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Infliximab for the treatment of acute exacerbations of ulcerative colitis

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1 SUMMARY

1.1 Scope of the submission

The submission considers the effectiveness and cost-effectiveness of infliximab in the treatment of acute exacerbations of ulcerative colitis that require hospitalisation. Further, patients are assumed to have had an inadequate response to conventional therapy including corticosteroids and 6-mercaptopurine (MP) or azathioprine (AZA), or who are intolerant to or have medical contraindications for such therapies.

1.2 Summary of submitted clinical effectiveness evidence

The manufacturer's submission reviews systematic reviews and RCTs of infliximab and ciclosporin, the main alternative treatment option. The review also examined non-RCT evidence, particularly case-series of infliximab in the patient group of interest.

The main evidence identified is well known, four RCTs, two comparing infliximab with placebo in patients not responsive to initial treatment with intra-venous corticosteroids and one comparing ciclosporin with placebo. A fourth RCT compares ciclosporin with iv corticosteroids as the initial treatment after hospitalisation. The evidence on effectiveness is combined through a mixed treatment comparison model.

The review and the model contribute to the two main conclusions offered in the manufacturer's submission:

- That infliximab provides clinical benefit to patients with acute severe, steroid-refractory ulcerative colitis (UC) and is well tolerated

Infliximab provides additional clinical benefits over ciclosporin particularly avoidance of colectomy.

1.3 Summary of submitted cost effectiveness evidence

No published economic evaluations of infliximab in acute UC were identified and so the cost-effectiveness work focuses entirely on the *de novo* model and economic evaluation undertaken by the manufacturer. A decision tree model was built to compare infliximab to strategies involving ciclosporin, standard care and surgery. The main evidence used to estimate some of the key probabilities in the model derived from the main trials but data on resource use and costs were only available from an expert panel. Utility data were taken from an observational cohort (the HODaR study). The results revealed dominance in the comparison of standard care and with ciclosporin. On the basis of the results, 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. After correcting a small number of errors in the model the revised base case ICER for infliximab compared to ciclosporin is £20,000. However, sensitivity analyses revealed considerable uncertainty in this result to the weight of the patient, the timeframe considered and, most importantly, the colectomy rates used. When a more appropriate mix of trials was included in the estimation of colectomy rates, the ICER for infliximab rose to £48,000.

1.4 Commentary on the robustness of submitted evidence

1.4.1 Strengths

The review of effectiveness is generally systematic in approach, building on previous work in the area.

The submission reports a *de novo* model-based economic evaluation that has considered the cost-effectiveness of infliximab in UC. The use of a decision tree model is appropriate as the focus is on the acute phase of the disease. The main probability inputs have been derived from trial data.

Probabilistic sensitivity analysis and one-way sensitivity analyses have been performed.

1.4.2 Weaknesses

Although generally systematic the review of clinical effectiveness has some errors most notably failing to distinguish that the effect measured by one of the included RCTs is qualitatively different from the other trials and should not be combined with them. There is concern that the considerable uncertainty surrounding the estimates of effectiveness arising from the very small number of RCTs, which are themselves small, is understated. Although the mixed treatment comparison model is interesting, it is debatable whether the very limited amount of data available warrants such a sophisticated approach.

The model has not considered side-effect issues or mortality events. The resource use estimates used in the model are from an expert panel. The key model inputs on colectomy rates are derived from a small number of small trials, some of which may not be directly relevant to the policy question being addressed.

1.4.3 Areas of uncertainty

- There is considerable uncertainty about the evidence on effectiveness of infliximab and ciclosporin. Primarily this emanates from the very limited amount of RCT data, the impact of which is somewhat understated in the manufacturer submission. This is compounded by a debatable decision about “combining” the data for an RCT with a control arm of iv cortiocsteroids with RCTs with placebo control arms and the use of a mixed treatment comparison model to generate estimates of the effect infliximab versus ciclosporin for which there is no direct evidence. This however has also led to estimates of effect of infliximab and ciclosporin which differ in important respects from the original trials.

- The results consistently indicate that the move from standard care to ciclosporin is highly cost-effective. Thus, the appropriate policy

question is not uncertain. The question to be addressed is: should we make a subsequent move from ciclosporin to infliximab? And so the only appropriate comparator for infliximab is ciclosporin.

- There is considerable uncertainty concerning what colectomy rates should be used.
- The weight of the patient is important – if patients tend to be 60kg or less then the cost-effectiveness of infliximab is more attractive.
- The timeframe of the model is also important – extrapolating beyond 12 months is the approach that is consistent with the NICE methods guide. Such extrapolation indicates worsening cost-effectiveness for infliximab in general.

1.5 Key issues

The appraisal appears to hinge on the three issues:

- Is the effectiveness of both infliximab and ciclosporin accurately portrayed by the manufacturer submission, particularly through the "inclusion" of the RCT of ciclosporin by D'Haens et al, and through the use of the mixed treatment comparison model to summarise and estimate parameters for the economic model?
- Does the manufacturer's submitted model fully capture and convey the uncertainty arising from the problems with the effectiveness data?
- From the information available is it likely that improved estimates of effectiveness, and so cost-effectiveness, will arise from the on-going trials of infliximab versus ciclosporin identified?

2 BACKGROUND

2.1 Critique of manufacturer's description of underlying health problem

The manufacturer's description of the underlying health problem is reasonable and introduces all the aspects of the management of ulcerative colitis relevant to this appraisal.

2.2 Critique of manufacturer's overview of current service provision

Again the overview is reasonable. Arguably there is too great an emphasis on the limitations of ciclosporin. The implication that infliximab does not appear in management guidelines just because it was not licensed at the time the guidelines were compiled also seeks to divert attention from the fact that there is continuing genuine debate about the place of infliximab in the management of ulcerative colitis.

3 Critique of manufacturer's definition of decision problem

The discussion which occurred during the first STA on infliximab for ulcerative colitis had already done much to clarify the problems with the decision problems surrounding use of infliximab, particularly that its use in patients still out-patients and patients requiring hospitalisation were distinct. As it was the latter that was not completely addressed in the first STA, this STA was intended to focus on use of infliximab in the acute situation. The manufacturer's statement of the decision problem is consistent with this.

3.1 Population

The NICE final scope indicates, "Adults with acute exacerbations of severely active ulcerative colitis who have had an inadequate response to conventional therapy including corticosteroids and 6-mercaptopurine or azathioprine, or who are intolerant to or have medical contraindications for such therapies, and whose clinical management require hospitalisation."

The manufacturer's submission addresses this population.

It might also have been worth clarifying that in the UK context, unless contraindicated, the initial management of a patient hospitalised with acute ulcerative colitis would be intravenous corticosteroids for at least three days. Patients who fail to respond to such treatment, are "steroid-refractory" and are

the main target population for alternative rescue therapies such as infliximab, ciclosporin or surgery.

3.2 Intervention

The NICE final scope indicates this to be infliximab.

The manufacturer's submission amplifies this as: "Infliximab 5 mg/kg given as an intravenous infusion over a 2 hour period followed by additional 5 mg/kg infusion doses at 2 and 6 weeks after the first infusion."

This does raise issues about how research evaluating higher doses such as 10mg/kg and 20mg/kg should be treated, and whether excluding such research is unnecessarily restrictive.

3.3 Comparators

The comparators in the NICE final scope are stated to include:

- Standard clinical management which may include surgical intervention
- Ciclosporin

Again the manufacturer's submissions amplifies this:
"Current clinical management in UK for an acute exacerbation of UC not responding to 72 hours iv steroids consists of treatment with infliximab, ciclosporin, up to 1 week iv steroids as a bridge to maintenance immunomodulatory therapy or surgery. All the treatment options including infliximab upon failure may result in surgical intervention. Therefore the proposed submission will focus on surgical intervention as an outcome of inadequate response to treatment as well as a comparator. Therefore, the comparators will be

- Standard clinical management which may result in surgical intervention
- Ciclosporin which may result in surgical intervention
- Surgical intervention"

This amplification is appropriate and remains consistent with the NICE scope although strictly the issues raised relate primarily to the target population. Once this is defined as steroid-refractory patients, the nature of the comparators is automatically clarified to a great extent.

3.4 Outcomes

The NICE scope indicates the outcome measures to be considered should include:

- Health-related quality of life
- Survival
- Rates of and duration of response, relapse and remission
- Rates of surgical intervention
- Measures of disease activity
- Adverse effects of treatment

The manufacturer's submission also indicates its intention to target these outcomes.

3.5 Time frame

The NICE final scope suggests that the time horizon should be long enough to allow reasonable estimation of expected costs (including adverse events if applicable) and benefits for the intervention, but should also account for the disease specific feature, particularly fluctuation and unpredictability of symptoms.
The manufacturer's submission argues:

"The treatment goals for UC patients with an acute exacerbation are

- Avoiding surgery
- Avoiding prolonged hospitalisation
- Reduction in disease activity resulting in remission

Therefore, outcomes over a shorter time horizon such as 3 months (immediate) and 12 months (short-term) are considered to be significant. The current evidence for infliximab and its competitors in this setting is also restricted for a shorter time horizon. Therefore, a base case analysis of 12 months with a sensitivity analysis of 3 months will be provided."
This argument seems reasonable.

3.6 Other relevant factors

As other relevant factors the NICE final scope indicates:

"Where evidence permits, the appraisal of infliximab for the acute exacerbation of severely active UC should identify patient subgroups for whom the technology is most appropriate.

Where evidence permits, the appraisal of infliximab for the acute exacerbation of severely active UC should consider different posology or methods of administration, treatment continuation strategies and lengths of treatment required when patients have responded to infliximab.

Guidance will only be issued in accordance with the Summary of Product Characteristics"

The manufaturer's submission observes:
"Depending on the availability of evidence a sub-group analysis for newly diagnosed UC patients contraindicated to immunomodulators will be provided.

The submission will focus on a full induction dose of infliximab (weeks 0, 2 & 6) followed by 'bridge' to immunomodulator therapy."

This again seems consistent with the final scope.

4 CLINICAL EFFECTIVENESS

4.1 Critique of manufacturer's approach

This is based on a formal critical appraisal recorded in Appendix 1. Two additional appraisals (Appendices 2 & 3) were conducted on two Cochrane reviews which appeared to have informed the manufacturer review of clinical evidence. The four key studies used in the manufacturer's approach were reappraised and the abstracted data rechecked as documented in Appendices 4-7. Finally the mixed treatment comparison model, for which specific code was provided the manufacturer was re-run.

4.1.1 Description of manufacturers search strategy and comment on whether the search strategy was appropriate.

For infliximab the search strategy of both the submission and the underlying Cochrane review were strong with respect to published data, but possibly slightly limited with respect to unpublished data. For ciclosporin the search strategy was weaker. The terms used to search MEDLINE and EMBASE for the economic evaluation were limited and a syntax error was noted (see set 3). The ERG verified search strategies and checked for on-going studies . We identified no additional included RCTs for either infliximab or ciclosporin. We identified one additional on-going trial. This is based in the UK and is comparing infliximab with ciclosporin in steroid-refractory acute severe ulcerative colitis in hospitalised patients.

4.1.2 Statement of the inclusion/exclusion criteria used in the study selection and comment on whether they were appropriate.

The main inclusion/exclusion criteria for the submission were RCTs of infliximab and ciclosporin in patients with acute severe ulcerative colitis in hospitalised patients. This was felt by the ERG to be appropriate as the main evidence base for this STA.

In addition non-randomised interventional studies and observational studies were sought too. However, this was only done for infliximab. Given that

observational studies tend to present exaggerated estimates of effect, the overall impression created by identifying case-series for infliximab, but not for ciclosporin may be to over-state the effectiveness of infliximab relative to ciclosporin.

4.1.3 Table of identified studies. What studies were included in the submission and what were excluded.

For infliximab two RCTs by Jarnerot et al[1] and Sands et al[2] were included. Both compared infliximab with placebo in acute severe ulcerative colitis in hospitalised patients who had not responded to initial treatment with iv corticosteroids. A list of excluded potential-include RCTs was provided with reasons for exclusion. A number of case-series were also included from the review of non-randomised interventional and observational studies.

For ciclosporin a further two RCTs by Lichtiger et al[3] and D'Haens et al[4] were included. The first of these was analogous to the two trials for infliximab in that it compared ciclosporin with placebo in acute severe ulcerative colitis in hospitalised patients who had not responded to initial treatment with iv corticosteroids. In contrast, the second RCT by D'Haens et al compared ciclosporin with iv corticosteroids in patients with acute severe ulcerative colitis requiring hospitalisation who had not yet received any intensive treatment. In the ERG's view it was not appropriate to include this RCT, and its very different nature ought to have been more clearly recognised as it has been in the Cochrane review by Shibolet et al[5]. The effect of including D'Haens et al is likely to have led to an underestimation of the effect of ciclosporin and so to an overestimation of the effect of infliximab relative to ciclosporin in the MTC model.

[1] Jarnerot G, Hertervig E, Friis-Liby I, Blomquist L, Karlen P, Granno C et al. Infliximab as rescue therapy in severe to moderately severe ulcerative colitis: a randomized, placebo-controlled study. Gastroenterology 2005:128(7);1805-1811.
[2] Sands BE, Tremaine WJ, Sandborn WJ, Rutgeerts PJ, Hanauer SB, Mayer L et al. Infliximab in the treatment of severe, steroid-refractory ulcerative colitis: A pilot study. Inflamm Bowel Dis. 2001;7(2):83-88.
[3] Lichtiger S, Present D, Kornbluth A, Gelernt I, Bauer J, Galler G et al. Cyclosporine in severe ulcerative colitis refractory to steroid therapy. N Engl J Med 1994;330(26):1841-5.
[4] D'Haens G, Lemmens L, Geboes K, Vandeputte L, Van Acker F, Mortlemans L et al. Intravenous cyclopsorine versus intravenous corticosteroids as single therapy for severe attacks of ulcerative colitis. Gastroenterology 2001;120(6):1323-1329.

4.1.4 Details of any relevant studies that were not included in the submission?

See appendix 8 for details of the additional on-going trial identified. No other relevant studies not included in the submission were identified.

4.1.5 Description and critique of manufacturers approach to validity assessment

The submission used an early version of the Jadad score to assess validity of the included RCTs, focusing particularly on allocation concealment of the randomisation. This is a well recognised approach and appears to have been reasonably conducted despite the handicap of being conducted by a single reviewer. In contrast there was very little assessment of the validity of the included case-series for infliximab. It is one reason why the results of this component of submission should receive little emphasis in drawing overall conclusions on effectiveness because openness to bias of such study designs does not appear to have been carefully considered

4.1.6 Description and critique of manufacturers outcome selection

The submission focuses on clinical response/induction of remission, colectomy rates and adverse events. While information on other outcomes such as duration of hospitalisation and health-related quality of life would have been ideal, appraisal of the four main included studies confirmed that this information was not available.

The process of data abstraction is vulnerable because it appears to have been conducted without any checking procedure. However, most of the key data appears to have been abstracted correctly, with minor error being identified (Table 5.4.1; D'Haens row; ciclosporin column; entry should be 5/14 (36%) rather than 6/14 (36%)).

[5] Shibolet O, Regushevskaya E, Brezis M, Soares-Weiser K. Cyclosporine A for induction of remission in severe ulcerative colitis. *Cochrane Database of Systematic Reviews* 2005, Issue 1. Art. No.: CD004277. DOI: 10.1002/14651858.CD004277.pub2.

4.1.7 Describe and critique the statistical approach used

The summary of the results is weak.

The submission relies on a mixed treatment comparison model to provide quantified summary estimates of effect, particularly of colectomy rates to use in the cost-effectiveness model. They claim they have not done meta-analysis, ignoring the fact that the mixed treatment comparison model has achieved the same aim.

The ERG has re-run the MTC model using the code provided by the manufacturer and has obtained the same numerical estimates. However the main concern is the face validity of the results, which bear little relation to actual estimates of effect obtained in the original trials. This is illustrated in the following three tables where the results of the original trials expressed as events rates and odds ratios are tabulated alongside the outputs of the MTC.

Table 1 Colectomy 0-3 month results (event rates & OR) from different parts of the report

Intervention	Jarnerot	Sands	Lichtiger	D'Haens		MTC model
Crude rates (%) [95% CI by Wilson's method]						
Infliximab	7/24 (0.29) [0.15, 0.49]	0/3 (0.0) [0.0, 0.56]				(0.23) [0.05, 0.56]
Ciclosporin			3/11 (0.27) [0.10, 0.57]	3/14 (0.21) [0.08, 0.48]		(0.58) [0.22, 0.88]
Placebo	14/21 (0.67) [0.45, 0.83]	3/3 (1.0) [0.44, 1.0]	4/9 (0.44) [0.19, 0.73]	3/15 (0.20) [0.07, 0.45]		(0.67) [0.46, 0.85]
Odds ratio [95% CI]						
Infliximab vs placebo	0.21 [0.06, 0.73]*	0*				0.13 [0.03, 0.44]
Ciclosporin vs placebo			0.47 [0.07, 3.04]**	1.09 [0.18, 6.58]		0.70 [0.18, 2.69]
Infliximab vs Ciclosporin	No direct comparisons					

Notes: * Combined result from meta-analysis of Jarnerot and Sands, supplied by manufacturer in response to request for supplementary information, summary OR (fixed effects) 0.16 [0.05, 0.53], Summary OR (random effects) 0.16 [0.04, 0.66]
** Equivalent to RR of 0.61 [0.18, 2.1]

Table 2 Colectomy 0-12 month results (event rates & OR) from different parts of the report

Intervention	Jarnerot	Sands	Lichtiger	D'Haens		MTC model
Crude rates (%) [95% CI by Wilson's method]						
Infliximab	10/24 (0.42) [0.25, 0.61]					
Ciclosporin				5/14 (0.36) [0.16, 0.61]		
Placebo	15/21 (0.71) [0.5, 0.86]			6/15 (0.40) [0.2, 0.64]		
Odds ratio [95% CI]						
Infliximab vs placebo	0.29 [0.08, 0.99]					
Ciclosporin vs placebo				0.83 [0.19, 3.75]		
Infliximab vs Ciclosporin	No direct comparisons					

Table 3 Colectomy 3-12 month results (event rates & OR) from different parts of the report

Intervention	Jarnerot	Sands	Lichtiger	D'Haens		MTC model
Crude rates (%) [95% CI by Wilson's method]						
Infliximab	3/17 (0.18) [0.06, 0.41]					(0.27) [0, 0.92]
Ciclosporin				3/11 (0.27) [0.10, 0.57]		(0.18) [0.0, 0.70]
Placebo	1/7 (0.14) [0.03, 0.51]			3/12 (0.25) [0.09, 0.53]		(0.14) [0.0, 0.47]
Odds ratio [95% CI]						
Infliximab vs placebo	1.3 [0.11, 15.0]					1.8 (0.13, 57)
Ciclosporin vs placebo				1.1 [0.18, 7.2]		1.1 (0.15, 8.5)
Infliximab vs Ciclosporin	No direct comparisons					

A particular example of the mismatch generated by use of the MTC is the 0-3 month colectomy event rates shown in the first table. The actual event rates in the trials were 0.27 and 0.21; the event rate predicted by the MTC, and the event used in the economic modelling, was 0.58. The lack of face validity not

only undermines the credibility of the model in summarising the available data and making an estimate of the unmeasured effect of infliximab relative to ciclosporin, but also challenges the validity of the effectiveness parameters used in the economic model, which are already challenged by the inclusion of the data by D'Haens et al, a study which measures a different effect.

