Scottish Medicines Consortium

Infliximab 100mg powder for concentrate for solution for Infusion, (Remicade®) No. (448/08)

Schering-Plough

11 February 2008

The Scottish Medicines Consortium 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 use within NHS Scotland for the treatment of severe, active Crohn's disease, in paediatric patients aged 6 to 17 years, who have 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.

In an open label study 88% of patients had a clinical response following the induction regimen and this was maintained at one year in significantly more patients receiving infliximab every 8 weeks compared with every 12 weeks.

Overleaf is the detailed advice on this product.

Chairman,
Scottish Medicines Consortium

Indication

Treatment of severe, active Crohn's disease, in paediatric patients aged 6 to 17 years, who have 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. Infliximab has been studied only in combination with conventional immunosuppressive therapy.

Dosing information

5 mg/kg given as an intravenous infusion over a 2-hour period followed by additional 5 mg/kg infusion doses at 2 and 6 weeks after the first infusion, then every 8 weeks thereafter. Some patients may require a shorter dosing interval to maintain clinical benefit, while for others a longer dosing interval may be sufficient.

Product availability date

30th May 2007

Summary of evidence on comparative efficacy

Infliximab 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 Crohn's disease (CD).

One randomised non-comparative, open-label study evaluated infliximab in children aged 6 to 17 years with moderate-to-severe CD (Paediatric Crohn's Disease Activity Index [PCDAI] >30) confirmed by endoscopy and biopsy at least 3 months before screening. The PCDAI is a validated tool that measures disease activity on a 0 to 100 scale with high values indicating severe disease. Patients were required to have initiated treatment with an immunomodulator (azathioprine, 6-mercaptopurine or methotrexate) at least 8 weeks before screening and be on a stable dose for at least 2 weeks. Concomitant treatments that were permitted included aminosalicylates, given at a stable dose for at least 2 weeks, oral corticosteroids at a daily dose of 60mg or less expressed in terms of prednisone, enteral nutrition on a stable regimen for at least 2 weeks and antibiotics on a stable dose for at least one week.

All patients received an induction regimen of infliximab 5 mg/kg via intravenous (IV) infusion at weeks 0, 2, and 6. At week 10, patients were evaluated for a clinical response defined as a reduction from the baseline PCDAI score of at least 15 points with a total score ≤ 30. Patients achieving a clinical response were randomised equally to receive subsequent infusions of infliximab 5 mg/kg IV every 8 weeks at weeks 14, 22, 30, 38, and 46, or every 12 weeks at weeks 18, 30, and 42. Patients who did not have a clinical response following induction were withdrawn from the study. In the maintenance period, patients who lost clinical response (defined as an increase in PCDAI of ≥15 points from randomisation on two consecutive visits or PCDAI > 30 points) were eligible to cross over once to receive treatment more frequently and/or at a higher dose. Patients who crossed over due to loss of response were considered non-responders in the intention-to-treat analyses.

The primary efficacy endpoint was the efficacy of the 3-dose induction regimen in terms of the proportion of patients who achieved a clinical response. Secondary endpoints included: the proportion of patients in clinical remission (PCDAI score ≤10 points) at week 10; proportions of patients in clinical response and in clinical remission at week 54; changes from baseline to week 54 in daily corticosteroid use; change from baseline in patient's height z-score, a measure of deviation of the patient's height from the expected height of an age- and sex-matched population (in patients with at least a 1-year delay in bone age); and health related quality of life.

