PUBLIC SUMMARY DOCUMENT
Product: Etanercept, injection set containing 4 vials powder for injection 25 mg and 50 mg and 4 pre-filled syringes solvent 1 mL, and injection 50 mg in 1 mL single use pre-filled syringes, 4, Enbrel®
Sponsor: Wyeth Australia Pty Ltd
Date of PBAC Consideration: July 2008

1. Purpose of Application

The submission sought an extension to the current PBS listing of etanercept for rheumatoid arthritis (RA) and psoriatic arthritis (PsA) to include patients with ≥ 10 tender and swollen joints or ≥ 2 major affected joints and to halve the thresholds for c-reactive protein (CRP) and erythrocyte sedimentation rate (ESR) levels.

2. Background

Etanercept for rheumatoid arthritis

Etanercept was recommended for listing at the December 2002 PBAC meeting on the basis of a high but acceptable cost-effectiveness ratio for adult patients with severe and active rheumatoid arthritis who met certain criteria. Listing was effective from 1 August 2003.

At the March 2005 meeting, the PBAC rejected a submission for etanercept seeking to reduce the minimum initial joint count from 20 to 14 active joints (retaining the 4 big joint criteria) and to change the continuing treatment criteria to reduce the active joint count from fewer than 10 to fewer than 7, because of uncertainty of the extent of reduced clinical benefit associated with a smaller reduction in active joint count and the resulting uncertain, but unacceptable cost-effectiveness.

Etanercept for psoriatic arthritis

At the March 2005 meeting, the PBAC recommended listing etanercept for treatment of patients with PsA on the basis of acceptable cost-effectiveness provided that the same indices of disease severity that applied to the listing in rheumatoid arthritis applied to the requested listing in psoriatic arthritis. The submission had claimed that patient with PsA with ≥ 14 active joints represent a similar burden of disease/extent of disutility compared to rheumatoid arthritis (≥ 20 joints) and evidence was presented to support a proposed lower CRP threshold for PsA (> 10 mg/L) compared to RA (> 15 mg/L). The PBAC was of the view that it could not accept the requested initiation criteria as insufficient evidence had been provided over whether the extent of disutility in psoriatic arthritis patients with 14 affected joints, in the requested listing, was comparable with the extent of utility accepted for rheumatoid arthritis patients with 20 affected joints. Listing was effective from 1 August 2006.

3. Registration Status

Etanercept is TGA registered for:

- Active, adult RA in patients who have had inadequate response to one or more disease modifying antirheumatic drugs (DMARDs).
- Severe, active, adult RA to slow progression of disease-associated structural damage in patients at high risk of erosive disease.
- Active polyarticular-course juvenile chronic arthritis.
- Active and progressive PsA in adults, when the response to previous disease-modifying antirheumatic therapy has been inadequate.
- Active ankylosing spondylitis

- Severe chronic plaque psoriasis.

4. Listing Requested and PBAC's View

A summary of the current and proposed eligibility criteria for initiation and continuation of treatment is provided in the table below:

Component	Current restriction	Requested restriction (as specified in the Pre-Subcommittee response)
Initiation criteria		
Prior use of DMARDs	Must have failed to achieve an adequate response to: Methotrexate of at least 20mg weekly for at least 3 months AND Sulfasalazine of at least 2g daily for at least 3 months OR Leflunomide of up to 20mg daily for at least 3 months.	No change
Definition of affected joint	Swollen AND tender	No change
Number of affected joints	At least 20 in total OR at least 4 major joints	At least 10 in total OR at least 2 major joints
ESR CPR	ESR >25mm/hr OR CRP >15mg/L	An ESR or CRP value outside of normal range for that test, specified as ESR >12.5mm/hr OR CRP >7.5mg/L
Overlap of eligibility for current and requested restrictions	NA	Do not meet the current bDMARD RA and PsA initiation criteria
Continuation criteria		
Timing of assessment	Between Weeks 12 and 16	No change
Number of affected joints	At least 50% reduction in total joint count from baseline; or At least 50% reduction in major joint count from baseline (from at least 4)	At least 50% reduction in total joint count from baseline OR At least 50% reduction in major joint count from baseline (from at least 2)
ESR	No greater than 25mm/hr OR ≥20% Δ ESR from baseline	No change
CRP	No greater than 15mg/L OR ≥20% Δ CRP from baseline	No change

For PBAC's view, see Recommendation and Reasons.

5. Comparator

The submission nominated placebo/standard care as the main comparator.

The PBAC considered that the cost-effectiveness in the requested population (marginal group), not the total population (current plus new populations), is the relevant consideration for this submission.

For PBAC's view, see Recommendation and Reasons.

