Public Summary Document

Product:	Etanercept, injection set containing 4 vials powder for injection 25 mg or 50 mg and 4 pre-filled syringes solvent 1 mL, Enbrel®
Sponsor:	Wyeth Australia Pty Ltd
Date of PBAC Consideration:	March 2006

1. Purpose of Application

The resubmission requested an authority required listing on the Pharmaceutical Benefits Scheme (PBS) for certain patients with severe chronic plaque psoriasis.

2. Background

At the July 2005 meeting, the Pharmaceutical Benefits Advisory Committee (PBAC) rejected a submission for etanercept for an authority required listing for certain adults with severe chronic plaque psoriasis because of uncertain and unacceptable cost-effectiveness.

3. Registration Status

Etanercept is registered for the treatment of adult patients with moderate to severe chronic plaque psoriasis, who are candidates for phototherapy or systemic therapy.

4. Listing Requested and PBAC's View

The sponsor requested an authority required PBS listing for a subset of patients within the registered indication. The PBAC's view was that the restriction be closely aligned to the PBS restriction for efalizumab. The PBAC noted that the sponsor had agreed to this.

5. Clinical Place for the Proposed Therapy

Psoriasis is a chronic, incurable inflammatory disorder that, although not life-threatening, can severely impact on a patient's quality of life. Current psoriasis therapies reduce the symptoms but do not provide a permanent cure for this chronic disease. Etanercept is proposed as a last line therapy for patients with severe psoriasis that are unresponsive to, contraindicated to, or intolerant to conventional psoriasis therapies.

6. Comparator

The submission nominated standard medical management (i.e placebo) as the main comparator.

For PBAC's view, see Recommendation and Reasons.

7. Clinical Trials

The key clinical evidence was from three randomised, double-blind, placebo-controlled, parallel-design, multi-centre trials (Leonardi et al, 2003; Gottlieb et al 2003 and Papp et al, 2005). Across the three trials, 415 patients were treated with etanercept 25mg twice weekly, 358 patients with 50mg twice weekly, and 414 patients with placebo.

(Note: the patient numbers 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. These differences do not affect the overall conclusions).

The primary outcome measure in all three trials was the PASI 75 (proportion of patients with ≥75% reduction from baseline PASI (Psoriasis Area and Severity Index (PASI)).
Two of the studies had been published at the time of submission and one trial has been published subsequently, as follows:

Trial/first author	Protocol/Publication title	Publication citation
Gottlieb AB	A randomized trial of etanercept as monotherapy for psoriasis.	Arch Dermatol 2003; 139:1627-1632.
Leonardi CL	Etanercept as monotherapy in patients with psoriasis.	N Engl J Med 2003; 349:2014-2022.
Papp KA	A global phase III randomized controlled trial of etanercept in psoriasis: safety, efficacy, and effect of dose reduction.	Brit J Derm 2005; 152:1304-1312

The submission also presented a subgroup analysis for patients with a baseline PASI score > 15, the patients who would receive PBS-subsidised treatment under the proposed listing restriction. This analysis has not been published.

8. Results of Trials

The Intent To Treat (ITT) results of the key trials are summarised in the following table for the outcome PASI 75 at 12 and 24 weeks of treatment.

(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. These differences do not affect the overall conclusions).

Trial	Week 12		ARD (95% CI)	RR (95% CI)	NNT (95% CI)
	Etanercept (25mg BIW)	**Placebo**			
Gottlieb et al	17/57 (30%)	1/55 (2%)	0.25 (0.14, 0.37)	16.0 (2.2, 116.8)	4 (3, 5)
Leonardi et al	55/162 (34%)	6/166 (4%)	0.28 (0.21, 0.36)	8.9 (3.9, 20.1)	3 (3, 4)
Papp et al	67/196 (34%)	6/193 (3%)	0.31 (0.24, 0.38)	11.0 (4.9, 24.8)	3 (3,4)
Pooled	**139/415 (33%)**	**13/414 (3%)**	**0.30 (0.26, 0.35)**	**10.7 (6.0, 18.5)**	**3 (3,4)**
	Week 24				
Gottlieb et al	**32/57 (56%)**	**3/55 (5%)**	**0.46 (0.32, 0.60)**	**10.0 (3.2, 31.0)**	**2 (2, 3)**
	Week 12				
	Etanercept (50mg BIW)	**Placebo**			
Papp et al	96/194 (49%)	6/193 (3%)	0.46 (0.39, 0.54)	15.9 (7.2, 35.4)	2 (2, 3)
Leonardi et al	81/164 (49%)	6/166 (4%)	0.43 (0.35, 0.52)	13.2 (5.9, 29.4)	2 (2, 3)
Pooled	**177/358 (49.4%)**	**12/359 (3.3%)**	**0.46 (0.41, 0.52)**	**14.8 (8.4, 26.1)**	**2 (2, 2.4)**
	Etanercept (50mg BIW)	**Etanercept (25mg BIW)**			
Papp et al	96/194 (49%)	67/196 (34%)	0.15 (0.06, 0.25)	1.45 (1.14, 1.84)	7 (4, 17)
Leonardi et al	81/164 (49%)	55/162 (34%)	0.15 (0.05, 0.25)	1.45 (1.13, 1.88)	7 (4,17)
Pooled	**177/358 (49%)**	**122/358 (34%)**	**0.15 (0.08,0.23)**	**1.45 (1.21,1.73)**	**7 (4, 13)**

All three trials showed that significantly more patients treated with etanercept at 25mg twice weekly or 50mg twice weekly exhibited a 75% improvement in PASI scores from baseline at 12 weeks and 24 weeks compared with patients treated under placebo conditions. In the subgroup of patients with baseline PASI > 15, similar proportions exhibited a 75% improvement in PASI as for the total trial population.

