Scottish Medicines Consortium

etanercept 25mg vial of powder for subcutaneous injection (Enbrel®) (No. 212/05)

Wyeth

New indication: severe active ankylosing spondylitis inadequately controlled by conventional therapy.

4 October 2005

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:

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

Etanercept improves signs and symptoms, physical function and quality of life in patients with severe active ankylosing spondylitis. 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.

Overleaf is the detailed advice on this product.

Chairman,
Scottish Medicines Consortium

etanercept 25mg powder for subcutaneous injection (Enbrel®)

Indication

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

Dosing information

25mg by subcutaneous injection twice a week.

UK launch date

16th January 2004

Comparator medications

Another tumour-necrosis factor (TNF) antagonist, infliximab, is the only other drug licensed in the UK for the treatment of patients with severe active ankylosing spondylitis (AS) who have an inadequate response to conventional therapies. It is indicated for the treatment of patients who have severe axial symptoms, elevated serological markers of inflammatory activity and who have responded inadequately to conventional therapy.

Cost per treatment period and relevant comparators

Drug	Dose	Annual cost (£)
Etanercept	**25mg twice a week**	**9296**
Infliximab	5mg/kg every 6 to 8 weeks	10894 to 14525*#

£14665 to £17877 in first year; * for 60kg to 80kg patient, for those weighing <60kg annual costs would be £8170 to £10894 (£10999 to £13408 in first year)

Summary of evidence on comparative efficacy

Etanercept is a cloned fusion protein consisting of the fixed component of human IgG1 and the ligand-binding portion of a TNF receptor. It binds to soluble and transmembrane forms of TNF, antagonising its biological activity.

Two double-blind trials recruited 84 and 277 adults fulfilling the modified New York criteria for AS who had active disease, as defined by an average score ≥30mm for duration and intensity of morning stiffness, measured on 100mm visual analogue scales (VAS), plus scores ≥30mm on 100mm VAS for two of the following: patient's global assessment of disease activity; Bath AS functional index (BASFI); or total back pain, which is the average of total back pain and nocturnal back pain. They were randomised in the respective studies to 12 and 24 weeks' treatment with placebo or etanercept 25mg by subcutaneous (sc) injection twice weekly. In both studies in intention-to-treat (ITT) analyses, significantly greater proportions of patients in the etanercept groups, compared to the placebo groups, achieved the primary outcome of at least 20% improvement on assessment of AS criteria (ASAS20) by 12 weeks. In the respective trials these were: 60% vs. 23% and 59% vs. 28%. Conditional upon achieving this primary outcome in the 24-week trial, ASAS20 responders at 24 weeks were analysed and found to be significantly greater with etanercept compared to placebo: 57% vs. 22%. Etanercept also improved other measures of disease activity, including the numbers of

ASAS50 and ASAS70 responders, Bath AS disease activity index (BASDAI), C-reactive protein (CRP) and patients' global assessments of disease activity. Function, assessed via Bath AS functional index (BASFI) and spinal mobility, assessed via Schober's test, chest expansion and occiput-to-wall measures, also improved with etanercept. These results are summarised in the tables.

Results of 12-week and 24-week placebo-controlled trials of etanercept in patients with severe ankylosing spondylitis.

	24 weeks		**12 weeks**	
	Etanercept n=138	**Placebo n=139**	**Etanercept n=45**	**Placebo n=39**
% of ASAS20 responders	57**	22	60 *	23
% of ASAS50 responders	42 **	10	49 *	10
% of ASAS70 responders	28 **	5	24	10
% of patients in partial remission+	17*	4	18	10

* p<0.001, ** p<0.0001 vs. placebo; + scores <20 on all assessment of AS (ASAS) criteria; ASAS20, ASAS50 and ASAS70 = improvement of ≥20%, 50%, 70%, respectively, on ≥3 ASAS criteria, plus absence of deterioration in the fourth criterion.

	24-week trial				**12-week trial**			
	Baseline		**Endpoint**		**Baseline**		**Endpoint**	
	PBO	**ETN**	**PBO**	**ETN**	**PBO**	**ETN**	**PBO**	**ETN**
BASDAI (0-100)	60	58	55	34.5[d]	59	61	50	34[c]
CRP (mg/dL)	2.0	1.9	1.9	0.6[d]	9.7	15.4	11.7	4.0[d]
Patient global assess (0-100)	63	63	56	36[d]	63	66	54	38[a]
Total back pain (0-100)	63.5	61	58	37[d]	56	60	51	31[d]
Stiffness (0-100)+	64	61	57	33[d]	63	68	53	36 [b]
BASFI (0-100)	56	52	55	36[d]	57	60	54	40[d]
Schober's test, cm	3.0	3.1	2.9	3.3[b]	2.8	2.2	2.7	2.7[b]
Chest expansion, cm	3.2	3.3	3.0	3.8[d]	3.9	3.3	4.1	3.8
Occiput-to-wall, cm	5.3	5.6	6.0	4.5[d]	4.6	7.3	4.0	6.2