6. Clinical Trials

The submissions presented seven randomised controlled trials comparing etanercept ± methotrexate or sulfasalazine and placebo ± methotrexate or sulfasalazine for patients with RA, and two randomised trials comparing etanercept ± methotrexate and placebo ± methotrexate in patients with PsA. All of the trials presented in this submission had previously been considered by the PBAC for both RA and PsA, with the exception of the trial reported by Combe (2007) that assessed the use of etanercept ± sulfasalazine in the treatment of RA.

The published trials included in the submission are reproduced in the table below:

Trial/First author	Protocol title/ Publication title	Publication citation
Direct randomised trials for RA		
16.0009 Moreland et al (1999)	Etanercept therapy in rheumatoid arthritis: A randomised, controlled trial.	Annals of Internal Medicine (1999) 130:478-486.
Mathias SD et al.	Health-related quality of life and functional status of patients with rheumatoid arthritis randomly assigned to receive etanercept or placebo.	Clinical Therapeutics (2000) 22:128-139.
Moreland LW et al.	Effect of etanercept on fatigue in patients with recent or established rheumatoid arthritis.	Arthritis Care and Research (2006) 55:287-293.
16.0014 Weinblatt et al (1999)	A trial of etanercept, a recombinant tumor necrosis factor receptor:Fc fusion protein, in patients with rheumatoid arthritis receiving methotrexate.	New England Journal of Medicine (1999) 340:253-259.
16.0036 Keystone et al (2004)	Once-Weekly Administration of 50 mg Etanercept in Patients with Active Rheumatoid Arthritis: Results of a Multicenter, Randomised, Double-Blind, Placebo-Controlled Trial.	Arthritis and Rheumatism (2004) 50:353-363.
308-EU TEMPO Klareskog et al (2004)	Therapeutic effect of the combination of etanercept and methotrexate compared with each treatment alone in patients with rheumatoid arthritis: Double-blind randomised controlled trial.	Lancet (2004) 363:675-681.
Zhou H et al.	Unaltered etanercept pharmacokinetics with concurrent methotrexate in patients with rheumatoid arthritis.	Journal of Clinical Pharmacology (2004) 44:1235-1243.
Van Der Heijde D et al.	Comparison of different definitions to classify remission and sustained remission: 1 Year TEMPO results.	Annals of the Rheumatic Diseases (2005) 64:1582-1587
Van Der Heijde D et al.	Presentation and analysis of data on radiographic outcome in clinical trials: Experience from the TEMPO study.	Arthritis and Rheumatism (2005) 52:49-60
Landewe R et al.	Disconnect between inflammation and joint destruction after treatment with etanercept plus methotrexate: Results from the trial of etanercept and methotrexate with radiographic and patient outcomes.	Arthritis and Rheumatism (2006) 54:3119-3125.
Van Der Heijde D et al.	Comparison of etanercept and methotrexate, alone and combined, in the treatment of rheumatoid arthritis: Two-year clinical and radiographic results from the TEMPO study, a double-blind,	Arthritis and Rheumatism (2006) 54:1063-1074.

	randomised trial.	
Van Der Heijde D et al.	Patient reported outcomes in a trial of combination therapy with etanercept and methotrexate for rheumatoid arthritis: The TEMPO trial.	Annals of the Rheumatic Diseases (2006) 65:328-334.
Lan et al (2004)	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 (2004) 103:618-623.
16.0030 Combe et al (2007)	Etanercept and sulfasalazine, alone and combined, in patients with active rheumatoid arthritis despite receiving sulfasalazine: A double-blind comparison.	Annals of the Rheumatic Diseases (2007) 65:1357-1362.
Direct randomised trials for PsA		
16.0612 Mease et al (2000)	Double-blind, Randomized, Placebo-controlled Study of Etanercept (Recombinant Human Tumor Necrosis Factor Receptor [p75] Fusion Protein: in the Treatment of Psoriatic Arthritis (PsA) and Psoriasis, with Open-label Extension	Lancet (2000) 356:385-390.
16.0030 Mease et al (2004)	Double-blind, Randomized, Placebo-controlled Phase 3 Study of Etanercept in the Treatment of Psoriatic Arthritis (PsA) and Psoriasis, with radiographic endpoints.	Arthritis Rheum (2004) 50:2264-72. Clin Exp Rheumatol (2002) 20:S116-S121. Various conference abstracts

7. Results of Trials

The results of the trials presented in the submission were not specifically relevant to the population for whom PBS listing was sought and did not form part of the modelled economic evaluation. The submission provided an analysis of individual patient data from two of the RA trials and one of the PsA trials to estimate the proportion of patients who would qualify to initiate and continue treatment with etanercept under the current and requested restrictions.

