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 accepted for restricted use within NHS Scotland.

**Indication under review**: Treatment of severely active ulcerative colitis in children and adolescents aged 6 to 17 years 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

**SMC restriction**: as an alternative to ciclosporin in patients with acute, severe paediatric ulcerative colitis (rescue therapy) who are steroid refractory.

Open-label, uncontrolled data indicate that infliximab induces remission of moderate to severe active ulcerative colitis in paediatric patients.

Overleaf is the detailed advice on this product.

Chairman,
Scottish Medicines Consortium
**Indication**
Treatment of severely active ulcerative colitis, in children and adolescents aged 6 to 17 years, 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.

**Dosing Information**
The induction phase comprises three intravenous infusions of 5mg/kg at weeks 0, 2 and 6. Maintenance infusions are administered every eight weeks thereafter. Available data do not support further infliximab treatment in paediatric patients not responding within the first eight weeks of treatment.

Infliximab treatment is to be initiated and supervised by qualified physicians experienced in the diagnosis and treatment of inflammatory bowel diseases. Infusions should be administered by qualified healthcare professionals trained to detect any infusion related issues. Patients treated with infliximab should be given the package leaflet and the special Alert card.

**Product availability date**
5 March 2012

**Summary of evidence on comparative efficacy**
Ulcerative colitis is characterised by diffuse mucosal inflammation of the colon. Common manifestations in children are blood loss, diarrhoea and abdominal pain. Severe acute ulcerative colitis is potentially life threatening. Infliximab is a monoclonal antibody that binds to both soluble and transmembrane forms of 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.

SMC has considered the use of infliximab for the treatment of moderately to severely active ulcerative colitis in adult 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 contraindications for such therapies. SMC issued not recommended advice for this indication in July 2009. This submission relates to an extension of the marketing authorisation in March 2012 to include use in children and adolescents aged 6 to 17 years. In this submission the company has requested that SMC considers infliximab for induction treatment (three doses) only, and when positioned for use as an alternative to ciclosporin in patients with acute, severe paediatric ulcerative colitis (rescue therapy) who are steroid refractory.

Evidence for this extension to the marketing authorisation is from one open-label study in paediatric patients,¹ with supportive data from two double-blind studies (ACT-1 and ACT-2) and one open-label study in adults.

The open-label paediatric study recruited 60 patients, aged 6 to 17 years, with biopsy-confirmed diagnosis of ulcerative colitis which was moderately to severely active (Mayo score 6 to 12 points,
including an endoscopy sub-score ≥2). Eligible patients had failed, or been intolerant of, adequate treatment with aminosalicylates, 6-mercaptopurine, azathioprine or corticosteroids.

In the initial eight-week induction of remission phase, all patients were assigned to treatment with infliximab 5mg/kg by intravenous (iv) infusion at weeks 0, 2 and 6. At baseline, all patients were receiving concomitant ulcerative colitis medication and the doses of corticosteroids and immunomodulators could be tapered and discontinued if clinically indicated, whilst other ulcerative colitis treatment remained stable. The primary outcome was clinical response at week 8, defined as a reduction in the Mayo score (range: 0 to 12, higher scores indicate more severe disease) of ≥30% and ≥3 points, with a rectal bleeding sub-score of 0 to 1 or a decrease of ≥1 points. It was pre-specified that the study would indicate efficacy if the lower limit of the 95% confidence interval (CI) for the proportion of patients achieving clinical response at week 8 exceeded 40%. This was based on pooled data from the ACT 1 and ACT 2 studies indicating that the upper limit of the 95% CI for the proportion of placebo-treated adults with a clinical response at week 8 was 39%. The proportion of patients who met the primary outcome was 73% (44/60), (95% CI: 62% to 84%), so efficacy was demonstrated. There were several secondary outcomes. At week 8, clinical remission, defined as Mayo score ≤2 with no individual sub-score >1, was achieved by 40% (24/60) patients; mucosal healing, defined as Mayo endoscopy sub-score of 0 or 1, was achieved by 68% patients (41/60); PUCAI clinical remission, defined as PUCAI score <10, was achieved by 33% (17/51) evaluable patients.

