The Scottish Medicines Consortium (SMC) has completed its assessment of the above product and advises NHS Boards and Area Drug and Therapeutic Committees (ADTCs) on its use in NHS Scotland. The advice is summarised as follows:

**ADVICE:** following a full submission

**infliximab (Remicade®)** is not recommended for use within NHS Scotland for the treatment of moderately to severely active ulcerative colitis in patients who have had an inadequate response to conventional therapy including corticosteroids and 6-mercaptopurine or azathioprine, or who are intolerant to or have medical contra-indications for such therapies.

As rescue therapy, infliximab has been shown to reduce the rate of colectomy compared with placebo in two small studies. However its relative efficacy and long-term benefits compared to existing management options remain unclear. The manufacturer did not present a sufficiently robust economic case to gain acceptance by SMC.

Overleaf is the detailed advice on this product.

Chairman
Scottish Medicines Consortium
**Indication**
For the treatment of moderately to severely active ulcerative colitis in patients who have had an inadequate response to conventional therapy including corticosteroids and 6-mercaptopurine or azathioprine or who are intolerant to or have medical contra-indications for such therapies.

**Dosing information**
5mg/kg given as an intravenous infusion over 2 hours followed by additional 5mg/kg infusion doses at 2 and 6 weeks after the first infusion, then every 8 weeks thereafter. Continued therapy should be carefully reconsidered in patients who show no evidence of therapeutic benefit within this time period. The submitting company’s proposed dose for the treatment of acute exacerbations of ulcerative colitis is 5mg/kg as a three dose induction regimen. Treatment is to be initiated and supervised by qualified physicians experienced in the diagnosis and treatment of inflammatory bowel disease.

**Product availability date**
Licence extension approved 28 February 2006

**Summary of evidence on comparative efficacy**
Infliximab is a monoclonal antibody that binds to both soluble and transmembrane forms of the human tumour necrosis factor (TNF)α, thereby inhibiting its functional activity. TNFα is a pro-inflammatory cytokine that plays a key role in the pathophysiology of ulcerative colitis.

The submitting company has requested that SMC considers the use of infliximab in a subset of the licensed indication including only patients with acute exacerbations of ulcerative colitis. The proposed dose is 5mg/kg as a three-dose induction regimen to induce clinical response and remission i.e. as a rescue therapy.

Two double-blind, randomised, placebo-controlled phase III studies assessed the safety and efficacy of infliximab in patients with active ulcerative colitis and support the licensed indication. Eligible patients had moderately to severely active disease as defined by a baseline Mayo score of between 6 and 12 inclusive (score range 0 to 12); were ambulatory and not considered likely to undergo colectomy within 3 months and had endoscopic evidence of active colitis (endoscopy subscore ≥2) with an inadequate response to conventional therapies.

Since the studies were of similar design, they were analysed both separately and together. The results presented here are for the pooled analysis. Patients were randomised to receive infliximab 5mg/kg (n=242), infliximab 10mg/kg (n=242), or placebo (n=244) at weeks 0, 2 and 6 and then every 8 weeks thereafter. Stable doses of oral 5-aminosalicylates, corticosteroids and/or immunomodulators were permitted during the studies. The primary endpoint was the induction of clinical response (defined by a ≥30% and ≥3 point reduction in
the Mayo score accompanied by a decrease in the rectal bleeding subscore of \( \geq 1 \) or a rectal bleeding score of 0 or one, evaluated at 8 weeks. This primary endpoint was achieved in significantly more infliximab 5mg/kg patients (67%) and infliximab 10mg/kg patients (65%) than placebo patients (33%). Colectomy was included as an additional efficacy endpoint and up to 54 weeks was reported in 12% (28/242), 7.4% (18/242) and 15% (36/244) of infliximab 5 and 10mg/kg and placebo patients respectively. However, the study populations were at relatively low risk for colectomy and the effect of the licensed dose of infliximab (5mg/kg) was not statistically significant in reducing the incidence of colectomy compared to placebo.

