

PUBLIC SUMMARY DOCUMENT

Product: Etanercept, injection set containing 4 vials powder for injection 25 mg and 4 pre-filled syringes solvent 1 mL; injections 50 mg in 1 mL single use pre-filled syringes; injection 50 mg in 1 mL single use auto-injector, Enbrel[®]

Sponsor: Pfizer Australia Pty Ltd

Date of PBAC Consideration: March 2012

1. Purpose of Application

The submission sought an extension to the current Section 85 Authority Required listing for etanercept to include treatment of severe chronic plaque psoriasis in patients under the age of 18 years.

2. Background

Etanercept had not been previously considered by the PBAC for this indication.

Etanercept is currently listed on the PBS as a Section 85 Authority Required listing for the following indications:

- Treatment of adult patients with severe active rheumatoid arthritis;
- Treatment of adult patients with severe active psoriatic arthritis;
- Treatment of adult patients with active ankylosing spondylitis;
- Treatment of adult patients with severe chronic plaque psoriasis;
- Treatment of adult patients with a history of juvenile idiopathic arthritis.

Etanercept is currently listed on the PBS under the Section 100 (Highly Specialised Drugs Program) for:

- Initial and continuing treatment of patients aged under 18 years with severe active juvenile idiopathic arthritis;
- Continuing treatment of patients aged 18 years or older with severe active juvenile idiopathic arthritis.

3. Registration Status

The TGA approved indications for etanercept were extended on 4 January 2012 to include “treatment of chronic, severe plaque psoriasis in children and adolescents from age 4 to 17 years, who are inadequately controlled by, or are intolerant to, other systemic therapies or phototherapies. Duration of therapy to be no longer than 24 weeks and treatment to be ceased after 12 weeks if a significant PASI response is not achieved.”

4. Listing Requested and PBAC’s View

An abbreviated version of the requested restriction is presented.

Authority Required

Initial treatment [Initial 1, Whole body (New patients — No prior biological agent)]

Initial treatment as systemic monotherapy (other than methotrexate) by a dermatologist **of a patient under 18 years**: (a) have severe chronic plaque psoriasis where lesions have been present for at least 6 months from the time of initial diagnosis; and

(b) have not received any prior PBS-subsidised treatment with a biological agent for this condition in this Treatment Cycle; and

(c) **whose parent or authorised guardian has signed a patient acknowledgement** indicating they understand and acknowledge that PBS-subsidised treatment will cease if they do not meet the predetermined response criterion for ongoing PBS-subsidised treatment, as outlined in the restriction for continuing treatment (whole body); and

(d) have failed to achieve an adequate response, as demonstrated by a Psoriasis Area and Severity Index (PASI) assessment, to at least 2 of the following 3 treatments:

- (i) phototherapy (UVB or PUVA) for 3 treatments per week for at least 6 weeks; and/or
- (ii) **methotrexate at a dose of at least 10 mg or 10mg/m² weekly (whichever is lowest)** for at least 6 weeks; and/or
- (iii) acitretin at a dose of at least 0.4 mg per kg per day for at least 6 weeks.

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Authority Required

Initial treatment [Initial 1, Face, hand, foot (New patients — No prior biological agent)]

Initial treatment as systemic monotherapy (other than methotrexate) by a dermatologist **of a patient under 18 years**:

- (a) have severe chronic plaque psoriasis of the face, or palm of a hand or sole of a foot where the plaque or plaques have been present for at least 6 months from the time of initial diagnosis; and
- (b) have not received any prior PBS-subsidised treatment with a biological agent for this condition in this Treatment Cycle; and
- (c) have signed a patient and prescriber acknowledgement indicating they understand and acknowledge that PBS-subsidised treatment will cease if they do not meet the predetermined response criterion for ongoing PBS-subsidised treatment, as outlined in the restriction for continuing treatment (face, hand, foot); and
- (d) have failed to achieve an adequate response, as demonstrated by a Psoriasis Area and Severity Index (PASI) assessment, to at least 3 of the following 4 treatments:
 - (i) phototherapy (UVB or PUVA) for 3 treatments per week for at least 6 weeks; and/or
 - (ii) **methotrexate at a dose of at least 10 mg or 10mg/m² weekly (whichever is lowest)** for at least 6 weeks; and/or
 - (iii) acitretin at a dose of at least 0.4 mg per kg per day for at least 6 weeks.