The sample of patients who represent the requested RA and PsA marginal listing populations was identified from the individual patient datasets for trials 16.0009/16.0014 and trial 16.0030; the modelled economic evaluations were based on the data from these samples for RA and PsA, respectively. The RA and PsA sample sizes are summarised in the table below.

Number of patients who represent the requested marginal listing population.

Scenario	Etanercept	Placebo
RA		
Marginal population with ≥10 total OR ≥2 major joints AND CRP >7.5mg/L OR ESR >12.5mm/hr*	**32**	**34**
PsA		
Marginal population with ≥10 total OR ≥2 major joints AND CRP >7.5mg/L OR ESR >12.5mm/hr*	**21**[c]	**28**

* Although the number of total and major joints affected are equal to or greater than 10 and 2, respectively, these numbers exclude any patients who qualify under the current criteria

The datasets from the RA and PsA trials respectively showed that there was a statistically significantly greater number of etanercept-treated patients than placebo-treated patients who

achieved adequate treatment response (i.e. the proportion of patients who met the PBS continuation criteria at week 12).

For PBAC's comments on these results, see Recommendation and Reasons.

8. Clinical Claim

The submission claimed that etanercept had significant advantages in terms of effectiveness over placebo, but was associated with greater toxicity.

The PBAC had previously accepted that based on the trial evidence presented, etanercept has an acceptable safety profile, but that it is more toxic than placebo.

For PBAC's view, see Recommendation and Reasons.

9. Premodelling studies

In translating the clinical evaluation to the listing requested for inclusion in the economic evaluation, the submission identified the following issues:

Type	Issue
Applicability	RA Application of eligibility criteria to mimic the current and proposed PBS eligibility criteria for etanercept to pooled individual trial data from two of the key trials presented (Moreland *et al* (1999), appropriately excluding the etanercept 10mg twice a week arm, and Weinblatt *et al* (1999)). PsA Application of eligibility criteria to mimic the current and proposed PBS eligibility criteria for etanercept to individual trial data from Mease 2004 presented. For each disease, three post-hoc sub-group analyses were undertaken *in the submission* comparing : (i) baseline demographics and disease characteristics of the subgroups; (ii) trial response rates (as defined by ACR 20, ACR 50 and ACR 70) of the subgroups; and (iii) the proportion of PBS continuers using the current and proposed eligibility criteria versus the proportion of "trial responders" using one of the trial definitions of response (ACR 50). The proportion of PBS continuers was measured as "incremental efficacy absolute risk difference" by the submission, and was used in the economic analysis in preference to the trial based ACR50 definition of response to estimate the number of eligible patients for initiation and continuation of treatment at week 12. The proportion of "PBS continuers" was estimated by the submission to be substantially higher than the proportion of ACR50 responders for the same population(s).
Extrapolation	Two extrapolation issues relevant to both RA and PsA were identified during the course of the evaluation: (i) extrapolation of trial results from a 24 week time period to a 5 year time horizon; and (ii) extrapolation of cross-sectional health service utilisation costs estimated for a three month period to a five year time horizon.
Transformation	Utility transformation (RA and PsA)

	RA trial based individual patient data included Health Assessment Questionnaire (HAQ) values as a measure of patient functional status; however no utility information was collected during the trials. The submission "triangulates", or uses an indirect comparison of three sources of information to transform HAQ scores into utility values using the Health Utility Index (HUI-3) instrument: (i) pooled individual patient data from Moreland *et al* (1999), excluding the etanercept 10 mg twice a week arm, and Weinblatt *et al* (1999); (ii) a cross-sectional utility and resource use study commissioned by the sponsor in 170 participants at four study sites; and (iii) an analysis of a sub-population of the Australian Rheumatology Association Database (ARAD), commissioned by the sponsor. The ARAD is a national voluntary register of patients in Australia being treated with biological disease modifying anti-rheumatic drugs (bDMARDs) which began recruiting patients in 2003. <u>Resource Use and Costs (RA and PsA)</u> Determination of resource use and costs involved in the treatment of RA by utilisation of data from the same utility study mentioned in (ii) above. Collected data on costs were combined to calculate fortnightly costs per patient and mapped to corresponding HAQ scores from the commissioned utility and resource use study.

For PBAC's view, see Recommendation and Reasons.

10. Economic Analysis

The submission presented a stepped economic evaluation.

The Pre-Sub-Committee Response presented updated modelled economic evaluations that included additional costs and cost-offsets compared with those presented in the submission.

- The costs of ongoing assessment for continuation of PBS subsidy had now been applied at the end of every 24 week period in the model following the initial week 12 assessment, with the same cost applied at every assessment point. The costs (with appropriate discounting at a rate of 5% per annum) – at week 12 (assessment for continuation) and every 24 weeks thereafter (coinciding with the assessment for continued response for additional scripts) have been appropriately applied.
- The costs associated with carers and home modifications had been taken from the Resource Use questions in the RA Utility Study presented in the submission. These costs for carer's time and home modifications had been used to derive a new linear relationship between Health Assessment Outcome (HAQ) scores versus resource use costs.