The submitting company presented a systematic review of the literature on the use of infliximab and comparator (ciclosporin) in hospitalised patients with severe ulcerative colitis refractory, intolerant or contra-indicated to conventional therapy and their efficacies in terms of avoiding colectomy. This review included two randomised, double-blind, placebo-controlled studies of infliximab. The first study was conducted in 45 patients with acute moderately-severe to severe ulcerative colitis unresponsive to at least 4 days of intravenous corticosteroids. The study was designed to enrol 140 patients but due to slow enrollment, interim analysis was conducted earlier than planned and the study was stopped. Eligible patients had a fulminating colitis index \( \geq 8 \) on day 3 after starting intravenous corticosteroids or a Seo index on days 5, 6, or 7 >150 (indicating a severe or moderately severe attack of ulcerative colitis that was not responding to corticosteroids). They were randomised to receive a single dose of infliximab (5mg/kg, n=24) or placebo (n=21). Intravenous corticosteroids were continued and mesalazine-based therapy, azathioprine and antibiotic prophylaxis against opportunistic infections were also permitted. The primary endpoint was colectomy or death within 90 days after infusion. Colectomy was performed in significantly more placebo patients (67% - 14/21) than infliximab patients (29% - 7/24) corresponding to an odds ratio of 4.9 (95% confidence intervals [CI]: 1.4 to 17). There were no deaths.

In the second smaller study, 11 patients with severe active ulcerative colitis who were unresponsive to at least 7 days of corticosteroids (of which at least 5 days included intravenous administration) were randomised to receive a single dose of infliximab 5mg/kg (n=3), 10mg/kg (n=3), 20mg/kg (n=2) or placebo (n=3). Patients could continue on stable doses of 5-aminosalicylates, antibiotics, 6-mercaptopurine, azathioprine or anti diarrhoeals. The primary endpoint was treatment failure at 2 weeks after study drug infusion defined by at least one of the following criteria: failure to achieve a clinical response (modified Truelove and Witts score <10 and a 5-point reduction compared with baseline); received >60mg corticosteroids daily or ciclosporin or other immunomodulator because of no improvement or clinical worsening; underwent non-elective or elective colectomy or died as a result of ulcerative colitis. The study was designed to enrol 60 patients but was stopped early because of slow accrual. All three patients who received placebo underwent colectomy within 2 weeks and were considered treatment failures. Two of three patients treated with infliximab (5mg/kg) were considered treatment successes.

| Summary of evidence on comparative safety |

The safety profile of infliximab in the treatment of ulcerative colitis was similar to its established safety in other indications. The most common side effects were infections, including tuberculosis and opportunistic infections. Infliximab has been associated with acute infusion-related reactions, including anaphylactic shock, and delayed hypersensitivity reactions. Since anti-TNF therapy is suspected to have a potential tumour-promoting effect, infliximab could affect the risk of malignancy associated with ulcerative colitis. The Summary of Product Characteristics recommends that all patients with ulcerative colitis who are at increased risk, or have a history of dysplasia or colon carcinoma, should be screened for dysplasia at regular intervals before therapy and throughout their disease course.
Summary of clinical effectiveness issues

The two phase III studies, described briefly above, support the licensed indication for ulcerative colitis. The company subsequently applied to the European Medicines Agency to change the ulcerative colitis indication to reflect the reduction in the incidence of colectomy in the study patient populations. However this change was not approved as it was considered an outcome of treatment rather than an indication. In addition, the results from the phase III studies did not show sufficiently convincing effect with the approved dose of infliximab (5mg/kg).

In their submission to SMC, the submitting company only presented data on the efficacy of infliximab in hospitalised patients with moderately-severe to severe ulcerative colitis refractory, intolerant or contra-indicated to conventional therapy, in terms of avoidance of colectomy. Treated patients received one single dose of infliximab compared to the three doses proposed by the submitting company in this submission and the three doses followed by eight weekly maintenance recommended in the licence. Infliximab has been shown to be effective in reducing the rate of colectomy when used as rescue therapy in these patients. However the key studies included small numbers of patients and in the second of these studies described above only three patients were treated with the licensed dose of infliximab (5mg/kg). In both infliximab studies, recruitment was terminated early because of slow accrual and both studies are therefore likely to be underpowered.

The studies used colectomy or death at 3 months or treatment failure at 2 weeks as primary endpoints. While these outcomes are relevant to this patient population, they assessed efficacy in the short-term and it is unclear how long the effect of infliximab rescue therapy lasted. There is also uncertainty over subsequent management of a second acute exacerbation since the safety and efficacy of re-administering infliximab outwith the licensed schedule of 8 weekly maintenance has not been established. In addition, there is concern that the risk of delayed hypersensitivity reactions increases when the infliximab-free interval is increased.

