PUBLIC SUMMARY DOCUMENT
Product: ETANERCEPT, powder for injection, 25 mg, ENBREL®
Sponsor: Wyeth Australia Pty Ltd
Date of PBAC Consideration: November 2005

1. Purpose of Application

To seek an additional Section 85 authority required listing of etanercept for the treatment, in combination with methotrexate, of adult patients with severe active rheumatoid arthritis who are at high risk of erosive disease in order to slow progression of disease-associated structural damage.

2. Background

Etanercept, a biological disease modifying anti-rheumatic drug (bDMARD), is currently Section 85 Authority required listed on the Pharmaceutical Benefits Scheme (PBS) for treatment of adults with severe active rheumatoid arthritis or active ankylosing spondylitis meeting certain specific criteria.

Also, under Section 100 (Highly Specialised Drugs), etanercept is authority required listed for patients with a documented history of severe active polyarticular course juvenile chronic arthritis with onset prior to the age of 18 years. Etanercept was recommended for the treatment of psoriatic arthritis at the March 2005 meeting. (Listing is yet to be implemented)

3. Registration Status

Etanercept is registered by the Therapeutic Goods Administration for the treatment of:

- active, adult rheumatoid arthritis (RA) in patients who have had inadequate response to one or more disease modifying antirheumatic drugs (DMARDs). Etanercept can be used in combination with methotrexate.
- Severe, active adult rheumatoid arthritis to slow progression of disease-associated structural damage in patients at high risk of erosive disease (see Clinical Trials).
- Active polyarticular-course juvenile chronic arthritis in patients (4-17 years) who have had inadequate response to one or more disease-modifying antirheumatic drugs. Etanercept has not been studied in children less than 4 years of age.
- The signs and symptoms of active and progressive psoriatic arthritis in adults, when the response to previous disease-modifying antirheumatic therapy has been inadequate.
- The signs and symptoms of active ankylosing spondylitis in adults.
- Treatment of adult patients with moderate to severe chronic plaque psoriasis, who are candidates for phototherapy or systemic therapy. Safety and efficacy beyond 12 months have not been demonstrated.

4. Listing Requested and PBAC's View

The sponsor requested an Authority Required listing for a subset of patients within the registered indication. Under the requested listing, treatment would be limited to patients with severe active rheumatoid arthritis who are at high risk of erosive disease. Eligibility for treatment would be determined against a set of criteria including radiographic evidence of bone erosion and blood chemistry.

See Recommendations and Reasons for the PBAC's view.

5. Clinical Place for the Proposed Therapy

The requested listing sought to make etanercept available for the early treatment of patients with severe rheumatoid arthritis who are considered to be at high risk of developing erosive bone disease.

6. Comparator

The submission nominated methotrexate monotherapy as the main comparator. The PBAC did not agree that this was the appropriate comparator.

See Recommendations and Reasons for the PBAC's view.

7. Clinical Trials

The submission presented three trials comparing etanercept + methotrexate and placebo + methotrexate (TEMPO (Klareskog et al, 2004), Weinblatt et al, 1999, Lan et al, 2004); two trials comparing etanercept monotherapy and methotrexate monotherapy (TEMPO (Klareskog et al, 2004) and Bathon et al, 2000). The details of the published trials are as follows:

Trial/First author	Protocol/Publication title	Publication citation
TEMPO 1.Klareskog et al, 2.Kobelt et al	Therapeutic effect of the combination of etanercept and methotrexate compared with each treatment alone in patients with rheumatoid arthritis: double-blind randomised controlled trial (TEMPO)	1.Lancet 2004; 363(9410):675-81. 2.Annals of the Rheumatic Diseases 2005; 64: 1174 – 1179
Lan et al	A comparative study of etanercept plus methotrexate and methotrexate alone in Taiwanese patients with active rheumatoid arthritis: a 12-week, double-blind, randomised, placebo-controlled study.	Journal of the Formosan Medical Association (Taiwan Yi Zhi) 2004; 103(8):618-23.
Weinblatt et al	A trial of etanercept, a recombinant tumour necrosis factor receptor:Fc fusion protein, in patients with rheumatoid arthritis receiving methotrexate.	New England Journal of Medicine 1999; 340(4):253-9.
Bathon et al	A comparison of etanercept and methotrexate in patients with early rheumatoid arthritis.	New England Journal of Medicine 2000; 343:1586-93.

