Scottish Medicines Consortium

infliximab 100mg powder for intravenous infusion (Remicade®) No. (363/07)

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 severe, active Crohn's disease, in patients who have 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. Infliximab for the treatment of acute severe, active Crohn's disease was approved by NICE in 2002.

Infliximab maintenance treatment, compared to placebo, is associated with higher rates of clinical remission and a longer time to loss of response in patients with active Crohn's disease. 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

Treatment of severe, active Crohn's disease, in patients who have 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.

Dosing information

5mg/kg by intravenous infusion over two hours and, for patients who respond by week 2, additional 5mg/kg by intravenous infusions at weeks 2 and 6, then every eight weeks or when signs and symptoms of the disease recur, if these recur within 16 weeks of the last infusion. The safety and efficacy of re-administration after a drug-free interval greater than 16 weeks has not been established.

Product availability date

May 2003 (for maintenance therapy) and September 2006 (for second-line treatment)

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 approved by the National Institute for Health and Clinical Excellence (NICE) in 2002 for treatment of active severe Crohn's disease and this indication permitted episodic treatment. The license variation under consideration in this submission allows for regular eight weekly maintenance treatment in severe active disease.

A double-blind trial recruited 573 TNF-antagonist-naïve adults with Crohn's disease for at least three months that was active as defined by a Crohn's disease activity index (CDAI) of 220 to 400. They received infliximab 5mg/kg intravenous (iv) infusion and were randomised, with stratification for study centre and duration of continuous exposure to corticosteroids, in a 1:1:1 ratio to iv infusions of placebo, infliximab 5mg/kg at weeks 2 and 6 then every eight weeks or infliximab 5mg/kg at weeks 2 and 6 then 10mg/kg every eight weeks up to one year. Other medications for Crohn's disease (aminosalicylates, antibiotics, corticosteroids, azathioprine, mercaptopurine and methotrexate), which had been taken at stable doses before the trial, were continued at these doses during it, except for corticosteroids, which were given at the stable doses until week 6 and could then be reduced and discontinued upon improvement of a patient's condition. The co-primary outcomes were assessed in the subgroup of patients who experienced at week 2 a response, defined as a decrease in CDAI score of at least 70 points and a reduction in CDAI score of at least 25%. One of these was the proportion of week-2 responders in clinical remission, defined as CDAI score lower than 150, at week 30. This was significantly greater than the placebo group, 21% (n=23/110), in the group that received the licensed dose of infliximab (5mg/kg), 39% (n=44/113) and in the group that received infliximab 10mg/kg as maintenance treatment, 45% (n=50/112). Similar results were observed at week 54 in the respective groups. The other primary outcome was time to loss of response, defined as CDAI of at least 175, a CDAI increase of at least 35% and a CDAI at least 70 points greater than the week-2 CDAI for at least two consecutive visits (21 days or longer). In an analysis that censored data for patients who discontinued the study for reasons other than lack of efficacy or loss of response and those with missing CDAI data, the median times to loss of response in both of the infliximab groups, 38 and >54 weeks, respectively, were significantly longer than the placebo group, 19 weeks.

Among week-2 responders, rates of clinical response, as defined previously, were significantly greater with infliximab 5mg/kg and 10mg/kg compared to placebo at week 30 and at week 54. Among 2-week responders who were receiving corticosteroids at baseline, significantly more patients in the infliximab 5mg/kg and 10mg/kg groups, compared to the placebo group, were in clinical remission and had discontinued corticosteroids at week 54.

Quality of life
In patients who were responders at week 2, quality of life was assessed via the inflammatory bowel disease questionnaire (IBDQ), with scores that ranged from 32 to 224, with higher scores for better quality of life. Infliximab regular maintenance treatment (5mg/kg at weeks 0, 2, 6 then every 8 weeks), compared to a single infliximab 5mg/kg dose followed by placebo, was associated with significantly greater mean improvements from baseline to week 10 (38 vs. 29), week 30 (27 vs. 14) and week 54 (22 vs. 9). It was also associated with significantly greater mean improvements on the 100-point short-form (SF-36) physical composite score from baseline to week 10 (8.6 vs. 4.9), week 30 (7.3 vs. 3.1) and week 54 (6.1 vs. 2.5).

