Scottish Medicines Consortium

adalimumab 40mg pre-filled syringe (Humira®) (No. 300/06)

Abbott Laboratories Ltd

10 November 2006

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

adalimumab (Humira®) is accepted for restricted use within NHS Scotland for the treatment of adults with severe active ankylosing spondylitis who have an inadequate response to conventional therapy. It is restricted to use in accordance with the British Society for Rheumatology (BSR) guidelines of July 2004.

Adalimumab improves signs, symptoms, physical function and quality of life in patients with severe active ankylosing spondylitis. It reduces spinal inflammation, but there is no radiological evidence that it decreases joint damage. An economic evaluation demonstrated that it is a cost-effective treatment option when used in tumour necrosis factor (TNF)-antagonist naïve patients in accordance with the BSR guidelines and where clear and rigorous stopping rules are applied.

Overleaf is the detailed advice on this product.

Chairman
Scottish Medicines Consortium

Indication

Treatment of adults with severe active ankylosing spondylitis who have an inadequate response to conventional therapy.

Dosing information

40mg by subcutaneous injection every two weeks.

Product availability date

6th June 2006

Summary of evidence on comparative efficacy

Adalimumab is a recombinant human IgG monoclonal antibody against tumour necrosis factor (TNF). It binds to TNF and antagonises its biological activity.

Two double-blind trials recruited 315 and 82 adults fulfilling the modified New York criteria for ankylosing spondylitis (AS) who had active disease, defined as two of the following criteria: Bath AS disease activity index (BASDAI) score ≥4; total back pain score ≥4 (both on 10cm visual analogue scales (VAS)); or morning stiffness ≥1 hour. All patients had an inadequate response or intolerance to at least one non-steroidal anti-inflammatory drug (NSAID) and were TNF-antagonist-naive. Patients were randomised in the larger study in a 2:1 ratio and, in the smaller study, in a 1:1 ratio to adalimumab 40mg by subcutaneous (sc) injection every two weeks or placebo for 24 weeks, with the option to receive open-label adalimumab after week 12 if an improvement of 20% on the assessment of AS (ASAS) criteria (ASAS20 response) had not been achieved. The following drugs could be continued during the study if they had been taken at stable doses for four weeks prior to study entry: NSAIDs, prednisone (≤10mg/day), sulphasalazine, methotrexate and hydroxychloroquine. All other disease-modifying anti-rheumatic drugs (DMARDs) were discontinued at least four weeks prior to randomisation. The primary outcome was the proportion of the intent-to-treat population, which comprised all randomised and treated patients, achieving an ASAS20 response at week 12. In the larger study this was significantly greater with adalimumab compared to placebo though in the smaller study the difference between treatments was not significant. In analyses at week 24, which classified patients receiving open-label adalimumab rescue after week 12 as non-responders, significantly more patients achieved an ASAS20 response with adalimumab compared to placebo in the larger study, though again in the smaller study the difference between drugs was not significant. Adalimumab also improved other measures of disease activity, including proportions of patients achieving ASAS50 and ASAS70 responses and ≥50% improvement on BASDAI score (BASDAI50). Function, assessed via Bath AS functional index (BASFI), and spinal mobility, assessed via Bath AS metrology index (BASMI) were also significantly improved with adalimumab compared to placebo.

Results at 12 and 24 weeks with adalimumab and placebo in patients with active ankylosing spondylitis.

	Study A				Study B			
	Adalimumab n=208		Placebo n=107		Adalimumab n=38		Placebo n=44	
Analysis at week	12	24	12	24	12	24	12	24
ASAS20 responders	58%*	50%*	21%	19%	47%	34%	27%	16%
ASAS50 responders	38%*	35%*	10%	11%	40%*	32%#	6.8%	11%
ASAS70 responders	23%*	24%*	4.7%	8.4%	21%#	29%#	2.3%	6.8%

p<0.001, # p<0.05 vs. placebo; Ankylosing spondylitis assessment (ASAS) 20, 50 and 70 = ≥20%, 50%, 70%, respectively, improvement on ≥3 ASAS criteria, plus absence of deterioration on the fourth; partial remission = scores <20 on all ASAS criteria.

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

Quality of life
Adalimumab, compared to placebo, was associated with significant improvements in mean change from baseline to week 12 and 24 in short-form (SF-36) physical summary and AS quality of life questionnaire (ASQoL) scores in both trials and, in the smaller study, in SF-36 mental summary score.

