NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

Overview

Infliximab and adalimumab for the treatment of Crohn's disease

The overview is written by members of the Institute's team of technical analysts. It forms part of the information received by the Appraisal Committee members before the first committee meeting. The overview summarises the evidence and views that have been submitted by consultees and evaluated by the Assessment Group, and highlights key issues and uncertainties. To allow sufficient time for the overview to be circulated to Appraisal Committee members before the meeting, it is prepared before the Institute receives consultees' comments on the assessment report. These comments are therefore not addressed in the overview.

A list of the sources of evidence used in the preparation of this document is given in appendix A.

1 Background

1.1 The condition

Crohn's disease is a chronic inflammatory condition of the gastrointestinal tract (gut) that may affect any part of the gut from the mouth to the anus. It has a particular tendency to affect the terminal ileum and ascending colon (ileocolic disease). People with Crohn's disease have recurrent attacks, with acute 'flares' of the disease interspersed with periods of remission or less active disease. These 'flares' may affect any part of the gut. They may be defined by location (terminal ileal, colonic, ileocolic, upper gastrointestinal), or by the pattern of the disease (inflammatory, fistulising, or stricturing).

In Crohn's disease the lining of the affected area of the gut is inflamed and may be ulcerated, with thickening of the wall of the intestine. The clinical features of Crohn's disease are variable and are determined partly by the site of the disease. The symptoms of Crohn's disease include diarrhoea,

abdominal pain and weight loss. Constitutional symptoms include malaise, lethargy, anorexia, nausea, vomiting and low-grade fever.

Crohn's disease can be complicated by the development of strictures (a narrowing of the intestine), obstructions, fistulae and perianal disease. Fistulae develop in 17–43% of people and are characterised by the formation of an abnormal connection between areas of the intestine or adjacent organs. Perianal disease includes fissures, fistulae and abscesses. Other complications of Crohn's disease include acute dilation, perforation and massive haemorrhage, and carcinoma of the small bowel or colon.

The prevalence of Crohn's disease in the UK is estimated to be about 50–100 per 100,000 people in the population, and it affects approximately 60,000 people. The incidence of Crohn's disease is greatest in people aged between 15 and 30 years. However, it may affect people of any age: 15% of people with the disease are older than 60 years at diagnosis and 20–30% are younger than 20 years. Mortality among people with Crohn's disease is only slightly higher than that in the general population.

A number of activity indices have been developed to assess the severity of Crohn's disease. The Crohn's disease activity index (CDAI) is one of the most frequently used indices. The index consists of eight variables related to the disease (number of liquid stools, daily abdominal pain, general wellbeing, extraintestinal complications, use of antidiarrhoeal drugs, abdominal mass, haematocrit and body weight); a full description is available on pages 28–29 of the assessment report. These variables are weighted according to their ability to predict disease activity. The total score ranges from 0 to 600. A CDAI score below 150 is considered remission. Moderate-to-severe active disease is defined as a CDAI score above 220. Severe active disease is defined as a CDAI score above 300. The PCDAI is a paediatric equivalent to this score and its means of classifying remission and active disease are comparable with those used for the CDAI.

The perianal disease activity index (PDAI) was developed to account for the morbidity and impairment of quality of life of patients with perianal disease, and to evaluate the effectiveness of treatment of perianal disease. Variables measured include discharge, pain during or restriction of activities, restrictions of sexual activity, type of perianal disease (including number of fistulae) and degree of induration (hardening of the tissue). Scores range from 0 to 20.

The inflammatory bowel disease questionnaire (IBDQ) is a health-related quality of life (HRQL) measure. It is a 32-item questionnaire and evaluates four-dimensions of quality of life: bowel function, emotional function, systemic function and social function. Scores range from 32 to 224.

1.2 Current management

Crohn's disease cannot be cured by either medical or surgical means. Treatment is aimed at reducing symptoms to maintain or improve quality of life while minimising short- and long-term toxicity.

Clinical management is dependent on the disease activity, site and pattern (inflammatory, stricturing, fistulising), response to previous medications, side-effect profile of medications, and extraintestinal manifestations. Because Crohn's disease is unpredictable in nature, successful treatment is focused on achieving and maintaining clinical remission.

Current treatment includes aminosalicylates, corticosteroids, immunosuppressants, tumour necrosis factor alfa (TNF-α) inhibitors, antibiotics and supportive agents, and dietary measures. Corticosteroids are typically used for short-term (4–8 weeks) treatment of active Crohn's disease. In severe active disease, hospital admission and intravenous administration of corticosteroids may be required. There is evidence that despite a good response, a proportion of patients will become resistant to corticosteroid treatment. Some others become dependent on corticosteroids, relapsing once the dose is reduced or treatment stopped.

Azathioprine and 6-mercaptopurine are widely used in the management of active Crohn's disease. Treatment with these drugs is associated with the risk of bone marrow suppression and pancreatitis, which necessitates patient monitoring.

Between 50 and 80% of patients with Crohn's disease will require surgery at some stage. The main reasons for surgery are:

- strictures causing blockages in the gut
- failure to respond to medical therapy
- complications such as fistulae and perianal disease.

Maintenance therapy after surgical resection has been shown to prolong remission of the disease. Without maintenance therapy, symptoms recur in approximately 35% of patients within 5 years and in approximately 73% of patients within 20 years

The National Institute for Health and Clinical Excellence (NICE) previously published guidance on the use of infliximab for the treatment of Crohn's disease (NICE technology appraisal 40). This guidance recommends the use of infliximab for the treatment of Crohn's disease in patients who fulfil all three of the following criteria:

- Patients who have severe active Crohn's disease (a CDAI score of 300 or more and a Harvey-Bradshaw index of 8/9 or above)
- Patients whose condition has not responded to treatment with immunomodulating drugs and corticosteroids, or who are intolerant to these treatments.
- Patients for whom surgery is inappropriate.

NICE technology appraisal 40 also states that treatment can be repeated for patients who have responded to the initial treatment course, but have then relapsed (episodic treatment). The full guidance is shown in appendix B.

2 The technologies

Table 1: Summary description of technologies

Non-proprietary name	Infliximab	Adalimumab
Proprietary name	Remicade	Humira
Manufacturer	Schering Plough Ltd	Abbott Laboratories Ltd
Dose	5 mg/kg given as an intravenous infusion over a 2-hour period. No evidence for continuing treatment after 2 weeks for non-responders. Responders: 1. Maintenance Additional infusions of 5 mg/kg at 2 and 6 weeks after the initial dose, followed by infusion of 5 mg/kg every 8 weeks 2. Re-administration If signs and symptoms recur an additional infusion of 5 mg/kg can be offered. **Fistulising active Crohn's disease** An initial 5 mg/kg infusion over a 2-hour period, to be followed by additional 5 mg/kg infusion doses at 2 and 6 weeks after the first infusion. If patient does not respond after 3 doses, no additional treatment with infliximab should be given. Responders: Additional infusions of 5 mg/kg every 8 weeks. Re-administration if treatment stopped in responders If signs and symptoms of the disease recur, followed by infusions of 5 mg/kg every 8 wks	80 mg (induction) at week 0 followed by 40 mg at week 2. Should be given in conjunction with corticosteroids. Can be given as monotherapy if intolerant to corticosteroids. For a more rapid response 160 mg (induction) at week 0, followed by 80 mg at week 2 can be used, with the awareness that the risk of adverse events is higher during induction. Some patients who experience a decrease in their response may benefit from an increase in dose intensity to 40 mg adalimumab every week. Some patients who have not responded by week 4 may benefit from continued maintenance therapy through to week 12. Continued therapy should be carefully reconsidered in a patient not responding within this time period. Maintenance 40 mg every other week via subcutaneous injection. Corticosteroids may be tapered in accordance with clinical practice guidelines. Re-administration If signs and symptoms recur, adalimumab can be re-administered. However, there is little evidence for re-administration after more than 8 weeks since the previous dose.
Acquisition cost (BNF edition 55)	Net price for a 100-mg vial = £419.62	Net price for a 40-mg prefilled syringe = £357.50

Tumour necrosis factor alfa (TNF-α) is a pro-inflammatory mediator. It is thought to play a role in the pathogenesis of Crohn's disease. Its over-expression is believed to be partly responsible for the chronic inflammatory processes in the intestinal tissue in many patients with Crohn's disease. Infliximab and adalimumab are monoclonal antibodies directed against TNF-α thereby inhibiting its action. The summaries of product characteristics indicate that the action of the drugs may be associated with the risk of tuberculosis, lymphoma, demyelination and worsening heart failure. Treatment with TNF-α inhibitor monoclonal antibodies is associated with the production of antibodies that can cause allergic reactions and a loss of response to treatment.

