has greater benefit than ciclosporin based on the indirect comparison to be unfounded." (Evaluation report; page 13)* The primary purpose of the indirect comparison in this appraisal was to synthesise a composite efficacy estimate based on the published trial evidence. However, ERG has selected to ignore the trial evidence and adjust their efficacy estimates based on the expert opinion. Such an approach is inconsistent with the Institute's own published guidelines and especially inappropriate given the availability of published trial data. In light of our response above, Schering-Plough would like the Appraisal Committee to reconsider its guidance and recommend infliximab in patients deemed inappropriate to receive ciclosporin.	The ERG's indirect comparison was based on existing published trial data; only difference being the exclusion of the D'Haens study, due to different population characteristics.

Consultee	Comment	Response
NACC	Further contact with clinicians has confirmed that there is considerable variation in the number of doses of infliximab commonly used. The committee is therefore correct to recognise this as an area of uncertainty and not to prescribe the number of doses to be used in those patients where ciclosporin is contra-indicated. In many cases it will be less than three, but scope should be left for the manufacturer's licensed regime to be used.	Guidance relates only to the use of infliximab within its marketing authorisation for an induction course of three doses of infliximab
NACC	We would like to see in the ACD greater provision to recognise the very great concerns patients may genuinely have about ciclosporin. As noted, both drugs have significant potential risks but patients are inevitably aware of the level of concern felt by gastroenterologists about using ciclosporin and that they generally have a greater sense of security with infliximab. (The IBD audit figures showing low use of rescue therapy are evidence of the extent of concern about ciclosporin.) Limiting the use of infliximab to patients with specific contraindications is, we feel, too restrictive. The ACD should recognise situations where the patient is very concerned about the side-effect profile of ciclosporin and recognise this as a valid justification for using infliximab for those patients. Ultimately patients ought to have a choice in this important decision and be able to make a decision with their clinician's guidance.	Comments noted. See FAD 4.5

Comments received from commentators

Commentator	Comment	Response
	None received	

Comments received from members of the public

Role*	Section	Comment	Response
NHS Professional 1	2	For recommendation 1.1 to be useful in practice and to assist funding decisions, specific guidance is required on the number of doses to be administered for this indication i.e. a single infusion or infusions at 0, 2 and 6. It should also be clear that maintenance dosing has not been addressed in this appraisal.	Guidance relates only to the use of infliximab within its marketing authorisation for an induction course of three doses of infliximab

* When comments are submitted via the Institute's web site, individuals are asked to identify their role by choosing from a list as follows: 'patent', 'carer', 'general public', 'health professional (within NHS)', 'health professional (private sector)', 'healthcare industry (pharmaceutical)', 'healthcare industry'(other)', 'local government professional' or, if none of these categories apply, 'other' with a separate box to enter a description.

Role*	Section	Comment	Response
NHS Professional 2	1	Ciclosporin is a drug fraught with side-effects. It causes disfiguring facial changes that make it a very undesirable drug to try, especially in teenage girls. This side effect does not prevent the introduction of the drug, but the facial hair, once established can be an on-going problem	Comment noted. The adverse effects associated with ciclosporin are addressed in the FAD section.
Non-consultee clinical expert (responding on behalf of the UK paediatric inflammatory bowel disease working group)		I would like to express the views of the UK paediatric inflammatory bowel disease (IBD) working group on the use of Infliximab in paediatric patients with severe ulcerative colitis. I am aware that it is not licensed for this use in children in the UK but we feel that it should have been considered in this appraisal. Children with severe colitis have very similar rates of colectomy as those in adult patients and recent data have shown patients in the paediatric age range are more likely to present with pancolitis (total colitis) at presentation and if not, to progress to total colitis more quickly than in the adult population. Thus the need for effective treatment quickly may be greater in the paediatric group.	Guidance relates only to the use of infliximab within its marketing authorisation for the treatment of acute exacerbations of severely active ulcerative colitis.
Non-consultee clinical expert (responding on behalf of the UK paediatric inflammatory bowel disease working group)		Intravenous steroids are used as in the adult population so after 3 days of intravenous steroids if not responding (> 8 stools per day or CRP >45mg/dl) further treatment is considered. Paediatric gastroenterologists would then commence intravenous cyclosporine 2mg/kg but it is extremely difficult to establish satisfactory blood levels which are the yardstick used to confirm effective dosage of cyclosporine. Inadequate trough levels in the blood then necessitate need to increase the dose of cyclosporine and obviously delay the time taken to reach effective intravenous levels. In addition, there is great concern about toxicity in patients receiving cyclosporine particularly adverse effects on renal function, hypertension, increased risk of infection and mortality. Surgeons are unhappy to operate on patients who are rendered more immunocompromised by their treatment in conjunction with their underlying colitis.	Guidance relates only to the use of infliximab within its marketing authorisation for the treatment of acute exacerbations of severely active ulcerative colitis

Role*	Section	Comment	Response
Non-consultee clinical expert (responding on behalf of the UK paediatric inflammatory bowel disease working group)		Paediatric gastroenterologists are increasingly using infliximab instead of cyclosporin as we have become familiar with its use and consider that it has fewer potential side-effects than cyclosporine. In addition, cost effectiveness in this population may be even more favourable that in the adult population as there may be fewer vials of Infliximab used per patient due to their lower weight. Although there has been no formal audit, it is not at all certain that in the setting of severe acute colitis whether all patients receive 3 doses but it is likely most will receive two. There is no need to emphasis how important it is for paediatric patients also to have time to adjust to the possibility that colectomy may become a necessity if medical treatment fails.	Guidance relates only to the use of infliximab within its marketing authorisation for the treatment of acute exacerbations of severely active ulcerative colitis