

PUBLIC SUMMARY DOCUMENT

Product: Etanercept, injection set containing 4 vials powder for injection 25 mg and 4 pre-filled syringes solvent 1 mL, and injection set containing 4 vials powder for injection 50 mg and 4 pre-filled syringes solvent 1 mL, Enbrel[®]

Sponsor: Wyeth Australia Pty Ltd

Date of PBAC Consideration: March 2007

1. Purpose of Application

To request that the PBAC consider changing the current PBS restriction for patients with severe chronic plaque psoriasis to include a mechanism for allowing a proportion of 'high needs' patients to access continuous treatment and also to allow an initial treatment period of 24 weeks for all patients instead of the currently approved 12 weeks.

2. Background

At the July 2005 meeting, the 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.

At the March 2006 meeting, the PBAC recommended listing for patients with severe chronic plaque psoriasis 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.

3. Registration Status

Etanercept is registered by the TGA (for use in psoriasis) for the 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 submission requested that patients be treated for an initial 24 weeks (instead of 12 weeks) with 50 mg per week (either as 25 mg twice weekly or 50 mg once weekly) and then undergo a mandatory period of treatment withdrawal period of 12 weeks, as per the current PBS listing. Those patients who relapse within this 12 week withdrawal period will be classified as early relapsers, and have the option of receiving treatment using a new continuous regimen at the same dose of 50 mg per week. Those patients who do not relapse within the 12 week withdrawal period remained eligible for intermittent therapy as per the current PBS listing. The proposed definition of relapse was a return to 75% of pre-treatment Psoriasis Activity and Severity Index (PASI) score. (A detailed restriction wording was proposed).

The PBAC did not comment on the requested restriction.

5. Clinical Place for the Proposed Therapy

A treatment for severe chronic plaque psoriasis.

6. Comparator

The submission nominated the current treatment algorithm i.e. etanercept 25mg twice weekly (or etanercept 50mg weekly) administered for 12 weeks initially and then, in responders, administered intermittently (at least 12 weeks off-therapy followed by another 12 weeks on therapy).

See Recommendations and Reasons for PBAC's view.

7. Clinical Trials

The submission presented two trials, CSR-51139 and CSR-51727, and a withdrawal and extension study of CSR-51727 (CSR-51820) which constituted the primary source of evidence.

These trials have been published at the time of submission as follows:

Primary Enbrel RCTs

Clinical Study Report No.	Title	Publication/s
CSR-51139	Double-blind, placebo-controlled, phase 2 study of etanercept (Enbrel) in the treatment of psoriasis: final report.	Gottlieb AB, Matheson RT, Lowe N et al. A randomized trial of etanercept as monotherapy for psoriasis. <i>Arch Dermatol</i> 2003; 139:1627-1632.
CSR-51727	Multicenter, dose-ranging study of the safety and efficacy of etanercept in psoriasis: final 24-week report.	Leonardi CL, Powers JL, Matheson RT et al. Etanercept as monotherapy in patients with psoriasis. <i>N Engl J Med</i> 2003; 349:2014-2022.
		Feldman SR, Kimball AB, Krueger GG, et al. Etanercept improves the health-related quality of life of patients with psoriasis: Results of a phase III randomized clinical trial. <i>J Am Acad Dermatol</i> 2005; 53(5):887-889.
CSR-51820	Multicenter dose-ranging study of the safety and efficacy of etanercept in psoriasis: withdrawal and retreatment final report.	Gordon KB, Gottlieb AB, Leonardi CL, et al. Clinical response in psoriasis patients discontinued from and then reinitiated on etanercept therapy. <i>J Dermatol Treat</i> 2006; 17(1):9-17
		Krueger GG, Elewski B, Papp K, et al. Patients with psoriasis respond to continuous open-label etanercept treatment after initial incomplete response in a randomized, placebo-controlled trial. <i>J Am Acad Dermatol</i> 2006; 54(3 SUPPL. 2):S112-S119
		Krishnan KR, Cella D, Woolley M, et al. Etanercept improves symptoms of depression and fatigue in patients with psoriasis. 158 th Annual Meeting of the American Psychiatric Association; 2005 May 21-26; Atlanta., GA

Other clinical trial data was presented as supportive evidence.