One hundred and twelve patients were enrolled in the study and received the induction regimen. One hundred and three patients were then randomised to a treatment regimen (52 in the every-8-weeks and 51 in the every-12-weeks groups) at week 10, 99/112 (88%, 95% confidence interval [CI] 83% to 94%) patients had a clinical response. Errors in randomisation lead to the discrepancy between responders at week 10 (n=99) and the numbers of patients randomised to the maintenance phase (n=103). Clinical remission was observed in 66/112 patients (59%, 95% CI 50% to 68%) at week 10. The response and remission rates at 54 weeks for the every-8-week group were significantly superior to the every-12-week group; 63% (33/52) and 56% (29/52) versus 33% (17/51) and 23% (12/51). Twice as many patients receiving infliximab every-12-weeks required to cross over and receive an increased dose or shorter dosing interval compared with patients receiving infliximab every-8-weeks (25/51 [49%] vs. 10/52 [19%]).

Fifteen out of 36 (42%) patients on corticosteroids at baseline had discontinued them at week 10 (12/24 and 3/12 patients in the every-8-weeks and every-12-weeks groups respectively). At week 54, 10/12 in the every-8-weeks group and 5/9 in the every-12-weeks group had discontinued corticosteroids. In patients with at least a 1-year delay in bone age at baseline (number not reported), there were significant improvements in height z-scores at week 30 and 54. Improvements in health-related quality of life (measured using IMPACT III and completed by 76 patients) showed significant improvements from baseline to week 30 and week 54. Improvements were numerically but not statistically superior for the every-8-weeks group compared with the every-12-weeks group.

Summary of evidence on comparative safety

No comparative safety data are available for infliximab in the indication under consideration. In the pivotal study, serious adverse events occurred in 8/53 (15%) patients treated with infliximab every-8-weeks and 7/50 (14%) patients receiving infliximab every-12-weeks. The most common serious adverse events were related to the gastrointestinal system.

Infections were reported more frequently for patients who received infliximab every-8-weeks compared with every-12-weeks (39/53 [74%] and 19/50 [38%]), while serious infections were reported for 3/53 (5.7%) patients in the every-8-week and 4/50 (8.0%) patients in the every-12-week groups. Three cases of pneumonia (one serious) and two cases of herpes zoster (both non-serious) were reported; there were no reports of tuberculosis.

Infusion reactions occurred at similar rates; 9/53 (17%) vs. 9/50 (18%) for the every-8-weeks and the every-12-weeks groups respectively. Common infusion reactions included flushing (eight patients); injection site infiltration and dyspnoea (four patients each); and sweating, urticaria, chest pain, vomiting, hypotension, and paraesthesia (each in two patients).

In post-marketing surveillance six cases of hepatosplenic T-cell lymphoma in CD patients treated with infliximab had been identified (5 cases in the age range 12 to 19 years). All cases occurred in patients receiving concomitant treatment with azathioprine or 6-mercaptopurine. The Summary of Product Characteristics (SPC) for infliximab notes that a risk for the development for hepatosplenic T-cell lymphoma in patients treated with infliximab cannot be excluded.

Summary of clinical effectiveness issues

In the pivotal trial only responders entered the randomised stage of the trial. Therefore in clinical practice the remission and response rates observed in an unselected patient population may be lower than those observed in the trial. However, the SPC for infliximab states that available data do not support further treatment in paediatric patients not responding within the first 10 weeks of treatment.

There are no safety and efficacy data for treatment of paediatric CD patients with infliximab beyond one year. An editorial published concurrently with the pivotal trial commented that the study did not address whether patients who have responded at one year can be changed to less frequent dosing or infliximab treatment be discontinued. The European Medicines Agency (EMEA) noted that short-term safety in the pivotal study was generally similar to adults even taking into account that the frequency of infections (and the frequency of serious infections) was higher in the paediatric population. They also noted that long-term safety is not known including, for example, whether the risk of malignancies is increased.

The EMEA commented that at week 54, whilst there was a significant decrease from baseline in steroid dose for the combined group, there was no significant difference from baseline between the two dosing regimens. The EMEA concluded that infliximab appeared to have a steroid sparing effect. However, it should be noted that only 35% of patients were prescribed steroids at baseline and therefore the trial population can not be considered as being steroid dependent.