Spinal inflammation
In the smaller study described previously, magnetic resonance imaging (MRI) of spinal and sacroiliac joints were conducted and inflammation scored on the Spondyloarthritis Research Consortium of Canada (SPARCC) index. This was significantly reduced from baseline to week 12 with adalimumab compared to placebo in both the spinal joints (mean change from baseline in the respective groups: -54% vs. -9%) and in sacroiliac joints (mean change from baseline in the respective groups: -53% vs. -13%).

Summary of evidence on comparative safety

No new safety issues were identified for adalimumab in the AS populations. Adalimumab and etanercept are associated with allergic reactions, but do not require administration in hospital. In contrast, infliximab must be administered in hospital, as it has been associated with serious acute infusion-related reactions, including anaphylactic shock, and delayed hypersensitivity reactions.

Summary of clinical effectiveness issues

One of the requirements of the British Society for Rheumatology (BSR) guidelines for prescribing TNF-α blockers in adults with AS is that patients have failed to respond to two or more NSAIDs. In the trials described previously all patients had either failed to respond or were intolerant to at least one NSAID. Adalimumab was associated with significant benefits compared to placebo in terms of ASAS20 and BASDAI50 responder rates, which were similar in the subgroup that had received two of more previous NSAIDs and the subgroup that had received only one previous NSAID.

Adalimumab reduces spinal inflammation, as measured by MRI. However, BSR guidelines note that a possible role for MRI as a prognostic predictor needs to be confirmed. There are

no radiological data indicating that adalimumab prevents or reduces structural joint damage compared to placebo.

There are no direct comparative trials of adalimumab with either etanercept or infliximab, the other TNF-antagonists licensed for treatment of adults with severe active AS. The efficacy and safety of adalimumab relative to these drugs in this indication are unclear.

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

Summary of comparative health economic evidence

The manufacturer provided a cost utility model comparing adalimumab versus 'conventional therapy' (NSAIDs, non-drug therapy) with adalimumab being used in the context of the BSR guidelines for the use of TNF-antagonists in AS patients. This was a micro-simulation model and used information from the two key clinical trials, described previously, to project the likely profile of costs and benefits over a 30-year time horizon. The model assumed that patients on conventional therapy would experience annual disease progression (a 0.05 point increase in the BASFI score each year) but that patients receiving adalimumab would not be subject to this deterioration for as long as they continued to respond to treatment. Costs in the model included drug costs, costs related to adverse events, monitoring costs and costs that related to the level of AS disease (e.g. hospitalisations, healthcare visits, aids and appliances).

The AS-related disease costs were estimated from a survey of patients in Europe and the responses then related to the level of their BASDAI score in order to generate cost profiles across the disease severity spectrum. Utility scores were generated directly from the BASDAI and BASFI scores from the two key clinical studies. The modelling approach and analysis were appropriate. The company also provided a more limited form of analysis to compare adalimumab to etanercept.

The cost per quality-adjusted life-year (QALY) in the baseline analysis was £23000, rising to £26000 if a five-year time horizon was used or £47000 if a 48-week horizon was taken. One-way and probabilistic sensitivity analyses indicated that there was little change in the results when other variables were altered. The indirect comparison with etanercept suggested that adalimumab was likely to have a similar level of cost-effectiveness to etanercept.

Summary of patient and public involvement

A Patient Interest Group Submission was not made.

Additional information: guidelines and protocols

The July 2004 BSR guideline for prescribing TNF-α blockers in adults with AS recommends that treatment with TNF blocking agents may be appropriate if a patient's disease satisfies the modified New York Criteria and their spinal disease is active (defined as two occasions at least 4 weeks apart without any change in treatment when BASDAI is $\geq$4cm and spinal pain in the last week is $\geq$4cm on 10cm VAS); and they have failed on conventional treatment with two or more NSAIDs each taken sequentially at maximum tolerated or recommended dosage for four weeks. Treatment with a TNF blocking agent should be stopped if severe adverse effects develop or the drug is ineffective (defined as failure to achieve 50% improvement or a fall of $\geq$2 units in BASDAI and/or a reduction of $\geq$2 units in spinal pain assessed on a VAS)

after three months of therapy. Responses should be reviewed every three months and treatment discontinued if these are not maintained.

An international consensus statement, developed in 2003 via review of published papers and a Delphi exercise, recommends TNF-antagonists for patients who fulfil the modified New York criteria for AS, have active disease for ≥4 weeks, defined by BASDAI ≥4 and expert opinion, and who have failed to respond to conventional treatment. It also recommends that they should only be continued in patients who have responded, defined by a 50% relative reduction or an absolute reduction of 2 points (on a 0-10 scale) in BASDAI and expert opinion, after 6-12 weeks.