The ERG re-ran the model without the D'Haens et al RCT. This resulted in some changes as indicated in the table below:

Table 4 Colectomy 0-3 month results (event rates & OR) from different parts of the report – MTC re-run without D'Haens et al

Intervention	Jarnerot	Sands	Lichtiger		MTC model	
Crude rates (%) [95% CI by Wilson's method]						
Infliximab	7/24 (0.29) [0.15, 0.49]	0/3 (0.0) [0.0, 0.56]			(0.24) [0.05, 0.56]	No change from original estimate
Ciclosporin			3/11 (0.27) [0.10, 0.57]		(0.48) [0.09, 0.89]	Change from 0.58 to 0.48
Placebo	14/21 (0.67) [0.45, 0.83]	3/3 (1.0) [0.44, 1.0]	4/9 (0.44) [0.19, 0.73]		(0.67) [0.46, 0.85]	No change from original estimate
Odds ratio [95% CI]						
Infliximab vs placebo	0.21 [0.06, 0.73]	0			0.13 [0.03, 0.44]	No change from original estimate
Ciclosporin vs placebo			0.47 [0.07, 3.04]		0.43 [0.06, 3.1]	0.70 to 0.43 Widening of 95% CI
Infliximab vs Ciclosporin	No direct comparisons					

The exclusion of D'Haens reduces the estimated colectomy rates for ciclosporin to some extent from 0.58 to 0.48, but these colectomy rates at 0-3 months are still much higher than would be expected in practice, and still far exceed the rate observed in the remaining ciclosporin RCT by Lichtiger et al (0.27)

The exclusion of D'Haens et al from the MTC also means that no rates can be derived for 3-12 months as it is the only study contributing data for ciclosporin over this period.

4.1.8 Summary statement

The evidence appears to be complete although it is always impossible to completely exclude the possibility of unpublished studies and the associated danger of publication bias. The chance of missed studies is greater for ciclosporin than infliximab. An important additional on-going RCT comparing infliximab with ciclosporin for the treatment of acute severe ulcerative colitis was identified; there are two such studies in progress.

The included studies were generally confirmed to be the most relevant to the decision problem. The RCT by D'Haens et al of ciclosporin should not have been included, or at least clearly distinguished from the two RCTs of infliximab and one RCT of ciclosporin which compared the active agents with placebo. In contrast D'Haens et al compared the active agent ciclosporin with another active agent, iv steroids. The additional review of case-series of infliximab unfortunately added little.

The general conduct of the review was adequate, although use of a single reviewer is not ideal. The major problem however was the quantitative summary using a mixed treatment comparison model to summarise the extremely heterogenous results from the data provided by the very limited number of small RCTs. Even with the debatable inclusion of the D'Haens et al, the total number of patients investigated is 100 (27 allocated to infliximab, 25 to ciclosporin, 33 to placebo and 15 to intravenous steroids). The results of the mixed treatment comparison model are inconsistent with the results actually obtained in the RCTs, which in turn calls into question the economic model which directly uses the colectomy rates produced by the MTC as its main effectiveness parameters.

4.2 Summary of submitted evidence

4.2.1 Summary of results

There is no succinct summary of results.

Section 5.9 (page 32) Interpretation of clinical evidence, offers the following two paragraphs:

> All studies summarised acute severe treatment refractory UC; no studies looked specifically at patients intolerant or contraindicated to corticosteroids, 6-mercaptopurine or azathioprine. Comparison with ciclosporin was only reported as a subgroup of a single observational study; few patients were treated (6 with infliximab and 15 with ciclosporin) and the differences were relatively small. High quality head-to-head RCTs were not found of infliximab and ciclosporin; all infliximab and ciclosporin RCTs compared the study drug to placebo or steroids.
>
> The evidence identified from two small RCTs and nine largely small, open, uncontrolled observational studies (three of which reported subgroups only) suggest that infliximab provides clinical benefit to patients with acute severe, steroid-refractory UC and is well tolerated. Our indirect comparison against ciclosporin suggests that infliximab provides additional clinical benefit in terms of colectomy avoidance beyond that available with other, currently-used therapies.

The main output of the clinical effectiveness section carried forward to the health economic modelling are the results of the mixed treatment comparison model set out in Tables 5.6.1 and 5.6.2 (both marked as aic in manufacturer's submission, page 26).

Table 5.6.1 Log*Odds Ratios of Colectomy compared to Placebo

Treatment	Timepoint	Mean	SD	2.5% CI	97.5% CI
Infliximab	0-3 Months	-2.07	0.66	-3.40	-0.82
Infliximab	3-12 Months	0.65	1.55	-2.03	4.01
Ciclosporin	0-3 Months	-0.33	0.69	-1.70	1.01
Ciclosporin	3-12 Months	0.12	1.02	-1.92	2.16

Note: Logs assumed to be natural logarithms

Table 5.6.2 Predicted Probabilities of Colectomy

Treatment	Timepoint	Mean	SD	2.5% CI	97.5% CI
Placebo	0-3 Months	0.67	0.10	0.46	0.85
Placebo	3-12 Months	0.14	0.12	0.00	0.47
Infliximab	0-3 Months	0.23	0.13	0.05	0.56
Infliximab	3-12 Months	0.27	0.27	0.00	0.92
Ciclosporin	0-3 Months	0.58	0.18	0.22	0.88
Ciclosporin	3-12 Months	0.18	0.19	0.00	0.70

4.2.2 Critique of submitted evidence syntheses

The summary correctly conveys that there is some RCT evidence supporting the conclusion that infliximab is effective in producing a clinical response and reducing the rate of colectomy relative to placebo in patients hospitalised with an acute severe flare of ulcerative colitis requiring hospital treatment, but not responsive to initial intensive treatment with iv corticosteroids. The amount of uncertainty arising from the small numbers of participants in the two RCTs is understated. There do not appear to be major adverse events associated with using infliximab in this situation, but the confidence about this statement is again affected by the small number of patients examined.

In their summary the manufacturer submission fails to clearly indicate that there is similar or slightly less strong evidence that ciclosporin is effective in producing a clinical response and reducing the rate of colectomy relative to placebo in patients hospitalised with an acute severe flare of ulcerative colitis requiring hospital treatment, but not responsive to initial intensive treatment with iv corticosteroids. Within the limits of the small amount of evidence available, the adverse events associated with ciclosporin appear more frequent than with infliximab.

The assertion that infliximab has greater benefit than ciclosporin based on the indirect comparison is unfounded. The mixed treatment comparison model in question, not only includes a study, D'Haens et al which is inappropriate, but also generates results which are inconsistent with the original trial results.

This also challenges the validity of the effectiveness parameters used in the economic model.

Finally the manufacturer submission fails to reflect the potential importance of on-going RCTs in improving the evidence base of clinical decisions on the management of acute severe flares of ulcerative colitis. RCTs comparing infliximab and ciclosporin could be particularly useful. One on-going study of this type was identified in the submission; a further study was identified by the ERG (see appendix 8).

4.2.3 Summary

The review of clinical evidence was free of many of the errors seen in the first submission on infliximab.

However some substantial problems remain:

- The quality of searching for ciclosporin was much less comprehensive than searches for infliximab.
- The inclusion of the D'Haens et al RCT was an error as it does not measure the same effect (active agent vs placebo in patients not responsive iv corticosteroids) as the other three included RCTs. The differences in the D'Haens et al trial should have been more clearly recognised in the mixed treatment comparison, and overall estimates of effect should have been conducted without its inclusion, or as a sensitivity analysis.
- The review of case-series of infliximab adds very little to the assessment of effectiveness and should be substantially disregarded. The marked variation in colectomy rates between case-series does serve to indicate extreme sensitivity to small differences in case-mix and/or the experience of centres undertaking the study. This in turn points to the clear need to employ randomisation if at all possible to avoid confounding in accurately evaluating effectiveness of treatments for acute severe flares of ulcerative colitis.

- There was at least one simple data abstraction error pointing to the danger of a review of evidence conducted by a single reviewer

- Although we managed to replicate the results of the mixed treatment comparison, we have substantial concerns about the face validity of the estimates of colectomy rates which are then used without modification in the economic model. If as is likely the MTC model does not appropriately estimate the true effects of the different treatment options in the model, the validity of the cost-effectiveness estimates are also undermined. The estimates of particular concern are for ciclosporin's effectiveness where the colectomy rates hypothesised by the MTC model are nearly twice those actually observed. The existence of evidence for the superior effectiveness of infliximab over ciclosporin cannot be substantiated and as a result any observed advantage in cost-effectiveness of infliximab over ciclosporin must be carefully scrutinised.

- The section on on-going trials is likely to be of particular importance in this appraisal because the amount of rigorous evidence is so limited. The manufacturer submission only captures one of the two on-going trials we identified which address the key issue of the relative effectiveness of infliximab and ciclosporin. In addition to the trial based in France, there is a study, CONSTRUCT, in the UK.

Overall the clinical evidence review does identify that there is evidence for the effectiveness in terms of clinical response and colectomy of both infliximab and ciclosporin relative to placebo in patients refractory to iv steroids in acute severe flares of ulcerative colitis. The combined summary odds ratio for infliximab relative to placebo, meta-analysing the results of Jarnerot et al and Sands et al, calculated by the manufacturer as part of a response to requests for supplementary information was: Summary OR (fixed effects) 0.16 [95% CI 0.05, 0.53]. With a baseline risk of 40% this is equivalent to a number needed to treat (NNT) to avoid one colectomy over three months of 3.3 [95%CI 2.7, 7.2]. With a baseline risk of 70% the NNT is better at 2.3 [95%CI 1.7, 6.8]. For ciclosporin a summary measure cannot be obtained if the results of D'Haens

et al are not included. The size of effect measured in Lichtiger et al is OR 0.47 [95% CI 0.07 to 3.04]. With the baseline risk that occurred in the study, 44%, the NNT was 5.8 [95% CI 1.7, -4.1] (NB minus value for an NNT indicates harm). If the baseline risk was 70%, the NNT would be 3.7.

Whether it is the effect of infliximab or ciclosporin which is being measured. there is a high level of uncertainty, not sufficiently acknowledged in the conclusions. This results from very small numbers of participants included in the very limited number of RCTs. Small numbers included in RCTs not just affects uncertainty due to chance, but also impairs the ability of randomisation to deliver base-line and avoidance of confounding. This is most clearly seen in the study by Sands et al in which 11 participants are allocated, albeit randomly, across 4 trials arms.

The adverse event profile of ciclosporin appears from the clinical evidence review to be more intrusive, but the strength of this conclusion is also impinged on by the small number of participants examined and the short-duration of observation. Infliximab is also not given in any of the included RCTs in the manner suggested in the licence, with repeat dosing at 2 and 6 weeks. This seems likely to have a greater effect on the identified side-effects than the measured response rates.

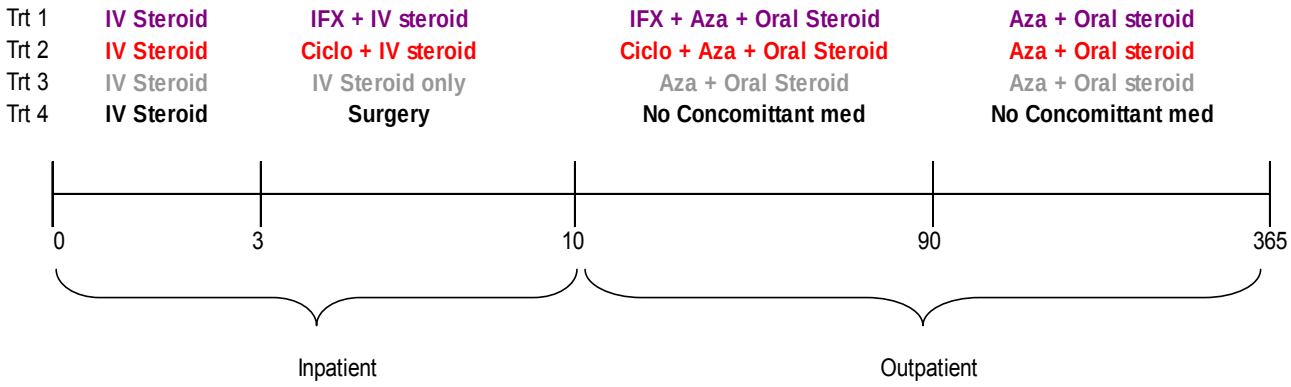
There is no direct information on health-related quality of life or length of hospital stay.

5 ECONOMIC EVALUATION

5.1 Overview of manufacturer's economic evaluation

The manufacturer identified no published economic evaluations of infliximab in UC and this finding is supported by the ERG's own literature search. Thus, the report of the cost-effectiveness work focused entirely on the *de novo* model and economic evaluation undertaken by the manufacturer.

A decision tree model was built using Excel to compare four treatment strategies. The strategies are outlined in the Figure below, taken from the submission (Figure 6.2.1.1, page 36).



On admission, all patients were assumed to receive 72 hours of intravenous corticosteroid treatment (i.e. 400 mg/day Hydrocortisone). Only patients who did not respond to the initial IV steroid treatment were then followed in the model and given one of four subsequent therapies: continued standard care (IV steroids), infliximab with standard care, ciclosporin with standard care or surgical intervention.

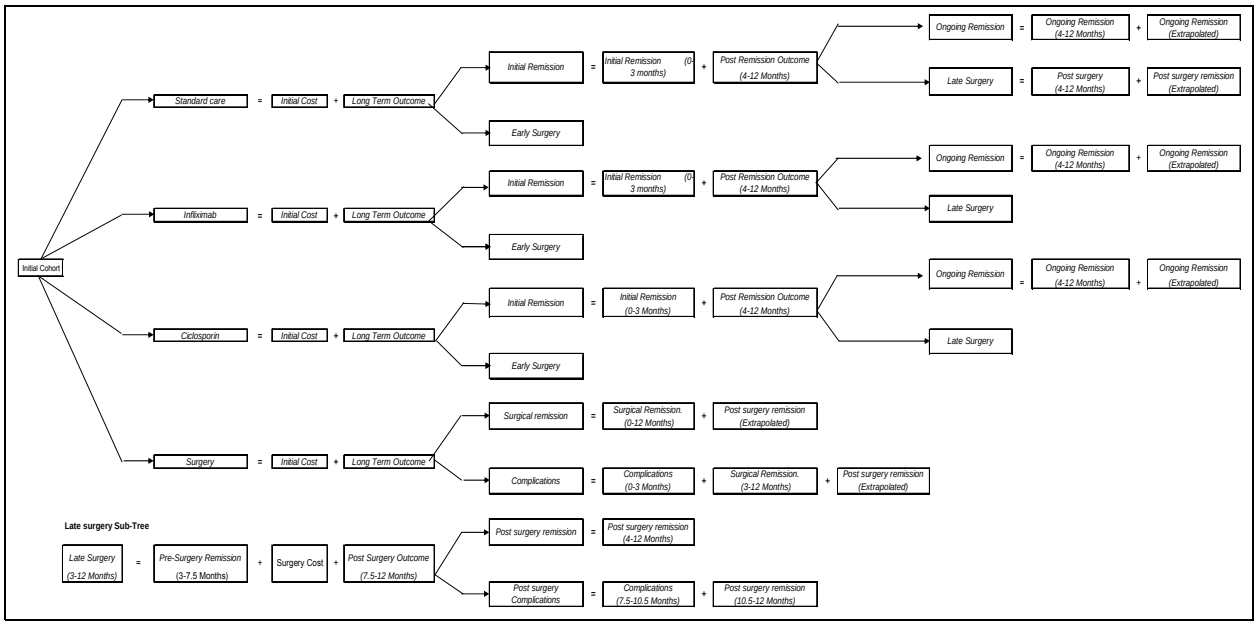
- The standard care treatment simply comprised continuation of 400 mg/day Hydrocortisone for an additional 7 days. Following discharge from hospital, responders are switched to combination therapy

comprising of oral corticosteroids (60 mg/day of Prednisolone) and Azathioprine (2 mg/kg) for 3 months.

- Infliximab treatment included a first full induction dose of 5 mg/kg of infliximab on day 4, followed by additional 5 mg/kg infusion doses at 2 and 6 weeks. These patients also received concomitant standard care of IV corticosteroid treatment for an additional 7 days. Responders to infliximab were assumed to respond within 7 days of the first infusion. Following discharge from hospital, all infliximab responders received oral corticosteroids (60 mg/day of Prednisolone) and Azathioprine (2 mg/kg) for 3 months. In addition, responders also received the two remaining doses of infliximab 5 mg/kg at weeks 2 and 6 following the first infusion.
- Ciclosporin therapy was assumed to be a 4 mg/kg daily dose of IV ciclosporin starting on day 4 for a period of 7 days. These patients also receive standard care comprising of IV corticosteroid treatment during this period. Following discharge from hospital, ciclosporin responders are switched to oral ciclosporin (2 mg/kg/day) until the end of 3 months. In addition to oral ciclosporin, these patients also receive oral corticosteroids (60 mg/day of Prednisolone) and Azathioprine (2 mg/kg) during this period.
- Surgical intervention represents a further alternative treatment strategy whereby patients undergo colectomy following non-response to IV steroids by day 3. Surgical intervention is also included as a treatment outcome for patients not responding to one of the medical treatment strategies on or before day 10.

In the longer-term, all patients receiving medical therapy and with a continued response were assumed to move onto combination therapy comprising oral corticosteroids (60 mg/day of Prednisolone) and Azathioprine (2 mg/kg). Further, they continued to receive combination therapy for the remainder of the analysis timeframe (i.e. up to 1 year following the hospitalisation event). The base case model only considered costs and effects over a 1 year time period. This was extended as a sensitivity analysis to go to 20 years using a Markov process.

The full detail of the base-case model structure is given in the Figure below (Figure 6.2.6.1.1, page 40).



The main evidence used to estimate some of the key probabilities in the model derived from Jarnerot et al and Sands et al for infliximab, and from D'Haens et al and Lichtiger et al for ciclosporin. However, one of the key drivers of the model is avoidance of surgery and this outcome was available only from the studies by Jarnerot et al and D'Haens et al where the follow-up duration was 1 year. Table 6.2.6.1 (page 42) provides the main parameter estimates used in the model (see section 5.1.2 of this report).

The base-case results of the economic analysis presented in the submission are given below in Tables 6.3.3.1 and 6.3.3.2 (from page 58).

Table 6.3.3.1 Costs and benefits associated with each treatment

Treatment	Total costs	Total QALYs	Incremental costs	Incremental QALYs	ICER
Surgery	£17,067	0.58			
Ciclosporin	£18,162	0.70	£1,095	0.12	£9,374
Standard care	£18,550	0.68	£388	-0.02	Dominated
Infliximab	£19,890	0.80	£1,729	0.10	£18,425

Table 6.3.3.2 Incremental cost effectiveness ratios of infliximab compared to the alternative treatments

Treatment comparisons	Incremental costs	Incremental QALYs	ICER
Infliximab vs Standard care	£1,341	0.12	£11,589
Infliximab vs Ciclosporin	£1,729	0.09	£18,425
Infliximab vs Surgery	£2,824	0.21	£13,407

On the basis of these results, 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.

5.1.1 Natural history

The cost-effectiveness section of the report does not describe the natural history of UC.

5.1.2 Treatment effectiveness within the submission

The effectiveness estimates used in the model were derived from the trials of infliximab and of ciclosporin as described above. The infliximab trials are those by Jarnerot and Sands, and the ciclosporin trials are those by Lichtiger and D'Haens. For information, the raw data from the trials, as used as a basis for populating the model, are presented in the tables below. This re-emphasises the paucity of high quality data available in this clinical area. Thus, for one of the key parameters in the model (i.e. avoidance of surgery), data are only available from the modestly powered studies by Jarnerot et al and D'Haens et al where the follow-up duration was 1 year. As indicated above, there are serious concerns about the relevance on the D'Haens trial to this clinical question.

Table 5: Short-term (0-3 months) colectomy rates

	Placebo		Infliximab		Ciclosprorin	
	N	Colectomies	N	Colectomies	N	Colectomies
Jarnerot 2005	21	14	24	7		
Sands 2001	3	3	3	0		
Lichtiger 1994	9	4			11	3
D'Haens 2001	15	3			14	3

Table 6: Medium-term (4-12 months) colectomy rates

	Placebo		Infliximab		Ciclosprorin	
	N	Colectomies	N	Colectomies	N	Colectomies
Jarnerot 2005	21	15	24	10		
Sands 2001						
Lichtiger 1994						
D'Haens 2001	15	6			14	6

Table 6.2.6.1 (page 42 in the submission) provides the main parameter estimates used in the model. The synthesis of the relative treatment effects observed in the trials, and thus the conversion of the raw trial data into these rates, was undertaken in WinBUGS using a Bayesian hierarchical model using Markov Chain Monte Carlo Methods (MCMC).

