

**adalimumab 40mg injection in pre-filled pen and syringe
(Humira®) No. (417/07)**

Abbott Laboratories Ltd

5 October 2007

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

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.

Overleaf is the detailed advice on this product.

**Chairman,
Scottish Medicines Consortium**

Indication

For the treatment of severe, active Crohn's disease, in adult 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

Recommended induction dose regimen is 80 mg by subcutaneous injection (sc) at week 0 followed by 40 mg at week 2. For more rapid response to therapy, 160 mg sc at week 0 can be administered followed by 80 mg at week 2. For induction treatment, adalimumab should be given in combination with corticosteroids.

After induction treatment, the recommended dose is 40 mg sc every other week. During maintenance treatment, corticosteroids may be tapered in accordance with clinical practice guidelines. Some patients who experience decrease in their response may benefit from an increase in dose intensity to 40 mg sc every week.

Adalimumab can be given as monotherapy in case of intolerance to corticosteroids or when continued treatment with corticosteroids is inappropriate.

If a patient has stopped adalimumab and signs and symptoms of disease recur, adalimumab may be re-administered. There is little experience from re-administration after more than 8 weeks since the previous dose.

Product availability date

June 2007

Summary of evidence on comparative efficacy

Crohn's disease is an incurable, chronic relapsing remitting inflammatory disease which occurs in a relatively young population. Adalimumab is a recombinant human IgG₁ monoclonal antibody specific for human tumour necrosis factor alpha (TNF- α). TNF is a naturally occurring cytokine involved in inflammatory and immune responses. By binding specifically to TNF- α , adalimumab blocks the interaction with its cell surface receptors thus reducing the immune-mediated response.

The evidence for this licence extension is from 4 phase III studies, 2 induction and 2 maintenance studies in adult patients with moderate to severely active Crohn's disease of at least 4 months duration confirmed by endoscopy or radiologic evaluation. All patients included in the studies had a Crohn's Disease Activity Index (CDAI) score of 220-450 points (<220 represents mild disease, 220-450 moderate disease, and >450 severe disease) and were on stable doses of concurrent therapies for Crohn's disease including azathioprine, 6-mercaptopurine, methotrexate, mesalazine, sulphasalazine, budesonide and prednisone. The primary outcome in all the studies was the proportion of patients achieving clinical remission, CDAI<150 points, with secondary outcomes including the decrease in CDAI of ≥ 70 and ≥ 100 points (CR-70 and CR-100) and the Inflammatory Bowel Disease Questionnaire (IBDQ) administered to assess patient-reported outcomes.

The pivotal induction study was a 4-week, randomised, double-blind, placebo-controlled, dose-ranging study evaluating the safety and efficacy of adalimumab in 299 anti-TNF- α naïve patients. The enrolled patients represented a heterogeneous group; 50% taking neither steroids nor immunosuppressants at inclusion and around 20% not having received steroids or immunosuppressant prior to the study or at baseline. Patients were randomised to placebo (n=74), adalimumab 40mg at baseline (week 0) followed by 20mg at week 2 (n=74), adalimumab 80mg at week 0 and 40mg at week 2 (n=75) or adalimumab 160mg at week 0 and 80mg at week 2 (n= 76). The rate of clinical remission in the 4 groups was assessed at week 4. Significantly more patients treated with adalimumab 160mg/80mg achieved clinical remission than placebo patients (36% [27/76] vs 12% [9/74] respectively). The difference in clinical remission for the adalimumab 80mg/40mg group versus placebo was not significant, with only 24% [18/75] of patients achieving clinical remission. A significantly greater proportion of the adalimumab 160mg/80mg group than the placebo group had a CR-100 response (50% vs 25%) at week 4. Only the CR-70 outcome was significant for the 2 lower-dose adalimumab groups.

The other 4-week, double-blind, placebo-controlled, induction study, randomised 325 patients, who had initially responded to infliximab but stopped responding, or who were intolerant to infliximab, to placebo or adalimumab 160 mg at week 0 followed by 80 mg at week 2. Primary non-responders to infliximab were excluded from the study. The patients represented a more severely ill population compared to the previous study. More patients in this study were treated with either steroids or immunosuppressants at inclusion, but around 30% had not received steroids or immunosuppressants prior to the study or at baseline. At week 4 the proportion of patients who achieved clinical remission was significantly greater in the adalimumab 160/80mg group compared to placebo (21% [34/159] vs 7% [12/166]). The absolute difference in the rates of clinical remission was 14% (95% CI, 6.7%-22%). Significantly more patients in the adalimumab group achieved a CR-100 response (38% vs 25%).

