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 requested two changes to the current etanercept PBS listing for patients with psoriasis:

I. To change the initial treatment period to enable patients who achieve a PASI response of at least 50 at week 12 to be treated with a further 12 weeks of initial therapy to achieve a PASI 75 response (patients with a PASI response <50 at week 12 would discontinue treatment).

II. To change the continuing criteria to allow patients who qualify for continuing treatment and achieve at least a PASI 75 response after 24 weeks treatment with etanercept to receive treatment with a continuous etanercept 50 mg/week regimen or an intermittent flexible regimen.

2. Background

At the July 2005 meeting, the PBAC rejected a submission for etanercept for severe chronic plaque psoriasis because of uncertain and unacceptable cost-effectiveness. However, the PBAC noted that etanercept is an effective drug in terms of both a PASI 50 and a PASI 75 improvement. *(See PBAC Public Summary Document – July 2005)*

At the March 2006 meeting, the PBAC recommended listing of etanercept 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. 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 was determined to be equivalent to efalizumab 1 mg/kg/week for a total of 48 weeks for pricing relativity purposes. The PBAC rejected a request for an initial 50 mg twice weekly regimen of etanercept as the incremental cost effectiveness ratio was considered to be unacceptably high. *(See PBAC Public Summary Document – March 2006)*

Etanercept for chronic plaque psoriasis was listed on the PBS from 1 August 2006.

At the March 2007 meeting, the PBAC rejected a submission to change the restriction for etanercept for psoriasis which would allow a proportion of 'high needs' patients access to continuous treatment and also allow an initial treatment period of 24 weeks for all patients instead of the currently approved 12 weeks 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. *(See Public Summary Document – March 2007)*

3. Registration Status

Etanercept was TGA registered on 26 March 2004 for severe chronic plaque psoriasis.

It is TGA registered for the following indications:

- rheumatoid arthritis (RA)
- active polyarticular course juvenile chronic arthritis
- psoriatic arthritis
- ankylosing spondylitis
- 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 following were the proposed changes to the restriction:

Proposed changes to initial treatment regimen

- Patients who have not achieved at least a PASI 50 treatment response at the end of the 12-week initial treatment period be discontinued,
- All patients achieving at least a PASI 50 response at Week 12 be allowed to continue etanercept for a subsequent 12 weeks (this equals a total of 24 weeks initial treatment for all subjects who achieved a PASI 50 or better response by week 12).
- At week 24, all patients who have not achieved a PASI 75 treatment response must discontinue etanercept treatment whilst those achieving a PASI 75 qualify as continuers.

Proposed changes to continuation criteria

- Patients who achieve a PASI 75 after 12 or 24 weeks of initial therapy be treated with continuous etanercept 50 mg per week or a flexible intermittent dosing regimen which allows 'treatment breaks' for the patient's convenience, at the discretion of the clinician and patient.

Proposed assessment of response

- Initial assessment of treatment response at week 12 (patients who achieve a PASI 75 would be classified as continuers at this point).
- Second assessment of treatment response at week 24.
- Assessment of response in continuers every 24 weeks prior to reapplication for prescription (but must occur at least 12 weeks after 'treatment breaks').

For PBAC's view, see Recommendation and Reasons.

5. Comparator

The submission nominated the current treatment algorithm (as permitted by the current listing of etanercept) of etanercept 25 mg twice weekly (BIW) or etanercept 50 mg weekly (QW) administered for 12 weeks initially and then, in responders, administered intermittently (at least 12 weeks off-therapy followed by another 12 weeks on therapy) as the main comparator. The submission nominated efalizumab and infliximab as secondary comparators.

The PBAC considered this was appropriate as although the continuous etanercept treatment is likely to predominantly replace the current intermittent regimen, introduction of a continuous etanercept regimen will likely replace some use of infliximab and efalizumab.

6. Clinical Trials

The submission presented two trials, CRYSTEL and EASE, as the primary source of evidence. CRYSTEL, a randomised open-label trial, tested the hypothesis that the continuous, low dose 25 mg twice weekly (BIW) regimen would be at least as effective as the intermittent, high dose 50 mg BIW, with step-down regimen (25 mg BIW after week 12), over 54 weeks in adults with stable, active plaque psoriasis involving ≥ 10% of body surface area (BSA) and Physician's Global Assessment (PGA) status of "moderate" or "worse" at screening and baseline visits. Patients also had to have failed one of the following systemic therapies at an adequate dose of sufficient duration, have a contraindication or intolerance to methotrexate, cyclosporin, psoralen plus ultraviolet A (PUVA).