Table 6.2.6.1: Parameter estimates

Parameter		Estimate	Range used for SA
Short-term outcomes (0-3 months): colectomy rate			
	Infliximab	0.23	0.01 – 0.84
	Ciclosporin	0.58	0.03 – 0.98
	Standard care	0.67	0.24 – 0.96
Medium-term outcomes (4-12 months): colelectomy rate			
	Infliximab	0.27	0.0 – 1.0
	Ciclosporin	0.18	0.0 – 0.97
	Standard care	0.14	0.0 – 0.80
Surgical complications		23.49%	
Post-operative wound infection		8.95%	
Post-operative rectal stump complications		1.12%	
Post-operative bleeding		1.54%	
Post operative sepsis		4.2%	
Anastomical leakage		1.7%	
Small bowel obstruction		3.0%	
Stoma complications		3.0%	
Patient weight		80kg	60kg – 80kg
Time horizon		1 year	1 – 10 years

5.1.3 Health related quality of life

Table 6.2.8.2 (page 47) reports the health states used in the model with their associated utility values and the sources of the values. The primary source is the HODaR study; the same source as was used by the manufacturer in the earlier submission on UC. The HODaR study was a cross-sectional cohort study of 171 patients with a diagnosis of UC, recruited in South Wales. Utilities were measured using the EQ-5D instrument. The work is reported in Appendix 9.12 (page 130). The entire appendix is marked as CIC but the utility estimates reported in the table are not.

The health effects measured were patients' health-related quality of life associated with the ill-health states. Utilities were estimated for remission, active UC and surgery health states.

Since separate sets of utilities were available for IPAA and ileostomy post-surgery remission health states, a weighted average utility value was estimated based on the prevalence of these surgical techniques. No data were found on the utility associated with surgery and so it was assumed the

same utility as in the post surgery remission health state. The utility associated with post surgery complications was not available from HODaR and so the utility associated with post-surgery complications available in Arsenau (2006) was used.

Table 6.2.8.2 Utility estimates associated with health states

Health state	Arseneau (TTO)		HODaR (EQ-5D)	
	Mean	SD	Mean	SD
Remission	0.79	0.24	0.88	0.14
Active UC	0.32	0.31	0.42	0.32
Surgical remission	0.63	0.30	0.60	0.38
Surgical complications	0.49	0.32	-	-

The model did not include any consideration of the side effects of the treatments being compared. This is discussed further below.

5.1.4 Resource use and costs

Overview

Resource use included in the economic model were categorised as:

a) drug costs associated with infliximab

b) concomitant medications

c) diagnostic procedures

d) surgical procedures

e) hospital admissions

Data on the quantities of resources used by UC patients in each health state was not available and so this information has been taken from estimates made by a panel of UK gastroenterologists.

Resource use was valued by applying unit costs from UK-specific sources including the British National Formulary, the NHS Reference Costs Schedule 2006-2007. The details of unit costs are reported in Table 6.2.9.3 (page 53).

In relation to surgery costs some specific assumptions were made that were stated to be conservative, potentially inflating the ICERs for medical treatments compared to surgery. The total cost of ileostomy was assumed to be twice the cost of a 'complex procedure in gastroenterology' to reflect the fact that ileostomy involves two separate surgical procedures in the space of 3 months. Although both illeostomies and ileoanal pouch anal anastomosis (IPAA) procedures are carried out in the UK, the exact proportions were unavailable and so the assumption was made that all procedures were illeostomies.

Unit costs were indexed to a 2007 price year.

Medications

Unit costs and doses of drug therapy used in the analysis (both for infliximab and concomitant medications) were taken from the BNF.

Diagnostic procedures

The use of diagnostic procedures was estimated by a panel of UK gastroenterologists and the unit costs were taken from published NHS Reference costs for 2006/07.

Surgery

The primary surgical procedure for patients with acute UC is colectomy which comprises both IPAA and ileostomy. Expert opinion was used to make a number of assumptions in the costing.

- All patients undergoing colectomy would would first receive an ileostomy which itself involves two separate surgical procedures. Thus, the cost of an ileostomy was taken as twice the cost of a 'complex procedure in gastroenterology'.

- A small proportion of patients will additionally undergo a third procedure called IPAA. However, because of a lack of data on the proportions of patients having which procedure, it was assumed that all surgical procedures were illeostomies.

5.1.5 Discounting

The base case only considered a 12 month time horizon and so there was no discounting applied but the extrapolation to 20 years as a sensitivity analysis applied a discount rate of 3.5% to both costs and health outcomes, consistent with NICE reference case.

5.1.6 Sensitivity analyses

One-way sensitivity analysis was undertaken to consider variation in patient's weight, utility values, long-term treatment effect, infliximab administration cost, hospital stay following initiation of therapy and hospital stay following post-surgery complications.

Time frame and treatment effect

The base case analysis adopted a 1-year time frame only. Univariate sensitivity analysis was performed using a Markov process to extrapolate to 20 years, with a 9 month time cycle. Three scenarios were used:

- Continuing treatment effect, where the colectomy rate in the mdium term (4-12 months) was assumed to continue at a constant rate.
- Maximum treatment effect, where all patients continued in remission and there were no further colectomies beyond 12 months.
- Minimum treatment effect, where all patients were assumed to undergo colectomy within the first cycle after 12 months.

Patient weight

The base case used an estimate of 80kg and it was suggested that this is at the upper end of the range likely to be seen in acute UC patients. Alternative weights of 60kg and 70kg (with vial sharing assumed) were also considered.

Utility estimates

The alternative utility values used in the sensitivity analysis are those from the Arseneau study and are given in Table 6.2.8.2 (page 47), reported below.

Table 6.2.11.1.2 Utility estimates used in sensitivity analysis

Health state	**Utilities (Arseneau) – sensitivity analysis**		**Utilities (HODaR) – base case**	
	Mean	**SD**	**Mean**	**SD**
Remission	0.79	0.24	0.88	0.14
Active UC	0.32	0.31	0.42	0.32
Surgical remission	0.63	0.30	0.60	0.38
Surgical complications	0.49	0.32	-	-

Infliximab administration cost

The base case administration cost was assumed to be £94 per infusion. This was varied within a range of £65.02 to £124.00.

Hospitalisation period

The base case assumed a 7 day hospital stay following initiation of the treatment of interest and 10 days post surgery complications. These were varied between 4 and 10 days and 7 and 13 days respectively.

Probabilistic sensitivity analysis

In order to further explore the importance of parameter uncertainty in the model, probabilistic sensitivity analysis (PSA) was also used (Table 6.2.11.1; page 56). The PSA was partial and placed distributions around some of the outcome probabilities (beta distributions), the health state utility estimates (beta distributions) and some of the unit costs (normal distributions).

5.1.7 Model validation

Model validation processes were described by the manufacturer and included the following

- The model structure and content were approved by a panel of UK gastroenterologists and 'external consultants'.
- Predictive validity was assessed through comparison of the patient flows in the model with those observed in the relevant trials. For longer-term outcomes the data was very limited given the short-term nature of the trials.

5.2 Critique of approach used

Model type and structure

The use of a decision tree model is appropriate as the focus here is on the acute phase of the disease. The base case analysis has a 1-year time horizon with predictions of costs and effects up to that time point. The justification for this is the lack of any longer-term data on probabilities, costs and effects. However, as a sensitivity analysis, the time horizon is extended using a Markov process, with the some extreme scenarios (i.e. no further colectomies beyond 12 months, and all patients to receive colectomy at 12 months) modelled.

Two structural issues are worthy of comment. First, The model lacks any consideration of adverse events. Trials of infliximab in UC patients have described 'serious adverse events', 'infections requiring antimicrobial treatment', and 'serious infections' (bacterial infection, etc) are these are not accounted for in the model. Similarly any adverse effects associated with the other treatments, notably ciclosporin which has known adverse events, are also ignored. Thus, any costs or dis-utilities associated with serious adverse events have been excluded.

Second, patients cannot die in this model! Mortality issues are ignored and so, for example, peri-operative mortality associated with the surgery option is not considered.

Key input parameters

Clinical advice has raised some serious questions concerning the appropriateness of including the D'Haens study because of concerns in relation to the nature of the comparison being made, as described in detail earlier.

Related to this was surprise at the colectomy rate used in the model for the ciclosporin treatment option. The mixed treatment comparison in the submission gives a rate of 0.58 for the 0 – 3 month period. We have been advised that this is 'completely inconsistent with the current evidence and with clinical experience' (clinical advice to the ERG). A lower rate would make ciclosporin more attractive from a cost-effectiveness point of view and would thus increase the ICER for infliximab compared to ciclosporin. This issue is explored further in the further work by the ERG.

The key uncertainties in the analyses are the colectomy rates (both in the short and medium terms) for the strategies being compared.

Resource use and costs

Unit costs and doses of drug therapy used in the analysis (both for infliximab and concomitant medications) were checked against current BNF prices. Two discrepancies were identified:

- In the submission oral ciclosporin was priced at £27.83 for 30 50mg capsules. The BNF price is £30.68.
- In the submission oral azathioprine was priced at £11.80 for 56 50mg tablets. The BNF price is £9.48.

These revised prices have been used in the ERG re-analysis.

Most resource use inputs into the model are based on judgements from the clinical advisory panel as no empirical data were available. The assumptions need to be verified. Clinical advice to the ERG suggested:

- The surgery costs looked reasonable although the proportion of patients receiving the IPAA may be higher, possibly at 50%.
- The number and type of endoscopies for those going into remission was too high – many of the endoscopies would probably be rigid sigmoidoscopies rather that fibre-optic.
- There may be some additional screening tests before commencing on infliximab such as tests for TB.

All of these issues were explored by varying some of the cost inputs into the model and the impact on the final results was not large.

Sensitivity analysis

The univariate sensitivity analysis has very helpfully explored the robustness of results to variation in some of the key parameters. It has highlighted the importance of both the patient weight and the timeframe of the analysis as two important issues that drive the model result. However, the central driver of the model is the colectomy rates (in the short and medium terms) associated with the alternative treatment strategies and these have not been varied as part of the univariate analyses.

The probabilistic sensitivity analysis (PSA) has been undertaken in a very partial manner, with distributions placed around selected parameters only. The level of uncertainty in the model results is therefore underestimated for this technology.

5.3 Results included in manufacturer's submission

Base-case analysis

The base-case results of the economic analysis presented in the submission are given below in Tables 6.3.3.1 and 6.3.3.2 (from page 58).

Table 6.3.3.1 Costs and benefits associated with each treatment

Treatment	Total costs	Total QALYs	Incremental costs	Incremental QALYs	ICER
Surgery	£17,067	0.58			
Ciclosporin	£18,162	0.70	£1,095	0.12	£9,374
Standard care	£18,550	0.68	£388	-0.02	Dominated
Infliximab	£19,890	0.80	£1,729	0.10	£18,425

Table 6.3.3.2 Incremental cost effectiveness ratios of infliximab compared to the alternative treatments

Treatment comparisons	Incremental costs	Incremental QALYs	ICER
Infliximab vs Standard care	£1,341	0.12	£11,589
Infliximab vs Ciclosporin	£1,729	0.09	£18,425
Infliximab vs Surgery	£2,824	0.21	£13,407

Sensitivity analysis

The results of the univariate sensitivity analysis are given in Table 6.3.3.1.1 (page 58) of the original submission. This is reproduced below.

Table 6.3.3.1.1 One-way sensitivity analysis

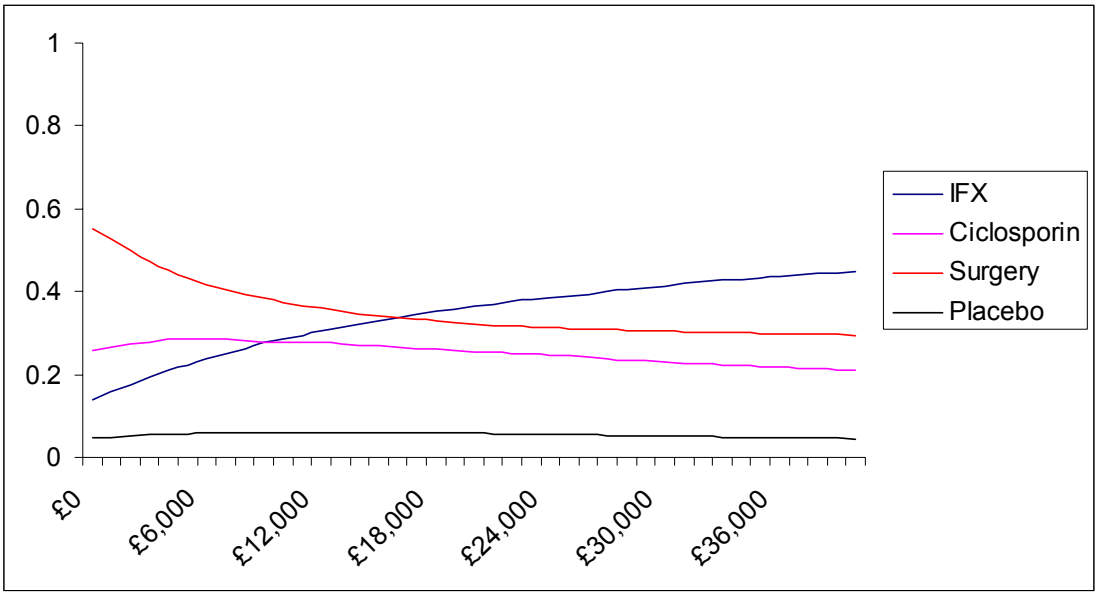
Parameter	Base-case estimate	Sensitivity estimate	IFX vs SC	IFX vs Cic	IFX vs surgery
Patient weight	80kg	60kg	£512	£5,759	£7,169
		70kg	£6,050	£12,092	£10,287
Utility estimates	HODaR	Arseneau	£17,078	£27,128	£20,552
Long-term treatment effect	1 year	Constant Tx effect	£35,739	£34,104	£18,765
		Max Tx effect	£997	£1,429	£1,471
		Min Tx effect	£56,319	£64,486	£65,290
Infliximab administration cost	£94.00	£65.02	£11,088	£17,808	£13,132
		£124	£12,107	£19,065	£13,692
Hospital stay following therapy start	7 days	4 days	£11,589	£18,425	£9,523
		10 days	£11,589	£18,425	£17,291
Hospital stay post surgical complications	10 days	7 days	£12,046	£18,881	£13,919
		13 days	£11,132	£17,970	£12,895

On the basis of the univariate sensitivity analysis results, the manufacturer highlighted the patient weight and the longer term treatment effect issues as being key uncertainties in the model-based analysis.

Probabilistic sensitivity analysis

The PSA results were reported using cost-effectiveness acceptability curves (CEACs), shown in Figure 6.3.1 (page 59), and shown below.

Figure 6.3.1 Cost effectiveness acceptability curves



5.4 Comment on validity of results presented with reference to methodology used

The ERG had access to the Excel spreadsheet model in an executable form and the results reported in the submission have been replicated using the input values reported in the submission. There were some minor errors in the model, none of which changed the results to any great extent, and these are discussed further in section 6.

The manufacturer provided some further analysis results as part of their response to points raised in the clarification letters from NICE. For information, these further analyses are reported verbatim from the manufacturer's response in the box below.

B5.	Please discuss the validity of using an average of utilities for IPPA and ileostomy from Arseneau and HODaR study. Also, please justify the use Arseneau utilities in the sensitivity analysis instead of the range reported on the HODar study.

The approach of using an average of utilities was validated by the panel of UK gastroenterologists.

Since, we only used ileostomy as the surgical procedure in the base case, an alternative way of approaching this is to use HODaR utility for ileostomy in the base case and Arseneau utility for in the one-way sensitivity analysis. The results obtained using this approach, are displayed below.

Base case: using HODaR utilities

Treatments	QALY Gain		Total QALYs	Costs		Total Costs
	0-3 months	4-12 months		0-3 months	4-12 months	
Infliximab	0.20	0.61	0.81	£15,108	£4,782	£19,890
Placebo	0.17	0.53	0.70	£16,584	£1,966	£18,550
Ciclosporin	0.18	0.54	0.72	£15,676	£2,486	£18,162
Surgery	0.15	0.47	0.62	£16,214	£853	£17,067

Treatments	Total Costs	Total QALYs	ICER of IFX vs competitors
Infliximab	£19,890	0.81	N/A
Placebo	£18,550	0.70	£12,574
Ciclosporin	£18,162	0.72	£19,987
Surgery	£17,067	0.62	£14,696

	Inc Cost	Inc QALY	ICER
IFX Vs Placebo	£1,341	0.11	£12,574
IFX vs ciclosporin	£1,729	0.09	£19,987
IFX vs Surgery	£2,824	0.19	£14,696

The tables above display the base case analysis using the utility of ileostomy from the HODaR database. Over a one year time frame, use of infliximab results in higher QALY gains at a higher cost compared to all available alternatives. The ICERs are within acceptable thresholds of cost effectiveness. In the analysis using a shorter time horizon (3 months), infliximab dominates all the competitors with a higher QALY gains at a lower costs.

Sensitivity analysis: using Arseneau utilities

Treatments	QALY Gain		Total QALYs	Costs		Total Costs
	0-3 months	4-12 months		0-3 months	4-12 months	
Infliximab	0.18	0.55	0.73	£15,108	£4,782	£19,890
Placebo	0.16	0.48	0.64	£16,584	£1,966	£18,550
Ciclosporin	0.16	0.50	0.66	£15,676	£2,486	£18,162
Surgery	0.14	0.43	0.57	£16,214	£853	£17,067

Treatments	Total Costs	Total QALYs	ICER of IFX vs competitors
Infliximab	£19,890	0.73	N/A
Placebo	£18,550	0.64	£14,455
Ciclosporin	£18,162	0.66	£22,975
Surgery	£17,067	0.57	£16,966

	Inc Cost	Inc QALY	ICER
IFX Vs Placebo	£1,341	0.09	£14,455
IFX vs ciclosporin	£1,729	0.08	£22,975
IFX vs Surgery	£2,824	0.17	£16,966

The sensitivity analysis conducted using Arseneau utilities results in lower QALYs compared to base case. The results however confirm the cost effectiveness of infliximab within the acceptable threshold. A shorter time horizon (3 months) indicates trends similar to base case wherein infliximab dominates all the alternatives.

The Arseneau utilities were used in the one-way sensitivity analysis only. The rationale was to estimate the impact of a different set of utilities on the resultant ICERs. In contrast, the PSA was designed to estimate the uncertainty around the base case estimates. Here, we used the range reported around HODaR utilities.

B6. Please provide the rationale for the assumption that all surgical procedures carried out were illeostomies.

The assumption that all surgical procedures are illeostomies is conservative. Ileostomy and Ileal Pouch Anal Anastomosis (IPAA) are the most commonly performed surgeries in patients with acute UC failing medical therapies. There is however conflicting evidence on the proportion of patients undergoing these procedures. The panel of UK gastroenterologists estimated that 70% patients undergoing surgery would eventually undergo IPAA while the remaining 30% would undergo ileostomy (Scenario A). The UK IBD audit however indicated these numbers to be 29% and 24% respectively with the remainder of patients undergoing either protectomy, protocolectomy or subtotal colectomy. These three procedures usually lead to an ileostomy, thus making it the most common procedure in the UK setting (Scenario B).

An ileostomy is a two stage procedure carried out during a single hospital stay and an IPAA is a three stage procedure usually requiring two hospitalisation

episodes. The cost of an IPAA is significantly higher than the cost of an ileostomy. Our assumption that all procedures are illeostomies therefore reduces the cost of surgery and reduces the costs associated with treatment failures. This adversely affects cost effectiveness for infliximab, which has the least number of treatment failures. The ICERs using Scenario A and B are displayed below.

