PUBLIC SUMMARY DOCUMENT
Product: Efalizumab, injection set containing 4 vials powder for injection 125 mg and 4 pre-filled syringes diluent 1.3 mL, Raptiva®.
Sponsor: Merck Serono (Australia) Pty Ltd.
Date of PBAC Consideration: November 2008

1. Purpose of Application

The submission requested extension of the current listing for chronic plaque psoriasis to extend the initial treatment phase from 12 to 24 weeks.

2. Background

The PBAC has considered submissions for efalizumab for chronic plaque psoriasis on three previous occasions. At the November 2004 meeting, the PBAC rejected an application to list efalizumab as an Authority Required listing because of unacceptable cost-effectiveness.

At the July 2005 meeting, the PBAC rejected an application to list efalizumab under Section 100 because of unacceptable cost-effectiveness. (See also Public Summary Document for July 2005).

At the November 2005 meeting, the PBAC recommended listing of efalizumab on the PBS under Section 85 for the treatment of severe refractory psoriasis on the basis of acceptable cost-effectiveness compared to no systemic treatment in the defined population. The PBAC noted a change to the response criteria from a Psoriasis Area and Severity Index (PASI) PASI-50 to a PASI-75 improvement in the restriction, and a price reduction compared to the July 2005 submission. (See also Public Summary Document for November 2005).

With the criteria to be met in order to qualify for continuing therapy with efalizumab, the PBAC recommended that at least a 75 % improvement in the patient's baseline PASI score following at least 12 weeks of therapy would be required. The restriction should also include the requirement for patients to complete the informed consent process included in the PBS restriction for the biological DMARDs for the treatment of rheumatoid arthritis, so they are aware of the criteria to be met to qualify for ongoing therapy, prior to commencing treatment. Listing was effective 1 April 2006.

3. Registration Status

Efalizumab was TGA registered on 5 October 2004 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 established.

4. Listing Requested and PBAC's View

The current listing includes an initial treatment period of 16 weeks with PASI assessment conducted after at least 12 weeks. This submission sought to extend *initial* treatment with efalizumab to 28 weeks with PASI assessment conducted after at least 24 weeks. No further changes were requested to the current authority listing. As a result of this change, the maximum number of repeats for initial treatment would increase from 3 to 6.

No change to the current listing for *continuing* treatment was proposed.

For PBAC's view see Recommendation and Reasons.

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 for this chronic disease. Efalizumab is proposed as a treatment for patients with severe refractory psoriasis who have little or no alternative therapies.

6. Comparator

The submission nominated current use of efalizumab using a 12-week initial treatment period as the main comparator. Following the initial assessment at week 12, and subsequent assessment every 24 weeks, patients who achieve a PASI $\geq$ 75 % reduction continue on efalizumab. If at the initial 12 weeks assessment (or any subsequent assessment point) the PASI > 75 % response is not met, patients switch to etanercept or infliximab, within a 5-year period. This was accepted by the PBAC.

7. Clinical Trials

The submission presented 6 placebo controlled trials of efalizumab, 4 placebo controlled trials of etanercept and 4 placebo controlled trials of infliximab.

Details of the key trials and associated reports published at the time of the submission are presented in the table below.

Trial ID	Publication title	Publication citation
Efalizumab trials		
Efalizumab 12 weeks response		
- 24011	Clinical experience acquired with the efalizumab (Raptiva®) (CLEAR) trial in patients with moderate to severe plaque psoriasis: results from a phase III, international, randomised, placebo controlled trial. Impact of efalizumab on patient reported outcomes in high-need psoriasis patients: results of the international, randomised, placebo-controlled phase III Clinical Experience Acquired with Raptiva (CLEAR) trial [NCT00256139]. Clinical Experience Acquired with Raptiva (CLEAR) trial in patients with moderate to severe plaque psoriasis: results from extended treatment in an international, phase III, placebo-controlled trial.	Dubertret, L et al (2006), *Br J Dermatol* 155: 170-181. Ortonne, J et al (2005), *BMC Dermatol* 5: Article no. 13. Sterry, W et al (2006), *JDDG – J Germ Soc Dermatol* 4: 947-957.
- 2058	Extended efalizumab therapy improves chronic plaque psoriasis: results from a randomised phase III trial.	Leonardi, C et al (2005), *J Am Acad Dermatol* 52 (3, Part 1) 425-433.
- 2059	A novel targeted T-cell modulator, Efalizumab, for plaque psoriasis.	Lebwohl, M et al (2003), *NEJM* 349: 2004-2013.
- 2390	Efalizumab for patients with moderate to severe plaque psoriasis: a randomised controlled trial.	Gordon, K et al (2003), JAMA 290: 3073-3080.
- 2600	Safety of efalizumab in adults with chronic moderate to severe plaque psoriasis: A phase IIIb, randomized, controlled trial	Papp, K et al (2006a), *Int J Dermatol* 45: 605-614.
Efalizumab 24 weeks response		
- 24011	As above	As above
- 2391	Efficacy and safety ovserved during 24 weeks of	Menter, A et al (2005), *Arch*