In the second, maintenance therapy phase of this study, 45 patients who had a clinical response at week 8 were randomised to receive infliximab 5mg/kg iv infusions every eight weeks or every twelve weeks, for one year. If the response at week 8 was subsequently lost, patients receiving 5mg/kg every eight weeks could increase to 10mg/kg every eight weeks. Patients receiving 5mg/kg every twelve weeks who lost response within eight weeks of the previous infusion could increase to 10mg/kg every eight weeks and those who lost response between eight and twelve weeks could change to 5mg/kg every eight weeks.

At week 54, PUCAI clinical remission was achieved by 38% (8/21) in the 8-weekly infliximab group versus 18% (4/22) in the 12-weekly infliximab group, p=0.146. Corticosteroid-free PUCAI clinical remission was achieved by five patients in the 8-weekly infliximab group and none in the 12-weekly infliximab group, (14 patients in each dosage group had been receiving corticosteroids at baseline). Overall, 8.3% (5/60) patients required colectomy within the 54 weeks after baseline: 13% (2/15) non-randomised patients, 4.5% (1/22) 8-weekly infliximab patients and 8.7% (2/23) 12-weekly infliximab patients.

The submission included supportive evidence from two similar double-blind phase III studies (ACT 1 and ACT 2), which recruited adults with moderately to severely active ulcerative colitis (baseline Mayo score 6 to 12, with endoscopy subscore ≥2) who were ambulatory, unlikely to undergo colectomy within three months and had an inadequate response to conventional therapies. Patients were randomised to iv infusion of infliximab 5mg/kg (n=242), infliximab 10mg/kg (n=242), or placebo (n=244) at weeks 0, 2 and 6, and then every eight weeks thereafter. Stable doses of oral 5-aminosalicylates and/or immunomodulators were permitted. Corticosteroids could be tapered to zero after week 8. The primary outcome was the same as for the paediatric study described above and was achieved in significantly more infliximab 5mg/kg patients (67%) and infliximab 10mg/kg patients (65%) than placebo patients (33%). An extension study that included 229 of 484 infliximab-treated patients from the ACT studies concluded that long-term treatment with infliximab for up to three additional years was effective and well tolerated.

Further supportive data was presented from an open-label study which recruited 115 adults with an acute severe flare of ulcerative colitis, Lichtiger score >10 points (>10 indicates severe disease; total range is 0 to 21), who had failed treatment with high-dose iv steroids and not previously received
ciclosporin or infliximab. They were randomised equally to ciclosporin (2mg/kg iv infusion daily for one week, then oral ciclosporin to day 98) or infliximab (5mg/kg iv infusion on days 0, 14, and 42). In both groups, azathioprine was started at day 7 in patients with a clinical response. The primary outcome was treatment failure defined as absence of a clinical response at day 7, a relapse between day 7 and day 98, absence of steroid-free remission at day 98 or a severe adverse event leading to treatment interruption, colectomy, or death. Treatment failure occurred in 60% (35/58) of patients on ciclosporin and 54% (31/57) of patients on infliximab (absolute risk difference 6% [95% CI: −7 to 19], p=0·52). Nine (16%) patients in the ciclosporin group and 14 (25%) in the infliximab group had severe adverse events.

Other data were also assessed but remain commercially confidential.*

**Summary of evidence on comparative safety**

The pivotal study did not reveal any new safety concerns; however, younger children (6 to 11 years) seem to have more adverse events, especially infections, than adolescents which may be due to more severe disease in the younger group. The young age of the patients and potentially longer disease and treatment duration, warrant increased caution regarding infliximab’s known safety profile including toxicity relating to colon dysplasia, malignancy and hepatosplenic T-cell lymphoma (HSTCL), which is usually fatal. All infliximab-related cases of HSTCL have been in patients with inflammatory bowel disease and most were reported in adolescent or young adult males. The European Medicines Agency (EMA) has restricted the indication to the most severely ill paediatric patients and recommends that infliximab be used as monotherapy in the paediatric population as HSTCL is more likely with concomitant use of azathioprine/6-mercaptopurine.