8. Results of Trials

Both radiographic and clinical outcomes from the 4 trials and from a subgroup within a trial were presented in the submission. Not all results presented in the submission have been published to date. The ACR50 (American College of Rheumatology criteria), Total Sharp Scores (TSS) and Health Assessment Score (HAQ) results that have been published are provided in the following tables.

(Note: the results reported in this Public Summary Document are taken from the cited publications. They may vary slightly from the numbers considered by PBAC which were taken from the sponsor's internal reports.)

ACR50 response rates observed in the trials comparing etanercept + methotrexate with methotrexate monotherapy

Trial	Proportion of patients, n/N (%)		RD (95% CI)	RR (95% CI)
	Etanercept + MTX	Placebo + MTX		
3 months/12 weeks				
Lan et al, 2004	19/29 (65.5%)	3/29 (10.3%)	0.55 (0.35, 0.76)	6.33 (2.10, 19.09)
Weinblatt et al, 1999	25/59 (42.4%)	0/30 (0.0%)	0.42 (0.29, 0.56)	26.35 (1.66, 418.44)
6 months/24 weeks				
Weinblatt et al, 1999	23/59 (39.0%)	1/30 (3.3%)	0.36 (0.22, 0.50)	11.69 (1.66, 87.67)
12 months/52 weeks				
TEMPO (Klareskog et al, 2004)	69%	43%	0.27 (0.18, 0.35)	1.63 (1.37, 1.94)

MTX=methotrexate; n=number of patients achieving outcome; N=number of patients in ITT (intention-to-treat) population; RD=risk difference; RR=relative risk

The mean changes in Total Sharp Score (TSS) in etanercept +MTX combination therapy and in MTX monotherapy in the analysed radiographic ITT population from the TEMPO trial (Klareskog et al, 2004) at 12 months are tabulated below. TSS is a radiographic measure, which is the sum of erosions and joints space narrowing measured on a defined scale.

Population	Months	N		Mean change (95% CI)	
		Etanercept + MTX	Placebo + MTX	Etanercept + MTX	Placebo + MTX
All patients	12	218	212	-0.54 (-1.00, -0.07)	2.8 (1.08, 4.51)

TSS=total Sharp score; MTX=methotrexate; N=number of patients;

Results for health assessment questionnaire (HAQ) for the TEMPO trial (Kobelt et al, 2005)

Duration of treatment	Patient number		Mean (SD)	
	Etanercept + MTX	Placebo + MTX	Etanercept + MTX	Placebo + MTX
Baseline	231	228	1.8 (0.6)	1.7 (0.7)
1 year	193	159	0.7 (0.7)	0.9 (0.8)
2 years	161	118	0.7 (0.7)	0.9 (0.8)

SD=standard deviation

The pooled differences across treatment groups in discontinuations due to adverse events did not reach statistical significance at any time point. The rate of injection-site reactions were higher in patients treated with etanercept

See Recommendations and Reasons for the PBAC's views on the trial results.

9. Clinical Claim

The submission described etanercept in combination with MTX as having significant advantages in effectiveness over MTX monotherapy and having similar or less toxicity.

Although this claim may have been reasonable, the PBAC considered the comparison was not informative, given its view about the comparator.

10. Economic Analysis

A preliminary economic evaluation adopting a cost-effectiveness approach was presented. The only resource included in the preliminary economic evaluation was drug costs.

A modelled economic evaluation was also conducted. The resources included were drug costs, hospitalisation costs and costs for specialist visits.

The base case modelled incremental discounted cost/extra discounted quality adjusted life year (QALY) gained was between $45,000 to $75,000.