Adalimumab is indicated for the treatment of severe active Crohn's disease in patients whose condition has not responded despite full and adequate treatment with an immunosuppressant and/or corticosteroid. Its marketing authorisation indicates that for induction therapy adalimumab should be administered in combination with corticosteroids. Adalimumab can be given as monotherapy if a patient has an intolerance to corticosteroids or when continued treatment with corticosteroids is inappropriate.

Infliximab is licensed for the following indications:

- Patients with severe active Crohn's disease, whose condition has not responded despite a full and adequate course of therapy with a corticosteroid and/or an immunosuppressant; or who are intolerant to or have medical contraindications for such therapies.

- Patients with fistulising, active Crohn's disease, whose condition has not responded despite a full and adequate course of therapy with conventional treatment (including antibiotics, drainage and immunosuppressive therapy).

- Children and adolescents aged 6 to 17 years with severe active Crohn's disease, whose condition has not responded to conventional therapy including a corticosteroid, an immunomodulator and primary

nutrition therapy; or who are intolerant to or have contraindications for such therapies.

The manufacturer of infliximab estimated that, of patients treated with infliximab for Crohn's disease, approximately 15% receive a single induction infusion only, 25% receive episodic treatment and 60% receive maintenance treatment. Episodic treatment involves infrequent infusions at irregular intervals; maintenance therapy involves regular dosing at intervals of 8 weeks after the induction doses. Information from the British Society of Gastroenterology (BSG) suggests that adalimumab is being reserved for those who are not suitable to continue infliximab treatment, because of either hypersensitivity reactions or loss of response to treatment. The BSG note that in clinical practice a proportion of patients will respond to 40 mg of adalimumab every other week. However, approximately 50–60% of patients will require dose escalation to 40 mg of adalimumab every week.

The United States Food and Drug Administration (FDA) is currently investigating the possible association between the use of TNF α inhibitors and the development of lymphoma and other cancers in children and young adults. The FDA is investigating approximately 30 reports of cancer in children and young adults. These reports were submitted to the FDA's adverse event reporting system over a 10-year interval. The FDA has asked the manufacturers of the TNF-α inhibitors approved for use in children (infliximab, etanercept and adalimumab) to provide information about all cases of cancer reported in children taking TNF-α inhibitors. The FDA has contacted medical experts to assess the potential association between TNF-α inhibitors and cancer, including lymphoma. They are also attempting to determine if there are children and young adults with juvenile idiopathic arthritis and Crohn's disease who may be at particular risk of developing lymphoma or other cancer.

2.1 Treatment schedules

The Assessment Group noted that the differentiation of treatment into induction, episodic and maintenance regimens was not straightforward.

Induction therapy can be defined as patients receiving treatment with TNF-α inhibitors for a short duration to get a favourable clinical response. In the clinical trials the definition of clinical response varied. However, the Assessment Group considered that in clinical practice the most suitable measure would be the achievement of remission.

Episodic treatment is characterised by infrequent infusions either set apart at long intervals or given as needed; that is, when a patient relapses. The Assessment Group considered that this was more clinically relevant than induction therapy and should be used in the de novo model.

Episodic treatment was defined differently depending on the setting. NICE technology appraisal 40 defined episodic treatment as giving treatment when a patient experiences a relapse. Maintenance treatment can be defined as patients receiving an induction dose and then continued doses of TNF-α inhibitors to maintain a response. However, other definitions were proposed in the clinical trials and in cost-effectiveness studies. It could mean any scheduled maintenance treatment, any continuing treatment (scheduled or episodic), or any treatment that includes an induction and maintenance phase.

3 The evidence

3.1 Clinical effectiveness

Twelve relevant randomised controlled trials (RCTs) were identified by the Assessment Group as meeting the criteria for the systematic review. The trials varied in type of treatment (induction or maintenance) and the population treated (severe active disease, fistulising disease and children) and are listed in table 2.

Table 2 Overview of included trials

Patient population	Induction	Maintenance
Severe active	CLASSIC I (adalimumab) GAIN (adalimumab) D'Haens et al. (1999) (infliximab) Targan et al. (1997) (infliximab)	CHARM (adalimumab) CLASSIC II (adalimumab) ACCENT I (infliximab) Rutgeerts et al. (1999) (infliximab)
Fistulising	Present et al. (1999) (infliximab)	ACCENT II (infliximab)
Paediatric	Baldassano et al. (2003) (infliximab)	REACH (infliximab)

The Assessment Group stated that it did not carry out a meta-analysis or indirect comparison because the trials differed significantly in design, end point and follow-up. There was also heterogeneity in the trial populations in terms of CDAI scores, the outcomes in the placebo group and the reporting of subgroup-only results at follow-up. Results from the trials were presented at several time points. The results described below relate to the last recorded event unless specified otherwise. The Assessment Group identified a Cochrane review which analysed maintenance therapy with TNF-α inhibitors for Crohn's disease. This review included all the maintenance trials in table 2 except for the two paediatric studies (REACH and Baldassano et al. 2003). The Cochrane review analysed the infliximab trial results (ACCENT I and Rutgeerts et al. 1999) by pooling all the treatment arms. The Assessment Group considered the pooling of the infliximab maintenance trials to be inappropriate given the difference in defining responders and previous exposure to infliximab. The Cochrane review states that the two studies evaluating adalimumab were evaluated separately due to heterogeneity between the two trials (that is CLASSIC II and CHARM).

3.2 Induction therapy

The induction-therapy trials included by the Assessment Group are summarised in table 3.

Table 3 Summary of trials of induction therapy in people with Crohn's disease

Drug	Trial	Population (size)	Length (weeks)	Withdrawal rate (%)	Dosage	Severity
Adalimumab	CLASSIC I	Active severe n = 299	4	5	Placebo 40 mg/ 20 mg 80 mg/ 40 mg 160 mg/ 80 mg	CDAI 220–450
	GAIN	Active severe n = 325	4	4	Placebo 160 mg/ 80 mg	
Infliximab	D'Haens et al. (1999)	Active severe n = 30	4	–	Placebo 5 mg/kg 10 mg/kg 20 mg/kg	CDAI 220–400
	Targan et al. (1997)	Active severe n = 108	4	0		CDAI 220–450
	Present et al. (1999)	Fistulising n = 94	12	6	5 mg/kg 10 mg/kg	Mean PDAI 9 Mean CDAI 192.9
	Baldassano et al. (2003)	Paediatric n = 21	12	10	1 mg/kg 5 mg/kg 10 mg/kg	PCDAI > 30 or modified CDAI > 200

CDAI, Crohn's disease activity index; PCDAI, paediatric Crohn's disease activity index; PDAI, perianal disease activity index.

A number of the trials included dosing schedules that do not reflect those specified in the marketing authorisations. However, the summaries of product characteristics for both infliximab and adalimumab allow for dose escalation. Therefore the results of these studies are included in this overview.