The National Institute for Health and Clinical Excellence (NICE) is conducting a health technology assessment of adalimumab, etanercept and infliximab in AS that is to be published in February 2007.

Additional information: previous SMC advice

After review of a full submission, the SMC issued advice on 4th October 2005 that etanercept (Enbrel®) is accepted for restricted use within NHS Scotland for the treatment of adults with severe active AS who have had an inadequate response to conventional therapy. It is restricted to use in accordance with the BSR guidelines of July 2004. Etanercept improves signs and symptoms, physical function and quality of life in patients with severe active AS. It reduces acute spinal inflammation, but there is no radiological evidence that it decreases joint damage. An economic evaluation, including an assumption that etanercept reduces disease progression, demonstrated that it is a cost-effective treatment option when used in accordance with the BSR guidelines and where clear and rigorous stopping rules are applied.

After review of a resubmission, the SMC issued advice on 9th September 2005 that infliximab (Remicade®) is accepted for restricted use within NHS Scotland for the treatment of AS in patients who have severe axial symptoms, elevated serological markers of inflammatory activity and who have responded inadequately to conventional therapy. Infliximab demonstrated improvements in signs and symptoms, quality of life and physical functioning and also reductions in spinal inflammation activity. As yet the magnitude of any effect on disease progression is unclear. The treatment provides value for money only where clear and rigorous stopping rules are followed. It is restricted to use in accordance with BSR guidelines of July 2004.

Additional information: comparators

The other two TNF-antagonists, etanercept and infliximab, licensed for treatment of adults with severe active AS who have an inadequate response to conventional therapy have been accepted by the SMC for restricted use within NHS Scotland, in accordance with the BSR guidelines of July 2004.

Additional information: costs

Drug	Dose	Annual cost (£)
Adalimumab	**40mg every two weeks**	**9295**
Infliximab	5mg/kg every 6 to 8 weeks	10910 to 14547*#
Etanercept	25mg twice weekly or 50mg weekly	9295

£14687 to £17903 in first year; * for 60kg to 80kg patient, for those weighing <60kg annual costs would be £8183 to £10910 (£11015 to £13428 in first year); costs from eVadis accessed on 31st August 2006 and the 51st edition of the British National Formulary; doses do not imply therapeutic equivalence.

Additional information: budget impact

The manufacturer estimated that the budget impact of using adalimumab in all eligible patients was £2.72m, £2.25m, £2.34m, £2.43m and 2.53m in the years 2006 to 2010, respectively. This is the same budget impact that using etanercept would have and is less that the budget impact if all eligible patients were given infliximab. The figures assume that 7% (45 patients from 455) of AS patients would be eligible for treatment and that 50% of patients would stop treatment at 12 weeks due to non-response. Adalimumab is one of several anti-TNF treatments and therefore the net impact is likely to be limited.

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 13 October 2006.

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.

Van der Heijde D, Kivitz A, Schiff AK et al. Efficacy and safety of adalimumab in patients with ankylosing spondylitis. Arthritis Rheum 2006; 54: 2136-46

Van der Heijde D, Kivitz A, Schiff AK et al. Adalimumab therapy results in significant reduction of signs and symptoms in subjects with ankylosing spondylitis: the ATLAS trial. American College of Rheumatology Annual Meeting, San Diego, USA, Nov 2005, Abstract no. 691. Oral presentation.

Van der Heijde D, Luo M, Matsumoto A et al. Adalimumab improves health-related quality of life in patients with active ankylosing spondylitis-the ATLAS trial. American College of Rheumatology Annual Meeting, San Diego, USA, Nov 2005, Abstract no. 490. Poster presentation.

Maksymowych WP, Rahman P, Keystone E et al. Efficacy of adalimumab in active ankylosing spondylitis (AS)-results of the Canadian AS study. American College of Rheumatology Annual Meeting, San Diego, USA, Nov 2005, Abstract no. 505.

Lambert RGW, Salonen D, Rahman P et al. Adalimumab reduces spinal and sacroiliac joint inflammation in patients with ankylosing spondylitis (AS) – 52 week magnetic resonance imaging (MRI) results from the Canadian AS study. European League against Rheumatism (EULAR), Annual European Congress of Rheumatology, June 2006. Abstract OP0038.