Scottish Medicines Consortium

infliximab 100mg powder for intravenous infusion (Remicade®) No. (364/07)

Schering-Plough UK Ltd

6 April 2007

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 maintenance treatment of fistulising, active Crohn's disease, in patients who have not responded despite a full and adequate course of therapy with conventional treatment (including antibiotics, drainage and immunosuppressive therapy). Infliximab was not approved by NICE in 2002 for patients with fistulating Crohn's disease who do not have the other criteria for severe active Crohn's disease.

Infliximab maintenance treatment, compared to placebo, was associated with a longer time to loss of fistula response in patients with fistulising Crohn's disease. The manufacturer's justification of the treatment cost in relation to its health benefits was not sufficient to gain acceptance by SMC.

Overleaf is the detailed advice on this product.

Chairman
Scottish Medicines Consortium

Indication

Treatment of fistulising, active Crohn's disease, in patients who have not responded despite a full and adequate course of therapy with conventional treatment (including antibiotics, drainage and immunosuppressive therapy).

Dosing information

5mg/kg by intravenous infusion over two hours at weeks 0, 2 and 6 and, for patients who respond, 5mg/kg by intravenous infusion every eight weeks or, if signs and symptoms of disease recur, re-administration followed by 5mg/kg intravenous infusion every eight weeks.

Product availability date

October 2003

Summary of evidence on comparative efficacy

The tumour necrosis factor (TNF)-antagonist, infliximab, is a human-murine monoclonal antibody against TNF. It binds to TNF and antagonises its biological activity Infliximab was not approved by National Institute for Health and Clinical Excellence (NICE) in 2002 for patients with fistulating Crohn's disease who do not have the other criteria for severe active Crohn's disease which included episodic treatment. This submission focussed on regular eight weekly maintenance treatment of fistulising active Crohn's disease.

A double-blind trial recruited TNF-antagonist-naïve adults with Crohn's disease who had at least one draining fistula for at least three months. They received infliximab 5mg/kg by intravenous (iv) infusion at weeks 0, 2 and 6. At week 14 they were assessed for response and randomised, with stratification for number of fistula (1 or >1) and presence or absence of active inflammatory bowel disease (defined as a Crohn's disease activity index (CDAI) ≥150), to placebo or infliximab 5mg/kg iv infusion every eight weeks for the rest of the year. Other medications for Crohn's disease (aminosalicylates, antibiotics, corticosteroids, azathioprine, mercaptopurine, mycophenolate mofetil and methotrexate) were permitted during the study at stable doses. The primary outcome time to loss of response was defined as recrudescence of draining fistulas, need for change in medication for Crohn's disease or for additional therapy for persistent or worsening luminal disease activity, need for surgical procedure for Crohn's disease or discontinuation of study medication due to lack of efficacy. This was primarily assessed in patients who had a response at week 14, defined as a reduction of at least 50% compared to baseline in the number of draining fistulas at both weeks 10 and 14. After randomisation, median time to loss of response was significantly longer for maintenance therapy with infliximab, compared to placebo: >40 vs. 14 weeks. Among the responders at 14 weeks, 42% (n=40/96) and 62% (n=61/99) of patients in the respective groups had a loss of response by week 54. The two most common criteria for this were: a need for change in medication for Crohn's disease (25% and 38% in respective groups), mainly corticosteroids or antibiotics; and recrudescence of fistula (16% and 22% in the respective groups). Among patients who did not have a response at week 14, there was no significant difference between the infliximab and placebo maintenance groups in the number of patients who subsequently had a response: 21% (n=9/43) and 16% (n=7/44), respectively. Data from this trial reviewed by the European regulatory authority indicated that infliximab did not show superiority over placebo with regard to sustained healing of all fistulas, 24% vs. 16%, and that infliximab did not reduce the number of new fistulas compared with placebo. However, subgroup analysis indicated that long-term treatment was superior to placebo in patients with active fistulising Crohn's disease. It was considered that symptomatic benefit for the patient had not been shown.