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Authority Required

Continuing treatment (Whole body)

Continuing PBS-subsidised treatment as systemic monotherapy (other than methotrexate) by a dermatologist **of a patient under 18 years**:

- (a) who have a documented history of severe chronic plaque psoriasis; and
- (b) whose most recent course of PBS-subsidised biological treatment for this condition in this Treatment Cycle was with etanercept; and
- (c) who have demonstrated an adequate response to their most recent course of treatment with etanercept.

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Authority Required

Continuing treatment (Face, hand, foot)

Continuing PBS-subsidised treatment as systemic monotherapy (other than methotrexate) by a dermatologist **of a patient under 18 years**:

- (a) who have a documented history of severe chronic plaque psoriasis of the face, or palm of a hand or sole of a foot; and
- (b) whose most recent course of PBS-subsidised biological treatment for this condition in this Treatment Cycle was with etanercept; and
- (c) who have demonstrated an adequate response to treatment with etanercept.

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For PBAC's view, see Recommendation and Reasons.

5. Clinical Place for the Proposed Therapy

Therapeutic Guidelines - Dermatology (2009) describes psoriasis as an inflammatory and hyperplastic disease of the skin, characterised by erythema and scale. It is strongly familial and the primary defect may be an abnormally activated immune response in the skin. The

clinical manifestations are numerous and range from minor inflammation at one or two sites on the skin to total skin involvement with postulation and constitutional symptoms.

In plaque psoriasis, plaques are well demarcated, pink and surmounted with a silvery scale. Common sites are the elbows, knees, sacrum and scalp. Lesions may be single or numerous and individual plaques may coalesce into large confluent areas, sometimes 30 cm or more in diameter.

The submission proposed that the place in therapy of etanercept is as a last line treatment for paediatric patients with severe chronic plaque psoriasis, who have failed at least 2 prior therapies.

6. Comparator

The submission nominated best supportive care (which may consist of high dose systemic treatments including methotrexate, and acitretin (as monotherapy or in combination), intermittent hospitalisation for intensive treatment (e.g. Ingram's regime), topical therapies and phototherapy (possibly in combination with systemic therapies) as the main comparator. This was accepted by the PBAC as the appropriate comparator.

7. Clinical Trials

The submission presented one randomised, double-blind, placebo controlled comparing etanercept 0.8 mg/kg up to a maximum dose of 50 mg once weekly with placebo in paediatric patients aged 4 to 17 years with moderate to severe chronic plaque psoriasis (Study 20030211). The submission also provided 96 weeks of treatment data from extension study 20050111.

Details of the trials published at the time of submission are in the table below.

Trials and associated reports presented in the submission

Trial ID	Protocol title/ Publication title	Publication citation
Direct randomised trial (Study 20030211 and Study 20050111)		
Paller, 2008	Etanercept treatment for children and adolescents with plaque psoriasis.	<i>The New England Journal of Medicine</i> , 358(3), 241-251.
Paller, 2010	Long-term etanercept in pediatric patients with plaque psoriasis.	<i>Journal of the American Academy of Dermatology</i> , 63(5), 762-768.
Langley, 2011	Patient-reported outcomes in pediatric patients with psoriasis undergoing etanercept treatment: 12-week results from a phase III randomised controlled trial.	<i>Journal of the American Academy of Dermatology</i> , 64[1], 64-70.
Landells 2010	Efficacy and safety of etanercept in children and adolescents aged > or = 8 years with severe plaque psoriasis.	<i>European Journal of Dermatology</i> , 20(3), 323-328
Siegfried, 2006	Etanercept in children and adolescents with psoriasis. Abstract P2880.	<i>American Academy of Dermatology</i> 64th Annual Meeting March 3-7
Paller, 2010	Interim results of a long-term safety and tolerability study of etanercept treatment in	<i>European Journal of Pediatric Dermatology</i> , 20[1], 52-53