The pivotal study evaluating the maintenance of remission with adalimumab was a 56-week, randomised, double-blind, placebo-controlled study in 845 anti-TNF- α naïve and experienced patients. Patients received open-label induction therapy with adalimumab 80 mg at week 0 followed by 40 mg at week 2. At week 4, patients were assessed and stratified by responder status (reduction in CDAI score of ≥ 70 points, 'the randomised responders') and previous exposure to anti-TNF- α agents. Patients were then randomised to placebo (n=261), adalimumab 40 mg every other week (n=260) or adalimumab 40 mg weekly (n=257) to week 56. From week 12, patients whose disease was not controlled could switch to open-label adalimumab. The co-primary efficacy endpoints were the percentage of week-4 randomised responders who had sustained clinical remission at week 26 and week 56. Thus the primary analysis population included 499 patients with the 279 non-responders included in the safety analysis. At weeks 26 and 56 significantly more patients in the adalimumab groups achieved clinical remission. (Table 1)

Table 1: Primary efficacy endpoint at weeks 26 and 56 for 'randomised responders'

Randomised responders	Placebo (n=170)	Adalimumab 40mg every other week (n=172)	Adalimumab 40mg weekly (n=157)
Week 26	29 (17%)	68 (40%)	73 (47%)
Week 56	20 (12%)	62 (36%)	65 (41%)

At week 8, patients receiving corticosteroids who experienced a decrease in CDAI of ≥ 70 points could reduce their corticosteroid dose. At week 56, 6%, 29% and 23% of patients treated with placebo, adalimumab 40mg every other week and adalimumab 40mg weekly achieved corticosteroid-free remission.

Patients from the pivotal induction study could enroll in a 56-week maintenance study. This double-blind, placebo-controlled rollover study included 275 anti-TNF- α naïve patients from the original study. Patients received open-label adalimumab 40mg at week 0 (week 4 of the induction study) and at week 2. At week 4, the 55 patients who were in clinical remission at both weeks 0 and 4 were randomised to placebo, adalimumab 40mg every other week or adalimumab 40mg weekly. Patients not in remission at both weeks 0 and 4 were assigned open-label adalimumab. The primary efficacy endpoint was the maintenance of clinical remission at week 56. Significantly more patients were in clinical remission at 56 weeks in the adalimumab 40mg every other week group and adalimumab 40mg weekly groups (79% [15/19] and 83% [15/18], respectively) compared with 44% (8/18) in the placebo group and this was significant for each adalimumab group vs. placebo.

Of these 55 patients, 49% were receiving systemic corticosteroids or budesonide at baseline. At week 56, 67% (4/6) and 88% (7/8) of patients in the adalimumab 40mg every other week and adalimumab 40mg weekly groups had completely discontinued steroid treatment, compared with 57% (4/7) of patients in the placebo group.

Summary of evidence on comparative safety

The adverse event profile of adalimumab in Crohn's disease was similar to that reported previously. No new safety concerns were raised. The incidence of adverse events, including serious and severe adverse events was greater with the higher dosage regimen of 160mg/80mg, although numbers for comparison were small.

Summary of clinical effectiveness issues

Adalimumab is not licensed for fistulating disease as the Committee for Medicinal Products for Human Use (CHMP) believed patient numbers in the studies were small and the data were not robust enough. There is no direct comparison with infliximab, the other licensed anti-TNF- α product for this indication.

Patients included in the studies had moderate to severely active disease. The CHMP accepted the manufacturer's definition of severe disease as a CDAI >300 with concomitant Crohn's disease therapy and this is supported by the National Institute of Health and Clinical Excellence (NICE). However, in the published literature there are discrepancies as to the definition of severe disease on the CDAI scale, e.g. CDAI >450 is defined as severe, extremely severe and very severe disease according to source. Clinical remission as CDAI <150 points is well accepted.

The patients in the studies represented a heterogeneous group since only about a third of patients had severe disease and not all patients had received a full and adequate course of therapy with a corticosteroid and/or an immunosuppressant prior to enrolment. The minority of truly refractory patients in the trial in relation to the proposed indication was acknowledged by the CHMP but accepted. The CHMP recommended, however, that the indication should be restricted to patients with severely active disease, due to the safety profile of adalimumab.

The licensed dose is a compromise between efficacy and safety, and the pivotal induction study included only 75 patients treated with the licensed dose, not all of whom would have had severely active disease.

Patients previously treated with infliximab with no initial response were excluded from the studies so there is no information as to whether primary non-responders to infliximab will respond to adalimumab.

Thus, for a variety of reasons, the patients treated in the studies may not reflect those who will be treated in practice in respect of either disease severity or previous treatment.

There are some practical differences between infliximab and adalimumab both in administration and stopping rules. After initial supervision, fortnightly/weekly sc injections of adalimumab can be self-administered after training compared with an infusion every 8 weeks in an outpatients department for infliximab. If there is no response to infliximab after 2 weeks in severe disease (i.e. after 2 treatments), the treatment should be stopped, whereas adalimumab may be administered for up to 12 weeks before it is stopped in non-responders (a possible 6-10 treatments).

Summary of comparative health economic evidence

The manufacturer submitted a cost-utility analysis of adalimumab every other week in various scenarios. Comparators included standard care and infliximab, patient groups included moderate/severe and severe sub-groups, and the time horizon for the evaluation was set to 56 weeks and the lifetime of patients.