8. Results of Trials

In addition to the ITT data presented below, additional analyses were conducted. The submission claimed that the analyses presented suggested that more patients treated with etanercept 25mg given twice weekly achieved PASI responses at week 24 than at week 12. The model presented in the submission applied the response rates observed for the sub-group of patients with PASI ≥ 15 following 12 weeks and 24 weeks of etanercept therapy.

(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).

Achievement of PASI 75 response at Week 12 and Week 24 in patients treated with etanercept 25mg BIW

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)
	Week 24				
Gottlieb et al	32/57 (56%)	3/5 (5%)	0.46 (0.32,0.60)	10.0 (3.2, 31.0)	2 (2, 3)

The PBAC noted an issue with the comparison of outcomes at 12 weeks with those at 24 weeks that was not discussed in the submission was the potential for confounding of results that occurs in the context of a disease that generally flares and recedes over time. In such a condition, the potential for regression to a mean state over time becomes an important consideration.

Results for the PASI outcomes for the comparison of the placebo (for 12 weeks followed by etanercept 25mg for 12 weeks) and etanercept 25mg for 24 weeks arms of CSR-51727 at 24 weeks were presented in the submission. It was acknowledged that this comparison was not the ideal comparison (as the arm where etanercept was delivered for 12 weeks had patients initially treated with placebo followed by 12 weeks of etanercept) however the comparison across arms was performed at the same time point which may be important in the context of a disease that flares and recedes over time.

The submission presented results of analyses of time to disease relapse from CSR-51820 and CSR-51139, the former as pivotal evidence and the latter as supportive evidence.

According to the current (and requested restriction) patients are eligible for continued treatment with etanercept if they achieve the equivalent of a PASI 75 response. In the requested restriction, relapse was defined as a return to 75% of baseline PASI score. In CSR-51820, patients were eligible for re-treatment if they achieved a PASI 50 response at week 24 and the definition of relapse was a 50% loss of PASI improvement. The submission presented results of a post hoc analysis based on patients achieving a PASI 75 at week 24.

The median time to relapse was 12 weeks for PASI 75 responders in the placebo-crossover ITT group. By comparison, the median time to relapse for PASI 75 responders in the etanercept ITT group was 16 weeks. The submission claimed that the results appear to suggest that treatment with etanercept 25mg twice weekly for 24 weeks might lead to longer time to relapse compared with treatment with the same dosage for 12 weeks.

The submission presented results from the treatment withdrawal and follow-up phase of trial CSR-51139. Time to disease relapse was defined in this trial as “a return to 75% of the baseline PASI or the start of systemic therapy, whichever came first”. As noted by the submission, although this definition was more consistent with the proposed PBS relapse criteria than the definition of relapse in CSR-51820, the number of subjects who entered the extended follow-up period was small (three subjects in the placebo arm and 17 subjects in the etanercept-treated arm).

The submission presents results of an analysis of response to re-treatment of PASI 50 responders from trial CSR-51820. Results comparing outcomes 24 weeks after re-treatment with outcomes after the initial treatment period were provided in the submission. On the basis of these results, the submission claimed that the overall effect of re-treatment was similar to the effect of initial treatment. On this basis, the model presented in the submission assumed that patients responding to the initial course of etanercept will continue to respond to future courses of continuing etanercept therapy. The applicability of these results to the PBS setting was uncertain given that the definition of response is PASI 50 rather than PASI 75.

9. Clinical Claim

The submission claimed that the proposed initial treatment period of 24 weeks has significant advantages over the current initial treatment period of 12 weeks, being significantly more effective than the current regimen but associated with increased toxicity due to the longer time on drug rather than decreased tolerance over time.