EASE was a randomised, open-label trial in which all patients received 50 mg etanercept BIW during the first 12 weeks, followed by either continuous or interrupted etanercept 50 mg once weekly (QW) in the next 12 weeks in adults with stable, active plaque psoriasis involving ≥10% of BSA and PGA status of "moderate" or "worse" at screening and baseline visits.

The trials and associated report published at the time of submission are as follows:

Trial/First author	Protocol title/Publication title	Publication citation
20030190 (also known as EASE) Gelfand et al, 2006	Health resource utilization and patient-reported outcomes during continuous and intermittent treatment with etanercept: 6-month results.	Abstract P2887. American Academy of Dermatology 64th Annual Meeting March 3-7, 2006. Journal of the American Academy of Dermatology Volume, Ab219 DOI:
Gordon et al, 2006.	Effectiveness and safety of continuous versus intermittent etanercept therapy in patients with psoriasis: Analysis of the EASE trial.	Abstract P2875. American Academy of Dermatology 64th Annual Meeting March 3-7, 2006. Journal of the American Academy of Dermatology: 54(3 Suppl 1): Ab216
Moore et al, 2007.	A randomized, open-label trial of continuous versus interrupted etanercept therapy in the treatment of psoriasis.	Journal of the American Academy of Dermatology 56(4): 598-603.
20030211 (referred to as CSR 70926 in the submission) Paller et al, 2008.	Etanercept treatment for children and adolescents with plaque psoriasis.	N Engl J Med Jan 17;358(3):241-51.

EASE: Etanercept: Assessment of Safety and Effectiveness in Psoriasis Study

7. Results of Trials

The results for the primary outcome in the CRYSTEL trial - the mean Physician's Global Assessment (PGA) score over 54 weeks – showed that the PGA score was statistically significantly better for subjects in the continuous therapy group compared to those in the intermittent group. The mean PGA score from week 12 to week 54 was also statistically significantly better for those in the continuous therapy group compared to subjects in the intermittent group.

The results of the primary outcome of the EASE trial - the proportion of PGA responders across various assessment time points - showed that the proportion of responders to continuous or intermittent therapy did not differ up to week 12 because both groups received

etanercept 50mg BIW for this period. After week 12, at which point responders in the intermittent arm discontinued treatment until relapse, differences between treatment groups were observed. The proportion of PGA responders in the continuous group was maintained from week 12 to week 24 while that for the intermittent group declined from week 12 to week 16 and week 20 with a slight rise at week 24.

The CRYSTEL trial results for achieving a ≥ 75% improvement from baseline in PASI score indicated no significant difference between the continuous and intermittent group at week 12. After that timepoint patients in the intermittent group who had achieved adequate treatment response took treatment breaks of variable duration based on clinical needs assessment, and all timepoints thereafter (weeks 18, 24, 30, 36, 42, 48, 54) indicated that the PASI 75 responder rate was significantly higher in the continuous group compared to the intermittent group.

The submission presented the results of PASI 75 responder rates in patients with a baseline PASI score of ≥ 15, from post-hoc analysis of data from the continuous arm of the CRYSTEL trial. These analyses were done to address the applicability issue that the more severe patients eligible for etanercept under PBS criteria (PASI ≥15) might have a different response to treatment than the moderate to severe patients enrolled in the CRYSTEL trial (PASI ≥10). The results showed that the PASI 75 responder rates were numerically higher among the PASI≥15 subgroup compared to the whole trial population, both at 12 and 24 weeks. This observation was also confirmed by a post hoc analysis of data from another study (Trial 51727, referred to in the submission as study 1639) that was presented previously to the PBAC in March 2007. PASI 75 responder rates were numerically higher among the PASI≥15 subgroup (who are more likely to represent the PBS population) compared to the whole trial ITT population.

The submission sourced utilities for patients with psoriasis from Zug et al, 1995. This is a report of a study of patient preferences for health in 87 patients with psoriasis being managed by dermatologists at tertiary medical centres in the USA. The study assumed that there was a link between affected BSA and utility, and used three different methods (vertical rating scale (VRS), time trade-off (TTO) and standard gamble (SG)) to assess the utilities for three categories of psoriasis severity. For patients with severe disease, Zug et al. 1995 reported an improvement of 0.30 associated with treatment using the time trade-off (TTO) method.

The submission also presented quality of life data (EQ5D) from the CRYSTEL study. The mean values for all patients in the continuous and intermittent arms did not show a difference between the treatment arms. For patients with PASI ≥15 at baseline, an improvement of 0.19 (observed data) was observed from baseline to week 54 in continuous patients and 0.16 in intermittent patients.

Utility estimates were not available from the EASE trial.

Safety results were also presented in this submission, which were similar to those presented in previous submissions.

