PUBLIC SUMMARY DOCUMENT
Product: Etanercept, injection set containing 4 vials powder for injection, 25 mg and 4 pre-filled syringes solvent 1 mL, injection set containing 4 vials powder for injection, 50 mg and 4 pre-filled syringes solvent 1 mL, injections, 50 mg in 1 mL single use pre-filled syringes, Enbrel®
Sponsor: Wyeth Australia Pty Ltd
Date of PBAC Consideration: March 2009

1. Purpose of Application

The re-submission requested an amendment to the treatment regimen for etanercept in chronic plaque psoriasis to allow etanercept 50 mg/week for 12 weeks of initial treatment to be followed by continuous treatment of 50 mg/week, or, a flexible intermittent dosing regimen, for those patients who meet the continuation criteria.

2. Background

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 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 versus intermittent treatment, and because of a high and uncertain cost effectiveness ratio.

At the July 2008 meeting, the PBAC rejected a submission for etanercept to extend the initial treatment period for psoriasis to 24 weeks for patients who achieve a Psoriasis Area and Severity Index (PASI) 50 at week 12, and to allow continuing treatment to be a continuous regimen or a flexible intermittent regimen on the basis of uncertainty in the clinical data and economic model, resulting in a high and uncertain cost-effectiveness ratio.

3. Registration Status

Etanercept is TGA registered for:

- 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 are the requested changes to the restriction.

Requested change to continuing treatment regimen

- Patients who achieve a PASI 75 response after initial therapy be treated with either continuous etanercept 50 mg/week or a flexible intermittent dosing regimen which allows treatment breaks, at the discretion of the clinician and patient (a minimum of 12-weeks re-treatment with etanercept 50 mg/week is required before a subsequent break can be taken).

Current continuing treatment regimen

- Patients who achieve a PASI 75 response after 12 weeks initial therapy (and subsequently undergo an initial 12 week biological treatment-free period) can begin continuing treatment with etanercept 50 mg/week on a cyclical basis consisting of 12 weeks on-treatment followed by a minimum 12-week biological treatment-free period.
- Patients who have a break in therapy may recommence treatment with etanercept under Initial 2 providing they have not failed treatment with etanercept.

Proposed assessment of response

- Initial assessment of treatment response at week 12.
- For patients prescribed the continuous dosing regimen, continuing treatment response assessment every 24 weeks.
- For patients prescribed the flexible intermittent dosing regimen, continuing treatment response assessment completed at the end of each active treatment cycle (minimum 12 weeks with maximum 24 weeks of etanercept treatment), and no later than 4 weeks after treatment cessation.

Current assessment of response

- Initial assessment of treatment response at week 12.
- Continuing treatment response assessment after 12 weeks of etanercept treatment and no later than 4 weeks from cessation of that treatment course.

For PBAC's view see Recommendation and Reasons.

5. Clinical Place for the Proposed Therapy

The requested change to the listing alters the current treatment algorithm (12 weeks initial treatment followed by 12 week treatment break then further 12 week treatment for responders) to 12 week initial treatment followed by either continuous treatment or intermittent treatment for responders, and would continue to provide a PBS listed treated option for chronic plaque psoriasis.

6. Comparator

The submission nominated efalizumab as the main comparator, rather than the current treatment regimen with etanercept. This was accepted by the PBAC.

7. Clinical Trials

The re-submission included four previously presented etanercept trials, and five previously presented efalizumab trials (Dubertret 2006[1]; Gordon 2003[2]; Lebwohl 2003[3]; Leonardi 2005[4];

[1] Dubertret et al, Group CMS. Clinical experience acquired with the efalizumab (Raptiva) (CLEAR) trial in patients with moderate-to-severe plaque psoriasis: results from a phase III international randomized, placebo-controlled trial, The British Journal of Dermatology 2006;155:170-81.

Papp 2006[5]) were used to provide an indirect comparison of initial treatment response using placebo the common comparator.

Publication details of the two cohort studies follow:

- Berends M.A.M., Driessen R.J.B., Langewouters A.M.G., Boezeman J.B., van de Kerkhof P.C.M., de Jong E.M.G.J, Etanercept and efalizumab treatment for high-need psoriasis: Effects and side effects in a prospective cohort study in outpatient clinical practice, Journal of Dermatological Treatment, 2007;18:76-83.

- Driessen, R.J.B., Berends M.A.M., Boezeman J.B., van de Kerkhof P.C.M., de Jong E.M.G.J, Psoriasis treatment with etanercept and efalizumab: clinical strategies influencing treatment outcome, British Journal of Dermatology, 2008;158:1098-106.

8. Results of Trials

The table below provides the results of the indirect comparisons presented by the re-submission comparing etanercept and efalizumab for achievement of initial PASI 75 response at 12 weeks. The re-submission provided analyses using 95% and 75% confidence intervals.