Patient populations were described as having moderate-to-severe Crohn's disease, with the exception of those in the study by D'Haens and coworkers (D'Haens et al. 1999) that included people with refractory active Crohn's disease. The Assessment Group noted that the marketing authorisations for infliximab and adalimumab specify severe Crohn's disease as the therapeutic indication, although the definition of severe is not given.

The infliximab trials excluded patients who had previous treatment with 'experimental' agents (D'Haens et al. 1999) or with monoclonal antibodies (Targan et al. 1997). Of the adalimumab studies, the CLASSIC I trial excluded patients treated previously with infliximab or another TNF-α inhibitor whereas the GAIN trial specifically included patients who were treated previously with infliximab and either lost response or had an intolerance to infliximab treatment.

3.2.1 Induction – severe active disease

Table 4 shows the rate ratios (intervention rate divided by placebo rate) for remission (CDAI score below 150) and for response 70 and 100 values (a 70-point and 100-point reduction, respectively, in CDAI score) for the induction trials in adults. All trials reported a significant decrease across all measures compared with placebo apart from the low-dose adalimumab arm (80 mg/40 mg) in the CLASSIC I trial for remission (RR 1.97 CI 0.95 to 4.11) and response 100 (RR 1.56 CI 0.97 to 2.51). For infliximab the high doses of infliximab (10 and 20 mg/kg) failed to reach statistical significance. The Assessment Group noted that in the study by Targan and coworkers estimates were associated with considerable uncertainty as indicated by the wide confidence interval, possibly as a result of the relatively small sample size.

Table 4 Induction trial results – severe active Crohn's disease

Trial	Week	Dose	Remission		Response 70		Response 100	
			RR	95% CI	RR	95% CI	RR	95% CI
CLASSIC I	4	80 mg/ 40 mg	1.97	0.95 to 4.11	1.61	1.13 to 2.29	1.56	0.97 to 2.51
	4	160 mg/ 80 mg	2.92	1.48 to 5.78	1.62	1.14 to 2.31	1.95	1.24 to 3.05
GAIN	4	160 mg/ 80 mg	2.96	1.59 to 5.51	1.53	1.18 to 1.98	1.55	1.12 to 2.16
Targan et al. (1997)	4	5 mg/kg	12.04	1.70 to 85.44	5.09	2.04 to 12.73	N/A	N/A
	4	10 mg/kg	6.25	0.83 to 47.34	3.13	1.18 to 8.26	N/A	N/A
	4	20 mg/kg	6.25	0.83 to 47.34	4.02	1.57 to 10.28	N/A	N/A
D'Haens et al. (1999)	4	5 mg/kg	N/A	N/A	N/A	N/A	N/A	N/A
	4	10 mg/kg	N/A	N/A	N/A	N/A	N/A	N/A
	4	20 mg/kg	N/A	N/A	N/A	N/A	N/A	N/A

The Assessment Group noted the variability in the outcomes seen in the placebo arms of the trials. An example of this is the remission rates, as shown in table 5. Similar results were obtained from other outcome measures.

Table 5 Proportion of patients achieving remission

Trial	Intervention remission (%)	Placebo remission (%)	Difference
CLASSIC I	24	12	12
GAIN	52	34	14
Targan et al. (1997)	48	4	44

The Assessment Group noted that the remission rate in the placebo arm of the study by Targan and coworkers was considerably lower than those seen in the adalimumab trials and the induction phase of the infliximab maintenance trials (Targan et al. 1997). Additionally the Assessment Group noted that the C-reactive protein (CRP) concentration in the placebo group was lower than that in the active treatment group in the study by Targan and coworkers. The impact of this difference was difficult to determine. The Assessment Group suggested that the low CRP concentration and low

remission rate in the placebo group may indicate an atypical placebo population stemming from the small sample size of the group.

The Assessment Group considered that the high and varied remission rates in the placebo group seen in the adalimumab trials and the induction phase of the maintenance trials (infliximab and adalimumab) could, to some extent, be attributed to three influences:

- patients being in relapse and the tendency with time (irrespective of treatment) for their condition to improve
- a placebo effect
- the effect of concomitant treatments allowed in the trials.

3.2.2 Induction – fistulising disease

One study directly examined induction therapy with infliximab in patients with fistulising disease (Present et al. 1999). Intestinal areas affected by Crohn's disease were mainly the ileum and the colon. The main concomitant medications were aminosalicylates, 6-mercaptopurine or azathioprine, corticosteroids and antibiotics.

The rate difference (rate for intervention minus the rate for placebo) from the trial for a greater than 50% reduction in the number of draining fistulae relative to baseline was 0.42 (95% CI 0.19 to 0.64) for 5 mg/kg infliximab and 0.30 (95% CI 0.07 to 0.54) for 10 mg/kg infliximab. For a secondary outcome of complete absence of fistulae for 5 mg/kg infliximab the rate difference was 0.42 (95% CI 0.21 to 0.63) and for 10 mg/kg infliximab it was 0.25 (95% CI 0.04 to 0.45). Infliximab resulted in statistically significant improvements in CDAI and PDAI scores at week 2. The statistical significance of the difference had disappeared by week 18, although there was still a difference in the scores.

The GAIN trial (in patients with severe active Crohn's disease) reported the effectiveness of adalimumab for fistula closure. At the end of follow-up

(4 weeks) similar rates of fistula improvements were recorded for the adalimumab and placebo groups (3 out of 20 and 5 out of 25, respectively).

The Assessment Group noted that infliximab maintenance therapy promoted fistula closure to a greater extent than placebo. However, it also noted that fistula closure may not always be the most desirable outcome as it may result in increased development of abscesses.

3.2.3 Induction therapy – children

One trial studied infliximab in children (aged 18 years or under) with Crohn's disease (Baldassano et al. 2003). Patients had moderate-to-severe active disease, with a PCDAI score of above 30. The median PCDAI score was between 41 and 56. The population does not exactly reflect the population stated in marketing authorisation, which includes those with severe disease only. Details on the randomisation and concealment of allocation were unclear. Patients were randomised to three different infliximab doses (1, 5 and 10 mg/kg) and there was no placebo arm.

The results are summarised in figure 29 on page 117 of the assessment report. All estimates were associated with great uncertainty due to the small number of participants. The proportion of patients whose condition responded to treatment (defined as at least 10 point reduction in PCDAI or at least 70 point reduction in modified CDAI score) approached 100% after 1 week in all groups and tended to decline during follow-up. For remission, no clear pattern relating to dose or length of follow-up was apparent. The results presented demonstrated that PCDAI decreased and response to treatment improved with infliximab. Please see table 38 on page 119 of the assessment report for more information.

The Assessment Group stated that the absence of a control arm meant that it was not possible to determine the contribution of infliximab to the observed results.

3.3 Maintenance therapy

The maintenance trials are summarised in table 6. The trials aimed to identify those patients who are still responders or in remission through time. However, the Assessment Group noted that in all four trials patients who were responders or in remission at any time are counted in the results. Therefore no information is provided on the amount of time individuals spend in remission.

For the ACCENT I, CHARM and ACCENT II trials the patients received treatment with the study drug during an induction period before randomisation was carried out. For the CLASSIC II study, patients were drawn from a previous study (CLASSIC I) but it was unclear to the Assessment Group whether responders could be drawn from the placebo group of the previous induction trial as well as from the infliximab arm. Both responders and non-responders were randomised in the ACCENT I and CHARM trials, whereas in the CLASSIC II and ACCENT II trials only those who had responded were included.

In CHARM and CLASSIC II, patients were given the opportunity to switch to open-label treatment in cases of sustained non-response or a disease flare. In ACCENT I, patients could cross over from placebo to episodic infliximab treatment from week 14. However, it was unclear if only responders were allowed to cross over. In addition, patients on scheduled infliximab treatment were allowed to cross over to episodic treatment. This meant that there were patients who had received episodic treatment (those who had received placebo and then infliximab) and those who had always received scheduled infliximab combined in the same arms. For a valid comparison the Assessment Group stated that patients needed to be re-randomised at week 14.