All values are means, except CRP in the 12-week trial, which is the median; a p<0.05, b p≤0.01, c p<0.001, d p<0.0001 etanercept vs. placebo for percent change from baseline at endpoint; BASDAI = Bath ankylosing spondylitis disease activity index ; BASFI = Bath AS function index; CRP = C-reactive protein; PBO = placebo; ETN = etanercept 25mg twice weekly; + mean of duration and intensity of morning stiffness

In an open-label extension to the 24-week trial described previously, 257 patients received etanercept 25mg subcutaneous (sc) twice weekly for 72 weeks. Of the 128 patients who entered the study from the etanercept arm of the double-blind trial, 55% had an ASAS20 response at endpoint, with similar response rates for those who had received placebo in the double-blind trial.

A double-blind trial recruited 40 patients with active AS, defined as presence of inflammatory back pain, morning stiffness ≥45 minutes and at least moderate disease activity in assessments by the patient and physician. Etanercept 25mg sc twice weekly, compared to placebo, significantly improved from baseline to four months the composite physical health and mental health scores of the short form 36 (SF-36) quality of life questionnaire and the SF-36 domains of physical functioning, physical role, bodily pain, vitality, social function and mental health.

In a subgroup of 40 patients within the 24-week trial described previously, etanercept 25mg sc twice daily was associated with a significant reduction compared to baseline in the mean number of acute inflammatory lesions per vertebral unit, assessed via magnetic resonance images (MRI), at 12 and 24 weeks, with no change from baseline in the placebo group. A comparison of the two groups for these outcomes was not reported. The mean numbers of chronic spinal changes, assessed via MRI, increased from baseline at weeks 12 and 24 in both groups, with significant changes in the placebo group.

In a subgroup of 40 patients within the 24-week trial described previously, etanercept 25mg sc twice daily was associated with a significantly greater percent improvement from baseline to 24 weeks in spinal bone mineral density compared to placebo: 3.2% vs. 0.7%. Hip bone mineral density increased from baseline to 24 weeks in the etanercept group by 0.4% and decreased in the placebo group by 0.1%, with the between-group difference not significant.

Other data were also assessed but remain commercially confidential.*

Summary of evidence on comparative safety

In common with other TNF-antagonists, etanercept is associated with an increased incidence of infection, including opportunistic infections and tuberculosis, probably due to suppression of the immune system, which may also mask signs of fever. The relative deficiency of TNF produced by TNF-antagonists may also initiate autoimmune processes, with development of antinuclear and double-stranded DNA antibodies and lupus-like syndromes, although the latter remain uncommon. Etanercept, in common with other TNF-antagonists, has been associated with rare cases of demyelinating disease, including multiple sclerosis. There is also concern that TNF-antagonists, by continually inhibiting pro-inflammatory molecules may increase the risk of cancer, particularly lymphoproliferative malignancies. Currently there is no clinical evidence of this. However, long-term data are required to exclude it.

Etanercept is associated with allergic reactions, but does not need to be administered in hospital. In contrast, infliximab must be administered in hospital, as it has been associated with serious acute infusion-related reactions, including anaphylatic shock, and delayed hypersensitivity reactions. Unlike etanercept, infliximab is contra-indicated in patients with heart failure after results of a trial investigating its use for congestive heart failure at doses of 5mg/kg or 10mg/kg demonstrated higher incidences of mortality and worsening of heart failure in those treated with this drug compared to those given placebo.

Summary of clinical effectiveness issues

One of the requirements within 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 non-steroidal anti-inflammatory drugs (NSAIDs). Patients were not required to have failed treatment with NSAIDs for inclusion in the trials described previously and the numbers of patients within the studies who had not responded to at least two of these drugs are unknown. However, as patients had severe disease with mean duration of at least 10 years, it is likely that many patients would have been treated with at least 2 different NSAIDs.

Etanercept reduces spinal inflammation, as measured by MRI. However, the BSR guidelines note that a possible role for MRI as a prognostic predictor needs to be confirmed. There are no radiological data indicating that etanercept prevents or reduces structural joint damage compared to placebo.

There are no direct comparative trials with infliximab, the other TNF-antagonist licensed for the treatment of adults with severe AS. The relative efficacy and safety of these drugs in this indication are therefore unclear.