In the subgroup of patients who had a CDAI score ≥220 at baseline, significantly more patients given infliximab maintenance therapy, compared to placebo, had a disease-activity clinical response, defined as a reduction from baseline in CDAI of at least 25% and 70 points, at 54 weeks: 36% (n=12/33) vs. 6% (n=2/31).

Quality of life
Among all patients randomised, the median increases from baseline in inflammatory bowel disease questionnaire (IBDQ), which ranges from 32 to 224, with higher scores for better quality of life, were significantly greater with infliximab maintenance therapy, compared to placebo, at week 30 (14 vs. 4) and week 54 (10 vs. 5).

Hospital admission and surgery for Crohn's disease
Analyses of Crohn's disease-related hospital admission and surgery rates included data from patients after crossover to rescue re-treatment with infliximab at doses 5mg/kg higher than their initial assigned treatment. Among responders at week 14, significantly fewer patients had a Crohn's disease-related hospital admission in those initially assigned to the infliximab group than the placebo group: 7.3% (n=7/96) vs. 18% (n=18/99). Similar results were noted in all randomised patients: 8.6% (n=12/139) vs. 19% (n=27/143). Among all randomised patients, infliximab, compared to placebo was associated with fewer patients having major surgery for Crohn's disease, 3 vs. 12 and with fewer major surgery operations: 3 vs. 18.

*Other data were also assessed but remain commercially confidential.**

Summary of evidence on comparative safety

Infliximab is associated with increased incidences of infection, including opportunistic infections and tuberculosis, probably due to suppression of the immune system, which may also mask signs of fever. There is concern that drugs that modify the immune system may increase the risk of malignancies. There is no clinical evidence of this; however, long-term data are required to exclude this. The relative deficiency of TNF produced by TNF-antagonists may initiate auto-immune processes, with development of antinuclear and double-stranded DNA antibodies and lupus-like syndromes, although the latter remain uncommon. TNF-antagonists have also been associated with rare cases of demyelinating disease, including multiple sclerosis. Infliximab is associated with serious acute infusion reactions, including anaphylactic shock, and with delayed hypersensitivity reactions. There is an increased risk for delayed hypersensitivity with increasing drug-free intervals.

Summary of clinical effectiveness issues

When infliximab is prescribed in accordance with its Summary of Product Characteristics it would only be given to patients with active fistulising Crohn's disease. Benefits within the subgroup of patients who have active disease would therefore provide the best estimate of the size of treatment effects on fistula, which would be expected in practice.

The analyses of hospital admission and Crohn's disease-related surgeries included data from patients after crossover to rescue re-treatment with infliximab at a dose 5mg/kg higher than their initial assigned treatment, i.e. 5mg/kg and 10mg/kg for patients initially assigned to placebo and infliximab 5mg/kg maintenance groups, respectively. This higher dose of infliximab is not licensed. No data were provided on rates of Crohn's disease-related hospital admissions and surgeries with the licensed maintenance dose of infliximab, thus, effects on these outcomes in practice are unknown.

In the study more than 90% of patients had previously received treatment with antibiotics and about two-thirds had received treatment with the immunosuppressants, azathioprine or mercaptopurine. Concomitant medications, which were stable prior to study initiation and continued during it, included aminosalicylates, azathioprine or mercaptopurine, antibiotics and corticosteroids for 47%, 33%, 29% and 29% of patients, respectively. No data were available on the number of patients who had had an inadequate response to previous treatments.

The current treatment of active fistulising Crohn's disease which has not responded despite a full and adequate course of therapy with conventional treatment (including antibiotics, drainage and immunosuppressive therapy) is not well defined. It may include surgery or treatment with a different immunomodulator. There are no trials comparing infliximab with an alternative treatment strategy therefore comparative efficacy and safety are unknown.