Table 6 Summary of maintenance trials

Trial	Duration (size)	Population	Induction	Maintenance dose	Time point for division into responders and non-responders	Subjects for randomisation	Definition of responder
CHARM	56 weeks n=778	CDAI 220–450	Week 2: adalimumab 80 mg subcutaneously followed by 40 mg dose	40 mg adalimumab weekly 40 mg adalimumab eow Not stated if placebo weekly or eow	Week 4	Responders and non-responders	Patient with CDAI score reduced by 70 points at week 4 relative to baseline
CLASSIC II	56 weeks n=55	Patient subgroup from CLASSIC I all patients in remission Mean CDAI: Placebo 107 Adalimumab eow 106 Adalimumab weekly 88	Week 2: adalimumab 80 mg subcutaneously, followed by 40 mg dose (after 4 weeks of CLASSIC I and further 4 weeks) All patients in remission	40 mg adalimumab weekly 40 mg adalimumab eow Not stated if placebo weekly or eow	Week 8	Responders only	Patient in remission (CDAI below 150) at week 0 and 4
Rutgeerts et al. (1999)	48 weeks n=73	CDAI 220–400 Median CDAI: Placebo 305 Infliximab 310	Either as in Targan et al.(1997) or during open-label extension of same trial	Placebo 10 mg/kg infliximab every 8 wks	Up to week 12	Responders only	Patient with CDAI score reduced by 70 points at week 8 relative to baseline
ACCENT I	54 weeks n=573	CDAI 200–450	Week 0: intravenous infusion of infliximab 5 mg/kg	Placebo 5 mg/kg infliximab every 8 wks 10 mg/kg infliximab every 8 wks	Week 2	Responders and non-responders	Patient with CDAI score reduced by 70 points at week 2 relative to baseline
ACCENT II	54 weeks n=282	Single or multiple draining fistulae for at least 3 months	Weeks 0, 2 and 6: infliximab 5 mg/kg	Placebo 5 mg/kg infliximab every 8 wks	Week 14	Responders and non-responders	50% reduction in draining fistulae relative to baseline observed at both weeks 10 and 14
REACH	54 weeks n=103	PCDAI above 30	Weeks 0, 2 and 6: infliximab 5 mg/kg	5 mg/kg infliximab every 8 wks 5 mg/kg infliximab every 12 wks	Week 10	Responders only	Patient with PCDAI score reduced by at least 15 points and who had a score of 30 or less at week 10
CDAI, Crohn's disease activity index; eow, every other week; PCDAI, paediatric Crohn's disease activity index.							

Details of follow-up in the six trials are summarised in table 7. The most common reasons for withdrawal were adverse events, lack of efficacy or worsening of disease, and withdrawal of consent. Lack of efficacy or worsening of disease was also the main reason for crossover. The Assessment Group noted that the maintenance trials did not report results for those whose condition did not respond to treatment, thereby possibly losing valuable information regarding the response to the treatment that was being studied.

Table 7 indicates that there was a relatively high level of crossover in the maintenance trials and therefore a low number of people completing the study in the arm they were originally randomised to. The high level of crossover meant that identifying the target population, the population of interest and the precise therapy provided was difficult.

None of the maintenance trials contained a true placebo arm and therefore the effectiveness of the treatments in comparison with placebo is unknown.

Table 7 Follow-up of patients in maintenance trials

Study	Responders/ non-responders	Withdrawals (%)	Crossover or switch to open label (%)	Loss to follow-up (%)	Completed as randomised (%)
CHARM	Responders and non-responders	35	32.5	–	32.5
	Responders only	29	–	–	38
CLASSIC II	NA	16	24	2	58
ACCENT I	Responders and non-responders	22	35	–	43
Rutgeerts et al. (1999)	NA	33	0	0	67
ACCENT II	Responders and non-responders	–*	34	–	–
	Responders only	–*	40	–	–
REACH		9	34	0	57
*Patients were followed for an average of 51 weeks;					

3.3.1 Maintenance – severe active disease

The results from the four relevant trials are summarised in table 8. Analysis of all patients of the ACCENT I trial indicated that the median decrease in CDAI score was 292 to 205 for placebo and 300 to 185 for infliximab. The difference in CDAI score reduction between the arms may have been due to crossover from the placebo arm to episodic infliximab treatment. There are no data on the time spent in remission.

Table 8 Maintenance trial results – severe active Crohn's disease

Trial	Dose schedule	Week	Remission		Response 70		Response 100	
			RR	95% CI	RR	95% CI	RR	95% CI
CHARM	40 mg eow	56	3.06	1.94– 4.84	2.44	1.69–3.52	2.51	1.71–3.67
	40 mg weekly	56	3.46	2.20– 5.45	2.78	1.94–3.99	2.90	1.99–4.22
CLASSIC II	40 mg eow	56	1.78	1.01– 3.13	1.09	0.76–1.58	1.42	0.8–2.28
	40 mg weekly	56	1.88	1.08–3.27	1.23	0.89–1.71	1.60	1.03–2.50
Rutgeerts et al. (1999)	10 mg/kg	48	1.81	–	1.70	–	N/A	N/A
ACCENT I	5 mg/kg	54	2.08	1.19– 3.61	2.46	1.50–4.05	N/A	N/A
	10 mg/kg	54	2.82	1.66–4.76	3.06	1.90–4.94	N/A	N/A
All compared with placebo. CI, confidence interval; eow, every other week; N/A, not applicable; RR, rate ratio.								

The Assessment Group carried out an analysis to determine the ability of the treatments to maintain remission in defined responders. For the ACCENT I trial the median time to treatment failure (defined as an increase in 70 CDAI points) was 133 days for placebo and 266 days for infliximab 5 mg/kg. In the CHARM trial, the median duration of remission for responders who achieved remission was 127 days for the placebo group, 378 days for the 40 mg/kg (every other week) group and greater than 392 days for the 40 mg/kg weekly group.

The Assessment Group considered that the separating of patients into responders and non-responders is only clinically meaningful if a response at the time of separation is a good prognostic tool for identifying those patients most likely to benefit from treatment. This requires the comparison of results for responders and non-responders. The usefulness of data produced only from responders is therefore questionable. The Assessment Group noted that in ACCENT I the decision to separate people into responders and non-responders at 2 weeks was based on the small trial by Targan and coworkers (see above). However, it was possible that people would respond at a later date. Data from ACCENT I suggested that a number of patients achieved remission after this point and therefore that defining responders after 2 weeks was probably premature and may not be clinically meaningful.

The Assessment Group noted that while the data suggest that the interventions were more effective at achieving maintenance of response than placebo, the benefit was accrued early in the trial period, and over time the rate difference decreased or remained stable.

The Cochrane review pooled data from the ACCENT I trial and the study by Rugeerts and coworkers. The results are shown in table 9. The review suggests that infliximab is associated with statistically significant improvements in remission, clinical response and sparing corticosteroid treatment. The Assessment Group noted that the trials differed in the patients' prior exposure to infliximab and in the selection of responders. The Assessment Group concluded that the pooling of these results was unlikely to be informative.

Table 9 Cochrane review results

	Trials pooled	Relative risk	95% CI	I^2
Clinical remission	Hanauer et al. (2002)[a] Rutgeerts et al. (1999)	2.50[b]	1.64 to 3.80	0%
Clinical response	Hanauer et al. (2002) Rutgeerts et al. (1999)	2.19[c]	1.27 to 3.75	59.9%
Corticosteroid sparing	Hanauer et al. (2002)	3.13[b]	1.25 to 7.81	N/A

[a] Published article on ACCENT I trial.