	children and adolescents age 8 to 17 years with plaque psoriasis.	
Paller, 2007	A 12-week phase 3 study of efficacy and safety of etanercept therapy in children and adolescents with moderate to severe plaque psoriasis Abstract P2783.	American Academy of Dermatology 65th Annual Meeting February 2-6
Siegfried, 2010	Intermittent etanercept therapy in pediatric patients with psoriasis.	<i>Journal of the American Academy of Dermatology</i> 63(5), 769-774.
Paller, 2010	Safety and efficacy of etanercept treatment in children and adolescents with plaque psoriasis: 96-week results of open-label extension study.	<i>Journal of the American Academy of Dermatology</i> 62[3 SUPPL. 1], AB11. 2010.
Paller, 2008	Etanercept treatment in children and adolescents with plaque psoriasis.	<i>J.Am.Acad.Dermatol.</i> 58[Suppl. 2 No. 2], AbsP2300.

8. Results of Trials

The table below summarises the results for the primary endpoint in trial 20030211 of proportion of patients achieving a Psoriasis Area and Severity Index (PASI) 75 response at 12 weeks for etanercept and placebo.

Primary endpoint analysis of PASI 75 at week 12 (ITT analysis)

Trial ID	Etanercept n with event/N (%)	Placebo n with event/N (%)	Absolute difference RD± (95% CI)	Relative difference RR (95% CI)
Study 20030211	60/106 (57%)	12/105 (11%)	45% (34%, 56%)	4.95 (2.93, 8.65)
P-value: p < 0.0001				

Statistically significantly more patients in the ITT group achieved positive efficacy responses due to treatment with etanercept compared with placebo at week 12. (57% versus 11%; p<0.0001).

The PBAC noted the patients in the trial had less severe disease and were more treatment naïve and were therefore not representative of the PBS patients who would receive etanercept. The Pre-Sub-Committee Response provided subgroup analyses of the ‘PBS population’ based on subjects with a PASI score >15 and prior therapy as per the restriction. The PBAC noted that this revised analysis based on the proposed PBS population subgroup demonstrated a similar response rate.

The submission presented adverse event data from study 20030211. The PBAC noted the differences in adverse events between the etanercept and placebo groups: upper respiratory tract infections (17% vs. 11.4%), influenza (7.5% vs. 1.9%) and gastroenteritis (5.7% vs. 0%). No deaths were reported throughout the trial. No serious adverse events or infections occurred during the 12 week double-blind treatment or during the withdrawal-retreatment periods of the study. During the open-label period, one serious infection (pneumonia) attributable to etanercept and resulting in study withdrawal was reported and one subject had 2 serious events (dehydration and gastroenteritis) in the incomplete responder arm.

Long-term toxicity data was presented from the open-label extension study 20050111. A total of 145 out of 181 patients reported at least one adverse event during the study and five serious adverse event occurred in three patients (anxiety, intestinal obstruction, dehydration, abdominal pain, and abortion), but none were related to treatment. Two adverse events led to study withdrawal (sinusitis and Crohn disease) and no patients died. The PBAC considered that the overall safety of etanercept in patients with plaque psoriasis remains uncertain given only 96 weeks of safety data are available coupled with the fact that studies have reported an increase in the risk of severe infections in children taking biologics.

For PBAC's view, see Recommendation and Reasons.

9. Clinical Claim

The submission described etanercept as superior in terms of comparative effectiveness and non-inferior in terms of comparative safety over placebo. The PBAC considered that the claim of superior effectiveness of etanercept over placebo was reasonable, although some questions remain about the applicability of the trial population to the proposed PBS population. The PBAC considered that the claim of non-inferiority in terms of comparative safety over placebo was not reasonable given the overall safety concerns of bDMARD agents in paediatric patients.