There is no comparative safety data for infliximab in children with ulcerative colitis. In the pivotal study, 95% (57/60) patients had adverse events and 23% (14/60) had serious adverse events. Other than worsening of ulcerative colitis, no serious adverse event was reported in more than one patient. Fewer patients in the 8-weekly group than the 12-weekly group discontinued study treatment because of adverse events: 14% (3/22) (one each for worsening of ulcerative colitis, alopecia and both cyanosis and dyspnoea) versus 26% (6/23) (all for worsening of ulcerative colitis), respectively. One non-randomised patient experienced severe neutropenia. One patient receiving infliximab 8-weekly developed the serious adverse event of lupus erythematosus syndrome after week 54.

Infections were reported in 52% (31/60) patients and serious infections in seven patients: 6.7% (1/15) non-randomised, 14% (3/22) receiving infliximab 8-weekly and 13% (3/23) receiving infliximab 12-weekly. The summary of product characteristics for infliximab recommends close monitoring for infections including tuberculosis before, during and for six months after treatment with infliximab and notes that infections have been reported in a higher proportion of paediatric than adult patients. Although not reported in the pivotal study, infliximab has been associated with acute infusion-related reactions, including anaphylactic shock, and delayed hypersensitivity reactions.


**Summary of clinical effectiveness issues**

Infliximab is the first anti-TNF medicine to be licensed in the UK for use in children and adolescents with ulcerative colitis. The submitting company has requested that SMC considers infliximab for induction treatment only and when positioned for use as an alternative to ciclosporin in patients with
acute, severe paediatric ulcerative colitis (rescue therapy) who are steroid refractory. The proposed positioning differs from current paediatric guidance which recommends the use of infliximab for both induction and maintenance treatment of severely active ulcerative colitis.7

There is no evidence of efficacy versus an active or placebo comparator in the paediatric population. The authors of the pivotal study concluded that the effect of treatment with infliximab in the paediatric population with moderate to severe active ulcerative colitis was comparable with that in adults. However, the study had several limitations. The primary outcome was pre-defined clinical response and was achieved by 73% (44/60) patients; however, this phase of the study was uncontrolled. Clinical remission, which may be considered a more relevant outcome, was achieved by 40% (24/60) patients. The Committee for Medicinal Products for Human Use of the EMA accepted the open-label, non-placebo controlled design of the study because of the methodological and ethical challenges of undertaking a placebo-controlled study in this population. The randomised second phase of the study had insufficient power to detect a difference between the treatment groups.

Most study patients had less severe disease than would be eligible for treatment according to the infliximab marketing authorisation. Only 10% (6/60) of the study population had severe active baseline disease measured by the Mayo index. The supportive ACT studies in adults also included only a small subgroup (11%) of patients with severe disease. There is no universally accepted classification of the severity of ulcerative colitis, which complicates the assessment of disease state at baseline and the changes in disease course throughout the pivotal study, as well as comparisons with other studies. The pivotal study collected data based on the Mayo and PUCAI indices. The Mayo score has not been formally validated. The PUCAI has been validated and is specific to paediatric patients, but the collection of PUCAI data started some time after study initiation as the result of a protocol amendment, so some values were missing. The economic model is based on 15 patients with severe ulcerative colitis at baseline based on PUCAI; however, if using the Mayo index, only six patients were categorised as having severe disease. It is not known how many patients who failed induction therapy had severe disease. The European Public Assessment Report notes that a higher proportion of this group, 73% (11/15), reported obvious blood with stool most of the time for the Mayo rectal bleeding sub-score at baseline, compared with 47% (21/45) in the responder group.8

The number of evaluable patients in the longer term assessment was limited. Thirty of the 60 patients enrolled discontinued prematurely. Only 15 patients in the 6 to 11 years age group were randomised and only nine were evaluable for PUCAI scores at week 54.

Long-term efficacy is uncertain as in 41% (9/22) of patients who responded to induction therapy and were randomised to infliximab the dose was increased to 10mg/kg (unlicensed dose) because of loss of response.