With few exceptions, there was no statistically significant difference in any trial between the numbers of subjects reporting adverse events (either infectious or non-infectious) in groups treated with either 25mg twice weekly or 50mg twice weekly of etanercept compared with placebo over a 12 week period. However, significantly more subjects treated with 50mg or 25mg twice weekly of etanercept reported injection-site reactions compared with placebo. Monitoring of adverse events was not reported beyond 24 weeks after initiation of treatment.

9. Clinical Claim

The submission claimed that etanercept had significant clinical advantages over placebo. It is significantly more effective than placebo but had moderately more toxicity.

The submission did not provide an adequate evidentiary basis to fully determine the comparative effectiveness and toxicity of etanercept and efalizumab. The PBAC considered that given that an indirect comparison of randomised placebo controlled trials would most likely form this evidence basis, the evidence presented was sufficient to justify a recommendation to list on a cost-minimisation basis.

10. Economic Analysis

The submission presented a trial based cost-effectiveness analysis as the preliminary economic evaluation.

In the modelled economic evaluation, the incremental discounted cost per extra discounted quality adjusted life year (QALY) associated with Enbrel treatment was estimated to be in the range of $15,000 - $45,000 for patients treated with 25mg twice weekly for 12 weeks, then with 25mg twice weekly for 12 week periods at relapse for eligible responders.

The PBAC did not consider that the modelling presented in the submission substantiated the claim of cost-effectiveness at the initial higher dose of 50mg etanercept twice per week for the first 12 weeks. The PBAC did not consider the modelled economic evaluation to be helpful because it was based on a comparison with placebo rather than with efalizumab.

11. Estimated PBS Usage and Financial Implications

The submission estimated the number of patients suitable for Enbrel therapy with severe disease (PASI ≥ 15) to be < 10,000 per year in year 4 of listing.

The submission estimated the financial cost per year to the PBS to be up to $10 – 30 million per year for patients with a baseline PASI ≥15 and a PASI 75 response with the 25 mg twice weekly regimen in the fifth year of listing. The cost of etanercept was now likely to be shared with efalizumab.

12. Recommendation and Reasons

The PBAC recommended listing on a cost-minimisation basis concluding that, based on an indirect comparison, etanercept was no worse than efalizumab for the treatment of severe

refractory chronic plaque psoriasis. The equi-effective doses are etanercept 25 mg twice per week on a 12 week cyclical basis to provide for a total of 24 weeks of active etanercept treatment over 48 weeks and efalizumab 1 mg/kg/week for a total of 48 weeks.

The PBAC had concerns regarding the submission's nomination of placebo as the comparator, in light of its recent recommendation to list efalizumab on the PBS for the treatment of severe refractory chronic plaque psoriasis. Furthermore, based on the comparison with the 25 mg twice weekly regimen presented in the evaluation which appropriately compared the two listing options proposed in the submission, the incremental cost effectiveness ratio for 50 mg twice weekly was considered to be unacceptably high. The PBAC therefore rejected listing for the initial 50 mg twice weekly regimen.

The PBAC considered the modelled economic evaluation to be unhelpful because it was based on a comparison with placebo rather than with efalizumab. Further, the Committee noted that there was uncertainty relating to the conversion of the Body Surface Area score to utilities and re-treatment success rates.

The PBAC recommended that the restriction be as closely aligned to the ratified restriction for efalizumab, noting that there would need to be some adjustments to take into account the intermittent dosage regimen for etanercept versus continuous dosing for efalizumab. The PBAC also noted that the requested restriction limited re-treatment following demonstration of response, to patients whose condition rebounded to a level of 75% of their original PASI score. The Committee did not accept this requirement and considered that timing of re-treatment should be left up to clinical judgement, although the PBS restriction would still need to provide for cyclical dosing with at least a 12-week period between 12-week courses of etanercept as provided for in the above conclusion of equi-effectiveness.

The PBAC considered that interchangeability arrangements with efalizumab, similar to those applying to the biological agents for the treatment of rheumatoid arthritis and ankylosing spondylitis be developed, and that a 5 year exclusion period should apply following failure to demonstrate a response. Consultation with the sponsors and other relevant stakeholders will be required in developing interchangeability rules.

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 recommendation by the PBAC to list Enbrel on the PBS will offer significant benefits to patients with severe psoriasis who are uncontrolled by current systemic therapy.