Other data were also assessed but remain commercially confidential.*

Summary of comparative health economic evidence

The company submitted an individual patient-based cost utility model comparing etanercept with NSAID treatment for patients who had shown an inadequate response to two NSAIDs. The model examined costs and benefits over a fifteen-year time horizon. The effectiveness side of the model used the data from the 24-week placebo-controlled etanercept trial, described previously, re-analysed to show responders and non-responders according to the BSR criteria. The level of the response in terms of BASDAI and BASFI was calculated using a regression analysis of the trial data and responders to treatment were assumed to maintain this level for the duration of their response. It was also necessary to make an assumption regarding disease progression. It was assumed that patients who responded to treatment experienced no disease progression on the basis of data from the open-label extension of this study. A 10% withdrawal rate per annum was assumed. Utility values were derived using regression analysis of data from the open-label extension study. Costs associated with various levels of function and disability were estimated using data from a postal survey of 1413 UK AS patients.

The result of the base case model was an incremental cost per QALY ratio of £11,700 at fifteen years and this was tested in extensive one-way sensitivity analyses. These indicated that the result was sensitive to changes in the assumption of halted disease progression with etanercept; if the effect on disease progression is very small then the cost per QALY sits around the £30,000 mark. Similarly, the results were relatively sensitive to the costs assumed for the disease states and the baseline analysis used the costings that were most favourable for etanercept. The results were less sensitive to the responder rate, utility values and withdrawal rates used. The inclusion of wider social care costs improved the cost-effectiveness ratio.

In summary, the model was well constructed and used an appropriate comparator. The cost-effectiveness of the product improved as the time span of the model increased but relied on etanercept showing effects on disease progression over that time.

Patient and public involvement

Patient Interest Group Submission – National Ankylosing Spondylitis Society (NASS)

Budget impact

The company estimated the budget impact to be £3.8M in year one, £4.5M in year two and £4.9M in year three. These calculations assumed that 54% of patients would discontinue treatment after three months due to lack of effect, 10% would drop out of treatment each year thereafter and 90% of patients on treatment would receive the treatment at home rather than in hospital. The figures assumed a prevalence of AS of 0.1%.

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 ≥4cm and spinal pain in the last week is ≥4cm on a VAS); and they have failed on conventional treatment with 2 or more NSAIDs each taken sequentially at maximum tolerated or recommended dosage for 4 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 ≥2 units in BASDAI and/or a reduction of ≥2 units in spinal pain assessed on a VAS) after 3 months of therapy. Responses should be reviewed every 3 months and treatment discontinued if these are not maintained.

An AS Assessment Group (ASAS) 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.

Additional information

After review of a full submission, SMC issued advice on the 12th July 2004 that infliximab is not recommended for 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. In one relatively small study, it demonstrated improvements in signs and symptoms, quality of life and physical functioning. However, there is no evidence of a decrease in joint damage. The economic case is not demonstrated. The licence holder have made a resubmission and advice will be published on the SMC website on 10 October, 2005.

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 September, 2005.

Drug prices are those available at the time the papers were issued to SMC for consideration.

** 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. Those shaded grey are additional to those supplied with the submission.

Davis JC, Van Der Heijde D, Braun J et al. Recombinant human tumor necrosis factor receptor (etanercept) for treating ankylosing spondylitis: a randomized, controlled trial. Arthritis & Rheum 2003; 48:3230-6.

Calin A, Dijkmans BAC, Emery P et al. Outcomes of a multicentre randomised clinical trial of etanercept to treat ankylosing spondylitis. Ann Rheum Dis 2004; 63:1594-1600.

Davis JCJ, van der Heijde DM, Braun J et al. Sustained durability and tolerability of etanercept in ankylosing spondylitis for 96 weeks. Ann Rheum Dis 2005 (awaiting publication)

Gorman JD, Sack KE, Davis JC Jr. Treatment of ankylosing spondylitis by inhibition of tumor necrosis factor alpha. New Engl J Med 2002; 346:1349-1356.

Baraliakos X, Davis J, Tsuji W, Braun J. Magnetic resonance imaging examinations of the spine in patients with ankylosing spondylitis before and after therapy with the tumor necrosis factor alpha receptor fusion protein etanercept. Arthritis Rheum 2005; 52: 1216-23.

Davis JC Jr., Fleischmann R, Molitor J et al. Effects of Etanercept (ENBREL®) on Spinal and Hip Bone Mineral Density in Patients With Ankylosing Spondylitis: 24-Week Data. American College of Rheumatology Annual Meeting 2003; Abstract 365.

European Medicines Agency. European public assessment report for Enbrel. 1st October 2004. http://www.emea.eu.int/humandocs/Humans/EPAR/enbrel/enbrel.htm

Amgen. Briefing document for Enbrel (etanercept) for the treatment of ankylosing spondylitis. 28th May 2003. http://www.fda.gov/ohrms/dockets/ac/03/briefing/3967B2_01_Amgen.pdf