Scenario A: (29% IPAA, 71% ileostomy)

	Inc Cost	Inc QALY	ICER
IFX Vs Placebo	£1,006	0.12	£8,699
IFX vs ciclosporin	£1,459	0.09	£15,544
IFX vs Surgery	£2,142	0.21	£10,171

Scenario B: (70% IPAA, 30% Ileostomy)

	Inc Cost	Inc QALY	ICER
IFX Vs Placebo	£534	0.12	£4,613
IFX vs ciclosporin	£1,076	0.09	£11,470
IFX vs Surgery	£1,179	0.21	£5,597

5.5 Summary of uncertainties and issues

- The results consistently indicate that the move from standard care to ciclosporin is highly cost-effective. Thus, the policy question is clear: should we make a subsequent move from ciclosporin to infliximab? And so the only appropriate comparator for infliximab is ciclosporin
- There is considerable uncertainty concerning what colectomy rates should be used. This issue will be explored further in section 6.
- The weight of the patient is important – if patients tend to be 60kg or less then the cost-effectiveness of infliximab is more attractive.

- The timeframe of the model is also important – extrapotaing beyond 12 months is the approach that is consistent with the NICE methods guide. Such extrapolation indicates worsening cost-effectiveness for infliximab in general but depends crucially on the assumptions made about the ongoing effectiveness of infliximab. Such long-term data are not available.

6 Additional work undertaken by the ERG

Simple input errors

The workings of the model have been audited and whilst we have found some errors in programming, none of them are serious in that they do not change the results in a meaningful way. These errors are described below:

- According to the treatment pathway description, patients receiving ciclosporin treatment receive 7 daily doses of intravenous ciclosporin during the Day 4-10 period. However, in the table summarising the concomitant medication use (p. 50) it is mistakenly indicated that patients received 10 doses of intravenous ciclosporin during this period. The spreadsheet also mistakenly had the value of 10. The revised base case adjusting for this (changing the value of 10 to the value of 7).

- Two small costing errors were also identified. In the submission oral ciclosporin was priced at £27.83 for 30 50mg capsules. The BNF price is £30.68. In the submission oral azathioprine was priced at £11.80 for 56 50mg tablets. The BNF price is £9.48. These revised prices have been used in the ERG re-analysis and the revised base case has made these changes.

The revised base case results are given in the table below.

Table 7: Revised base case results

	Costs	QALY
IFX	£19,847	0.810
Ciclo	£18,122	0.723
Surgery	£17,067	0.618
Placebo	£18,524	0.703

	Inc Cost	Inc QALY	ICER
IFX Vs Placebo	£1,323	0.107	£12,407
IFX vs ciclosporin	£1,725	0.087	£19,946
IFX vs Surgery	£2,780	0.192	£14,470

Revised inputs for colectomy rates

As a verification for the mixed treatment comparison model, using the dataset described in the industry report, we re-ran the model in WinBUGS and produced similar results as shown in the tables below.

Table 8: Log-Odds Ratios of Colectomy compared to Placebo (verification re-run)

Treatment	Timepoint	Mean	SD	2.5%CI	97.5%CI
Infliximab	0-3 Months	-2.07	0.66	-3.40	-0.83
Infliximab	3-12 Months	0.61	1.53	-2.02	4.04
Ciclosporin	0-3 Months	-0.35	0.69	-1.72	0.99
Ciclosporin	3-12 Months	0.13	1.02	-1.88	2.14

Table 9: Predicted Probabilities of Colectomy (verification re-run)

Treatment	Timepoint	Mean	SD	2.5%CI	97.5%CI
Placebo	0-3 Months	0.67	0.10	0.46	0.85
Placebo	3-12 Months	0.14	0.12	0.00	0.46
Infliximab	0-3 Months	0.24	0.13	0.05	0.56
Infliximab	3-12 Months	0.26	0.26	0.00	0.92
Ciclosporin	0-3 Months	0.58	0.18	0.22	0.88
Ciclosporin	3-12 Months	0.18	0.19	0.00	0.70

The slight difference between the results and those given in the submission may be caused by the number of iterations and the prior values used in running the model. When these colectomy rates are used in the revised base case model the results are as below.

Table 10: Revised base case results-colectomy rates

	Costs	QALY
IFX	£19,822	0.809
Ciclo	£18,122	0.723
Surgery	£17,067	0.618
Placebo	£18,524	0.703

	Inc Cost	Inc QALY	ICER
IFX vs Placebo	£1,298	0.106	£12,307
IFX vs ciclosporin	£1,701	0.085	£19,922
IFX vs Surgery	£2,756	0.191	£14,427

One of the main concerns we have in relation to the colectomy rate estimates is the use of the D'Haens study, as discussed earlier. Thus, we have re-run the mixed treatment comparison model excluding the D'Haens data. The results are shown below.

Table 11: Log-Odds Ratios of Colectomy compared to Placebo (re-run with D'Haens removed)

Treatment	Timepoint	Mean	SD	2.5%CI	97.5%CI
Infliximab	0-3 Months	-2.069	0.654	-3.400	-0.834
Infliximab	3-12 Months	0.603	1.512	-2.010	3.987
Ciclosporin	0-3 Months	-0.837	1.018	-2.886	1.123
Ciclosporin	3-12 Months				

Table 12: Predicted Probabilities of Colectomy (re-run with D'Haens removed)

Treatment	Timepoint	Mean	SD	2.5%CI	97.5%CI
Placebo	0-3 Months	0.667	0.101	0.458	0.846
Placebo	3-12 Months	0.143	0.124	0.004	0.459
Infliximab	0-3 Months	0.235	0.134	0.050	0.558
Infliximab	3-12 Months	0.259	0.263	0.003	0.913
Ciclosporin	0-3 Months	0.480	0.225	0.087	0.888
Ciclosporin	3-12 Months				

For the cost-effectiveness analysis using these revised colectomy rates we have a problem as there is no prediction for ciclosporin in the medium term, given the lack of any data on that parameter. Thus, we have assumed a rate of 0.18 for ciclosporin 3-12 months as in the revised base case model. The revised cost-effectiveness results are given below.

Table 13: Revised cost-effectiveness results assuming rate 0.18 for ciclosporin

	Costs	QALY	
IFX	£19,759	0.810	
Ciclo	£16,864	0.750	
Surgery	£17,067	0.618	
Placebo	£18,528	0.703	
	Inc Cost	Inc QALY	ICER
IFX vs Placebo	£1,230	0.107	£11,503
IFX vs ciclosporin	£2,895	0.060	£48,367

	Costs	QALY	
IFX vs Surgery	£2,692	0.192	£13,998

7 Discussion

7.1 Summary of clinical effectiveness issues

- There are no major issues concerning the scope
- Although the review generally followed systematic processes, albeit using a single reviewer, there are a number of issues arising which in the ERG view are likely to have an impact on the appraisal.
- The evidence on the effectiveness of infliximab is accurately portrayed, with the exception that the review of case-series should be disregarded, particularly as this was not attempted for the main comparator of interest ciclosporin. The uncertainty surrounding the evidence on effectiveness of infliximab is underplayed in the manufacturer submission in the ERG's view.
- The evidence on the effectiveness of ciclosporin is inaccurately portrayed. It is inappropriate to include the study by D'Haens et al alongside the placebo-controlled trials of Jarnerot et al and Sands et al for infliximab and Lichtiger et al for ciclosporin. The effect of this is to understate the effectiveness of ciclosporin in the submission. This view takes into account the well recognised problems associated with ciclosporin use.
- There is no research providing direct evidence on the relative effectiveness of infliximab with ciclosporin. Conclusions in the appraisal are based on a mixed treatment comparison model which in the ERG's view misrepresents the available data, accentuating the probable effectiveness of infliximab and underestimating the effectiveness of ciclosporin.
- These issues should not disguise that the fundamental problem is the very limited amount of RCT evidence underpinning decisions on the management of severe acute flares of ulcerative colitis in hospitalised patients unresponsive to initial treatment with iv corticosteroids

- This appears to be the view of the clinical community with two on-going RCTs (one identified in the manufacturer's submission and another identified via our clinical adviser) of infliximab versus ciclosporin in the patient group of interest

7.2 Summary of cost effectiveness issues

- The results consistently indicate that the move from standard care to ciclosporin is highly cost-effective. Thus, the policy question is clear: should we make a subsequent move from ciclosporin to infliximab? And so the only appropriate comparator for infliximab is ciclosporin
- There is considerable uncertainty concerning what colectomy rates should be used. This issue has explored by the ERG and when the inappropriate D'Haens study is removed the ICER for infliximab compared to ciclosporin increases dramatically to over £48,000 per QALY gained. Similarly the further work by the ERG has indicated the high sensitivity of the ICERs to variation in the colectomy rates, parameters that are very uncertain because of the paucity of high quality data.
- The weight of the patient is important – if patients tend to be 60kg or less then the cost-effectiveness of infliximab is more attractive.

- The timeframe of the model is also important – extrapotaing beyond 12 months is the approach that is consistent with the NICE methods guide. Such extrapolation indicates worsening cost-effectiveness for infliximab in general but depends crucially on the assumptions made about the ongoing effectiveness of infliximab. Such long-term data are not available.

7.3 Implications for research

- There is a desperate need for larger, high quality trials that compare infliximab and ciclosporin. Support for the existing trials in this area would seem appropriate.

Appendix 1: ERG formal appraisal of review underpinning Clinical evidence section of submission

PURPOSE OF THIS APPRAISAL:
Critical appraisals attempt to identify the strengths and weaknesses of pieces of information, often research literature, so that readers may apply that information within the limits identified. There are two important sets of limits:

a) the INTERNAL validity of the information ie how the information was collected and/or summarised
b) the EXTERNAL validity of the information ie how relevant the information is to any specific question posed by a reader

This appraisal checklist is specifically designed for reviews of research information. It is based on: Oxman AD. Checklists for review articles. BMJ, 1994;309:648-51. Updated version in: Chalmers I & Altman DG (eds). *Systematic reviews.* London: BMJ Publishing, 1995. This has in turn been modified on the basis of ARIF's experience reviewing many different types of reviews of research retrieved in its responses to requests for research information on the effects/effectiveness of health care interventions.

Implicit in the checklist is our belief that the following elements of a review are particularly important:

- Clear, explicit statement of method (in sufficient detail that another person undertaking the same review might be able to repeat the processes and arrive at the same conclusion AND that a reader can make an assessment of any bias that the reviewer has introduced in the way that the research was identified and summarised).
- Comprehensive ascertainment of all the available research literature relevant to the question the reviewer sets out to answer.
- Processing the ascertained literature in a way which reduces bias or makes explicit any bias which has been introduced, so that the reviewers or the reader can make allowance for this in their conclusions.
- An appropriate numerical summary of the size of any effect (or equivalent), including its confidence intervals.

If a review meets the first three general criteria a review would be a "systematic review"; if a review met all four criteria it would be a "systematic review with meta-analysis".

ASSESSOR'S SCREENING QUESTIONS

On first reading is there sufficient information to make a detailed appraisal?

Yes

IN RELATION TO WHAT QUESTION IS THIS REVIEW BEING APPRAISED (TARGET QUESTION)?

This appraisal relates to the ""Clinical Evidence" component of the manufacturer submission for the STA "Infliximab for the treatment of acute exacerbations of ulcerative colitis". Other sections of the report, particularly the "Cost effectiveness" section are not dealt with here

State question, in terms of:

Question type - effects/effectiveness
Population/condition - adults patients diagnosed acute exacerbations of severe ulcerative colitis with either an inadequate response to conventional therapy (corticosteroids, 6-mecaptopurine, azathioprine) or intolerance to or medical contraindications to such therapies and are hospitalised for treatment
Intervention – infliximab
Comparator – standard clinical management (including surgical intervention); ciclosporin; placebo (or steroids)
Outcomes - survival; rates of surgical intervention; measures of disease activity; rates of and duration of response, relapse and remission; adverse effects of treatment; health-related quality of life

All of these question components are as specified in the final scope as set out by NICE

HAS A CLEAR QUESTION BEEN DEFINED (REVIEW QUESTION)?

State specific question, to which the further assessment of this review relates, in terms of:
Question type - effects/effectiveness
Population/condition – yes, as above
Intervention – infliximab (evidence on effectiveness of cyclosproin also targeted)
Comparator – yes, as above
Outcomes – yes, as above

****

Comments relating to internal validity:
The review question is sufficiently clear that the review could be executed systematically.

Comments relating to external validity:
The review question matches the target question.

****

WHAT ARE THE IMPLICATIONS FOR THE VALIDITY OF THE REVIEW OF THE TYPE AND RANGE OF STUDY DESIGNS INCLUDED?

State type/types of study designs which were included:
Randomised controlled trials and observational studies
(Observational studies not searched for in review of evidence on effectiveness of ciclosporin)

****

Comments:
The general validity of the included study designs to answer the review question was high, with the exception of observational studies which relatively are much more susceptible to bias

****

WERE INCLUSION/EXCLUSION CRITERIA CLEARLY STATED?

Yes see 9.2.6 p 67

List any INCLUSION criteria:

- Population (all of)
  - Adult
  - Acute severe UC refractory, or intolerant or contraindicated to standard treatment (including corticosteroids, 6-mercaptopurine, azathioprine)
  - Hospitalised
- Intervention
  - Infliximab or
  - Ciclosporin
- Comparator
  - Standard clinical treatment options (including surgery), ciclosporin or placebo
- Design and status (at least one of)
  - Systematic review OR
  - RCTs (with appropriate comparator) OR
  - Non RCTs (observational studies)
  - Published in full (single case reports, abstracts, letters and correspondence excluded)
  - English language

List any EXCLUSION criteria:

- No specific exclusion criteria bar single case reports, abstracts, letters and correspondence as indicated above

****

Comments:

The inclusion/exclusion criteria were consistent with the review question and were stated with sufficient clarity that it is likely that they could be applied reliably and the internal validity of the review assured as a result.

****

WAS THE SEARCH STRATEGY ADOPTED LIKELY TO HAVE MISSED MANY POTENTIALLY RELEVANT STUDIES?

State the search strategy:
Detailed in 9.2.4 p66
The following databases were searched in February 2008 using the search strategies given in the appendices:
Infliximab:

- MEDLINE
- EMBASE
- Cochrane Library (Issue 1, 2008)

There was no restriction by study design
Reference lists of potentially relevant studies also appear to have been searched (p68)
Ciclosporin

- MEDLINE
- EMBASE

Both were restricted to RCTs
The Cochrane Library does not appear to have been searched for RCTs of ciclosporin.

The drug licence holder Centocor was also contacted and clinicaltrials.gov searched for on-going trials.

****

Comments:
The search strategy was consistent with the review question.
The search was moderately rigorous and unlikely to have missed relevant studies for infliximab; the existence of prior systematic reviews, including a Cochrane Review (Lawson et al) which have comprehensively searched for RCTs of infliximab in ulcerative colitis greatly adds to the confidence concerning complete ascertainment

The search was less rigorous and likely to have missed relevant studies for cyclopsporin. The prior Cochrane Review by Shibolet et al does not provide the same reassurance about the completeness of the search for RCTs of ciclosporin for ulcerative colitis.

****

HOW WERE INCLUSION/EXCLUSION CRITERIA APPLIED?

QUOROM flow diagram for the infliximab component of the review is provided on p69
450 studies were identified; 2 RCTs and 9 other studies were included
A list of excluded studies with reasons for exclusion was provided

Minimal details on the ciclosporin component of the review

WAS THE VALIDITY OF INCLUDED STUDIES ASSESSED?

a) Validity implicit in inclusion/exclusion criteria
b) Validity of all included studies re-examined
c) Both
d) Apparently not assessed at all

The main method of quality assessment was re-checking of the validity of included studies ie (b)

State whether the criteria used to assess validity were reasonable OR
Whether a recognised validity checklist was employed (that is one which has had its validity assessed):

Review used an early version of the well recognised Jadad scale

State how information on the validity of the included studies was used:
a) To provide narrative or tabulated information on the strengths and weaknesses of the included studies

b) As a check on the nature of the included studies to identify “late exclusions” (potentially inappropriate)
c) As a check on the nature of the included studies to identify wide variation in characteristics, suggesting that meta-analysis was not appropriate
d) Where meta-analysis was employed, to conduct sensitivity analyses to check robustness of findings
e) Other (please state)
f) Apparently not at all (potentially inappropriate if variation in important characteristics of included studies was likely)

The review provided narrative information (pp22-3) on the strengths and weaknesses of the included studies ie (a). This was restricted to RCTs. There was minimal appraisal of the observational studies included, despite claims that this information was presented in Appendix 9.9

****

Comments:

There was an adequate assessment of the validity of included studies which were RCTs. There was inadequate assessment of the observational studies.

****

WAS THE PROCESS OF DATA ABSTRACTION ADEQUATE?

State how the relevant data items were extracted:

a) Reference to pre-determined list
b) Use of data abstraction sheet
c) Other (please state)
d) No detail

Single reviewer using a standardised data extraction sheet (p69)

****

Comments:
The use of a single reviewer without any evidence of accuracy checks is inadequate

****

WERE THE IMPORTANT STEPS IN THE REVIEW REPRODUCIBLE & BIAS FREE?

State whether the repeatability of the following steps was examined, reported and acted upon:

Searching for all potentially relevant studies - No
Applying study inclusion/exclusion criteria - No
Assessment of validity of included studies - No
Data abstraction - No

****

Comments:
The repeatability of important steps in the review could not be tested as these appear to have been performed by a single reviewer

****

WHAT WAS(WERE) THE RELEVANT AND JUSTIFIABLE REVIEW BOTTOM LINE(S) - AS STATED IN THE REVIEW ?

The summary of results was difficult to identify. 5.9.1 offers the following (underlining added):
“Several studies included in other systematic reviews (e.g., Gisbert et al 2007) were excluded from the current study; largely this selection was a consequence of our report focussing only on severely affected hospitalised patients with refractory disease (several case reports, abstracts, and correspondence included in Gisbert et al 2007 were also excluded here). No other systematic review looking specifically at this patient population was found.

All studies summarised acute severe treatment refractory UC; no studies looked specifically at patients intolerant or contraindicated to corticosteroids, 6-mercaptopurine or azathioprine. Comparison with ciclosporin was only reported as a subgroup of a single observational study; few patients were treated (6 with infliximab and 15 with ciclosporin) and the differences were relatively small. High quality head-to-head RCTs were not found of infliximab and ciclosporin; all infliximab and ciclosporin RCTs compared the study drug to placebo or steroids.

The evidence identified from two small RCTs and nine largely small, open, uncontrolled observational studies (three of which reported subgroups only) suggest that infliximab provides clinical benefit to patients with acute severe, steroid-refractory UC and is well tolerated. Our indirect comparison against ciclosporin suggests that infliximab provides additional clinical benefit in terms of colectomy avoidance beyond that available with other, currently-used therapies."

State whether meta-analysis was used:
The report indicates that there was no quantitative summary. The report does however use a indirect/mixed treatment comparison model which provides a quantified summary in the same way as meta-analysis. It is this which provides the effectiveness parameters for the economic model. The summary results are thus Tables 5.6.1 and 5.6.2 (both marked aic):

Table 5.6.1 Log-Odds Ratios of Colectomy compared to Placebo

Treatment	Timepoint	Mean	SD	2.5% CI	97.5% CI
Infliximab	0-3 Months	-2.07	0.66	-3.40	-0.82
Infliximab	3-12 Months	0.65	1.55	-2.03	4.01
Ciclosporin	0-3 Months	-0.33	0.69	-1.70	1.01
Ciclosporin	3-12 Months	0.12	1.02	-1.92	2.16

Table 5.6.2 Predicted Probabilities of Colectomy

Treatment	Timepoint	Mean	SD	2.5% CI	97.5% CI
Placebo	0-3 Months	0.67	0.10	0.46	0.85
Placebo	3-12 Months	0.14	0.12	0.00	0.47
Infliximab	0-3 Months	0.23	0.13	0.05	0.56
Infliximab	3-12 Months	0.27	0.27	0.00	0.92
Ciclosporin	0-3 Months	0.58	0.18	0.22	0.88
Ciclosporin	3-12 Months	0.18	0.19	0.00	0.70

The model used to create these findings was re-run and the same results obtained. However, as discussed in the main report there are some issues about whether the model provides useful and reliable additional information.

WAS THE REVIEW UP-TO-DATE?