See Recommendations and Reasons for PBAC's view.

10. Economic Analysis

A preliminary economic evaluation was presented. The only resource included was drug costs. The trial-based incremental per extra PASI 75 responder over 24 weeks was between \$15,000 and \$45,000.

A modelled economic evaluation was presented. Outcomes were expressed in terms of QALYs, which are derived from affected BSA (body surface area) scores. The resources included were drug costs and hospitalisation costs. The base case modelled incremental discounted cost per extra discounted QALY gained over 10 years was between \$45,000 and \$75,000.

The PBAC noted the results of the modelled economic evaluation represented a best-case scenario. The PBAC also noted issues concerning the modelled economic evaluation.

11. Estimated PBS Usage and Financial Implications

The submission estimated that the likely number of packs per year (accounting for market share) was up to 28,857 in Year 5 following change to restriction (with an associated cost of between \$30 to \$60 million). The net financial cost per year to the PBS from extension of the listing of etanercept was estimated to be \$10 to \$30 million per year.

12. Recommendation and Reasons

The PBAC noted that none of the trials presented by the submission addressed the appropriate clinical question (i.e. the comparative efficacy and safety of: (i) etanercept 50 mg/week or 25 mg twice weekly administered for 12 weeks initially (followed by a 12-week discontinuation period) to patients satisfying the PBS eligibility criteria and then, in responders, used intermittently (12 weeks on-treatment, 12 weeks off-treatment) versus (ii) etanercept 50 mg/week or 25 mg twice weekly administered for 24 weeks to patients satisfying the PBS eligibility criteria and then used intermittently (12 weeks on-treatment, 12 weeks off-treatment) in some patients (responders to treatment who do not relapse within a 12-week discontinuation period) and used continuously in other responders (patients who relapse within the 12 week discontinuation period).

Although, some evidence was presented to support increasing the initial treatment period to 24 weeks, this was based on the results of a post-hoc analysis.

The submission provided insufficient evidence to support a claim that continuous etanercept (50mg/week) has advantages over intermittent etanercept (50mg/week for 12 weeks followed by a 12-week treatment-free period) in patients who relapse within 12 weeks of discontinuing etanercept after response to initial treatment. The Pre-Sub-Committee Response argument that there is a clinical need for continuous treatment and that it is unreasonable to require these patients to have to return to their severe baseline, before being eligible to resume treatment, did not assist in addressing the lack of evidence.

The PBAC acknowledged that, although efalizumab was also an appropriate comparator, it had previously accepted that etanercept given intermittently, with a 12-week initiation course, was of similar safety and efficacy to continuous efalizumab. However, a comparison with efalizumab would have given extra support to support a claim of superiority.

The PBAC also noted a number of issues raised concerning the modelled economic evaluation, which meant there was uncertainty about the resulting incremental cost effectiveness ratio. The ESC advised that the cost per QALY of between \$45,000 and \$75,000 represented a 'best-case' scenario because, in general, the assumptions used in the model were likely to maximise the difference between intermittent and continuous etanercept treatment regimens, and thus favour the proposed continuous treatment regimen. Despite arguments in the Pre-PBAC Response contending that a cost per QALY between \$15,000 and \$45,000 was the 'best-case' scenario, the PBAC agreed that a higher per QALY represented the more plausible cost-effectiveness ratio that still favours etanercept.

The PBAC thus rejected the submission because of uncertainty about the clinical evidence for the proposed model of treatment and inadequate evidence supporting the role of continuous vs intermittent treatment, and because of a high and uncertain cost effectiveness ratio.

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

Wyeth will determine a course of action based on an evaluation of the PBAC's comments. Wyeth continues to believe that there is a small group of psoriasis patients who would benefit significantly from continuous therapy with etanercept. A re-evaluation of the available evidence and available economic modelling methods is required to address the views of the PBAC.