The manufacturer stated it was not possible to carry out an economic evaluation alongside the clinical trials because the maintenance studies either had a high switch rate from standard care to adalimumab or had no true standard care group. To compensate, extensive modelling work was required both to extend the trial data to the lifetime horizon and to compensate for the weaknesses in the clinical data. An indirect comparison was used for the comparison with infliximab.

For utility data a published study was identified, original data obtained and a further model constructed to estimate values for the desired health states. Resource use was taken from a published paper but hospitalisation rates for very severe disease were not available; an additional model was used to estimate these.

A number of results were produced, but focusing on the case for adalimumab versus standard care over the lifetime of patients, the additional cost of the adalimumab arm was £109,767 minus a predicted saving of £98,161 to give a net cost of £11,666. The QALY gain was 2.13 over the lifetime of the patients and so the additional cost per QALY gained was £5,479.

The problems with the analysis can be summarised under two headings: lack of transparency and inappropriately optimistic assumptions.

In terms of transparency, the submission was complicated by the extensive modelling work. There was inevitable uncertainty in each of the 5 models and in combining them the uncertainty was compounded. The predictions of the models were either not validated against actual observations or, where they were cross-checked, seemed to predict poorly for the 'very severe' state (which incurs extremes of cost and QALY loss). The submission was further complicated by inappropriate comparators, inappropriate groups of patients (moderate/severe does not match the licence) and a time horizon of 56 weeks, which would have been best confined to a sensitivity analysis. It was not apparent from the submission that Scottish expert clinicians had been consulted on the patients most likely to be treated with infliximab. The complexity of the model was compounded by lack of clarity in the submission, making it inaccessible to non-specialists.

The submission was also thought to be excessively optimistic in several respects:

- The hospitalisation costs for patients with 'very severe' patients were modelled but the prediction was that a person in this state would be in hospital for 116 days per year, costing over £56k per year. In the standard care arm this was applied to 16% of patients versus 7% in the adalimumab arm. No patients were considered for surgery. This large difference in costs per year explained the very large savings predicted for adalimumab over the lifetime of the patient, virtually offsetting the cost of the drug itself.
- Patients in the clinical trials were in their late 30s on average. In the lifetime model if they were still on adalimumab at the end of the 56-week trial they were assumed to maintain the same level of effectiveness until they died.
- The model estimated 18% of patients would switch from dosing every-other-week to weekly but clinical expert opinion stated that 50-60% would be more realistic. This raised further doubts about the validity of the modelling.
- Modelling used last-value-carried-forward in modelling disease states (in one of the trials used in the modelling nearly half of patients were categorised as missing values by 52 weeks) yet in a relapsing-remitting condition this seems an inappropriate assumption.

To compound all of these factors, the submission included only limited sensitivity analysis and it was confined to the economic evaluation with a 56-week time horizon.

Summary of patient and public involvement

Patient Interest Group Submission: National Association for Colitis and Crohn's Disease

Additional information: previous SMC advice

In April 2007, following a full submission, SMC advised 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. 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.

Additional information: comparators

Infliximab

Cost of relevant comparators

Drug	Dose regimen	Cost per year (£)
Adalimumab	80mg sc at week 0 then 40mg at week 2 then 40mg every two weeks thereafter	10,010
	or 80mg sc at week 0 then 40mg at week 2 then 40mg every week thereafter	18,948
Infliximab	5mg/kg intravenously at weeks 0,2 and 6 and every 8 weeks thereafter	10,910*

Doses are for general comparison and do not imply therapeutic equivalence. Costs from eVadis on 30th July 2007. *This cost is based on a 60-80kg patient. Costs for a patient weighing less than <60kg is £8,138

Additional information: budget impact

The manufacturer estimated an annual gross drug cost of £1.1m in year one based on 121 patients receiving adalimumab. With an additional 17 new patients treated each year thereafter, the gross drug budget impact at year 5 was estimated at £1.7m. Note that these figures were based upon an average annual cost of adalimumab of £9,247 which may tend to underestimate the budget impact if significant numbers of patients proceed to weekly dosing. There is also uncertainty around the likely market share of adalimumab.

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 14 September 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.

The undernoted references were supplied with the submission. The reference, shaded grey, is additional to information supplied with the submission.

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Sandborn W, Rutgeerts P, Enns R, Hanauer S, Colombel J, Pannacione R et al. Adalimumab Induction Therapy for Crohn Disease Previously Treated with Infliximab. Annals of Internal Medicine 2007;146(12):829-839

Colombel J, Sandborn W, Rutgeerts P, Enns R, Hanauer S, Panaccione R, Schreiber S, Byczkowski, Li J, Jent J, Pollack P. Adalimumab for Maintenance of Clinical Response and Remission in Patients With Crohn's Disease: The CHARM Trial. Gastroenterology 2007;132:52-65

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European Medicines Agency (EMA). European Public Assessment Report (EPAR). Scientific Discussion for adalimumab (Humira®) www.emea.europa.eu accessed on the 3/07/07