Yes. Searches conducted up to February 2008

GENERAL COMMENTS

The review incorporated the following elements:

a) Clear statement of method
b) Comprehensive ascertainment of relevant literature
c) Minimal/explicit bias (for which adjustment can be made) introduced in the process of summarising the available literature
d) Appropriate meta-analysis
e) Other useful features (please state)

The key features were a clear statement of method and comprehensive ascertainment of relevant literature for infliximab (a & b) above. There were doubts about how complete the ascertainment of relevant literature was for the review of ciclosporin. The mixed treatment comparison was correctly

conducted, but there are doubts about whether it adds meaningfully to the summarised clinical effectiveness in this particular report.

On this basis the review can be classified as:

A. Systematic review with a meta-analysis
B. Systematic review with no meta-analysis (or with a generally inappropriate meta-analysis, the results of which should be ignored)
C. Comprehensive overview, with clearly stated method
D. Review with clearly stated method
E. General review
F. Other (please state)

The report would thus be best described as a comprehensive overview, with clearly stated method (C above) for the summary of evidence on infliximab and a review with clearly stated method (D above) for the summary of evidence on ciclosporin

REFERENCES

- Lawson MM, Thomas AG, Akobeng AK. Tumour necrosis factor alpha blocking agents for induction of remission in ulcerative colitis. *Cochrane Database of Systematic Reviews* 2006, Issue 3. Art. No.:CD00051112. DOI: 10.1002/14651858.CD0005112.pub2.
- Shibolet O, Regushevskaya E, Brezis M, Soares-Weiser K. Cyclosporine A for induction of remission in severe ulcerative colitis. *Cochrane Database of Systematic Reviews* 2005, Issue 1. Art. No.: CD004277. DOI: 10.1002/14651858.CD004277.pub2.

Appendix 2: ERG formal appraisal Cochrane review on infliximab

Lawson MM, Thomas AG, Akobeng AK. Tumour necrosis factor alpha blocking agents for induction of remission in ulcerative colitis. *Cochrane Database of Systematic Reviews* 2006, Issue 3. Art. No.:CD00051112. DOI: 10.1002/14651858.CD0005112.pub2.

PURPOSE OF THIS APPRAISAL: As for Appendix 1.

ASSESSOR'S SCREENING QUESTIONS

On first reading is there sufficient information to make a detailed appraisal?

Yes

IN RELATION TO WHAT QUESTION IS THIS REVIEW BEING APPRAISED (TARGET QUESTION)?

This appraisal relates to a Cochrane Review cited in the "Clinical Evidence" component of the manufacturer submission for the STA "Infliximab for the treatment of acute exacerbations of ulcerative colitis". The Cochrane Review appears to have been influential in the conduct of the review in the manufacturer submission and has been appraised as a result. The target question, is the same as that for the STA report, namely the question indicated in the scope from NICE.

State question, in terms of:

Question type - effects/effectiveness

Population/condition - adult patients diagnosed with acute exacerbations of severe ulcerative colitis with either an inadequate response to conventional therapy (corticosteroids, 6-mecaptopurine, azathioprine) or intolerance to or medical contraindications to such therapies and are hospitalised for treatment

Intervention – infliximab
Comparator – standard clinical management (including surgical intervention); ciclosporin; placebo (or steroids)
Outcomes - survival; rates of surgical intervention; measures of disease activity; rates of and duration of response, relapse and remission; adverse effects of treatment; health-related quality of life

All of these question components are as specified in the final scope as set out by NICE

HAS A CLEAR QUESTION BEEN DEFINED (REVIEW QUESTION)?

Objectives of review:

1. To evaluate the efficacy of TNF-α antibody for the induction of remission in ulcerative colitis
2. To determine adverse events associated with TNF-α antibody treatment in ulcerative colitis

State specific question, to which the further assessment of this review relates, in terms of:
Question type - effects/effectiveness
Population/condition – ulcerative colitis
Intervention – TNF-α antibody (infliximab)
Comparator – placebo or other drugs
Outcomes – induction of remission; clinical, histological, endoscopic improvement; improvement in quality of life as measured by a validated quality of life tool; adverse events (infusion reactions, antibodies to infliximab, development of auto-antibodies with or without a lupus like syndrome, secondary infections eg tuberculosis, lymphoma and death

****

Comments relating to internal validity:
Review question is sufficiently clear that the review could be executed systematically.

Comments relating to external validity:
The review question appears to generally match the target question.

****

WHAT ARE THE IMPLICATIONS FOR THE VALIDITY OF THE REVIEW OF THE TYPE AND RANGE OF STUDY DESIGNS INCLUDED?

State type/types of study designs which were included:
Randomised controlled trials

****

Comments:
The general validity of the included study designs to answer the review question was high

****

WERE INCLUSION/EXCLUSION CRITERIA CLEARLY STATED?

Yes

List any INCLUSION criteria:

- RCTs
- Ulcerative colitis patients of any age
- TNF-α antibody (infliximab) versus either placebo or other drugs
- Outcomes of: induction of remission; clinical, histological, endoscopic improvement; improvement in quality of life as measured by a validated quality of life tool; adverse events (infusion reactions, antibodies to

infliximab, development of auto-antibodies with or without a lupus like syndrome, secondary infections eg tuberculosis, lymphoma and death).

List any EXCLUSION criteria:
No specific exclusion criteria listed

****

Comments:
The inclusion/exclusion criteria were consistent with the review question and were stated with sufficient clarity that it is likely that they could be applied reliably and the internal validity of the review assured as a result.

****

WAS THE SEARCH STRATEGY ADOPTED LIKELY TO HAVE MISSED MANY POTENTIALLY RELEVANT STUDIES?

State the search strategy:

A. Electronic search of

- MEDLINE (1966 to 2005)
- EMBASE (1984 to 2005)
- Cochrane Central Register of Controlled Trials (Issue 3, 2004)
- Cochrane Inflammatory Bowel Disease and Functional Bowel Disorders (IBD/FBD) Group Specialised Trial Register

There was no language limit on the search

Search strategies were detailed in full. They were constructed on terms capturing the intervention of interest, the condition and the study design

B. Reference searching
The references of all identified studies were inspected for more trials

C. Personal contacts

****

Comments:
The search strategy was consistent with the review question.
Given the rigorous nature of the electronic searches it is unlikely that many relevant studies were missed.
The steps to identify unpublished and on-going trials were however relatively weak. The original protocol contained a proposal to hand-search conference abstracts. This was not implemented in the full review

****

HOW WERE INCLUSION/EXCLUSION CRITERIA APPLIED?

24 studies were identified as being potentially relevant
17 articles were excluded following review of the full articles
5 included RCTs compared infliximab with placebo
2 included RCTs compared infliximab with corticosteroids

State whether a list of excluded studies was available and whether any excluded articles were examined:
References and reasons for exclusion of excluded studies given. Most excluded because studies were case-series

****

Comments:
The number of articles examined (24) is unusually low for a systematic review
This may be because it does not include the number of citations examined initially to identify the 24 studies which were felt to be impossible to exclude without reference to the full text

****

WAS THE VALIDITY OF INCLUDED STUDIES ASSESSED?

a) Validity implicit in inclusion/exclusion criteria
b) Validity of all included studies re-examined
c) Both
d) Apparently not assessed at all

Category c) of the above
Two recognised frameworks were employed (Criteria described in the Cochrane Handbook & the Jadad score). Both consider the quality of randomisation; in addition the Jadad score assesses blinding and loss to follow-up.

State how information on the validity of the included studies was used:
a) To provide narrative or tabulated information on the strengths and weaknesses of the included studies
b) As a check on the nature of the included studies to identify “late exclusions” (potentially inappropriate)
c) As a check on the nature of the included studies to identify wide variation in characteristics, suggesting that meta-analysis was not appropriate
d) Where meta-analysis was employed, to conduct sensitivity analyses to check robustness of findings
e) Other (please state)
f) Apparently not at all (potentially inappropriate if variation in important characteristics of included studies was likely)

Categories a) & b) above

****
Comments:

Overall, an adequate assessment of the validity of included studies was made, although no comments were made about loss to follow-up – see below - and nor was the Jadad score reported.

Included studies were restricted to RCTs

No overall concerns were highlighted arising from the quality of the included studies. Detailed analysis indicated that there was limited information about some aspects of quality in some studies:

- Random sequence: [vs placebo Jarnerot et al; Sands et al] [vs corticosteroids Armuzzi et al]
- Double blind: [vs placebo Jarnerot et al; Rutgeerts et al (ACT I & II)] [vs corticosteroids Armuzzi et al; Ochsenkuhn et al (both did not claim to be double-blind)]
- Random allocation concealment: [vs placebo allocation concealment clear in all trials in this group] [vs corticosteroids Armuzzi et al; Ochsenkuhn et al (both did not claim to be double-blind)]
- Loss to follow-up: No comments offered about this feature

Three key included RCTs (ACT1 & 2; Jarnerot) were reappraised by the ERG and the accuracy of the data presented in this review confirmed. In the case of ACT1 & 2, additional data from the clinical trial reports submitted for licensing was available.

****

WAS THE PROCESS OF DATA ABSTRACTION ADEQUATE?

State how the relevant data items were extracted:

a) Reference to pre-determined list

b) Use of data abstraction sheet

c) Other (please state)

d) No detail

Category b) above

****

Comments:
The data abstracted was consistent with the review question and the method used was one likely to maintain the validity of the review

****

WERE THE IMPORTANT STEPS IN THE REVIEW REPRODUCIBLE & BIAS FREE?

State whether the repeatability of the following steps was examined, reported and acted upon:

Searching for all potentially relevant studies - No
Applying study inclusion/exclusion criteria – Yes – but level of agreement/disagreement not reported
Assessment of validity of included studies - Yes – but level of agreement/disagreement not reported
Data abstraction - Yes – but level of agreement/disagreement not reported

****

Comments:
The repeatability of important steps in the review was examined but not reported

The accuracy of the abstracted data for key outcomes in the Jarnerot study was checked by the ERG and found to be accurate

****

WHAT WAS(WERE) THE RELEVANT AND JUSTIFIABLE REVIEW BOTTOM LINE(S) - AS STATED IN THE REVIEW ?

The following focuses on the studies comparing infliximab with placebo. Note however that in addition there were two small studies (n= 20 & 13) comparing infliximab with corticosteroids, which showed no difference between the two arms (although the under-powered nature of the studies must be considered in this respect)

Concerning infliximab vs placebo, like the S-P submission, there was no separation between acute/"rescue" applications (Sands & Jarnerot) and the trials considering sub-acute applications initiated out of hospital (Probert, ACT1 & 2)

State whether meta-analysis was used: Yes

The meta-analyses only include the results of Rutgeerts et al (ACT1 & 2). Although the combined size (728) of these is much greater than the three other smaller studies (Jarnerot n=45; Sands n=11; & Probert n=43), the validity of this decision is debatable. In both ACT1 & 2 there are two treatment arms giving IFX at 5mg/kg and 10mg/kg. The meta-analysis considers these together initially and then investigates whether the overall result differs if the just the results of the licenced does 5mg/kg are considered.

If meta-analysis was used, state for each outcome, subgroup or comparison, the review stated as being part of the question it would address:

a) How homogeneous or heterogeneous the results of the individual studies were - I^2 >50% is taken to indicate marked heterogeneity in this review
b) What the summary estimate of effect (or equivalent) was
c) The confidence interval, or equivalent indication of the role of chance

- Clinical remission (Mayo score $\leq$2, no individual score >1) 8 weeks

Marked heterogeneity (I^2 =72%)

RR (fixed) 3.2 (95% CI 2.2 to 4.8)

RR (random) 3.4 (95% CI 1.5 to 7.7)

RR (analysis restricted to IFX 5mg/kg) (fixed) 3.5 (95% CI 2.4 to 5.3) (I^2 =70%)

Direction of effect of other studies measuring this outcome at 6 weeks & 3m (Probert et al and Jarnerot et al) both favour infliximab

- Clinical response (Mayo score decrease by at least 3 points or 30% from baseline, and accompanied by a decrease in rectal bleeding score of 1, or an absolute rectal bleeding score of 0 or 1) 8 weeks

Borderline heterogeneity (I^2 =45%)

RR (fixed) 2.0 (95% CI 1.7 to 2.4)

RR (random) 2.0 (95% CI 1.5 to 2.6)

- Mucosal healing (Mayo – absolute endoscopy sub-score of 0 or 1) 8 weeks

No heterogeneity (I^2 =0%)

RR (fixed) 1.9 (95% CI 1.5 to 2.3)

RR (random) 2.0 (95% CI 1.5 to 2.6)

Direction of effect of other studies measuring this outcome at 6 weeks & 3m (Probert et al and Jarnerot et al): first favours infliximab, second favours placebo, but neither is statistically significant

- Colectomy (trial duration – 3 months for Jarnerot)

Data only included for Jarnerot et al (patients hospitalised rather than outpatients)

RR 0.4 95% (CI 0.2 to 0.9)

- Deaths (trial durations)

Notes only one death in the included studies comparing IFX with placebo

1 death from histoplasmosis and acute respiratory distress syndrome, in ACT2, IFX arm

- Disease activity scores (Baron, UCSS, Truelove and Witts, Mayo, Partial Mayo)

Not reported directly

- Health related quality of life (IBDQ, EuroQol) 6 weeks

Only reported for Probert et al - however results misquoted

Should be (with reference original paper)
IBDQ: IFX mean improvement in score 36; Pbo mean improvement in score 25; WMD 11 (favouring IFX [not placebo as indicated in Cochrane review])
EuroQol (results not reported in Cochrane review for this outcome): IFX mean improvement in score 7; Pbo mean improvement in score 4; WMD 3 favouring IFX
Data for ACT I & II are known to exist but are presumably not reported because they have not been formally published

- Safety (adverse events, discontinuation of treatment)

No marked difference in adverse events between placebo and IFX arms

- Hospitalisations

Data for ACT I & II are known to exist (see S-P submission and ACT I & II trial reports) but are presumably not reported because they have not been formally published

WAS THE REVIEW UP-TO-DATE?

Yes. Searches conducted up to 2005

GENERAL COMMENTS

The review incorporated the following elements:

a) Clear statement of method
b) Comprehensive ascertainment of relevant literature
c) Minimal/explicit bias (for which adjustment can be made) introduced in the process of summarising the available literature
d) Appropriate meta-analysis
e) Other useful features (please state)

Categories a), b), c) & d) of the above; there might be some debate about how appropriate the approach to the meta-analysis was

On this basis the review can be classified as:

A. Systematic review with a meta-analysis
B. Systematic review with no meta-analysis (or with a generally inappropriate meta-analysis, the results of which should be ignored)
C. Comprehensive overview, with clearly stated method
D. Review with clearly stated method
E. General review
F. Other (please state)

A. of the above with some provisos

- There may be some minor concerns about the ability of the search to identify unpublished data, the very small number of full articles examined during the inclusion/exclusion phase, failure to report loss to follow-up during the quality assessment and the decision not to include smaller studies in the meta-analysis.
- One error was noted in the Forest plot for QoL
- No consideration appeared to have been given in the analysis to the potential importance of the severity/setting at the point of randomisation, separating the studies which investigated “rescue” therapy (Sands et al; Jarnerot et al) from those investigating sub-acute situations in the out-patient setting (Probert et al; ACT1 & 2)
- The review may not include all available data particularly concerning colectomy rates, health-related quality of life data and hospitalisations

REFERENCES

- Armuzzi A, De Pasaclis B, Lupascu P, Fedeli P, Leo D, Mentella MC et al. Infliximab in the treatment of steroid–dependent ulcerative colitis. Eur Rev Med Pharmaco Sci 2004;8(5):231-233.
- Jarnerot G, Hertervig E, Friis-Liby I, Blomquist L, Karlen P, Granno C et al. Infliximab as rescue therapy in severe to moderately severe ulcerative colitis: a randomized, placebo-controlled study. Gastroenterology 2005:128(7);1805-1811.
- Ochsenkuhn T, Sackmann M, Goke B. Infliximab for acute, not steroid-refractory ulcerative colitis: a randomized pilot study. Eur J Gastroenterol Hepatol 2004; 16(11):1167-71.
- Probert CS, Hearing SD, Schreiber S, Kuhbacker T, Ghosh S, Arnott ID et al. Infliximab in moderately severe glucocorticoid resistant ulcerative colitis: a randomised controlled trial. Gut 2003;52(7):998-1002.
- Rutgeerts P, Sandborn WJ, Feagan BG, Reinisch W, Olson A, Johanns J et al. Infliximab for induction and maintenance therapy for ulcerative colitis. N Engl L Med 2005;353(23):2462-76. [ACT I & II]
- Sands BE, Tremaine WJ, Sandborn WJ, Rutgeerts PJ, Hanauer SB, Mayer L et al. Infliximab in the treatment of severe, steroid-refractory ulcerative colitis: A pilot study. Inflamm Bowel Dis. 2001;7(2):83-88.

Appendix 3: ERG formal appraisal Cochrane review on ciclosporin in ulcerative colitis

Shibolet O, Regushevskaya E, Brezis M, Soares-Weiser K. Ciclosporine A for induction of remission in severe ulcerative colitis. *Cochrane Database of Systematic Reviews* 2005, Issue 1. Art. No.: CD004277. DOI: 10.1002/14651858.CD004277.pub2.

PURPOSE OF THIS APPRAISAL:
As for Appendix 1.

ASSESSOR'S SCREENING QUESTIONS

On first reading is there sufficient information to make a detailed appraisal?
Yes

IN RELATION TO WHAT QUESTION IS THIS REVIEW BEING APPRAISED (TARGET QUESTION)?

This appraisal relates to a Cochrane Review cited in the "Clinical Evidence" component of the manufacturer submission for the STA "Infliximab for the treatment of acute exacerbations of ulcerative colitis". The Cochrane Review appears to have been influential in the conduct of the review in the manufacturer submission and has been appraised as a result. The target question, is the same as that for the STA report, namely the question indicated in the scope from NICE.

State question, in terms of:

Question type - effects/effectiveness
Population/condition - adult patients diagnosed with acute exacerbations of severe ulcerative colitis with either an inadequate response to conventional

therapy (corticosteroids, 6-mecaptopurine, azathioprine) or intolerance to or medical contraindications to such therapies and are hospitalised for treatment
Intervention – infliximab
Comparator – standard clinical management (including surgical intervention); ciclosporin; placebo (or steroids)
Outcomes - survival; rates of surgical intervention; measures of disease activity; rates of and duration of response, relapse and remission; adverse effects of treatment; health-related quality of life

All of these question components are as specified in the final scope as set out by NICE

HAS A CLEAR QUESTION BEEN DEFINED (REVIEW QUESTION)?

Objectives of review:
To evaluate the effectiveness of ciclosporin A for patients with ulcerative colitis

State specific question, to which the further assessment of this review relates, in terms of:
Question type - effects/effectiveness
Population/condition – adults with severe acute ulcerative colitis
Intervention – ciclosporin regardless of route of administration added to standard care
Comparator – no additional treatment over standard care or placebo
Outcomes – clinical improvement or remission (primary); death; patients requiring surgery; adverse events

****

Comments relating to internal validity:
Review question is sufficiently clear that the review could be executed systematically.

Comments relating to external validity:
The review question addresses a question related to the target question, in that cyclopsporin is an important alternative treatment option when iv corticosteroids fail in a patient with an acute severe flare of ulcerative colitis requiring hospitalisation. It should be noted that direct comparisons between ciclosporin and infliximab are not strictly speaking within the scope of this Cochrane Review (they would however be within the scope of the Cochrane Review on infliximab for ulcerative colitis appraised in Appendix 2).

****

WHAT ARE THE IMPLICATIONS FOR THE VALIDITY OF THE REVIEW OF THE TYPE AND RANGE OF STUDY DESIGNS INCLUDED?

State type/types of study designs which were included:
Randomised controlled trials

****

Comments:
The general validity of the included study designs to answer the review question was high

****

WERE INCLUSION/EXCLUSION CRITERIA CLEARLY STATED?

Yes

List any INCLUSION criteria:
As for review question above

List any EXCLUSION criteria:
No specific exclusion criteria listed

****

Comments:
The inclusion/exclusion criteria as expressed in “Criteria for considering studies for this review” were consistent with the review question and were stated with sufficient clarity that it is likely that they could be applied reliably and the internal validity of the review assured as a result.

****

WAS THE SEARCH STRATEGY ADOPTED LIKELY TO HAVE MISSED MANY POTENTIALLY RELEVANT STUDIES?