In the sponsor's pre-PBAC response, the base case incremental cost-effective ratios were recalculated for the marginal populations to be consistent with the intent of the requested restriction. The results estimated the ICERs to be between $50,000 - $100,000 per QALY gained for RA and between $50,000 to $100,000 per QALY gained for PsA.

For PBAC's view, see Recommendation and Reasons.

11. Estimated PBS Usage and Financial Implications

The likely number of eligible patients per year was estimated to be less than 10,000 for both RA and PsA in Year 5. These figures were based on prevalence and incidence estimates.

The financial cost per year to the PBS was estimated to be between $10 – 30 million in Year 5 for RA and less than $10 million in Year 5 for PsA. The submission's estimates were considered uncertain given the submission's assumptions, including the number of patients eligible for the proposed restriction, the uptake rates and market share of etanercept.

12. Recommendation and Reasons

The PBAC noted the Sponsor's request in the submission, pre-subcommittee response and hearing, that the new population would be exclusively eligible for etanercept (ie no interchangeability with other bDMARDs). However the Committee was concerned that this limited the choice of agents for initiation, in patients with less severe disease, created inequity for patients treated under the proposed criteria compared to the current criteria, and leaves the proportion of the new population who fail treatment with etanercept without the opportunity to try an alternate bDMARD until their condition deteriorates sufficiently to be eligible under the current criteria.

The PBAC considered that there is uncertainty in the clinical effectiveness of etanercept for rheumatoid arthritis and psoriatic arthritis in the proposed (marginal) population as it is based on a very small number of patients from the two trials (RA) and 1 trial (PsA) for which individual patient data was available. The PBAC noted that of the available evidence for RA the two pivotal trials were the older studies published by Moreland (1999) and Weinblatt (1999), and that the latter study reported a relative risk that differed substantially from other relevant trials.

The PBAC noted that the short and medium-term toxicity of etanercept is well established, however the long term toxicity remains uncertain. This may be important in the new population who would commence treatment with etanercept earlier in their disease.

The PBAC considered that there was uncertainty in the model, relating to applicability, transformation and extrapolation. In terms of applicability, while the approach taken is reasonable, the small number of patients from the trials who meet the PBS criteria results in confidence intervals around the estimates of risk difference that are relatively wide and increases the uncertainty of the results. The PBAC considered that the model's extrapolation of the outcomes from the 24 week trials to 5 years, and of the 3 month cross-sectional observational data on health system resource use to a 5 year period, resulted in additional uncertainty. There is also uncertainty in the transformation of trial-based individual patient data Health Assessment Questionnaire (HAQ) scores to utilities based on the 'triangulation' approach presented in the submission (literature review, analysis of the commissioned Australian Utility Study, and analysis of the Australian Rheumatology Association Database (ARAD)). The PBAC noted two key issues with the utility study (a) that the patients in the Australian Utility Study overall have less severe disease than the requested PBS population and the relationship between utility and joint involvement may not be the same across populations, and (b) as many patients are not on bDMARDs, the study does not take account of treatment with etanercept and its impact on utility. Of further concern was that the relationship between HAQ and utility at 24 weeks is assumed to be maintained to 5 years and the HAQ at 24 weeks is assumed constant for 5 years (except where a patient discontinues treatment). This was not considered to represent the nature of RA and PsA. The PBAC accepted the advice from ESC that, as generally observed in cross-sectional studies, there was a large variation in utility scores. The relationship between HAQ scores and utilities appeared to be driven by relatively few observation of individuals with large number of

involved joints. Therefore, it may not be valid to extrapolate from a cross-sectional relationship to a relationship in individuals over time. Overall, the PBAC considered that the incremental cost-effectiveness ratios (ICERs) presented in the submission are uncertain.

The PBAC considered that the cost-effectiveness in the requested population (marginal group) is the relevant consideration for this submission. The PBAC noted that the ICERs in the marginal RA and PsA populations were high and unacceptable.

Therefore, the PBAC rejected the application on the basis of uncertain clinical effectiveness and uncertain and high cost-effectiveness.

The PBAC considered that it would be timely to conduct a review of bDMARDS with input from Sponsors and the Australian Rheumatology Association (ARA), to examine use of these agents in the current population and to consider if subsidy in a broader population is appropriate.

Recommendation
Reject

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 would welcome a review of bDMARDs for earlier treatment of these rheumatic diseases. The sponsor will be considering its position regarding any future course of action, and refers you to its own website at http://www.wyeth.com.au/go/top-navigation/media-room for further comment.