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

8. Clinical Claim

The submission claimed that the proposed continuous etanercept treatment regimen had significant advantages in effectiveness over the current intermittent etanercept treatment regimen and had similar or less toxicity. The submission also claimed that the proposed intermittent flexible regimen is more effective than the current inflexible intermittent regimen.

The PBAC considered new clinical evidence in the form of two randomised open-label trials, CRYSTEL and EASE, but noted that neither trial allows for the appropriate comparisons of the requested restriction to the current PBS restriction.

For PBAC's view, see Recommendation and Reasons.

9. Economic Analysis

The submission presented one modelled economic evaluation where both a 24 week initiation period and continuous treatment with etanercept were considered simultaneously. The resources included were drug costs. Efficacy results from the CRYSTEL trial were applied in the economic model. The mean utility values obtained from the time trade-off method from the Zug et al study are incorporated in the economic model. The base case incremental cost effectiveness ratio (ICER) was estimated to be between $25,000 - $50,000 per QALY gained, with sensitivity analyses indicating that the ICER could be in the range of $50,000 - $100,000.

For PBAC's view, see Recommendation and Reasons.

10. Estimated PBS Usage and Financial Implications

The likely number of patients/packs dispensed per year (accounting for market share) was estimated to be less than 10,000 patients in Year 5.

The financial cost per year to the PBS from extension of the listing of etanercept was estimated to be less than $10 million in Year 5 following changes to the current restrictions.

11. Recommendation and Reasons

The PBAC considered new clinical evidence in the form of two randomised open-label trials, CRYSTEL and EASE, but noted that neither trial allows for the appropriate comparisons of the requested restriction to the current PBS restriction.

Regarding the proposal to increase the initial treatment period to 24 weeks for patients who demonstrate a PASI improvement of 50% (PASI 50) at 12 weeks, the Committee agreed that the data presented is generally supportive that a small additional group of patients will go on to meet the continuation criteria if a longer initial treatment period is allowed. This is based on a subgroup analysis of patients in the continuous arm of the CRYSTEL trial which indicates that approximately half of patients who achieve a PASI 50-75 at week 12, will go on to achieve PASI >75 at week 24. This corresponds to approximately an additional 19% of all patients initiated on etanercept meeting the continuation criteria by week 24.

Regarding the proposal to allow continuous or flexible intermittent continuing treatment, the PBAC recognises that some patients regress in the mandatory 12 week off period with the current PBS regimen and that this is clinically undesirable. The PBAC noted that in the CRYSTEL and EASE trials continuous treatment appears to result in a better outcome than

intermittent therapy, but considered that the comparison of efficacy is limited as the intermittent regimens in these trials do not reflect the current PBS regimen. The Committee also recalled that the original recommendation (March 2006 PBAC meeting) was based on the submission's request for flexible intermittent therapy in establishing the cost-effectiveness of etanercept in psoriasis.

With respect to safety, the PBAC noted that there are no differences in toxicity presented between the two treatment regimens, but considered that there may be more toxicity with the proposed compared to the current regimen due to a longer total time of exposure to etanercept treatment.

The PBAC noted that the results from the intermittent arms of the CRYSTEL trial did not form the basis of the economic model, but rather a previously presented trial (51727 and its extension, 51820) is used to model the current PBS regimen. The continuous arm of the CRYSTEL trial is used to model the proposed regimen. The PBAC considered that there are a number of additional issues with the economic model that introduce uncertainty including that the treatment benefit at 1 year is maintained at 4 years, and the assumptions relating to the proportion of patients who will take a treatment break and the duration of such breaks.

The PBAC noted that the CRYSTEL trial demonstrated minimal quality of life differences between the continuous and intermittent arms. The PBAC considered that use of the Zug et al (1995) utilities in the economic modelling is reasonable as these have been accepted by the PBAC previously, but noted that that the sensitivity analyses conducted during the evaluation indicate that there is considerable uncertainty, and that the Zug et al utility values may present a best case scenario of the QALY impacts when compared with the direct evidence from the trial.

Overall, the PBAC considered that while it appears that more patients achieve a PASI 75 after 24 weeks compared to 12 weeks of initial therapy, that the continuous regimen offers advantages over the intermittent regimen in maintaining PASI 75 response, and that both the continuous and flexible intermittent regimens in the CRYSTAL trial were effective, the comparison of the proposed listing change (to allow continuing treatment to be either continuous or flexible intermittent) is hindered because the new trial evidence does not allow comparison with the current regimen. As a result, and considering uncertainties in the economic model, the PBAC considered that the cost-effectiveness of the proposed changes to the continuing treatment period has not been established compared to the current listing restrictions.

Therefore, the PBAC rejected the application on the basis of uncertainty in the economic model, resulting in a high and uncertain cost-effectiveness ratio.

Recommendation
Reject

12. 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.

13. Sponsor's Comment

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.