State the search strategy:

A. Electronic search of

- MEDLINE (1966 to March 2004)
- EMBASE (1980 to March 2004)
- Cochrane Library (Issue 1, 2004)

There was no language limit on the search

Search strategy was described, but appears to be incomplete, containing just terms concerning the condition and the drug. There are apparently no terms to restrict by study design which would be essential in any searches of MEDLINE and EMBASE.

B. Reference searching
The references of all identified studies were inspected for more trials

C. Personal contacts
Corresponding authors of included trials and researchers active in the field were contacted for unpublished trials and complementary information on their own trials

****

Comments:
The search strategy was consistent with the review question.
As reported, the electronic searches do not look comprehensive and it is possible that included studies could have been missed.
There were apparently no steps to identify on-going trials.
There was some attempt through contact with researchers active in the field to identify unpublished material.

****

HOW WERE INCLUSION/EXCLUSION CRITERIA APPLIED?

36 studies were identified as being potentially relevant
2 included RCTs compared cyclopsporin with placebo

State whether a list of excluded studies was available and whether any excluded articles were examined:
References and reasons for exclusion of excluded studies given. Most excluded because the studies were not RCTs

****

Comments:
The number of articles examined (36) is low for a systematic review
This may be because it does not include the number of citations examined initially to identify the 24 studies which were felt to be impossible to exclude without reference to the full text

****

WAS THE VALIDITY OF INCLUDED STUDIES ASSESSED?

a) Validity implicit in inclusion/exclusion criteria
b) Validity of all included studies re-examined
c) Both
d) Apparently not assessed at all

Validity was both implicit in inclusion/exclusion criteria and was re-examined in all included studies ie c) above). Studies were primarily categorised as to risk of bias (low, moderate or high) depending on allocation concealment.

State how information on the validity of the included studies was used:

a) To provide narrative or tabulated information on the strengths and weaknesses of the included studies
b) As a check on the nature of the included studies to identify “late exclusions” (potentially inappropriate)
c) As a check on the nature of the included studies to identify wide variation in characteristics, suggesting that meta-analysis was not appropriate
d) Where meta-analysis was employed, to conduct sensitivity analyses to check robustness of findings
e) Other (please state)
f) Apparently not at all (potentially inappropriate if variation in important characteristics of included studies was likely)

The quality assessments were used to provide narrative or tabulated information on the strengths and weaknesses of the included studies and as a check on the nature of the included studies to identify “late exclusions” ie a) & b) above

****

Comments:

Overall, an adequate assessment of the validity of included studies was made. Both included studies were double-blind RCTs. Both were classified as being at low risk of bias on the basis of additional information received from the study authors about the process of randomisation.

****

WAS THE PROCESS OF DATA ABSTRACTION ADEQUATE?

State how the relevant data items were extracted:
a) Reference to pre-determined list
b) Use of data abstraction sheet
c) Other (please state)
d) No detail

There is no detail on how data were collected

****

Comments:
It is not possible to say whether the validity of the review was threatened by the process of data abstraction. However, key features of the included studies are clearly tabulated

****

WERE THE IMPORTANT STEPS IN THE REVIEW REPRODUCIBLE & BIAS FREE?

State whether the repeatability of the following steps was examined, reported and acted upon:

Searching for all potentially relevant studies - No
Applying study inclusion/exclusion criteria – Yes – but level of agreement/disagreement not reported
Assessment of validity of included studies - Yes – but level of agreement/disagreement not reported
Data abstraction - Yes – but level of agreement/disagreement not reported

****

Comments:
The repeatability of important steps in the review was examined but not reported

The accuracy of the abstracted data for colectomies in the two included studies was checked by the ERG and found to be accurate

****

WHAT WAS(WERE) THE RELEVANT AND JUSTIFIABLE REVIEW BOTTOM LINE(S) - AS STATED IN THE REVIEW ?

In general terms the review strongly concludes that there is insufficient information to draw conclusions about the effectiveness of ciclosporin and that further good quality trials are required.

State whether meta-analysis was used: No

Although Forest plots are presented for the data, the results are not combined because the two included studies do not investigate the same problem. The first included study by Lichtiger et al, compares ciclosporin with placebo in patients who have not responded to initial iv corticosteroid treatment; the second included study by D'Haens compares ciclosporin with iv corticosteroids in the initial phase of treatment after hospitalisation

The pattern of results was as follows:

- Clinical remission
    - Lichtiger (use of ciclosporin after trial of iv steroids)
        - 2/11 failed to induce remission with ciclosporin
        - 9/9 failed to induce remission with placebo
        - RR 0.18 [95% CI 0.05, 0.64]
        - There was a marked increase in induction of remission with ciclosporin which was unlikely to have been a chance finding

- D'Haens (ciclosporin vs iv steroids as initial treatment)
  - 5/15 failed to induce remission with ciclosporin
  - 7/15 failed to induce remission with placebo
  - RR 0.71 [95% CI 0.29, 1.75]
  - There was an increase in induction of remission with ciclosporin which was likely to have been a chance finding

- Deaths

There was only one death reported across both studies occurring in the placebo arm of the study by Lichtiger et al

- Colectomy
  - Lichtiger (use of ciclosporin after trial of iv steroids)
    - 3/11 required colectomy with ciclosporin
    - 4/9 required colectomy with placebo
    - RR 0.61 [95% CI 0.18, 2.06]
    - There was a reduction in colectomy with ciclosporin which could have been a chance finding
  - D'Haens (ciclosporin vs iv steroids as initial treatment)
    - 3/15 required colectomy with ciclosporin
    - 3/15 required colectomy with placebo
    - RR 1.00 [95% CI 0.24, 4.18]
    - There was no difference in colectomy with, but both a decrease and increase are compatible with the result
    - The one year colectomy rate was 5/15 ciclosporin vs 6/15 iv steroids
- Health related quality of life

No information on this outcome from included studies

- Safety (adverse events, discontinuation of treatment)

The review notes difficulty because of varying definitions of adverse events. Data on the following events were recorded:

- Hypertension
  - 5/26 in ciclosporin; 1/24 placebo or iv steroids

        - Excess with ciclosporin; unknown whether this could have been accounted for by chance alone
    - Paraesthesiae
        - 4/26 in ciclosporin; 1/24 placebo or iv steroids
        - Excess with ciclosporin; unknown whether this could have been accounted for by chance alone
    - Vomiting
        - 2/26 in ciclosporin; 1/24 placebo or iv steroids
        - Excess with ciclosporin; unknown whether this could have been accounted for by chance alone
- Length of hospital stay

No information on this outcome from included studies

WAS THE REVIEW UP-TO-DATE?

Yes. Searches conducted up to March 2004

GENERAL COMMENTS

The review incorporated the following elements:

a) Clear statement of method
b) Comprehensive ascertainment of relevant literature
c) Minimal/explicit bias (for which adjustment can be made) introduced in the process of summarising the available literature
d) Appropriate meta-analysis
e) Other useful features (please state)

a), b) & c) of the above, although there might be some concern about the comprehensiveness of the search

On this basis the review can be classified as:

A. Systematic review with a meta-analysis

B. Systematic review with no meta-analysis (or with a generally inappropriate meta-analysis, the results of which should be ignored)
C. Comprehensive overview, with clearly stated method
D. Review with clearly stated method
E. General review
F. Other (please state)

B. of the above

REFERENCES

- Lichtiger S, Present D, Kornbluth A, Gelernt I, Bauer J, Galler G et al. Cyclosporine in severe ulcerative colitis refractory to steroid therapy. N Engl J Med 1994;330(26):1841-5.
- D'Haens G, Lemmens L, Geboes K, Vandeputte L, Van Acker F, Mortlemans L et al. Intravenous cyclopsorine versus intravenous corticosteroids as single therapy for severe attacks of ulcerative colitis. Gastroenterology 2001;120(6):1323-1329.

Appendix 4: ERG check of abstracted data for Jarnerot et al

Summary:

The data abstracted in the submission by the manufacturer for one of the key studies on the effectiveness of infliximab by Jarnerot et al was checked against the original paper. The data were generally consistent, and confirm that the study although small was generally well conducted and that there was a positive effect of infliximab in reducing colectomy rates at 3 months. This benefit is suggested to extend to 1 year, but it is unclear where these results were published.

Detail:

The general format for the following is that a copy of the data presented in the submission is first provided, followed by a commentary on whether the results of the verification process.

A Table 5.2.3.1

Design	Population	Comparator	Intervention	Endpoints & Notes
Jarnerot et al 2005				
Randomised, double blind, parallel groups AC: adequate Oxford score R 1/2 DB 1/2 WD 1/1 Total 3/5	Acute severe/ moderately severe UC unresponsive to IV corticosteroids for at least 4 days N=45	Placebo plus IIVT therapy N=21	Infliximab 4mg/kg or 5mg/kg plus IIVT therapy N=24	Primary Colectomy or death within 3 months Secondary Clinical and endoscopic remission at 1 and 3 months Analyses undertaken early due to slow enrolment

No major inconsistencies were noted. To clarify: clinical remission was measured on the Seo index (<150 mild; 151 to 220 moderate; >220 severe active disease); remission rates were measured at 1 & 3 months; and included patients were hospitalized who were unresponsive to at least three days of intravenous corticosteroids. It seems likely, but is not completely clear, that the steroid treatment was continued in both arms after inflixmab or placebo were started. If steroids were stopped in the infliximab arm, it is unlikely that the trial was truly double-blind. Only one dose of infliximab was

given in the treatment arm rather than the three doses suggested in the summary of product characteristics.

The quality assessment score is accurate. It can be further noted that the method of randomisation as described seems likely to have achieved allocation in a truly random and concealed manner, although there are minimal details about how the random sequence was generated. No information is given on the nature of the placebo concerning the likelihood that it was indistinguishable from the intervention.

B Table 5.3.1 Methods

Infliximab: Jarnerot et al 2005

Jarnerot et al (2005 [*Gastroenterology & Evidence-Based Gastroenterology*]) conducted a randomised, parallel group, double blind, placebo controlled trial in patients from 10 centres in Sweden and Denmark.

Two treatment groups were included; 24 patients were randomised to additional treatment with a single dose of infliximab (5 mg/kg or a dose close to 5 mg/kg) plus IIVT therapy and 21 patients were randomised to placebo plus IIVT therapy.

Patients showing a response were switched to oral prednisone 40mg/day and tapered by 5 mg/day each week.

No inconsistencies were identified. However, it should be noted with respect to the last comment that patients responding to steroids were not part of the randomised trial. Only those refractory to steroids were randomised to infliximab or placebo.

C. 5.3.2 Participants

Infliximab: Jarnerot et al 2005

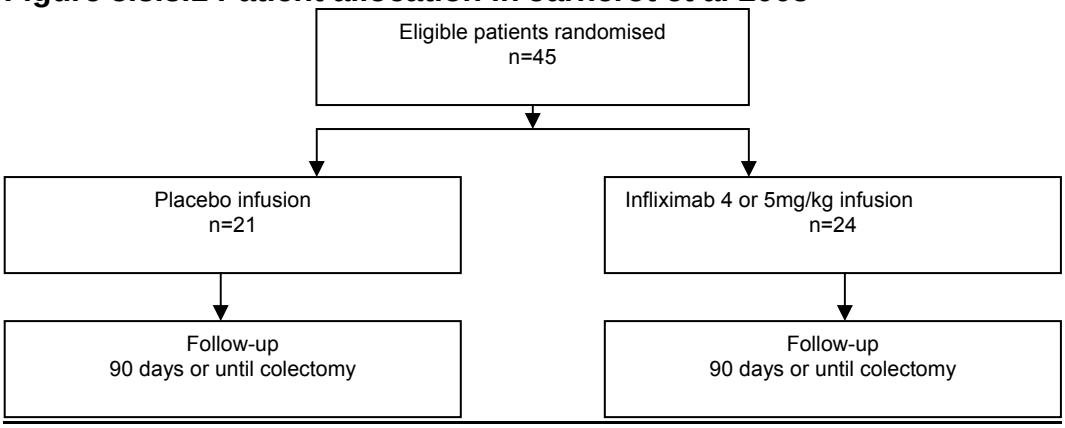
45 patients with acute severe or moderately severe UC unresponsive to intensive intravenous corticosteroids (IIVT [betamethasone 4 mg twice daily]) were recruited. All patients presented with a severe flare, and were at risk for urgent colectomy. Eligible patients had UC established by clinical history, endoscopy, and exclusion of infectious cause.

This information is consistent with the original paper.

D. 5.3.3 Patient numbers

Infliximab: Jarnerot et al 2005

Figure 5.3.3.1 Patient allocation in Jarnerot et al 2005



This information is consistent with the original paper.

E. 5.3.4 Outcomes

Infliximab: Jarnerot et al 2005

The primary endpoint was colectomy or death within 3 months after randomisation.

Secondary endpoints included clinical remission (defined as Seo Index <150) and endoscopic remission at 1 and 3 months after the infusions.

This information is consistent with the original paper.

F. 5.3.4 Statistics, Study Groups, Power

Infliximab: Jarnerot et al 2005

Forty-five patients were randomised: 24 to infliximab and 21 to placebo. Analyses were conducted on an intention-to-treat basis and included all 45 patients.

On the basis of published results, it was assumed that 35% in the infliximab group and 60% in the placebo group would have a colectomy. Seventy patients in each group would provide a statistical power of 80% and a significance level at 5%. It was planned that interim analysis would be performed and that the future of the study would be decided after 70 patients had been treated. The inclusion time was calculated as 1.5–2 years.

Categorical data were analyzed with the Fisher exact test (2-sided). The log-rank test, paired t test (2 sided), and logistic regression analysis were also used as appropriate.

Because this was an interim analysis, to reduce the risk of false- positive findings and to keep the overall significance level at 5%, a statistically significant P value should be <.029 instead of .05.

The information is consistent with the published paper. Attention should be drawn to the note about the adjustment to the cut-off level for the test of

statistical significance to take account of the early interim analysis. To note also that the reason for the early analysis was slow recruitment.

G. Study quality

Infliximab: Jarnerot 2005
The study was of acceptable quality and scored 3/5 on the Oxford quality scale. Two points were withheld as there was insufficient information on how the random sequence had been generated or how double-blinding was achieved. Allocation concealment was regarded as adequate. Also of note was that interim analyses were performed earlier than planned in the protocol due to slow recruitment. For this reason and to reduce the risk of false-positive findings, a statistically significant P value was assumed when <0.29 instead of 0.05. The study is still likely to be underpowered. Despite randomisation, a skewed distribution was observed with more male patients and more patients with a first attack of UC were randomised to the placebo group.

This information is consistent with the original paper.

The baseline characteristics are also available and are similar suggesting the general success of the randomisation process. However there is an imbalance between “male/female” and “earlier known UC/first attack of UC”, males and pre-existing UC being much commoner in the infliximab arm. The baseline characteristics also confirm the severe nature of the ulcerative colitis in the included patients.

Table 25. Baseline Demographics in Järnerot 2005

	Placebo (n= 21)	Infliximab (n = 24)
Male/female	8/13	16/8
Age, *y*, mean (range)	36.2 (19–61)	37.5 (20–60)
Smokers	2	0
Earlier known UC/first attack of UC	12/9	21/3
Extent of UC, total/extensive/distal	10/8/3	9/9/6
Seo index, day 0, mean (SD)	218 (30)	212 (30)
Included on fulminant colitis/Seo index	13/8	15/9
Fulminant colitis index, mean (range)	13.1 (8.1–25.3)	12.7 (8.1–22.5)
Seo index, mean (range)	195 (158–230)	196 (155–225)
Endoscopy at inclusion, severe/moderately severe inflammation	6/15	9/15
Hb, *g/L*, median (range)	119 (71–157)	130 (63–165)
Thrombocytes, 109/L, median (range)	444 (252–1131)	381 (154–763)
Albumin, *g/L*, median (range)	32 (16–48)	31 (15–48)
CRP, *mg/L*, median (range)	44 (8–324)	65 (5–296)

Hb, hemoglobin; CRP, C-reactive protein.

H. Results

Jarnerot et al 2005: results

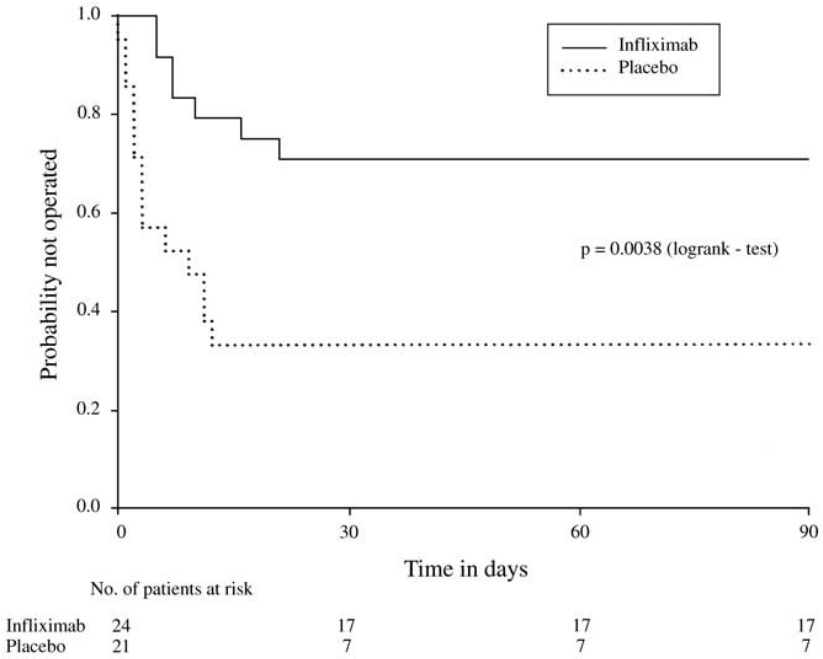
There was a statistically significant reduction in the primary outcome of colectomy rates in favour of infliximab OR 4.9 (1.4 to 17). Median time to colectomy after infusion was 8 days (range, 2 – 22 days) in the infliximab group and 4 days (range, 1 – 13 days) in the placebo group. Despite the skewed distribution, multivariate logistic regression analyses still showed results in favour of infliximab for both earlier known UC or first attack OR 3.6 (95% CI 1.0 to 1.37) and sex OR 5.7 (95% CI 1.4 to 2.2).

The efficacy findings for the secondary outcomes did not show statistically significant benefit of infliximab over placebo for either clinical remission or endoscopic remission. The clinical course (0 to 3 months) according to the SEO index is described as being similar in both groups (and is presented together in the paper).

Study	Placebo or Steroids	Infliximab	Ciclosporin
Colectomy at 3 months			
Järnerot 2005	14/21 (67%)	7/24 (29%)	-
Colectomy at 12 months			
Järnerot 2005	15/21 (71%)	10/24 (42%)	-

This information is consistent with the original paper. It is unclear where the 1 year colectomy data were derived from. Further detail was provided in the original infliximab submission on clinical remission and mucosal healing at 12 weeks. The paper also provides time to event data on colectomy:

Figure 8. Time to Colectomy Analysis in Järnerot 2005



This confirms that the difference in colectomy is highly statistically significant, even allowing for the adjustment in p value cut-off suggested in the statistical methods. It also confirms that the difference in colectomy rates is established within 4 weeks/1month of randomisation, as well as being apparent at the time-point stated.

The submission correctly reflects quality of life was not measured in the study by Jarnerot et al.

I. Results, adverse events

Infliximab: Jarnerot et al 2005

No deaths were reported and the frequency of adverse events appeared to be comparable between the infliximab and placebo groups; 9 patients treated with infliximab reported general side effects and 4 patients reported adverse postoperative events whereas 8 patients treated with placebo reported 8 general side effects and 5 patients reported adverse postoperative events.

This information is consistent with the original paper.

Appendix 5: ERG check of abstracted data for Sands et al

Summary:

The data abstracted in the submission by the manufacturer for one of the key studies on the effectiveness of infliximab by Sands et al was checked against the original paper. The data were generally consistent, and confirm that the study although small was generally well conducted and that there was a trend towards reducing colectomy rates at 2 weeks. The confidence intervals are however extremely wide, being compatible with both substantial increases and substantial decreases in colectomy rates, because of the very small number of patients distributed across 4 trial arms. As well as increasing uncertainty due to chance, the small number of participants may also have undermined the ability of randomisation to deliver baseline equivalence.