Ciclosporin therapy, either orally or intravenously, is not licensed for the treatment of ulcerative colitis although it is recommended by the British Society of Gastroenterology guidelines and is noted in the British National Formulary.

There are currently no direct comparative data on the relative efficacy and safety of infliximab and ciclosporin in this patient population. The limited available data, with small patient numbers, makes the results of an indirect comparison between infliximab and ciclosporin uncertain. Results of two ongoing studies are awaited to clarify their relative effectiveness.

Summary of comparative health economic evidence

The manufacturer submitted a cost-utility analysis using a decision-tree modelling approach in patients with active severe ulcerative colitis experiencing an acute exacerbation requiring hospital treatment, who had not responded to 72 hours of initial intravenous corticosteroid therapy. The three-dose infliximab induction regimen was compared to three different comparators: ciclosporin; surgery; and continued use of intravenous corticosteroid treatment. The most relevant comparators are ciclosporin and the use of early surgery.

The treatment pathways and associated healthcare resource use over a 1-year time horizon for each option were based on the opinion of a panel of UK gastroenterologists. The
pathway consisted of a 0-3 month phase with inpatient infliximab or ciclosporin treatment in addition to intravenous corticosteroid treatment for 7 days followed by outpatient infliximab or ciclosporin treatment plus azathioprine and oral steroid therapy, then a 4-12 month phase with azathioprine and oral steroid therapy. Non-responders received surgical intervention (colectomy) and then remained in a state of surgical remission and so required no further treatment within the year period. In the economic analysis, the aim of infliximab and ciclosporin rescue therapy is to achieve symptom-free remission and avoid or delay the need for colectomy surgery and the cost and disutility associated with this. The evidence for the relative efficacy of infliximab and ciclosporin in terms of the probability of surgery was from an indirect comparison of placebo-controlled trials for these drugs, with placebo representing the baseline rate of surgery with intravenous corticosteroid therapy alone. This indicated a 0.48 probability of requiring surgery for ciclosporin compared to 0.23 for infliximab in months 0-3, but a higher probability for infliximab in months 4-12 (0.26 compared to 0.18). Utility estimates for active disease (0.42), remission (0.88) and surgical remission (0.60) were from a study using the EQ 5D in patients with ulcerative colitis who had recently been treated for an acute exacerbation (including recent colectomy), and utilities for surgical complications (0.42) were derived estimates. Costs and disutility associated with drug adverse events were not included in the analysis.

The cost-effectiveness of infliximab versus ciclosporin was estimated to be £19,836 per QALY gained (incremental cost of £1,279 and 0.06 QALY gain), whereas infliximab was estimated to ‘dominate’ the surgery option (lower net costs of £1,667 and 0.21 greater QALYs per patient). The cost-effectiveness results were sensitive to patient weight – reducing the base case weight used from 80kg to 70kg improved the cost-effectiveness of infliximab versus ciclosporin to about £12,000 (although this assumed infliximab vial sharing which may not be appropriate in practice). An important driver of cost-effectiveness was the unit cost of surgery and hospital stay (also for complications) which was based on ISD Scotland sources. Whilst this source can be considered appropriate, in sensitivity analysis the use of NHS reference costs for the same codes produced cost/QALY estimates versus ciclosporin and surgery of £44,714 and £12,966 respectively.

There were a number of key limitations and weaknesses with the economic analysis, especially in the comparison versus ciclosporin:

- The indirect comparison used short-term trials with small sample sizes, hence the relative efficacy of infliximab and ciclosporin in terms of probability of surgery especially in the medium (4-12 months) and longer-term (beyond 1 year), phases is highly uncertain.