[b] Fixed effects model.

[c] Random effects model.

I^2 indicates the percentage of total variation across studies that is due to heterogeneity rather than chance. A value of 0% indicates no observed heterogeneity, and larger values show increasing heterogeneity.

3.3.2 Maintenance – fistulising disease

The Assessment Group identified one trial of infliximab maintenance therapy for patients with fistulising disease (ACCENT II). However, one other trial in patients with severe active Crohn's disease also reported results of fistula closure. The Assessment Group reported that randomisation and blinding appeared adequate in the maintenance trial for patients with fistulising disease (ACCENT II). It was also considered balanced at baseline in terms of CDAI, IBDQ and number of men or women. Data were censored before crossover occurred. Patients could cross over from placebo to treatment, or to a higher dose from week 22. Approximately 40% crossed over from placebo to receive 5 mg/kg infliximab. The trial population reflected the marketing authorisation. Main concomitant medications in both trials were aminosalicylates, 6-mercaptopurine or azathioprine, corticosteroids and antibiotics. The primary outcome was median time to loss of response in responders after randomisation. For placebo this was 14 weeks whereas for infliximab it was more than 40 weeks.

ACCENT II reported the rates of response (50% reduction in draining fistulae from baseline for at least two consecutive visits) and complete response (complete absence of draining fistulae). The results (in comparison with

placebo) for rate difference (rates for intervention minus rates for placebo) for responders only are summarised in table 10.

Table 10 Results from ACCENT II trial

Outcome	Week	Rate difference versus placebo	95% CI
Response	14	0.04	-0.04 to 0.12
	30	0.31	0.18 to 0.45
	54	0.21	0.08 to 0.34
Complete response	14	0.03	-0.10 to 0.16
	30	0.22	0.08 to 0.35
	54	0.17	0.04 to 0.29

The Assessment Group noted that most of the benefit of maintenance of response from active intervention was delivered between week 14 and week 30.

For non-responders in the placebo and intervention groups 16 and 21% respectively achieved a response. In ACCENT II the improvements in median CDAI and IBDQ were less than in ACCENT I study, but were statistically significant.

The Cochrane review noted the relative risk for fistula healing of 1.87 (95% CI 1.15 to 3.04) in ACCENT II.

CHARM reported on the effectiveness of adalimumab for fistula closure. In the CHARM trial, fistula remission at week 26 was reported for 30% (21/70) and 13% (6/47) of combined adalimumab group and the placebo group, respectively. At week 56 fistula remission was reported for 33% (23/70) and 13% (6/47), respectively.

The Assessment Group noted that the closure of fistulae did not necessarily lead to clinical improvements and may increase the number of abscesses. A post hoc analysis of patients participating in the ACCENT II trial found no significant difference in abscess incidence between two groups receiving different dosages of infliximab. The Assessment Group commented that

interpreting the results was problematical since there were no data on infliximab compared with placebo.

3.3.3 Maintenance therapy – children

One trial of maintenance therapy with infliximab was conducted in children (aged 18 years or under) (REACH). The trial population is described as having moderate-to-severe active disease, with a PCDAI score of above 30. The mean PCDAI score was between 40 and 42. The trial population does not exactly reflect the marketing authorisation (severe Crohn's disease). Patients previously treated with infliximab or another TNF-α inhibitor were excluded.

All patients initially received infliximab during an induction period and responders were then randomised at week 10. Patients could cross over to receive treatment more frequently or at a higher dose. Nine percent of patients withdrew and 34% crossed over or switched to open label.

The Assessment Group could not assess the treatment benefit of infliximab in children relative to standard care because there was no control arm in the studies. The results presented demonstrated that CDAI and PCDAI scores both decreased and response improved. Please see table 37 on page 116 of the assessment report for more details. The more frequent dosage regimen (infliximab 5 mg/kg every 8 weeks) resulted in statistically significant greater rates of response and remission compared with the less frequent dosage (infliximab 5 mg/kg every 12 weeks).

3.4 Adverse events

The Assessment Group found little difference between the placebo and treatment arms for selected adverse events. Please see page 124 of the assessment report for full details. The Assessment Group was also unable to conclude if one treatment was more likely to result in the production of antibodies. There is some evidence to suggest that episodic treatment with infliximab may lead to the production of fewer antibodies. However, the trial data were not randomised and it is uncertain how robust the results are. See pages 129–132 of the Assessment Group report for more details.

3.5 Additional quality of life data

The National Association for Colitis and Crohn's disease carried out a survey of its members who had experience of treatment or have been refused treatment with 'biological' drugs (infliximab and adalimumab) for Crohn's disease. The questionnaire consisted of sections concerning experiences of treatment and also an EQ-5D questionnaire where the person described their current quality of life (representing post-treatment) and were asked to recall their quality of life before treatment. The main outcomes of this survey were that the majority of the people who responded reported an improvement in their quality of life that was generally long lasting.

3.6 Cost effectiveness

3.6.1 Published literature

The Assessment Group identified four published economic analyses. All four studies examined infliximab. One study considered non-fistulising and fistulising disease, two considered non-fistulising disease only and one considered fistulising disease only.

The studies made extensive use of an epidemiological model constructed by Silverstein and coworkers (Silverstein et al. 1999). The model is based on 24 years of data (collected from 1970 to 1993) from 174 patients with Crohn's disease from Minnesota, USA. It includes patients with mild-to-severe Crohn's disease. Patients were TNF-α inhibitor naïve and did not receive any TNF-α inhibitors during the study. Patients did receive treatment with corticosteroids, immunosuppressants and 5-aminosalicylate. The model includes seven states (remission, mild disease, drug-responsive severe disease, drug-dependent severe disease, drug-refractory severe disease, surgery and postsurgical remission) plus death.

Taken together, the four economic analyses identified by the assessment group suggest that for all patient groups and dosing schedules infliximab has relatively high incremental cost-effectiveness ratios (ICERs) of above £50,000 per QALY gained in non-fistulising disease and £100,000 per QALY gained in

fistulising disease. For full details please see the pages 148–154 of the assessment report.

3.6.2 Schering Plough economic model – infliximab

The manufacturer of infliximab submitted a Markov model which compared infliximab with standard care in patients with severe active Crohn's disease (defined as a CDAI score of 220–400) or fistulising disease, and in paediatric populations, over a 5-year period. Two infliximab dosing schedules were modelled: maintenance therapy and infliximab clinical discretion. Infliximab clinical discretion corresponds to episodic treatment, although the Assessment Group noted that the definition doesn't guarantee the use of episodic treatment or rule out the use of maintenance treatment. Maintenance was modelled as 5 mg/kg at weeks 0, 2 and 6 and every 8 weeks thereafter. In the infliximab clinical discretion schedule, people received an induction dose of 5 mg/kg at week 0 and thereafter 5 mg/kg infliximab according to clinical discretion.

Health states included in the model were remission, on-treatment active, non-responding active, surgery, postsurgery remission, postsurgery complications and death. In addition to these states, the fistulising model expanded the 'active' state into four additional states (active + fistula closure, active + fistulae, remission + fistula closure and remission + fistulae). In the model all patients start in the on-treatment state. Response is determined after 2 weeks; if patients respond, they stay on treatment. Patients can achieve remission at any point while on treatment. If patients do not respond or stop treatment they cannot receive treatment for the duration of the model.

Estimates of the effectiveness of infliximab were derived from the individual arms of several trials which are summarised in tables 11 and 12. The placebo arms represented standard care.