Detail:

The general format for the following is that a copy of the data presented in the submission is first provided, followed by a commentary on whether the results of the verification process.

A. Table 5.2.3.1

Design	Population	Comparator	Intervention	Endpoints & Notes
Sands et al 2001				
Randomised, double blind, parallel groups AC: unclear Oxford score R 1/2 DB 2/2 WD 1 Total 4/5	Acute severe UC unresponsive to 7 days of corticosteroid therapy (of which 5+ days used intravenous admin) N=11	Placebo N=3	Infliximab 5mg/kg N=3 Infliximab 10mg/kg N=3 Infliximib 20mg/kg N=2	Primary Treatment failure at 2 weeks after infusion Secondary Change from baseline in modified Truelove & Witts score, physician's and patient's global response evaluation, ESR, CRP levels, sigmoidoscopic ratings, and histological disease scores Enrollment terminated early due to slow accrual

No major inconsistencies were noted. Included patients were unresponsive to seven days of corticosteroids, of which at least 5 days by an intravenous route. It seems likely, but is not completely clear, that the steroid treatment was continued in both arms after inflixmab or placebo were started. Only one

dose of infliximab was given in the treatment arm rather than the three doses suggested in the summary of product characteristics.

The quality assessment score is accurate. The only limitation was that there was no detailed information about method of randomisation and whether allocation was truly random and concealed.

B. Table 5.3.1 Methods

Infliximab: Sands et al 2001

Sands et al conducted a randomised, double-blind, parallel group trial of infliximab or placebo in 6 centers (5 in the US and 1 in Belguim).

Patients were randomly assigned to receive a single intravenous infusion of placebo or infliximab 5, 10, or 20mg/kg.

This information is consistent with the original paper.

C. 5.3.2 Participants

Infliximab: Sands et al 2001

The 11 recruited patients had active UC of at least 2 weeks duration diagnosed by clinical history, endoscopy, and histology. Disease severity was established using modified Truelove and Witts score, all patients had to have a score >10. Patients were excluded if their disease was so severe that endoscopy was contraindicated, or if they had toxic megacolon, perforation of the colon, or disease that did not extend beyond the rectum.

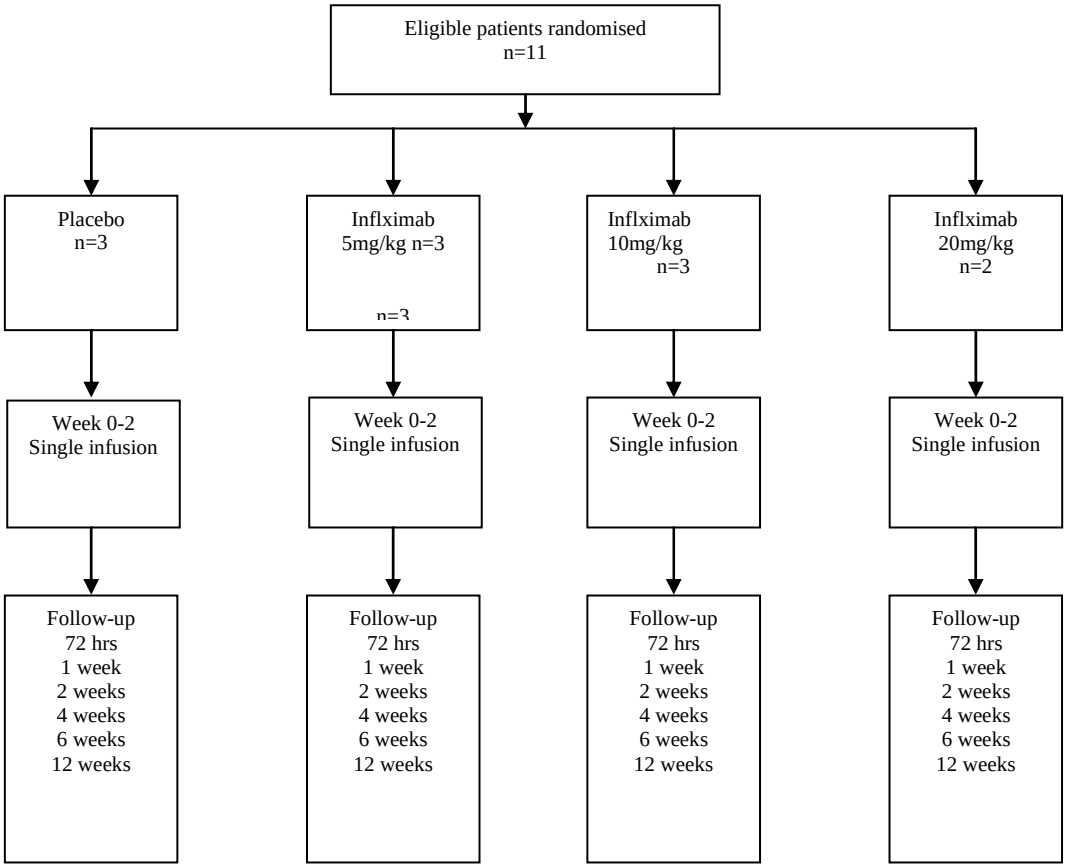
All patients had received at least 7 days of unsuccessful corticosteroid therapy (>40 to <60mg/day prednisone equivalent), of which at least 5 days included intravenous administration.

This information is consistent with the original paper.

D. 5.3.3 Patient numbers

Infliximab: Sands et al 2001

Figure 5.3.3.2 Patient allocation in Sands et al 2001



This information is consistent with the original paper.

E. 5.3.4 Outcomes

Infliximab: Sands et al 2001

The primary endpoint was treatment failure at 2 weeks after infusion (defined as failing to achieve a clinical response as defined by a modified Truelove and Witts score of <10 and a 5-point reduction from baseline, a dosage of >60mg/day corticosteroids or Ciclosporin A or other immunomodulators due to worsening condition, a nonelective or elective colectomy, or if the patient died as a result of UC).

Secondary endpoints included a comparison of the individual components of treatment failure, change from baseline for the modified Truelove and Witts score, physician's and patient's global response evaluation, ESR, CRP levels, sigmoidoscopic ratings, and histological disease activity scores.

This information is consistent with the original paper.

F. 5.3.4 Statistics, Study Groups, Power

Infliximab: Sands et al 2001

Enrollment was terminated prematurely; 3 patients were randomised to placebo, 3 patients to infliximab 5mg/kg, 3 patients to 10mg/kg, and 2 patients to 20mg/kg.

The study was designed to recruit 60 patients; however, enrolment was terminated prematurely because of slow accrual (11 patients were recruited in total).

Formal statistical analysis of results was not performed because of the small number of patients participating in the study.

The information is consistent with the published paper. Self-evidently the study was greatly underpowered, and the very small number of participants

randomised to each group would also have compromised the likelihood that there would be equivalence at baseline.

G. Study quality

Infliximab: Sands 2001
The study was of acceptable quality and scored 4/5 on the Oxford quality scale. One point was withheld, as there was insufficient information on how the random allocation sequence had been generated. A maximum two points were scored for double blinding as the use of an identical placebo was noted. Allocation concealment was regarded as unclear. Also of note is that recruitment was terminated early due to slow accrual. For this reason the authors did not undertake a formal statistical analyses of the results and the study is likely to be underpowered.

This information is consistent with the original paper.
There are quite marked differences in the baseline characteristics (see appendix 9.8 in manufacturer submission) between each of the four trial arms.

H. Results

Sands et al 2001: results

Fifty percent of patients treated with infliximab were considered a treatment success at two weeks; two patients treated with infliximab 5mg/kg, one patient treated with infliximab 10mg, and one patient treated with infliximab 20mg/kg. Of the patients treated with infliximab who did not respond two patients did not meet modified Truelove and Witts criteria for response (one patient treated with 10mg/kg and the other 20mg/kg), one patient received an increased corticosteroid dose and subsequent Ciclosporin (5mg/kg), and one patient underwent elective colectomy (treated with 10mg/kg). There were no responders amongst patients treated with placebo and all three underwent colectomy by two weeks (one elective and two non-elective).

Study	Placebo or Steroids	Infliximab	Ciclosporin
Colectomy at 3 months			
Sands 2001	3/3 (100%)	0/3 (0%)	-

This information is consistent with the original paper. The interpretation of the results on colectomy depends to an extent on whether all infliximab arms (10mg/kg and 20mg/kg as well as 5mg/kg) are regarded as providing useful effectiveness data and whether elective colectomies are regarded as severe adverse outcomes as non-elective colectomies. If all infliximab arms are included in the results the benefit associated with infliximab looks slightly less great: infliximab 1/8 vs placebo 3/3, RR 0.13 [95% CI ???, ???]. The trend towards benefit remains and the confidence intervals remain very wide as the number of participants is still very small.

Although other outcomes were measured, these were not reported in the manufacturer submission. However, these measures were also reported with minimal detail in the original paper. Some additional information on change in disease activity over time, as measured by Truelove and Witts score is provided in the original paper.

I. Results, adverse events

Infliximab: Sands et al 2001

No deaths were reported but all patients experienced at least one adverse event during the study. Most were mild to moderate and no patients discontinued the infusion due to adverse events. The events most frequently reported by infliximab patients were pruritus, headache and urinary tract infection (each occurring in two patients). Four patients reported five serious adverse events that required hospitalisation or prolonged the hospital stay, all resolved with appropriate treatment.

This information is consistent with the original paper. Two of the patients affected by serious adverse events were treated with placebo and two with infliximab.

Appendix 6: ERG check of abstracted data for Lichtiger et al

Summary:

The data abstracted in the submission by the manufacturer for one of the key studies on the effectiveness of ciclosporin by Lichtiger et al was checked against the original paper. The data were generally consistent, and confirm that the study although small was generally well conducted, possibly better than conveyed by the 3/5 rating allocated in the manufacturer submission. There was improved response rates and a trend towards reduced colectomy rates with ciclosporin, but the confidence intervals are extremely wide, being compatible with both substantial increases and substantial decreases in colectomy rates.

Detail:

The general format for the following is that a copy of the data presented in the submission is first provided, followed by a commentary on the results of the verification process.

A. Table 5.2.3.1

Design	Population	Comparator	Intervention	Endpoints & Notes
Lichtiger 1994				
Randomised, double blind, placebo controlled Single centre prospective study AC: adequate Oxford score R 1/2 DB 1/2 WD 1/1 Total 3/5	Acute severe UC refractory to IV corticosteroids after 7 or more days	Placebo N=9	Ciclosporin N=11	Primary Clinical activity score Response (clinical activity score of <10 on two consecutive days) within 14 days of starting treatment. Secondary Not defined

No major inconsistencies were noted. Included patients were unresponsive to seven days of intravenous corticosteroids, and the corticosteroids were continued as part of concurrent therapy in both the ciclosporin and placebo trial arms.

The quality assessment score is generally accurate. There was apparently no information about the process of randomisation beyond the description of the

study as a “randomized double-blind, controlled trial” in the abstract. However, the Cochrane Review by Shibolet et al indicates that they had confirmed the nature of the randomisation process with the authors, so that a higher quality score may be a better reflection of the study quality. The deduction of the quality assessment score for imperfect blinding may also be challenged – see below.

B. Table 5.3.1 Methods

Ciclosporin: Lichtiger 1994

This was a randomised, double-blind, placebo-controlled prospective study which was followed by an open-label period.

Patients assigned to receive ciclosporin were given a dose of 4 mg/kg per day by continuous infusion for up to 14 days. The patients assigned to placebo received an identical-appearing intravenous solution of cremaphor and alcohol.

This information is consistent with the original paper.

C. 5.3.2 Participants

Ciclosporin: Lichtiger 1994

All 20 patients included had a disease activity index of 10 or higher and had demonstrated no response to intravenous corticosteroid therapy, equivalent to a daily dose of 300mg hydrocortisone. Patients were excluded if they had bacterial or parasitic pathogens in stools, a positive test for Clostridium difficile toxin, septicemia, perforation of the bowel, megacolon, active fungal or viral infection, uncontrolled hypertension, or elevated levels of hepatic enzymes, creatinine, or cholesterol. Patients were also excluded if they had received mercatopurine, azathioprine or any investigational drug within the previous two weeks.

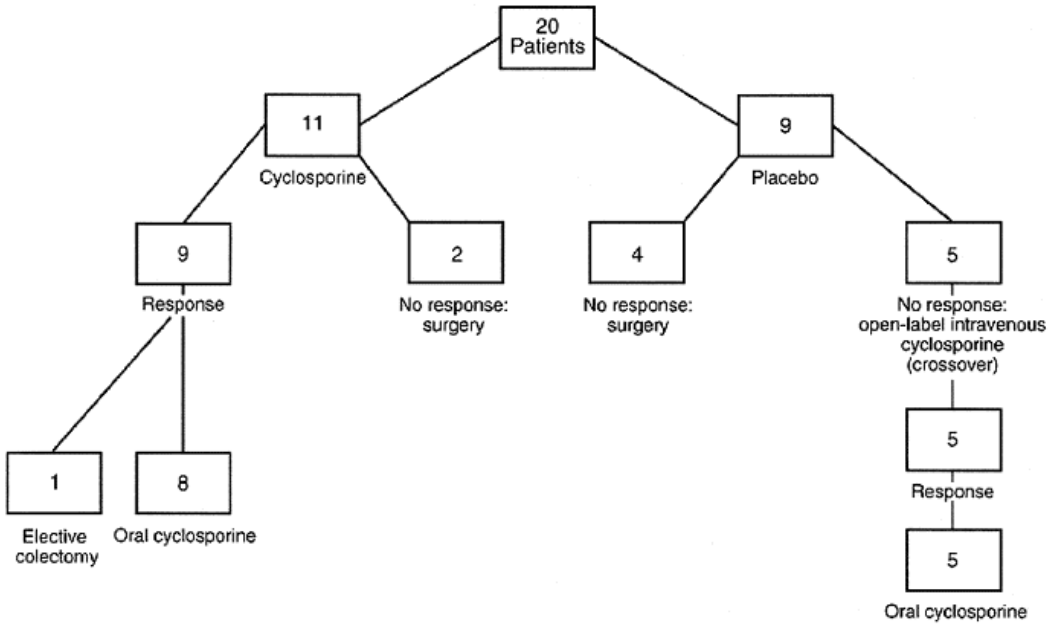
This information is consistent with the original paper.

D. 5.3.3 Patient numbers

Ciclosporin: Lichtiger 1994

All patients were treated according to the protocol. One patient in the ciclosporin group who had a response to therapy elected to undergo colectomy. All remaining patients with an initial response to ciclosporin were treated with oral ciclosporin and discharged from the hospital 48 hours later.

Figure 5.3.3.3 Patient allocation in Lichtiger 1994



This information is consistent with the original paper.

E. 5.3.4 Outcomes

Ciclosporin: Lichtiger 1994

The primary endpoint was defined as the clinical-activity score post treatment. A score of less than 10 on two consecutive days was considered to indicate a positive response to therapy. The score on the second of these two days was considered the final score. Patients whose clinical-activity scores did not fall below 10 for 2 consecutive days after 14 days of treatment or whose condition worsened were considered to have no response to treatment.

Secondary endpoints were not defined.

This information is consistent with the original paper.

F. 5.3.4 Statistics, Study Groups, Power

Ciclosporin: Lichtiger 1994

Two groups were defined – ciclosporin (n=11) and placebo (n=9).

The trial was terminated after 20 patients had been studied, when the physician who was aware of their treatment assignments noted a significant difference between the two groups, confirmed by the study monitor and two independent reviewers. No power calculations were reported.

Quantitative variables were compared with two-tailed Student's t-tests. Qualitative variables and differences between centers were compared with chi-square analysis with Yates' correction. All patients were assessed on an intention-to-treat basis.

The information is consistent with the published paper.

G. Study quality

Ciclosporin: Lichtiger 1994 & D'Haens 2001
These two RCTs have previously been evaluated for quality in the Cochrane review (Shibolet 2005) which indicated that both trials had adequate concealment. The review did note that the two trials have divergent comparators: while Lichtiger 1994 was a placebo-controlled trial, D'Haens 2001 randomised patients to either steroids or ciclosporin. On the Oxford scale, Lichtiger 1994 was awarded 3/5 because no details are provided on the methods of randomisation, and because investigators were not blinded. D'Haens 2001 scored 4/5 on the Oxford scale, because investigator blinding was not maintained beyond 8 days, and was of acceptable quality.

This information is generally consistent with the original paper. The information provided in the Cochrane Review by Shibolet et al from the original study authors, suggests that deduction of a point for imperfect randomisation may be harsh. The deduction of the point for failure to blind is also possibly harsh as the investigators did make attempts to blind assessment of outcome. In particular, the decision to recommend surgery was made by a surgeon who was unaware of treatment assignments. However, clinical activity scores were decided by two physicians one of whom was definitely aware of treatment assignment.

Baseline characteristics (see appendix 9.8 in manufacturer submission) showed some differences in age and duration of the disease.

H. Results

Ciclosporin: Lichtiger 1994

A total of 9 of 11 (82 percent) in the intravenous ciclosporin group had a response to therapy compared with 0/9 patients in the placebo group (P<0.001). The mean time to a response (second consecutive day on which the clinical-activity score was less than 10) was 7 days (range, 3 to 14). Mean clinical-activity score in the ciclosporin group fell from 13 (range, 10 to 16) to 6 (range, 2 to 8), and the mean score in the placebo group fell from 14 (range, 12 to 17) to 13 (range, 11 to 18). At the end of the study the mean decline in the clinical-activity score in the ciclosporin group was significantly greater than that in the placebo group (P<0.001).

One patient in the ciclosporin group who had a response to therapy elected to undergo colectomy. All 14 patients with a response, except the 1 who chose to undergo colectomy, were treated with oral ciclosporin and discharged from the hospital 48 hours later.

Study	Placebo or Steroids	Infliximab	Ciclosporin
Colectomy at 3 months			
Lichtiger 1994	4/9 (44%)	-	3/11 (27%)

This information is consistent with the original paper. The results of the trial in terms of response are more impressive than the number of colectomies. This is partly explained by the intention-to-treat analysis in which one elective colectomy in the cyclopsorin arm is counted as an adverse outcome. The relative risk for colectomy using the ITT approach is still 0.47 [95% CI 0.07 to 3.04]. The wide confidence intervals however indicate that the results are compatible with an increase in colectomies as well as a more marked decrease because of the small number of participants and events.

No other outcome data is provided in the original paper.

I. Results, adverse events

Ciclosporin: Lichtiger 1994

No deaths were reported. Four of 11 patients (36%) initially treated with ciclosporin had paresthesias compared with none of the patients in the placebo group. Hypertension, defined as a systolic blood pressure of more than 140 mm Hg or a diastolic blood pressure of more than 90 mm Hg for two consecutive days, was noted in 4/11 (36%) patients in the ciclosporin group, two of whom required treatment. Hypertension developed in one patient in the placebo group (11 percent). One patient in each group reported nausea and vomiting.

None of the patients had nephrotoxicity or hepatotoxicity. One patient treated with ciclosporin had a grand mal seizure after the initiation of therapy but had no more seizures after ciclosporin was discontinued. Headaches occurred as the only side effect in two of the patients who received ciclosporin after receiving placebo.

This information is as reported in the original paper. There is an excess of adverse events in the ciclosporin arm, but like the colectomy data, the small numbers of participants makes it difficult to exclude the possibility that these excesses occurred by chance alone.

Appendix 7: ERG check of abstracted data for D'Haens et al

Summary:

The data abstracted in the submission by the manufacturer for one of the key studies on the effectiveness of ciclosporin by D'Haens et al was checked against the original paper. The data were generally consistent, but clearly indicate that contrary to the argument advanced in the manufacturer's submission, this paper should not be considered to provide a valid estimate of the effect of cyclsoporin relative to placebo in patients refractory to iv steroids. D'Haens et al compares ciclosporin with iv steroids in the initial management of a severe acute flare of ulcerative colitis. As iv steroids are known to have activity in this situation, ciclosporin is being compared with an active agent rather than a placebo and so it is highly likely that the study will produce a lower estimate of ciclosporin's effect than a study comparing ciclosporin with placebo. This opinion is supported by the authors of the Cochrane review by Shibolet et al who felt that the RCTs by Lichtiger and D'Haens were too different in nature to combine in a meta-analysis.