10. Economic Analysis

The submission presented a trial-based cost per responder analysis of etanercept compared to placebo in paediatric patients based on the key clinical evidence from study 20030211. The evaluation estimated the incremental cost per PASI 75 response of etanercept compared to best supportive care over a 12-week period.

The incremental cost per PASI 75 response was less than \$15,000.

For PBAC's view, see Recommendation and Reasons.

11. Estimated PBS Usage and Financial Implications

The submission estimated the likely number of patients treated per year to be less than 10,000 in Year 5, at a net cost per year to the PBS of less than \$10 million in Year 5.

The PBAC considered the submission's financial estimate to be uncertain due to errors in the estimates, assumptions regarding the adult versus paediatric usage of biologics and the absence of any estimates of the effects of re-trialling.

12. Recommendation and Reasons

The PBAC recommended extending the Authority Required listing of etanercept powder for injection 25 mg and 50 mg to include the treatment of severe chronic plaque psoriasis in patients under 18 years of age who meet certain criteria on the basis of acceptable cost effectiveness to placebo in the context of a high clinical need.

In making this recommendation, the PBAC noted that chronic plaque psoriasis is a chronic inflammatory disorder that in its most severe form can considerably impact on a young person's quality of life. The PBAC further noted that the Paediatric Medicines Advisory Group (PMAG) had identified the clinical need for a treatment option for chronic plaque psoriasis in patients under 18 years of age.

The PBAC noted that the basis of the submission was a single randomised, double-blind control trial (Study 20030211) comparing etanercept 0.8 mg/kg up to a maximum dose of 50 mg once weekly with placebo in paediatric patients aged 4 to 17 years with moderate to severe plaque psoriasis. The primary endpoint of the study was the Psoriasis Area and Severity Index (PASI) 75 response at 12 weeks. The study found that statistically significantly more patients, in the ITT group at week 12, achieved positive efficacy responses due to treatment with etanercept compared with placebo (etanercept: PASI 75 responder of 57% versus placebo: PASI 75 responder of 11%). The PBAC noted that this equated to a statistically significant relative risk difference of 4.95 [95% CI: 2.93 to 8.65] and an absolute risk difference of 45% responders [95% CI: 34% to 56%]. The PBAC noted that a revised analysis based on the proposed PBS population subgroup demonstrated a similar response rate.

The PBAC agreed that the long term safety of treatment with tumour necrosis factor (TNF) inhibitors in paediatric populations continues to be of concern, however acknowledged that the Committee had previously considered that the risks of treatment with etanercept in paediatric populations were acceptable given the benefits.

The PBAC noted that the submission presented a trial-based cost per responder analysis, as determined by PASI 75 response to etanercept compared to best supportive care over a 12 week period, as the basis for the economic evaluation. The PBAC considered that although the absence of a cost utility analysis was not ideal there were precedents in previous paediatric submissions. The PBAC recommended that the cost of treatment with etanercept for the paediatric population with severe chronic plaque psoriasis should be no more than the cost in adults with the same condition.

The PBAC considered that the restriction should be consistent with the TGA registered indication regarding the duration of therapy with etanercept, which should be no longer than 24 weeks and treatment ceased after 12 weeks if a significant PASI response is not achieved.

In making this recommendation the PBAC noted the consumer comments on this item.

The PBAC recommended that etanercept is not suitable for inclusion in the PBS medicines for prescribing by nurse practitioners.

Recommendation:

ETANERCEPT, injection set containing 4 vials powder for injection 25 mg and 4 pre-filled syringes solvent 1 mL; injections 50 mg in 1 mL single use pre-filled syringes; injection 50 mg in 1 mL single use auto-injector.

Extend the current Authority Required listing to include treatment of severe chronic plaque psoriasis in patients under 18 years of age who meet certain criteria.

Restriction: **To be finalised**

Max quantity: 2 (25 mg – initial and continuing)

 1 (50 mg – initial and continuing)

Repeats: 3 (all strengths – initial)

5 (all strengths – continuing)

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 has no comments.