Results of the indirect comparisons of etanercept and efalizumab for initial response

	Pooled treatment effect RR (95% CI)		**Indirect estimate RR**	
Outcome	**Etanercept**	**Efalizumab**	**RR (95% CI)**	**RR (75% CI)**
PASI 75 response	**10.9 (6.4, 18.6)**	**7.5 (5.2, 10.3)**	1.5 (0.8, 2.8)	1.5 (1.0, 2.2)
Adverse event withdrawals	0.71 (0.33, 1.56)	1.41 (0.86, 2.30)	0.50 (0.20, 1.25)	0.50 (0.29, 0.86)
Serious adverse events	0.62 (0.20, 1.85)	1.25 (0.64, 2.45)	0.50 (0.13, 1.85)	0.50 (0.13, 1.07)
	Pooled treatment effect RD (95% CI)		**Indirect estimate RD**	
	Etanercept	**Efalizumab**	**RD (95% CI)**	**RD (75% CI)**
PASI 75 response	**31% (27%, 36%)**	**24% (19%, 30%)**	7% (1%, 13%)[a]	7% (3%, 11%)
Adverse event withdrawals	-1% (-3%, 2%)	1% (0%, 3%)	-2% (-4%, 0%)	-2% (-3%, -1%)
Serious adverse events	-1% (-4%, 2%)	1% (0%, 2%)	-2% (-5%, 1%)	-2% (-4%, 0%)

[a] *p=0.004*

[2] Gordon et al, Efalizumab Study G. Efalizumab for patients with moderate to severe plaque psoriasis: a randomized controlled trial. JAMA : the Journal of the American Medical Association 2003;290:3073-80.
[3] Lebwohl et al, Efalizumab Study G. A novel targeted T-cell modulator, efalizumab, for plaque psoriasis, The New England Journal of Medicine 2003;349:2004-13.
[4] Leonardi CL, Papp KA, Gordon KB, Menter A, Feldman SR, Caro I, Walicke PA, Compton PG, Gottlieb AB. Extended efalizumab therapy improves chronic plaque psoriasis: Results from a randomized phase III trial. J Am Acad Dermatol 2005;52:425-433.
[5] Papp et al, Efalizumab Study G. Safety of efalizumab in adults with chronic moderate to severe plaque psoriasis: a phase IIIb, randomized, controlled trial, International Journal of Dermatology 2006;45:605-14.

The re-submission claimed that the indirect comparisons indicate etanercept is at least as safe and effective as efalizumab and shows trends toward superiority over efalizumab, the latter claim based on the analyses using 75% confidence intervals.

The assessment of response during continuing treatment was done by reviewing: two prospective cohort studies assessing use of etanercept and efalizumab (Berends et al., 2007; Driessen et al., 2008); the CRYSTEL study (a randomised trial comparing intermittent and continuous etanercept) and an open-label etanercept follow-up study to a previously presented randomised trial of etanercept.

The re-submission claimed that the PASI 75 response for both etanercept and efalizumab is maintained over the longer term. The evidence in support of continuing treatment presented by the re-submission was as follows:

Efalizumab evidence: The re-submission presented a figure from the Leonardi et al (2008)[6] efalizumab trial and claimed no significant difference between the proportion of PASI 75 responders at week 12 and week 24.

Etanercept evidence: The re-submission did not provide any analysis of longer-term etanercept response but claimed that there is no observable decline in response and thus response will be maintained.

- The re-submission stated that the number of PASI 75 responders increased over time in the continuous treatment arm of the CRYSTEL trial (127/352 at week 12 and 196/352 at week 54). The re-submission also stated that there was a small decline in PASI 75 responder rates in the intermittent treatment arm in CRYSTEL.

The mean Physicians Global assessment of Psoriasis (PGA) score over 54 weeks was significantly better for subjects in the continuous therapy group compared to those in the intermittent group (1.98 versus. 2.51, P<0.001). The mean PGA score from week 12 to week 54 was also significantly better for those in the continuous therapy group compared to subjects in the intermittent group (1.80 versus. 2.46, p<0.001).

- Based on the Driessen et al (2008) cohort study, the re-submission claimed that eight patients with PASI 75 response at week 24 were the same patients with PASI 75 response at week 18.
- The re-submission, and Pre-Sub-Committee response, stated that in the open labelled etanercept follow-up study there were one hundred and forty (140) PASI 75 responders at baseline and one hundred and eighty five (185) PASI 75 responders at week 72, which demonstrated that PASI 75 responders increased over time.

~~Analysis of toxicity data following initial treatment was provided by the re-submission and it was concluded there are no statistically significant differences between etanercept and efalizumab in the occurrence of serious adverse events or withdrawals due to adverse events.~~

[6] Leonardi et al. Efalizumab: results of a 3-year continuous dosing study for the long-term control of psoriasis. British Journal of Dermatology 2008;158:1107-16.