Table 11 Trial arms used in economic models of severe active and fistulising disease

	Severe active			Fistulising	
Weeks	**Placebo**	**ICD**	**Maintenance**	**Placebo**	**Maintenance**
0–2	Targan et al. (1997) (placebo)	Targan et al. (1997) (treatment)	Targan et al. (1997) (treatment)	Present et al. (1999) (placebo)	Present et al. (1999) (treatment)
2–14	ACCENT I (placebo)	ACCENT I (treatment)	ACCENT I (treatment non-crossover)	Present et al. (1999) (placebo)	Present et al. (1999) (treatment)
14–54	ACCENT I (placebo non-crossover)	ACCENT I (treatment)	ACCENT I (treatment non-crossover)	ACCENT II (placebo non-crossover)	ACCENT II (treatment non-crossover)
ICD, infliximab clinical discretion.					

Table 12 Trial arms used in the paediatric economic models

Weeks	**Placebo**	**Weeks**	**Treatment**
0–2	Targan et al. (1997) (placebo)	0–2	Targan et al. (1997) (treatment)
2–14	ACCENT I (placebo)	2–10	REACH
14–54	ACCENT I (placebo non-crossover)	10–54	REACH (patients remaining on 8-weekly doses)

Data on rates of surgery and recurrence for patients with fistulising disease, were estimated from the literature and confirmed by clinical opinion. Surgery and recurrence rates for children were assumed to be equal to that for adult patients.

Costs were derived from published studies. Administration costs for infliximab (£96) were taken from a health technology assessment report for a previous NICE appraisal (Technology appraisal no.104: Psoriatic arthritis - etanercept and infliximab). Health-related utilities were derived from a variety of sources, including a published study of EQ-5D in Spanish patients with severe active Crohn's disease (using UK-based valuations) and a database of EQ-5D data from observational studies. The manufacturer noted that HRQL data were available for patients with fistulising disease and that these were significantly higher values (better quality of life) than those for patients with severe active

Crohn's disease. The manufacturer stated that this was not clinically reasonable. In addition, the manufacturer noted that the HRQL data for fistulising disease were collected in Crohn's disease patients and healthy individuals. Therefore, the manufacturer used the utility data from patients with severe active Crohn's disease and applied a decrement of 0.15 to represent presence of fistulae instead. The derivation of this figure was not discussed. The results of the cost-effectiveness analysis are presented in table 13.

Table 13 Results from the Schering Plough economic model

Patient population	Costs (£)	QALYs	ICER (per QALY gained)
Severe active			
Standard care	26,209	1.959	Dominated
ICD	25,501	2.133	–
Maintenance	31,040	2.145	£437,400
Fistulising			
Standard care	30,577	2.247	–
Maintenance	36,626	2.449	£30,000
Paediatric			
Standard care	27,672	2.146	–
Maintenance	33,504	2.566	£13,900
ICD, infliximab clinical discretion; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year.			

The Assessment Group noted that the model for severe active Crohn's disease relied heavily on the data from the ACCENT I trial. The Assessment Group expressed concerns about the use of data from the ACCENT I trial because the placebo arm included treatment with infliximab in non-responders and dose escalation was allowed for non-responders in the infliximab arm. The Assessment Group therefore considered that clinical effectiveness of infliximab may have been incorrectly estimated. The Assessment Group noted that the average body weight assumed in the model (60 kg) was lower than seen in the trials (68 to 74 kg), and so the cost of infliximab would be an underestimate.

With reference to the models of the population with fistulising disease and the paediatric population, the Assessment Group commented on the small trials used and the arbitrary time point used to identify responders and non-responders. The Assessment Group could not identify the source of the utility decrement applied to fistulising disease. The Assessment Group noted that the paediatric model contained numerous errors and could not be analysed effectively. The Assessment Group also noted that the cost-effectiveness acceptability curves that accompanied the analyses had been miscalculated.

In response to the Assessment Report, Schering Plough presented an updated analysis of data from paediatric patients aged 6 to 17 years. This differed from the original as the treatment costs were updated and the probabilistic sensitivity analysis was corrected. The calculation of infliximab costs included an assumption of progressive weight gain. This progression was linear from 40 kg to 60 kg at adulthood. The new analysis also examined two scenarios in addition to the base case. In 'scenario A' after the trial period of 54 weeks all patients were assumed to be off treatment and therefore switch to standard care. In 'scenario B' all efficacy data were based on the REACH trial. This was conducted to explore the uncertainty around extrapolating clinical data from adults to children. However, in REACH all patients received infliximab and therefore the less frequent dose arm (infliximab 5 mg/kg every 12 weeks) was assumed to represent standard care. The manufacturer stated that this represented a highly conservative possibility. These analyses have not been independently reviewed or checked by either the Assessment Group or the NICE technical team.

3.6.3 Abbott economic models – adalimumab

Abbott produced two economic models, one comparing the cost effectiveness of adalimumab as maintenance therapy with standard care, and one comparing the cost effectiveness of adalimumab with infliximab both given as maintenance therapies. The baseline age of patients in the model was 37 years and total life expectancy was assumed to be 66 years. The model is composed of four health states based around CDAI score: remission (CDAI

< 150), moderate (150 ≤ CDAI < 300), severe (300 ≤ CDAI < 450) and very severe (CDAI ≥ 450).

The adalimumab arm of the models was based on data from the CHARM trial, where 56-week data were extrapolated to a lifetime time horizon and the standard care arm was based on a regression of the CLASSIC I trial results. The models compared the 40 mg adalimumab (every other week) regimen with standard care. The models presented results for moderate and severe Crohn's disease and severe disease only (adalimumab has marketing authorisation for severe disease only). These populations were defined using the observed CDAI scores from the CLASSIC I and CHARM trials.

Health-related utilities were based on a re-analysis of a published study by Gregor and coworkers (Gregor et al.1997). Health-related utility values were obtained from 180 Canadian patients with Crohn's disease using a variety of different elicitation methods. The Abbott models used values obtained using the standard gamble method to obtain valuations of patients' own or hypothetical health states.

Costs excluding hospitalisation were estimated from a published cost-effectiveness study (Bassi et al. 2004). Since the disease states in this study were not identical to those in the study by Gregor and coworkers Abbott carried out a mapping exercise to calculate costs associated with the states. The results are presented in table 14.

Table 14 Results from the Abbott economic model for year 1

	Moderate and severe			Severe only		
	Adalimumab	Standard care	Difference	Adalimumab	Standard care	Difference
QALYs	0.8566	0.7743	0.0823	0.8384	0.7339	0.1045
Costs (£)	9,810	7,315	2,496	11,146	9,892	1,254
ICER (£ per QALY)			30,319			11,998
ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year.						

The manufacturer also presented sensitivity analyses. They used the last-value-carried-forward approach to missing data in the base case; the Assessment Group considered that this may be an optimistic assumption. The manufacturer presented results using the simulated placebo approach. Patients who left the CHARM trial did so because of disease flare or other issues requiring protocol-violating treatments, and so their health may have been poorer than an equivalent simulated standard care outcome. The Assessment Group considered the simulated placebo approach more neutral with respect to the prognosis of those leaving the CHARM trial. The manufacturer explored a variation of the extrapolation assumptions. It is assumed that patients who responded to adalimumab stayed on treatment for life in the base case. The manufacturer explored the results of relaxing this assumption and used drop-out rates from the 40 mg (every other week) arm of the CHARM trial. For the 56-week analysis this increased the ICERs for the 'severe only' group from £11,998 to £30,964 per QALY gained and for the 'severe and moderate group' from £30,319 to £56,621 per QALY gained. When the time horizon was increased from 56 weeks to 4 years this reduced the ICER for the moderate-to-severe group from £56,621 to £52,713 per QALY gained. If this was increased to a lifetime time horizon, the ICER fell to £24,385 per QALY gained.

The Assessment Group considered that the combination of these sensitivity analyses could underestimate adalimumab drug usage. However, it noted that the original analysis could overestimate adalimumab drug usage to a greater extent.