- The appropriate time horizon is longer than 1 year. However, no data were available to estimate the long run impact of treatment. A 10-year time horizon was explored in sensitivity analysis and the results were highly sensitive to assumptions for the probability of requiring surgery beyond 1 year. A scenario where the longer-term probability of surgery was the same as that estimated in months 4-12 ie a continued treatment effect, produced a cost/QALY of £125,921 versus ciclosporin, but was dominant if it was assumed that no further surgery was required. A minimum treatment effect scenario in which all patients were assumed to undergo colectomy within the first 3 months after the first year resulted in infliximab being dominated by ciclosporin. In the comparison versus early surgery, the cost/QALY ranged from £21,536 to £43,551 for the continued treatment effect and minimum treatment effect scenarios respectively. In the (clinically very unlikely) case of no further surgery being necessary, the ICER was £938. No further sensitivity analysis was provided on the data inputs to the 10 year time horizon model.
• Although Scotland was represented on the UK gastroenterologist panel used for clinical pathway verification and resource use estimates it is unclear whether the estimates used (e.g. for surgery, hospitalisation) were relevant for Scottish clinical practice.

• There is some suggestion that patients treated with infliximab who go on to receive surgery have an increased risk of perioperative complications including infections. This has not been explored in the economic analysis.

• Sensitivity analysis for relative colectomy rate probabilities during the 1-year time horizon (especially for months 4-12) did not provide reassurance that the cost-effectiveness of infliximab versus ciclosporin would be within acceptable levels.

• There is some concern that the utility value for patients in surgical remission, while acceptable for the one year time horizon, may be too low for the longer term analyses given that patients may adjust to having a colectomy over time. Allowing for this may worsen the ICER versus surgery.

Given the high level of uncertainty, especially in the long run outcomes associated with treatment, the manufacturer did not present a sufficiently robust case to demonstrate cost-effectiveness.

Summary of patient and public involvement

A Patient Interest Group Submission was not made.

Additional information: guidelines and protocols

The British Society of Gastroenterology published guidelines in 2004 for the management of inflammatory bowel disease including Crohn’s disease and ulcerative colitis in 2004. This predates infliximab’s licence for the treatment of ulcerative colitis. The guidelines recommend that treatment of severe ulcerative colitis involves intravenous corticosteroids, immediate surgical referral in selected patients and consideration of colectomy or intravenous ciclosporin if there is no improvement during the first 3 days.

Additional information: comparators

According to the British Society of Gastroenterology guidelines, the most appropriate comparators are surgery or ciclosporin which is not licensed for use in ulcerative colitis.

Cost of relevant comparators

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose regimen</th>
<th>Cost per course (£)</th>
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<tbody>
<tr>
<td>Infliximab</td>
<td>5mg/kg intravenously at 0, 2 and 6 weeks</td>
<td>3777 to 5035*</td>
</tr>
<tr>
<td>Ciclosporin</td>
<td>2mg/kg/day intravenously for 7 days then oral ciclosporin 4mg/kg/day for 3 months</td>
<td>41 to 54 then 504 to 649 **</td>
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Doses are for general comparison and do not imply therapeutic equivalence. Costs from eVadis on 2 April 2009. * costs are based on an adult patient weighing 60 to 80kg and using a unit dose of 300 to 400mg. ** Ciclosporin is not licensed for the treatment of ulcerative colitis but is included as a treatment option in the British National Formulary No. 57; costs are based on an adult weighing 60 to 80kg.
Additional information: budget impact

The manufacturer estimated that the drug budget impact of infliximab would be £25k per annum, based on an assumption of an additional 5 patients per annum with acute ulcerative colitis exacerbations receiving treatment with infliximab after intravenous corticosteroid non-response. This represents 2% of all eligible patients, which is the current use of infliximab estimated according to 2006 IBD audit data. This estimate assumes no displacement of ciclosporin. Current ciclosporin use is estimated to be 14 patients – if 50% of this use were displaced the total net budget impact is estimated to be £61K per annum. In addition, net resource savings from reduced colectomies were estimated.
Advice context:

No part of this advice may be used without the whole of the advice being quoted in full.

This advice represents the view of the Scottish Medicines Consortium and was arrived at after careful consideration and evaluation of the available evidence. It is provided to inform the considerations of Area Drug & Therapeutics Committees and NHS Boards in Scotland in determining medicines for local use or local formulary inclusion. This advice does not override the individual responsibility of health professionals to make decisions in the exercise of their clinical judgement in the circumstances of the individual patient, in consultation with the patient and/or guardian or carer.

This assessment is based on data submitted by the applicant company up to and including 15 May 2009.

Drug prices are those available at the time the papers were issued to SMC for consideration. These have been confirmed from the eVadis drug database.

The undernoted references were supplied with the submission.