Infliximab is licensed for the indication under review while ciclosporin is not, despite being used and recommended in guidelines.

SMC clinical experts have identified an unmet need for an effective licensed treatment in acute severe ulcerative colitis. They also highlighted the benefits of a medical rescue therapy as a valuable alternative to surgery in some patients. In addition, infliximab has some potential advantages over ciclosporin: it can be given to some children in whom ciclosporin would not be appropriate due to the risk of calcineurin toxicity; it is administered as short infusions while ciclosporin requires prolonged infusion; and infliximab treatment does not require biochemical and therapeutic drug monitoring.
The submitting company presented a cost-utility analysis comparing infliximab to ciclosporin for the acute (rescue) phase of treatment in the population of children and adolescents with severe ulcerative colitis who are steroid refractory. A 54 week time horizon was used. No analysis was provided by the submitting company on the cost-effectiveness of infliximab as a maintenance treatment.

A Markov model was used with health states for remission, mild/moderate disease and surgery (with and without complications). Patient entered the surgery state if they had severe disease. Clinical data to assess relative efficacy in the first cycle of the model were taken from the pivotal study for infliximab and for ciclosporin-treated patients, the odds ratio of a treatment failure (1.33) from an open-label randomised study of infliximab versus ciclosporin in 115 adult patients was used. Transition probabilities for other cycles in the model were estimated from other published studies in adult patients. Adverse events were estimated from a study in the literature which suggested a higher risk of developing serious adverse events with ciclosporin than infliximab.

In the acute treatment phase of the model, infliximab was assumed to be given as infusions at weeks 0, 2 and 6 and thereafter patients received maintenance treatment with aminosalicylates. Patients in the ciclosporin arm of the model were assumed to receive iv ciclosporin for 11 days and thereafter 45 days of oral ciclosporin before moving on to maintenance treatment with aminosalicylates. The model assumed, on the basis of expert opinion, that patients treated with infliximab would be hospitalised for 7 days during the acute treatment whereas ciclosporin-treated patients would have an 11 day length of stay.

Utility values were taken from a mapping exercise using data from the pivotal study. Resource use estimates were largely taken from a survey of clinicians.

The base case results showed infliximab to dominate ciclosporin (cheaper, more effective) given a saving of £7.32 and quality adjusted life year (QALY) gain of 0.0037.

A range of one way sensitivity analyses was presented in the submission and indicated that the results were most sensitive to the costs of infliximab (incremental cost effectiveness ratio [ICER] increased to £489k when infliximab cost doubled), the rate of adverse events with ciclosporin (ICER increased to £67k when rate was halved) and the costs of IV ciclosporin (ICER increased to £35k if the cost was halved). While these sensitivity analyses were helpful, a range of variables were not adequately tested in the initial presentation of results so the company was requested to provide further sensitivity analysis. The key findings from the additional analysis provided were as follows:

- The odds ratio from the study used to assess relative efficacy was non-significant, and when this difference was removed and treatments assumed to be equivalent, the ICER increased dramatically. Threshold analysis showed that the odds ratio needed to be 1.2195 before the ICER fell below £20,000 per QALY. As noted above, the recognised weaknesses in the clinical evidence base due to the nature of both the patient population and the condition lead to uncertainty about the extent of treatment benefits and thus cost-effectiveness.
- As noted above, the model assumed different lengths of stay between infliximab and ciclosporin for the initial hospitalisation (7 days versus 11 days). When no difference was assumed between treatments, the ICER rose to £466k per QALY. At a 3 day differential, the ICER was £115k. SMC clinical experts had mixed views on whether inpatient stay would be reduced in clinical practice as these patients are very ill.
- If no difference was assumed in adverse events, the ICER rose to £70k, and if adverse events were higher for infliximab (as per the source study for the efficacy odds ratio), the ICER increased.
to £91k.

- If all patients were assumed to receive 3 infusions of infliximab (unlike in the clinical study where there was some patient drop-out between the second and third infusions), the ICER increased to £44k.