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. Fewer Crohn's disease-related hospitalisations occurred in the group initially assigned to infliximab 5mg/kg and 10mg/kg than the placebo group: 23 and 24 vs. 38 per 100 patients, respectively, with the difference compared to placebo significant for the 10mg/kg group and of borderline significance (p=0.047) for the 5mg/kg group. Fewer patients assigned to the infliximab 5mg/kg and 10mg/kg groups had Crohn's disease-related intra-abdominal surgery than those in the placebo group: 2.6% (n=5/193) and 3.1% (n=6/192) vs. 7.4% (n=14/188), respectively.

Mucosal healing
A subgroup of patients participated in an endoscopic sub-study within the trial. Within those who were responders at week 2 and had mucosal ulceration at baseline, significantly more patients had complete mucosal healing at week 10 with the licensed infliximab induction dose (5mg/kg at weeks 0, 2, 6) compared to a infliximab 5mg/kg dose followed by placebo: 31% (n=10/32) vs. 0% (n=0/17) and at week 54 with regular infliximab maintenance every 8 weeks at the licensed dose (5mg/kg) and at a higher dose (10mg/kg) compared to a single 5mg/kg infliximab dose followed by placebo: 46% (n=5/11) and 53% (n=8/15), respectively, vs. 7% (n=1/14).

*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 as maintenance therapy to patients who had a response at week 2 following the initial infusion. In the trials described previously 42% of patients did not have a response at week 2. Therefore, of all the patients requiring treatment for active Crohn's disease, the licensed infliximab maintenance dose was associated with complete remissions and clinical responses at week 54 in approximately 17% and 22% of patients, respectively, compared to approximately 8% and 9% of patients given placebo maintenance (figures estimated from graphs). These figures may provide a better estimate of the size of treatment effects in this population than response rates in the week-2 responders. The European regulatory authority noted that this study population had moderately active disease and few patients had documented evidence of an inadequate response to standard therapy with both corticosteroids and immunomodulators. However, additional subgroup analyses showed efficacy in the restricted population defined in the indication. However, the magnitude of treatment effects with the 5mg/kg licensed dose of infliximab alone in this subgroup are unknown.

Analyses of Crohn's disease-related hospital admissions and surgeries included data from patients after they had crossed over to rescue re-treatment with infliximab at a dose 5mg/kg higher than their initial assigned treatment, i.e. 5mg/kg, 10mg/kg and 15mg/kg for the placebo, infliximab 5mg/kg and 10mg/kg maintenance groups, respectively. These higher doses of infliximab are unlicensed. No data were provided on the rates of Crohn's disease-related hospital admissions and surgeries with the licensed maintenance dose of infliximab.

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

Summary of comparative health economic evidence

The manufacturer provided a cost-utility analysis comparing infliximab maintenance treatment with episodic infliximab treatment over a five year time horizon.

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. Economic analysis was also conducted in the subgroup of patients with severe disease (CDAI >300) despite limited clinical data being presented in the submission for this subgroup. Hospitalisation and surgery rates were taken from published sources rather than the study on the basis that unlicensed doses of infliximab were possible in the trial and therefore the trial event rates would reflect this. Utilities were estimated from published literature sources.

The results indicated that the incremental cost per QALY was £28,678 at one year or £33,526 at five years. Limiting the analysis to only those patients with a CDAI >300 improved the cost-effectiveness ratio to £20,972 and £25,996 at years one and five respectively.

Clinical data to verify the model inputs for the subgroup of patients with CDAI>300 was received from the manufacturer but the trial results do not appear to be reflected in the economic model; the economic model appeared to overstate the remission rate advantage for infliximab maintenance compared to episodic treatment.

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 the initial 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

One brand of mesalazine tablet, (Asacol MR®), is indicated for maintenance of remission of Crohn's ileocolitis. No other aminosalicylate preparations 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 manufacturer estimated that the gross drug budget increase of infliximab in severe active Crohn's disease would be £2.4m in year one and £1.1m 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 £2.6m in year one and £1.16m by year five. It was assumed that 222 new patients would be eligible for treatment in the first year and an additional 124 new patients by year five.

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.

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.

** 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/

The undernoted references were supplied with the submission.

Hanauer SB, Feagan BG, Lichtenstein GR et al. Maintenance infliximab for Crohn's disease: the ACCENT I randomised trial. Lancet 2002; 359: 1541-9.

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Feagan BG, Yan S, Bala M et al. The effects of infliximab maintenance therapy on health-related quality of life. Am J Gastroenterol 2003; 98: 2232-8.

Rutgeerts P, Diamond RH, Bala M et al. Scheduled maintenance treatment with infliximab is superior to episodic treatment for the healing of mucosal ulceration associated with Crohn's disease. Gastrointest Endosc 2006; 63: 433-42.