11. Estimated PBS Usage and Financial Implications

The submission estimated the cost per year to the PBS of between $30 million to $60 million in Year 4 of listing, which was considered an underestimate by the PBAC

12. Recommendation and Reasons

The PBAC considered the requested restriction wording did not adequately define a group at high risk of erosive disease with sufficient clarity for PBS subsidy. The submission proposed only three variables as part of the criteria but the PBAC noted that other variables including rheumatoid factor, genetic tests (shared epitope containing HLA alleles), the AUC of CRP, failure to respond to therapy, educational status etc are also important predictors of poor outcome.

The submission's analyses appeared to imply that only patients with early disease (incidence population) at high risk of future further erosions would be treated. However, as requested, the restriction would tend to encompass the overall residual prevalence population of rheumatoid arthritis patients not already eligible for etanercept.

Further, the PBAC considered it would be appropriate for a restriction to include an active joint count and continuation criteria, as with the current restriction for severe active RA. Particular thresholds included in the restriction also needed clearer justification. The PBAC also anticipated that there might also be problems with any proposal to include the duration of disease as part of any restriction as this would be difficult to ascertain.

The PBAC did not accept the appropriate comparator to be 'methotrexate monotherapy'. Patients with early disease at high risk of erosive disease would tend now to be treated with combination DMARD therapy. The PBAC noted that supporting evidence for this approach to treatment had been available for some years. O'Dell et al 1996, New England Journal of Medicine examined the efficacy and toxicity of combination therapy vs methotrexate monotherapy and concluded that methotrexate, sulfasalazine and hydroxychloroquine combination therapy was more effective and no more toxic than methotrexate monotherapy. Subsequent studies – Mottonen et al and Boers et al have examined similar combination therapy in early RA patients and established similar efficacy.

No evidence was presented that the patients for whom the restriction was requested comparing the outcomes of the proposed combination of etanercept and methotrexate with those of other DMARD combination therapy. If the intent of the restriction was to capture a sub-group of high-risk patients, then the nominated main comparator of methotrexate monotherapy was inappropriate because such patients would more likely be treated with more aggressive combination, particularly methotrexate-based triple therapy.

The PBAC noted the evidence comprised a post hoc sub-analysis of patients with erosive disease, but only limited information was available on how the sub-group and erosive changes were selected. The patients included in this sub-group were not identified a priori, or

at the start of the trial, as potentially being at higher risk of progressive disease. The population proposed raised the question of the applicability of the results of the trials to the requested restriction.

The sub-group analysis comprises patients with some evidence of erosion who were classified to be at risk, but there is no evidence to show that these patients are at greater risk or have more aggressive disease than patients meeting the current eligibility criteria.

The results for radiographic outcomes (TSS scores) from the TEMPO (Klareskog) trial suggested that etanercept with methotrexate combination therapy was more effective than methotrexate alone, but there were no data to suggest that the extent of benefit would be different between patients in the identified sub-group as opposed to the entire intention-to-treat population.

The HAQ score showed a numerical advantage for the patients in the sub-group in comparison to the trial population as a whole, and was used in the submission to derive utility values. However, no statistical test for interaction was provided in order to assess whether a treatment effect modification was present in the sub-group. The confidence intervals suggested that a treatment effect modification was unlikely. Thus, the validity of the HAQ score to discriminate treatment effect was considered uncertain.

The PBAC rejected the submission on the grounds that the requested restriction failed to adequately identify and restrict usage to the intended PBS population and the choice of comparator was inappropriate.

13. Context for Decision

The PBAC helps decide whether and, if so, how medicines should be subsidised in Australia. It considers submissions in this context. A PBAC decision not to recommend listing or not to recommend changing a listing does not represent a final PBAC view about the merits of the medicine. A company can resubmit to the PBAC or seek independent review of the PBAC decision.

14. Sponsor's Comment

The Sponsor is considering its course of action and plans to provide a resubmission.