The Assessment Group noted concerns over the comparators used in the economic models. It considered that the standard care arm of the CHARM trial should have been used in the analysis of induction treatment, and a separate analysis carried out for maintenance treatment.

The Assessment Group commented that the trial data from CHARM suggested that patients who had not previously been treated with TNF-α inhibitor therapy had a better response to adalimumab. It therefore suggested

that adalimumab would be more cost effective in a TNF-α inhibitor naïve group.

Indirect comparison between infliximab and adalimumab

The manufacturer was unable to carry out a direct comparison because of a lack of evidence from the ACCENT I trial. Therefore the manufacturer simplified the model to examine the proportion of patients in remission and non-remission and the costs incurred. The result of this analysis was that adalimumab was more effective in achieving remission and was associated with lower costs than infliximab. The manufacturer therefore suggested that adalimumab dominated infliximab.

3.6.4 Assessment Group economic model

For the economic analysis the Assessment Group concluded that induction therapy was not useful as definition of the treatment schedule since it could not be straightforwardly distinguished from episodic therapy. This is because the decision to give the first induction course of treatment could not be divorced from future decisions to repeat treatment as needed (corresponding to episodic therapy). The Assessment Group therefore examined only TNF-α inhibitors given as required (episodic) and as scheduled treatment to maintain remission (maintenance) treatment for moderate and severe Crohn's disease.

The Assessment Group constructed a four-stage Markov model based on a reduced version of the Silverstein epidemiological model including only the following four health states (out of the original seven): remission, relapse, surgery and postsurgery remission (Silverstein et al. 1999).

All patients were assumed to start in the relapse state. Data from the Silverstein model were used to inform the course of the disease without TNF-α inhibitors. Infliximab and adalimumab were assumed to only affect the probability of a patient remaining in remission. The Assessment Group used data from the CLASSIC I trial (adalimumab) and the trial by Targan and coworkers (infliximab) to estimate the relative rate of remaining in remission for the episodic model. Data from the CHARM trial (adalimumab) and the

ACCENT I trial (infliximab) were used for the maintenance model. The Assessment Group noted that in the control arm of the trial by Targan and coworkers the remission rates were substantially lower than in the Silverstein data. They therefore used the data from the study by Silverstein and coworkers for the control arm in the infliximab analysis (Silverstein et al. 1999). The model did not assume differential rates of mortality since the Assessment Group did not identify any evidence of the condition impacting on mortality. The Assessment Group therefore adopted a 1-year time horizon (13 cycles).

Health-related utilities were taken from the study by Gregor and coworkers (time trade off utilities from 180 Canadian patients with Crohn's disease; Gregor et al. 1997), apart from the utility of major surgery which was based on the authors' assumption. The Assessment Group acknowledged that these were inconsistent with NICE's reference case since they did not use population-derived values and were from Canada. Costs were derived from NHS reference costs 2005–06. The exception was the cost of remission which came from the economic analysis by Bassi and coworkers (Bassi et al. 2004) indexed to present prices. Probabilistic sensitivity analysis was conducted. The results are presented in table 15.

Table 15 Cost-effectiveness results from Assessment Group model

	Standard care		TNF-α inhibitor		ICER (per QALY)
	Mean cost (£)	Mean QALY	Mean cost (£)	Mean QALYs	
Episodic					
Adalimumab moderate disease	6,687	0.964	6,405	0.977	Adalimumab dominates
Adalimumab severe disease	13,444	0.887	11,215	0.923	Adalimumab dominates
Infliximab moderate disease	6,858	0.965	10,010	0.994	£107,943
Infliximab severe disease	14,441	0.886	12,593	0.994	Infliximab dominates
Maintenance					
Adalimumab moderate disease	6,858	0.965	14,724	0.943	Standard care dominates
Adalimumab severe disease	13,447	0.886	22,177	0.827	Standard care dominates
Infliximab moderate disease	6,862	0.964	30,397	0.944	Standard care dominates
Infliximab severe disease	13,449	0.888	39,980	0.831	Standard care dominates

ICER, incremental cost-effectiveness ratio; TNF, tumour necrosis factor; QALY, quality-adjusted life year.

A sensitivity analysis exploring different time horizons was presented and suggested that if the time horizon was increased to 5, 10 or 20 years the conclusions of the analysis remained the same.

The Assessment Group considered that the estimates for maintenance therapy should be considered as exploratory because of the short placebo-controlled period for the trials. Therefore long-term efficacy would be subject to uncertainty.

Assessment Group analysis – fistulising disease

The Assessment Group did not conduct an analysis of fistulising disease because it did not identify any information on underlying disease progression. The Assessment Group concluded that in the absence of such evidence, the manufacturers' analyses provide the most appropriate estimates of cost effectiveness for patients with fistulising disease.

Assessment Group analysis – children

The Assessment Group stated that robust modelling of the cost effectiveness of TNF-α inhibitor therapy in a paediatric population was not possible because of a lack of placebo-controlled trials examining the effectiveness of infliximab in that population. The Assessment Group carried out a threshold analysis to determine the required effectiveness of infliximab. The Assessment Group stated that this analysis should be interpreted with caution as it extrapolated (non-drug) costs and utilities from adults to children. The Assessment Group stated that this was not a reasonable assumption since children are likely to require different services, such as carers, and have different priorities in terms of quality of life. The time horizon of the analysis was 1 year.

The Assessment Group altered the drug costs by accounting for the lower body weight of children. It carried out two analyses for between 40 kg and less than 60 kg, and between 20 kg and less than 40 kg. These analyses demonstrated that infliximab was not cost effective for maintenance therapy. If it was assumed that infliximab improved a child to full health (a full QALY) the Assessment Group concluded that infliximab still remained cost ineffective with ICERs of £539,333 to £193,328 per QALY gained for moderate and severe Crohn's disease, respectively. For induction treatment infliximab dominated standard care in children with severe Crohn's disease for all body weights. In the group of patients who weighed between 40 kg and less than 60 kg, infliximab had an ICER of £59,900 per QALY gained for moderate Crohn's disease. This fell to £51,071 per QALY gained when the effectiveness of infliximab was increased to returning people to full health. For the children who weighed between 20 kg and less than 40 kg, the ICER for children with moderate Crohn's disease was £13,573 per QALY gained. The Assessment Group investigated the cost effectiveness of the higher dose and concluded that infliximab was not cost effective for induction treatment with ICERs ranging from £746,902 to £231,002 per QALY gained for moderate and severe Crohn's disease, respectively. Standard care dominates infliximab for maintenance treatment.

Summary

Table 16 summarises the main cost effectiveness results from the submitted economic models. All the results are for severe active Crohn's disease patients and the time horizon is one year.

Table 16 Summary of incremental cost-effectiveness ratios compared with standard care

Model	Episodic		Maintenance		Fistulising	Paediatric episodic	Paediatric maintenance
	Infliximab	Adalimumab	Infliximab	Adalimumab			
Assessment Group	Dominates	Dominates	Dominated	Dominated	–	Dominates	Dominated
Schering Plough	Dominates	–	£25,900	–	£30,000	–	£13,900
Abbott	–	–	–	£12,000	–	–	–
Dominates: more effective and less expensive. Dominated: less effective and more expensive. ICERs: £ per QALY							

4 Issues for consideration

4.1 General

The Assessment Group were unable to compare adalimumab and infliximab because of the lack of direct trial evidence and the heterogeneity between the trial populations and designs. Can the Committee come to any conclusions on the relative effectiveness of the two treatments?

The Assessment Group noted that adalimumab would appear to be more cost effective in a TNF-α inhibitor naïve group than in those previously exposed to TNF-α inhibitors. Does the Committee believe that sequential use of TNF-α inhibitors would be clinically effective and cost effective?