Given the small cost and QALY differences in the base case, the ICER was relatively unstable when different assumptions were made around efficacy or cost parameters. It is acknowledged that there may be challenges in obtaining a robust evidence base to use in the health economic analysis in this patient population and that this will have introduced uncertainty into the results. On balance, despite these uncertainties, the economic case for infliximab as an acute treatment was demonstrated.

**Summary of patient and public involvement**

A Patient Interest Group Submission was received from Crohn's and Colitis UK (NACC)

**Additional information: guidelines and protocols**

The British Society of Paediatric Gastroenterology, Hepatology and Nutrition published Guidelines for the management of inflammatory bowel disease in children in the United Kingdom in 2008. For patients with acute severe colitis/toxic megacolon, the guidelines stress that early surgical opinion is essential and patients should be managed jointly between physician and surgeon. For induction of remission in children with acute severe ulcerative colitis they recommend that intravenous ciclosporin be considered in patients not responding to steroids as a temporary measure to delay/avoid colectomy allowing recovery and initiation of second line immunosuppressant. Tacrolimus may be an alternative. The guidelines note that there is some evidence that infliximab could be considered in non-responding acute severe ulcerative colitis.  

**Additional information: comparators**

Ciclosporin is the relevant comparator and tacrolimus has been cited by the British Society of Paediatric Gastroenterology, Hepatology and Nutrition as a possible alternative. However neither of these drugs is licensed for this indication.
Cost of relevant comparators

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose Regimen</th>
<th>Cost per induction period (12 weeks) treatment (£)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infliximab</td>
<td>Induction: 5mg/kg by intravenous infusion at weeks 0, 2 and 6</td>
<td>1,259 to 5,035</td>
</tr>
<tr>
<td>Tacrolimus*</td>
<td>100 micrograms/kg orally twice daily</td>
<td>481 to 1,378</td>
</tr>
<tr>
<td>Ciclosporin*</td>
<td>2mg/kg daily by continuous intravenous infusion till remission, then orally 5mg/kg to 8mg/kg daily in two divided doses</td>
<td>146 to 742</td>
</tr>
</tbody>
</table>

Doses are for general comparison and do not imply therapeutic equivalence. Costs for ciclosporin and tacrolimus from eVadis on 04.12.12; cost for infliximab from British National Formulary (BNF) No. 63 September 2012. Costs for 12 weeks (induction) only are shown as ciclosporin/tacrolimus are not recommended to be used in this indication for more than three or four months; induction treatment only is the proposed positioning for infliximab. Cost of ciclosporin is based on 10 days intravenous infusions, then oral treatment. Doses based on body weight range 20kg to 68kg (BNF average weights for children 6 to 17 years of age). Doses of ciclosporin and tacrolimus from Consensus for Managing Acute Severe Ulcerative Colitis in Children. * Off-label use.

Additional information: budget impact

The submitting company estimated the population eligible for treatment to be 94 in year 1 reducing to 82 in year 5, with an estimated uptake rate of 27% in year 1 and 40% in year 5. The gross impact on the medicines budget was estimated to be £95k in year 1 and £124k in year 5. As other drugs were assumed to be displaced, the net medicines budget impact is expected to be £87k in year 1 and £115k. The committee noted that SMC clinical experts have advised that there is currently some use of infliximab in clinical practice in this indication.
References

The undernoted references were supplied with the submission. The reference shaded in grey is additional to those supplied with the submission.


6. BMJ Group; British National Formulary for children


This assessment is based on data submitted by the applicant company up to and including 11 January 2013.

*Agreement between the Association of the British Pharmaceutical Industry (ABPI) and the SMC on guidelines for the release of company data into the public domain during a health technology appraisal: http://www.scottishmedicines.org.uk/About_SMC/Policy_Statements/Policy_Statements

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. SMC is aware that for some hospital-only products national or local contracts may be in place for comparator products that can significantly reduce the acquisition cost to Health Boards. These contract prices are commercial in confidence and cannot be put in the public domain, including via the SMC Detailed Advice Document. Area Drug and Therapeutics Committees and NHS Boards are therefore asked to consider contract pricing when reviewing advice on medicines accepted by SMC.
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.