Detail:

The general format for the following is that a copy of the data presented in the submission is first provided, followed by a commentary on the results of the verification process.

A. Table 5.2.3.1

Design	Population	Comparator	Intervention	Endpoints & Notes
D'Haens et al 2001				
Randomised, double blind Single-centre prospective study AC: adequate Oxford score R 2/2 DB 1/2 WD 1/1 Total 4/5	Patients hospitalised with severe attack of UC (clin. activity score ≥ 10)	Methylprednisolone N=15	Ciclosporin N=15	Primary Improvement in clinical activity score Response (clinical activity score of <10 on days 7 and 8 with a drop in the score from day 1 to day 8 of at least 3 points and the possibility of hospital discharge to the patients

No major inconsistencies were noted. For the included patients methylprednisolone or ciclosporin was the first line of treatment of their acute flare; unresponsive participants were offered combined steroid and ciclosporin treatment before proceeding to colectomy. The study thus compares ciclosporin with active treatment, and the main difference between patients would have been the order in which iv corticosteroids or ciclosporin were introduced into the treatment regimen, most patients being exposed to both treatments. In contrast in the study by Lichtiger et al patients allocated to placebo would not have received ciclosporin until the open phase of the study which occurred at least a week later, and would not have received at all if they had deteriorated to the point leading to colectomy while on placebo. It is thus unclear why the results of D'Haens et al are considered along-side those of Lichtiger et al, an approach also rejected by the Cochrane Review by Shibolet et al who judged the two RCTs to be sufficiently dissimilar not to meta-analyse their results.

The quality assessment score is generally accurate. Randomisation was well described and it seems likely that allocation was concealed. Blinding was maintained for the first 8 days of the RCT.

B. Table 5.3.1 Methods

Ciclosporin: D'Haens 2001

This was a randomised double-blind, single-centre prospective study.

Patients assigned to receive ciclosporin were given a continuous infusion of 4 mg/kg body wt per day for 8 days. Patients assigned to receive glucocorticosteroids were given 40 mg methylprednisolone per day.

This information is consistent with the original paper.

C. 5.3.2 Participants

Ciclosporin: D'Haens 2001

All 30 patients were admitted to hospital with a severe attack of UC having a clinical disease activity score of 10 or more. Similar to Lichtiger, patients were exclueded if they had parasites or Clostridium difficile, enteropathogens, uncontrolled hypertension or elevated hepatic enzymes, creatinine, or cholesterol. Patients were also excluded if they had received azathioprine for less than 3 months or if the dose had been changed in the 4 weeks prior to admission, or if they had exhibited recent response on glucocorticoids.

This information is consistent with the original paper.

D. 5.3.3 Patient numbers

Ciclosporin: D'Haens 2001

Overall 30 sequential patients presenting at emergency at outpatient clinics were recruited. 15 patients were each randomised to either ciclosporin or methylprednisolone. One patient in the ciclosporin group was found to have C. difficile toxins in faeces and was withdrawn on day 2. A graphic showing patient disposition was not supplied in the write-up of this study.

This information is consistent with the original paper.

E. 5.3.4 Outcomes

Ciclosporin: D'Haens 2001

The primary endpoint was defined as the level of improvement in clinical-activity score. Clinical 'response' was also assessed. This was defined as a score of <10 on days 7 and 8 with a drop in the score from day 1 to day 8 of at least 3 points and the possibility to discharge the patient.

Secondary endpoints were endoscopic and histologic response, urinary clearance, HMPAO white blood cell clearance.

This information is consistent with the original paper.

F. 5.3.4 Statistics, Study Groups, Power

Ciclosporin: D'Haens 2001

Sample size estimates showed that, with a sample size of 35 patients in each group, a 30% difference in the proportion of clinical responders could be demonstrated with 80% power (alpha 0.05), based on the assumption that 82% of patients would respond to 4 mg/kg and 50% to 2 mg/kg IV ciclosporin.

All patients were analyzed on an intention-to-treat basis. For quantitative data, statistical analysis was performed using 1-way analysis of variance for multiple comparisons, followed by a 2-tailed, paired t test for parametric, or Wilcoxon Rank sum test for nonparametric observations. Statistical significance was accepted at a P value 0.05. Mulivariate analysis with stepwise logistic regression was performed to test for parameters influencing clinical response.

The information is consistent with the published paper.

G. Study quality

Ciclosporin: Lichtiger 1994 & D'Haens 2001
These two RCTs have previously been evaluated for quality in the Cochrane review (Shibolet 2005) which indicated that both trials had adequate concealment. The review did note that the two trials have divergent comparators: while Lichtiger 1994 was a placebo-controlled trial, D'Haens 2001 randomised patients to either steroids or ciclosporin. On the Oxford scale, Lichtiger 1994 was awarded 3/5 because no details are provided on the methods of randomisation, and because investigators were not blinded. D'Haens 2001 scored 4/5 on the Oxford scale, because investigator blinding was not maintained beyond 8 days, and was of acceptable quality.

This information is consistent with the original paper and the information provided in the Cochrane Review by Shibolet et al.

Baseline characteristics (see appendix 9.8 in manufacturer submission) were generally well matched between the ciclosporin and methylprednisolone arms.

H. Results

Ciclosporin: D'Haens 2001

Nine of 14 patients (64%) had a response to ciclosporin therapy compared with 8 of 15 (53%) to methylprednisolone (P = 0.4). The mean dose of ciclosporin administered IV over the 8 days was 2.7 + 0.6 (range, 1.8 –3.5) mg/kg body wt per day, which corresponded to 196.7 + 18.1 (range, 91–263) mg/day; ciclosporin blood levels during IV treatment averaged 376 + 22 (range, 212– 488) ng/mL; concentrations in responders were not significantly different from those in nonresponders (means, 361 + 34 [212– 488] ng/mL vs. 385 + 30 [311– 482] ng/mL) (P = 0.6).

Mean decline in the clinical activity score was 5.4 (range, -1 to 14) with ciclosporin and 4.4 (range, -1 to 9) with methylprednisolone for all patients who completed the trial and 7.7 (range, 3–14) vs. 6.1 (range, 4 –9) in the responders.

The mean time to response was 5.2 + 0.9 days (range, 2– 8) in the ciclosporin group vs. 4.3 + 0.7 days range, 2– 8) in the methylprednisolone group (P = 0.2).

After day 8, blinding ended and interpretation of response and/or failure may have been subject to investigator bias.

Study	Placebo or Steroids	Infliximab	Ciclosporin
Colectomy at 3 months			
D'Haens 2001	3/15 (20%)	-	3/14 (21%)
Colectomy at 12 months			
D'Haens 2001	6/15 (40%)	-	6/14 (36%) INCORRECT – SHOULD BE 5/14 (36%)

This information is consistent with the original paper with the exception of a minor data abstraction error for colectomy rates at 12 months. They correctly reflect improvement in both arms of the trial. They also convey the non-statistically significant advantage of ciclosporin over methylprednisolone in the initial management of an acute ulcerative colitis flare with respect to clinical response and change in clinical activity score, and minimal difference in colectomy rates {at 3 months RR 1.09 [95% CI 0.18, 6.58]; at 12 months RR 0.9 [95% CI ???, ???]}

I. Results, adverse events

Ciclosporin: D'Haens 2001

No deaths were reported in the study. No patients discontinued due to adverse events and no dose reductions due to adverse events were necessary. Seizures did not occur, decreases in serum magnesium levels were observed in 2 and in serum potassium levels in 4 ciclosporin treated patients. For a detailed breakdown of AEs, see Appendix 9.8.

This information is as reported in the original paper. There is an excess of adverse events in the ciclosporin arm, but the small numbers of participants makes it difficult to exclude the possibility that these excesses occurred by chance alone. In addition to hypokalaemia and hypomagnesemia, there was a slight excess of hypertension, headache and vomiting, symptoms also seen

on the trial by Lichtiger et al. The trial also provided some evidence of a reduction on renal function in the ciclosporin arm, but not sufficient to influence creatinine levels.

Appendix 8: Validation of manufacturer's submissions search for on-going trials

Summary:

The limited existing evidence-base for clinical decisions on management of patients with acute flares of ulcerative colitis is a major problem identified in the manufacturer's submission. There appear to be two on-going trials which may substantially add to the evidence on clinical effectiveness by comparing infliximab with ciclosporin in steroid-refractory acute severe flares of ulcerative colitis. One was identified in the manufacturer's submission; the second has come to light through the ERG's clinical advisor, but was also mentioned in comments on the STA scope by the British Society of Gastroenterology.

Detail:

The general format for the following is that a copy of the data presented in the submission is first provided, followed by a commentary on the results of the verification process.

The main text of the section on clinical evidence states:

5.2.5 Ongoing studies

'ulcerative colitis' for relevant on-going or planned studies (Feb 2008). Five studies of infliximab in ulcerative colitis were found to be either active but not yet recruiting or recruiting (NCT00336492; NCT00537316; NCT00586807; NCT00207688; NCT00542152).

Only one study was relevant to this review (NCT00542152); a phase IV, multicentre, randomised, open label study of infliximab compared with ciclosporin in steroid-refractory severe attacks of ulcerative colitis in adults (sponsored by Groupe d'Etude Therapeutique des Affections Inflammatoires Digestives). Disease severity is defined as a severe acute flare of UC with a Lichtiger Index score > 10. Enrolled patients are to receive either infliximab 5mg/kg at weeks 0, 2, and 6 or ciclosporin 2mg/kg/day IV for 7 days followed by Neoral 4mg/kg/day orally for 3 months. This study is currently recruiting patients (target n=100).

The license holder, Centocor, was contacted by Schering-Plough with a request to search the company databases for any relevant ongoing trials. No trials were identified beyond those already revealed by our search of www.clinicaltrials.gov.

Some further information was provided in response to a request for further information to the manufacturer:

The following trials were identified through clinicaltrials.gov and their titles are shown in the table below. Please note that we currently have access only to the information available on clinicaltrials.gov. We have included summaries from clinicaltrials.gov on each trial in an appendix A attached with this response. The one ongoing trial which bears relevance to this submission is **NCT00542152**.

Trial ID	**Name**
NCT00336492	A Study of the Safety and Efficacy of Infliximab(REMICADE) in Pediatric Subjects With Moderately to SeverelyActive Ulcerative Colitis
NCT00537316	Efficacy & Safety of Infliximab Monotherapy Vs Combination Therapy Vs AZA Monotherapy in Ulcerative Colitis (Part 1) Maintenance Vs Intermittent Therapy for Maintaining Remission (Part 2)(Study P04807AM2)
NCT00586807	Metabolic Response to Infliximab in Pediatric Ulcerative Colitis
NCT00207688	A Long Term Safety Study of Infliximab (Remicade)
NCT00542152	Study Comparing Ciclosporin With Infliximab in Steroid-Refractory Severe Attacks of Ulcerative Colitis (cysif)

The ERG re-ran the searches on ClinicalTrials.gov as accessed 6/5/08. We confirmed that as claimed the only directly relevant on-going trial was NCT00542152 sponsored by the Group d'Etude Therapeutique des Affections Inflammatoires Digestif (GETAID). This is comparing the efficacy of ciclosporin with infliximab in steroid-refractory attacks of ulcerative colitis. It is an open-label RCT. The dose of infliximab is as licensed (5mg/kg at weeks 0, 2 & 6); the dose of ciclosporin is 2mg/kg iv for 7 days (a lower dose than used in the RCT by Lichtiger et al). The primary outcome is % of patients with treatment failure. The secondary outcome measures listed are:

- % clinical response
- % patients in remission
- Lichtiger index score
- MDAI score

- Time to discharge
- Endoscopic response
- Colectomy rate
- Steroid dosage
- Number of adverse events
- CMV infection

The target number of patients is 100 (50 per arm) and the study commenced in June 2007. It is based in France and Belgium.

In addition to this relevant on-going trial we also identified a further relevant on-going study comparing the effectiveness of ciclosporin with infliximab in the management of acute ulcerative colitis refractory to iv corticosteroids (CONSTRUCT – Comparison of iNfliximab and ciclopsporin in Steroid Resistant Ulcerative Colitis: a Trial). This has not started recruiting yet and is being coordinated by Professor JG Williams, School of Medicine, Swansea University (personal communication Dr B McCaig). Further details may be available at the first appraisal committee.

This trial is also referred to in a comment by the British Society of Gastroenterology on the scope:

> "The HTA-sponsored CONSTRUCT trial which starts late Spring, will compare infliximab with ciclosporin and provide a much more secure evidence base for policy. We would request that NICE recommends use of infliximab is restricted to patients in this trial until it is complete because this will speed recruitment immensely, for the common good and without any measurable decrement of established care for individuals until the results of that trial are known. It can be anticipated that provisional results could then be available within 1 year."

Appendix 9:Searches undertaken by the ERG

The searches undertaken for the previous report on Remicade for the treatment of ulcerative colitis were updated as follows:

- Systematic reviews from 2007 - 2008. Sources: Cochrane Library 2008 Issue 1, MEDLINE (Ovid), EMBASE (Ovid) and MEDLINE in Process & Other Non-Indexed Citations April 14 2008 (Ovid)
- Economic evaluations and models from 2007 to 2008. Sources: Cochrane Library (NHS EED) 2008 Issue 1, MEDLINE (Ovid) and EMBASE (Ovid)
- Randomised Controlled Trials from 2007 to 2008. Source: Cochrane Library (CENTRAL) 2008 Issue 1, MEDLINE (Ovid), EMBASE (Ovid) and MEDLINE in Process & Other Non-Indexed Citations April 14 2008 (Ovid)
- Quality of life associated with ulcerative colitis from 2007 to 2008. Source: MEDLINE (Ovid)
- In-going studies in the following sources: UKCRN Portfolio, ClinicalTrials.gov and Current Controlled Trials MetaRegister.

Search terms included text word and index terms for Infliximab, Remicade and ulcerative colitis. (See search strategies below)

On-going studies

The following sources were searched for on-going studies:
UKCRN Portfolio, ClinicalTrials.gov and Current Controlled Trials metaRegister (all accessed 17/04/2008). Search terms included Infliximab, Remicade and ulcerative colitis.

Systematic Reviews

Cochrane Library 2008 Issue 1

#1 infliximab or remicade

#2 ulcerative next colitis

#3 MeSH descriptor Colitis, Ulcerative,

#4 (#2 OR #3)

#5 (#1 AND #4)

MEDLINE (Ovid) 1950 - 2008

1 (infliximab or remicade).mp.

2 ulcerative colitis.mp.

3 colitis, ulcerative/

4 2 or 3

5 1 and 4

6 limit 5 to yr="2007 - 2008"

[Set 6 browsed for reviews]

EMBASE (Ovid) 1980 to 2008

1 (infliximab or remicade).mp.

2 ulcerative colitis.mp.

3 ulcerative colitis/

4 2 or 3

5 1 and 4

6 limit 5 to ("reviews (1 term high specificity)" and yr="2007 - 2008")

MEDLINE In-Process & Other Non-Indexed Citations April 14, 2008 (Ovid)

1 (infliximab or remicade).mp.

2 ulcerative colitis.mp.

3 1 and 2

Randomized Controlled Trials

Cochrane Library 2008 Issue 1

See strategy above

MEDLINE(Ovid)1950 - 2008

1 (infliximab or remicade).mp.
2 ulcerative colitis.mp.
3 colitis, ulcerative/
4 2 or 3
5 1 and 4
6 limit 5 to yr="2007 - 2008"
7 randomized controlled trial.pt.
8 controlled clinical trial.pt.
9 randomized.ab.
10 placebo.ab.
11 clinical trials as topic.sh.
12 randomly.ab.
13 trial.ti.
14 or/8-14
15 humans.sh
16 14 and 15
17 6 and 16

EMBASE (Ovid) 1980 - 2008

1 (infliximab or remicade).mp.
2 ulcerative colitis.mp.
3 ulcerative colitis/
4 2 or 3
5 1 and 4
6 limit 5 to yr="2007 - 2008"
7 crossover procedure/
8 double blind procedure/
9 randomized controlled trial/
10 single blind procedure/
11 (random$ or factorial$ or crossover$ or cross over$).tw.
12 (placebo$ or assign$ or allocat$ or volunteer$).tw.
13 (doubl$ adj blind$).tw.
14 (singl$ adj blind$).tw.

15 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14

16 6 and 15

MEDLINE In-Process & Other Non-Indexed Citations April 14, 2008 (Ovid)
See strategy above.

Economic evaluations and models

Cochrane Library (NHS EED) 2008 Issue 1
See strategy above

MEDLINE(Ovid) 1950 - 2008

1 (infliximab or remicade).mp.

2 ulcerative colitis.mp.

3 colitis, ulcerative/

4 2 or 3

5 1 and 4

6 economics/

7 exp "costs and cost analysis"/

8 cost of illness/

9 exp health care costs/

10 economic value of life/

11 exp economics medical/

12 exp economics hospital/

13 economics pharmaceutical/

14 exp "fees and charges"/

15 (econom$ or cost or costs or costly or costing or price or pricing or pharmacoeconomic$).tw.

16 (expenditure$ not energy).tw.

17 (value adj1 money).tw.

18 budget$.tw.

19 or/6-18

20 5 and 19

21 limit 20 to yr="2007 - 2008"

22 from 21 keep 1-2

23 decision support techniques/
24 markov.mp.
25 exp models economic/
26 decision analysis.mp.
27 cost benefit analysis/
28 economic model$.mp.
29 monte carlo method$.mp.
30 monte carlo.mp.
31 exp decision theory/
32 (decision$ adj2 (tree$ or analy$ or model$)).mp.
33 or/23-32
34 5 and 33

EMBASE (Ovid) 1980 - 2008

1 (infliximab or remicade).mp.
2 ulcerative colitis.mp.
3 ulcerative colitis/
4 2 or 3
5 1 and 4
6 "Cost Benefit Analysis"/
7 cost minimization analysis/
8 cost utility analysis/
9 economic evaluation/
10 (costs or cost or costed or costly or costing).tw
11 (economic$ or pharmacoeconomic$ or price$ or pricing).tw.
12 (technology adj assessment$).tw.
13 6 or 7 or 8 or 9 or 10 or 11 or 12
14 5 and 13
15 limit 14 to yr="2007 - 2008"
16 from 15 keep 1,5
17 from 16 keep 1-2
18 decision support techniques/
19 markov.mp
20 exp models economic/

21 decision analysis.mp.
22 cost benefit analysis/
23 economic model$.mp.
24 monte carlo.mp.
25 exp decision theory/
26 (decision$ adj2 (tree$ or model$)).mp.
27 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26
28 5 and 27
29 limit 28 to yr="2007 - 2008"

Quality of life for ulcerative colitis

MEDLINE (Ovid) 1950 -2008

1 ulcerative colitis.mp.
2 colitis, ulcerative/
3 1 or 2
4 quality of life/
5 life style/
6 health status/
7 health status indicators/
8 value of life/
9 quality adjusted life.mp.
10 or/4-9
11 3 and 10
12 limit 11 to yr="2007 - 2008"

Appendix 10: Quality Assessment using ScHARR-TAG economic modelling checklist (to be updated)

Title

Remicade® in the treatment of acute ulcerative colitis in England and Wales.

A statement of the problem

Yes, a statement of the problem has been given.

A discussion of the need for modelling

Yes, the need for modelling was determined.

A description of the relevant factors and outcomes

Yes, outcomes and relevant factors of the study has been reported and discussed.

A description of model including: type of model; time frame; perspective; and setting

The submission included a description of the type of the model, time frame, and perspective. The setting of the study was clearly specified – the study focuses on the acute population, likely to require hospitalisation.

A description of data sources, with description of respective strengths and weaknesses

Data sources and respective strengths and weakness were reported and described.

Key assumptions relating to model structure and data stated

A list of key assumptions was given.

Validation

A list of measures undertaken to validate and check the model were reported.