The Assessment Group commented on the division of patients into responders and non-responders in the maintenance trials to determine response. In addition, the Assessment Group considered the various ways response had been defined and concluded that remission was the most clinically valid. Does the Committee consider response criteria appropriate and, if so, how should response be defined?

Episodic treatment

Various definitions of episodic treatment were suggested. What does the Committee consider to be an appropriate definition of episodic treatment?

The Assessment Group concluded that treatment with TNF-α inhibitors was clinically effective, and according to all the models both treatments are cost effective in patients with severe Crohn's disease. Can the Committee reach conclusions on the relative effectiveness of the two treatments?

Are the higher doses and more intensive treatment schedules for TNF-α inhibitors (for example, the 10 mg/kg infliximab dose) likely to be cost effective?

Maintenance therapy

Taking into account the characteristics of the clinical trials (the lack of data on sustained response, the division of patients into responders and non-responders and the high proportion of crossover), do they provide an accurate assessment of the effectiveness of TNF-α inhibitors as maintenance treatment?

The analyses submitted by the manufacturers and the Assessment Group produced different cost-effectiveness results for the assessment of maintenance therapy. One of the key differences arises from the use of the data from Silverstein and coworkers (Silverstein et al. 1999) to reflect the course of the disease (Assessment Group) compared with relying solely on the trial data (manufacturer).The data from Silverstein and coworkers contained results for patients defined as having mild Crohn's disease and who were treatment-naïve (Silverstein et al. 1999), which is not included in the marketing authorisation for either TNF-α inhibitor. However, the Silverstein data may include people on more effective maintenance therapy than those in the placebo arms of the trials. Which sets of results do the Committee think are most appropriate?

Fistulising disease

The Assessment Group noted that the manufacturer's model for fistulising disease used the assumption of an average body weight 60 kg and was based on a responder-only analysis of ACCENT II. Does the Committee consider that the manufacturer's estimate of cost effectiveness for patients with fistulising disease is appropriate?

The Assessment Group noted the infliximab trials in patients with fistulising disease indicated a statistically significant increase in fistula healing. The Assessment Group cautioned that this may not be a clinically desirable outcome since it can lead to an increase in abscesses. However, consultees considered fistula healing to be an important clinical outcome to improve patient's quality of life. Does the Committee consider that this is an appropriate subgroup to examine?

Children

The Assessment Group stated that it could not come to any conclusions on the clinical effectiveness of infliximab in children because of the absence of placebo-controlled trials. Does the Committee agree?

The Assessment Group's exploratory threshold analysis concluded that infliximab was not cost effective for maintenance therapy in children regardless of the clinical effectiveness assumed. It should be noted that this analysis was restricted to a 1-year time horizon, and that the ICER would decrease over a longer period under the assumptions used in this particular analysis. In light of this evidence and that submitted by the manufacturer, does the Committee think that infliximab is cost effective in children?

5 Ongoing research

There are two ongoing trials for infliximab in Crohn's disease. One is investigating the long-term efficacy and safety of infliximab and methotrexate in combination. The second is investigating a new combination of infliximab and azathioprine.

There are ongoing trials of adalimumab that are investigating its ability to induce mucosal healing in children. The CARE trial is investigating safety and tolerability and the CHOICE trial is evaluating patient-reported outcomes and health economic outcomes.

No head-to-head trials have been identified.

6 Authors

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Appendix A: Sources of evidence considered in the preparation of the overview

A The assessment report for this appraisal was prepared by West Midlands Health Technology Assessment Collaboration.

- Dretzke J, Edlin R, Hulme C, Connock M, Czeczot J, Fry-Smith A, McCabe C, Meads C, Use of tumour necrosis factor alpha (TNF a) inhibitors adalimumab and infliximab for Crohn's disease. Systematic review and economic evaluation. July 2008

B Submissions or statements from the following organisations:

I Manufacturer/sponsor

- Schering Plough Ltd
- Abbott Laboratories Limited

II Professional/specialist, patient/carer and other groups:

- National Association for Colitis and Crohn's disease
- British Society of Gastroenterology
- Royal College of Nursing
- Royal College of Physicians
- Bedfordshire PCT

III Commentator organisations (without the right of appeal):

- British National Formulary
- Department of Health, Social Services and Public Safety for Northern Ireland
- NHS Quality Improvement Scotland
- Dr Falk Pharma UK Ltd
- Novartis Pharmaceuticals Ltd
- Pfizer Ltd
- Procter and Gamble Pharmaceuticals (UK) Ltd
- Sanofi-Aventis Ltd
- UCB Pharma Ltd

C Additional references used:

Baldassano R et al. (2003) Infliximab (REMICADE) therapy in the treatment of pediatric Crohn's disease. American Journal of Gastroenterology. 98(4):833-838.

Bassi A et al. (2004) Cost of illness of inflammatory bowel disease in the UK: a single centre retrospective study. Gut. 53:1471-1478.

Behm BW, Bickston SJ (2008) Tumor necrosis factor-alpha antibody for maintenance of remission in Crohn's disease. Cochrane database syst Rev; (1): CD006893

D'Haens G et al. (1999) Endoscopic and histological healing with infliximab anti-tumour necrosis factor antibodies in Crohn's disease. Gastroenterology. 116:1029-1034.

Early communication about an ongoing safety review of tumor necrosis factor (TNF) blockers (marketed as Remicade, Enbrel, Humira, and Cimzia), Food and Drug Administration: http://www.fda.gov/CDER/drug/early_comm/TNF_blockers.htm, retrieved 23/07/2008

Gregor J et al. (1997) An evaluation of utility measure in Crohn's disease. Inflammatory Bowel Disease. 3:265-276.

Present DH et al. (1999) Infliximab for the treatment of fistulae in patients with Crohn's disease. New England Journal of Medicine. 340:1398-1405.

Rutgeerts P et al. (1999) Efficacy and Safety of retreatment with anti-tumor necrosis factor antibody (infliximab) to maintain remission in Crohn's Disease. Gastroenterology. 117:761-769.

Silverstein MD et al. (1999) Clinical course and costs of care for Crohn's disease: Markov model analysis of a population-based cohort. Gastroenterology. 117:49-57.

Targan S et al. (1997) A short term study of chimeric monoclonal antibody cA2 to tumour necrosis factor alpha for Crohn's disease. New England Journal of Medicine. 337(15):1029-1035.

Appendix B: "The clinical effectiveness and cost effectiveness of infliximab for Crohn's Disease", Technology Appraisal No. 40 guidance

1.1 Infliximab is recommended for the treatment of patients with severe Crohn's disease who fulfil all three of the following criteria:

- Patients who have severe active Crohn's disease. These patients will already be in very poor general health with weight loss and sometimes fever, severe abdominal pain and usually frequent (3–4 or more) diarrhoeal stools daily. They may or may not be developing new fistulae or have extra-intestinal manifestations of the disease. This clinical definition normally corresponds to a Crohn's Disease Activity Index (CDAI) score of 300 or more and a Harvey-Bradshaw Index of 8/9 or above (see Appendix D)

- Patients whose condition has proved to be refractory to treatment with immunomodulating drugs (e.g. azathioprine or 6-mercaptopurine, methotrexate) and corticosteroids, or who have been intolerant of, or experienced toxicity from, these treatments.

- Patients for whom surgery is inappropriate (e.g. because of diffuse disease and/or a risk of short bowel syndrome).

1.2 Treatment can be repeated for those patients who match the above criteria and have responded to the initial treatment course, but then relapsed. A decision about whether or not to re-administer infliximab after the first course or subsequently should be made only after discussion with the patient who has been fully informed of the potential risks and benefits of repeated therapy (episodic treatment).

1.3 Infliximab should be prescribed by a gastroenterologist experienced in the management of Crohn's disease.

1.4 Infliximab is not recommended for patients with fistulising Crohn's disease who do not have the other criteria for severe active Crohn's disease as detailed in section 1.1.