Analysis of toxicity data following initial treatment was provided by the re-submission and it was concluded there are no statistically significant differences between etanercept and efalizumab in the occurrence of serious adverse events or withdrawals due to adverse events. The re-submission provided no assessment of comparative toxicity during continuing treatment and provided no extended assessment of comparative harms. ~~Although the re-submission did not provide an assessment of comparative toxicity during continuing treatment and provided no extended assessment of comparative harms, recent long term safety concerns have led to the withdrawal of efaluzimab from the market. The long term safety of etanercept, which has been available on the PBS since 2003, is well established.~~

9. Clinical Claim

The re-submission claimed the indirect comparison showed that etanercept is at least as safe and effective as efalizumab, and on the basis of 75% CI analysis, showed a trend towards superiority over efalizumab in proportion of patients with initial PASI 75 response.

The re-submission claimed that etanercept 50mg/week continuous therapy, or a flexible intermittent regimen that allows treatment breaks, is ~~at least~~ equi-effective to efalizumab 1mg/kg/week for maintenance treatment.

For PBAC's view see Recommendation and Reasons.

10. Economic Analysis

The re-submission presented a cost-minimisation analysis. The equi-effective doses were estimated as etanercept 50 mg/week and efalizumab 1 mg/kg/week during both the initial and maintenance treatment periods.

Three cost-minimisation analyses were presented, a base case analysis including trial-based and 'real-life' analyses, and two alternate analyses, one assuming both etanercept and efalizumab have 24 weeks initial treatment and the second comparing the current etanercept treatment regimen to efalizumab and to the requested etanercept regimen for a treatment duration of 48 weeks.

11. Estimated PBS Usage and Financial Implications

The submission estimated the number of one-month treatment courses per year to be less than 10,000 at a likely cost of < $10 million in Year 4. However, the PBAC noted that the assumptions and values used by the re-submission to arrive at the estimated cost have not been completely justified, and therefore these values are uncertain and should be interpreted with caution.

12. Recommendation and Reasons

The PBAC recommended amending the listing of etanercept to allow for continuous treatment in the management of chronic plaque psoriasis on the basis of cost-minimisation against efalizumab continuous treatment at the requested price. The equi-effective doses are etanercept 50 mg/week and efalizumab 1 mg/kg/week during both initial and maintenance treatment periods. The submission had sought an amended listing for either continuous or flexible intermittent use, or continuous use only.

The PBAC noted that after 12 weeks of therapy the indirect comparisons showed the effectiveness of etanercept based on a PASI 75 response is no worse than efalizumab.

The assessment of response during continuing treatment was done by reviewing: two prospective cohort studies assessing use of etanercept and efalizumab (Berends et al., 2007; Driessen et al., 2008); the CRYSTEL study (a randomised trial comparing intermittent and continuous etanercept) and an open-label etanercept follow-up study to a previously presented randomised trial of etanercept.

The 54 week results from CRYSTEL showed the mean Physician Global assessment of Psoriasis (PGA) score over 54 weeks was significantly better for subjects in the continuous therapy group compared to those in the intermittent group (1.98 versus. 2.51, P<0.001). The mean PGA score from week 12 to week 54 was also significantly better for those in the continuous therapy group compared to subjects in the intermittent group (1.80 versus. 2.46, p<0.001). The 54 week results also showed 55.7% of patients on continuous treatment compared to 34% on intermittent achieved a PASI 75 improvement from baseline.

The PBAC concluded from the data presented overall that efalizumab and etanercept are equally effective in patients with severe plaque psoriasis after 12 weeks of therapy and it is likely that continuous etanercept is ~~at least~~ as effective as efalizumab over 48 weeks of treatment. However, it was less clear that intermittent etanercept is as least as effective as efalizumab over 48 weeks of treatment. Therefore, the PBAC recommended etanercept be made for available for continuous treatment, noting that patients can have a break from treatment and later re-commence under the current listing criteria (initial 2), provided evidence of a response to etanercept within that treatment cycle is supplied to Medicare Australia.

As a general comment with respect to the biological Disease-Modifying Antirheumatic Drugs (bDMARDs) for the treatment of chronic plaque psoriasis, the PBAC noted that the different drugs have different patterns of effectiveness over time. The PBAC agreed the sponsor Wyeth should be offered the opportunity to request an amendment to the listing of etanercept such that a patient who achieved a PASI 50 response at three months be allowed to continue treatment for a further 3 months to achieve a PASI 75 response. However, the PASI 50 response at three months would be deemed a failure.

Recommendation

The PBS listing restriction can be found in the Schedule of Pharmaceutical Benefits at www.pbs.gov.au.

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 is pleased that etanercept will be available on the PBS for continuous use in chronic plaque psoriasis. It should be noted that since this submission was considered by the PBAC, efalizumab, the nominated comparator, has been withdrawn from the Australian market due to long term safety concerns. The long term safety of etanercept, which has been on the PBS since 2003, is well established with over 16 years and an estimated 1.8 million patient-years of collective clinical experience.~~Wyeth is pleased that etanercept will be available on the PBS for continuous use in chronic plaque psoriasis.~~