Summary of comparative health economic evidence

The manufacturer estimated the cost-effectiveness of infliximab relative to standard care for a representative 13 year old of weight 40kg over a 10-year time horizon. A cost-utility Markov model was used in which patients could enter remission, remain active but respond, or show no response. Those not responding stopped treatment and had a probability of surgery, which could result in complications but could also lead to remission.

The clinical data sources for infliximab were the paediatric trials, but as these were not placebo controlled, the clinical data source for standard care was taken to be the placebo arm of an adult trial of infliximab in Crohn's disease.

Quality of life data for those under treatment was taken from an EQ-5D study within the literature, while quality of life data for those undergoing surgery was drawn from a Welsh EQ-5D database. Significant non-drug resource savings were estimated for infliximab use from a before-and-after study of infliximab use in adults. Based on this approach, infliximab was estimated to result in small savings of £35 per patient, while providing an additional 0.708 QALYs over the 10-year time horizon. For heavier children of 50kg and 60kg, still 13 years of age, the cost effectiveness of infliximab was estimated as £6,650 per QALY and £13,169 per QALY respectively. However, a number of significant weaknesses were identified with this analysis.

In response to these issues, the manufacturer provided revised analyses, including using a five-year time horizon and adjusting the surgery rates, the quality of life values and non-drug resource savings. This resulted in an ICER of £20907 per QALY. Sensitivity analysis using more pessimistic clinical effectiveness estimates resulted in a likely maximum ICER of £25950.

Summary of patient and public involvement

A Patient Interest Group submission was not made.

Additional information: guidelines and protocols

The National Institute of Health and Clinical Excellence (NICE) published *guidance on use of infliximab in Crohn's disease* in 2002. This guideline predates the licensing of infliximab in paediatric CD patients.

NICE has agreed a final protocol for a technology assessment report entitled *use of tumour necrosis factor alpha (TNFα) inhibitors (adalimumab and infliximab [review]) for Crohn's disease.* Publication is expected in July 2008. This will include guidance on treatment of paediatric CD.

Additional information: previous SMC advice

After review of a full submission the Scottish Medicines Consortium (SMC) issued advice on 6 April, 2007 that 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. The manufacturer did not present a sufficiently robust economic case to gain acceptance by SMC.

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.

After review of a full submission the SMC issued advice on 5 October, 2007 that adalimumab (Humira®) is not recommended for use within NHS Scotland for the 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. In both induction and maintenance studies in patients with severe active Crohn's disease, more patients treated with adalimumab achieved and maintained clinical remission than with placebo. However, the manufacturer did not present a sufficiently robust economic case to gain acceptance by the SMC.

Additional information: comparators

There are no other TNFα inhibitors licensed for the treatment of paediatric CD and no other comparators relevant to the licensed indication.

Cost of relevant comparators

Drug	Dose regimen	Cost range per year (£)
Infliximab	**5mg/kg at 0, 2 and 6 weeks followed by 5mg/kg every 8 weeks**	**3,357 to 10,071** [a, b]
Infliximab	**5mg/kg every 8 weeks**	**2,937 to 8,812** [a, c]

Costs from BNF no. 54 (September 2007).
a. Weight range 20kg to 60kg; used to reflect paediatric population eligible for infliximab.
b. Cost for induction and maintenance for first year based on 8 doses (i.e. only up to week 46).
c. Cost of a year's maintenance therapy without the induction phase (i.e. 7 doses).

Additional information: budget impact

Based on a patient population of 148, the manufacturer estimated a gross drug cost of £456k in year 1, rising to £529k by year 5. Given other savings, this resulted in an overall net cost of £68k in year 1, rising to £171k by year 5.

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 January 2008.

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 reference was supplied with the submission.

Hyams J, Crandall W, Kugathasan S et al. Induction and Maintenance Infliximab Therapy for the Treatment of Moderate-to-Severe Crohn's Disease in Children. Gastroenterology. 2007;132: 863-73.