*Other data were also assessed but remain commercially confidential.**

Summary of comparative health economic evidence

The manufacturer provided a cost-utility analysis comparing regular infliximab treatment to three initial infliximab treatments followed by treatment with azathioprine, corticosteroids, immunomodulators and/or surgery. The time horizon for the model was five years.

The model structure was appropriate and included relevant disease states such as remission and surgery. The source of clinical evidence was the trial described previously. Hospitalisation and surgery rates were taken from published sources. Utilities were estimated from published literature sources. The results indicated that the incremental cost per quality-adjusted life year (QALY) was £19,000 at one year or £40,000 at five years. With a chronic disease a longer time horizon is more appropriate.

There were some limitations in the analysis. It was not always clear how the clinical data were used in the model to derive the results. The flow of patients in the model appeared to show an increasing remission rate over time with regular infliximab treatment despite the manufacturer stating that the response rate diminished over the course of the model. This was attributed to the effect of infliximab in producing underlying symptomatic disease improvement over the longer term.

Summary of patient and public involvement

A Patient Interest Group Submission was not made.

Additional information: guidelines and protocols

The April 2002 NICE guidance on the use of infliximab for Crohn's disease recommends infliximab for the treatment of patients with severe Crohn's disease who fulfil all three of the following criteria: severe active Crohn's disease; condition has proved to be refractory to treatment with immunomodulating drugs and corticosteroids, or patients have been intolerant of, or experienced toxicity from, these treatments; and patients for whom surgery is inappropriate (e.g. because of diffuse disease and/or risk of short bowel syndrome).

Treatment can be repeated for those patients who match the above criteria and have responded to initial the treatment course, but then relapsed. Infliximab is not recommended for patients with fistulising Crohn's disease who do not have the other criteria for severe active Crohn's disease.

The 2004 British Society of Gastroenterology guidelines for management of inflammatory bowel disease in adults note that infliximab is licensed but not yet approved by NICE for the maintenance therapy of Crohn's disease in the UK and national guidelines govern its use.

Additional information: comparators

No other medicines are licensed for treatment or maintenance of fistulising Crohn's disease. One brand of mesalazine tablet, (Asacol MR®), is indicated for maintenance of remission of Crohn's ileocolitis. However, no other aminosalicylates are licensed for maintenance of remission of Crohn's disease. Azathioprine, mercaptopurine and methotrexate have been used to maintain remission in Crohn's disease although they are not licensed for this.

Additional information: costs

Drug	Dosing regimen	Annual cost (£)[A]
Infliximab	**5mg/kg iv at weeks 0, 2 and 6 then every 8 weeks**	**10,910[B]**
Mesalazine m/r[C]	1200 to 2400mg orally each day	379-757
Mercaptopurine	1 to 1.5mg/kg orally each day	273-684
Azathioprine	2 to 2.5mg/kg orally each day	98-116
Methotrexate	15 to 25mg orally each week	36-60

A = costs based on a patient weighing 60-80kg; B = costs for a patient weighing <60kg, £8,183; costs in the first year would be £14,687 and £11,015 for patients weighing 60-80kg and <60kg, respectively; C = Asacol MR; iv = intravenous infusion.

Additional information: budget impact

The gross drug budget increase of fistulising disease was estimated by the manufacturer as being £48k in year one rising to £131k by year five. After taking account of savings in hospitalisations and surgery that might be associated with successful infliximab treatment, the manufacturer estimated that the overall net impact would be £1.1m in year one and £623k by year five. It was assumed that 222 patients would receive treatment in the first year and an additional 3 to 4 patients per year thereafter. The decline in budget impact reflects treatment drop-outs over time.

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 22 March 2007.

** 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/

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.

Sands BE, Anderson FH, Bernstein CN et al. Infliximab maintenance therapy for fistulizing Crohn's disease. N Engl J Med 2004; 350: 876-85.

Lichtenstein GR, Yan S, Bala M, Blank M, Sands BE. Infliximab maintenance treatment reduces hospitalizations, surgeries, and procedures in fistulizing Crohn's disease. Gastroenterology 2005; 128: 862-9.