	efalizumab therapy in patients with moderate to severe plaque paoriasis. *This is the open label extension phase of 2390*	*Dermatol* 141: 31-38.
- 2243	Extended efalizumab therapy sustains efficacy without increasing toxicity in patients with moderate to severe chronic plaque psoriasis. Long-term continuous efalizumab therapy in patients with moderate to severe chronic plaque psoriasis: updated results from an ongoing trial.	Gottlieb, A et al (2004a), *J Drugs Dermatol* 3 : 614-624. Gottlieb, A et al (2006a), *J Am Acad Dermatol* 54 (4) (Suppl) S154-S163.
Efalizumab attrition/loss of response studies		
- 2390/2391	As above	As above
- 2243	As above	As above
Etanercept trials		
Etanercept 12 weeks response		
- Gottlieb (2003a)	A randomised trial of etanercept as monotherapy for psoriasis.	Gottlieb, A et al (2003a), *Arch Dermatol* 139: 1627-1632
- Leonardi (2003) & Krueger (2006)	Etanercept as monotherapy in patients with psoriasis. Patients with psoriasis respond to continuous open-label etanercept therapy after initial incomplete response in a randomised placebo controlled trial.	Leonardi, C et al (2003), *NEJM* 349: 2014-2022. Krueger, G et al (2006), *J Am Acad Dermatol* 54 (3) (Suppl 2): S112-S119.
- Papp (2005b)& Elewski (2004)	A global, phase III, randomised controlled trial of etanercept in psoriasis: safety, efficacy and effectiveness of dose reduction. Efficacy and safety of etanercept in patients with psoriasis: results of a global phase III study.	Papp, K et al (2005b), *Br J Dermatol* 152: 1304-1312. Elewski, B et al (2004), *J Am Acad Dermatol* 50: 159.
Etanercept attrition/loss of responsiveness studies		
- Gordon 2006a	Clinical response in psoriasis patients discontinued from and then reinitiated on etanercept therapy. *This is an extension phase of trial reported by Leonardi (2003) and Kruger. The submission's assertion that Gordon 2006a and Gottlieb (2003a) are linked is incorrect.*	Gordon, K et al (2006a), *J Dermatol Treat* 17: 9-17.
Infliximab trials		
Infliximab 10 weeks response		
- Chaudari (2001)& Gottlieb (2003b)	Efficacy and safety of infliximab monotherapy for plaque type psoriasis: a randomised trial. Infliximab monotherapy provides rapid and sustained benefit for plaque type psoriasis.	Chaudhari, U et al (2001), *Lancet* 357: 1842-1847. Gottlieb, A et al (2003b), *J Am Acad Dermatol* 48 : 829-835
- Gottlieb (2004b) & Feldman (2005b)	Infliximab induction therapy for patients with severe plaque type psoriasis: A randomised, double blind placebo-controlled trial. Infliximab therapy results in significant improvement in the quality of life of patients with severe psoriasis: a double blind placebo-controlled trial.	Gottlieb, A et al (2004b), *J Am Acad Dermatol* 51: 534-542. Feldman, S et al (2005b), *Br J Dermatol* 152: 954-960.
- Reich (2005)	Infliximab induction with maintenance therapy for moderate to severe psoriasis: a phase III multicentre, double blind trial.	Reich, K et al (2005), Lancet 366: 1367-1374.
- Menter (2007b)	A randomised comparison of continuous vs. intermittent infliximab maintenance regimens over 1 year in the treatment of moderate to severe plaque psoriasis.	Menter, A et al (2007b), *J Am Acad Dermatol* 56 (1): 31.e1-31.e15.

Infliximab attrition/loss responsiveness studies		
- Reich (2005)	As above	As above.

8. Results of Trials

The submission estimated a difference in PASI ≥ 75 % response between efalizumab and placebo at week 12 from the efalizumab trials for patients with a baseline PASI > 15. Added to the pooled placebo response rate of approximately 3%, the submission estimated an overall efalizumab 12 weeks response rate of approximately 27% for patients with baseline PASI > 15.

Three efalizumab trials, (24011, 2390/2391 and 2243) reported PASI ≥ 75 % responses after 12 and 24 weeks. Only trials 24011 and 2390/2391 treated patients according to TGA approved product information (PI) doses of efalizumab of 1 mg /kg/week.

From the above two data sets the submission estimated for the modelled economic evaluation the PASI ≥ 75 % response rates for the proposed and current listings of initial efalizumab treatment. The efalizumab PASI ≥ 75 % response at Week 12 (pooled placebo response + risk difference for efalizumab versus placebo at Week 12) was >26%. The efalizumab response rate at Week 24 was >43%.

The response rates associated with an additional 12 weeks of efalizumab treatment in efalizumab non-responders at 12 weeks and the response rates reported for initial etanercept and infliximab treatment (applying the submission's assumption that patients will respond similarly regardless of prior therapies) indicate that the initial response rates to etanercept (33.4 %) and infliximab (79.6 %) are greater than for an additional 12 weeks of efalizumab treatment in patients who have failed to achieve a PASI ≥ 75 % response at 12 weeks (27.0 %). However, for patients who achieve a 50 % ≤ PASI < 75 % response at 12 weeks, the response rate to a further 12 weeks of efalizumab therapy was approximately 50%. For patients not achieving at least a PASI 50 % response by Week 12, the PASI 75 % response of an additional 12 weeks treatment with efalizumab was lower than the PASI 75 % response of patients receiving initial treatment with etanercept or infliximab.

9. Clinical Claim

The submission described efalizumab 28 weeks initial treatment as superior in terms of comparative effectiveness and equivalent in terms of comparative safety over efalizumab 16 weeks initial treatment.

For PBAC's view see Recommendation and Reasons.

10. Economic Analysis

A stepped economic evaluation was presented. The type of model used was a decision tree with a semi-Markov structure. Outcomes (PASI ≥ 75 % response from the trials) and costs (drug and physician costs only) were modelled to 5.31 years (24 weeks cycles), incremental cost effectiveness ratios (ICERs) were as cost/ Quality Adjusted Life Year (QALY). The model was driven by efficacy outcomes and utility values.

The model was sensitive to the attrition rates applied in each cycle of the model - the rate at which patients in maintenance phase lose their response to therapy. No sensitivity analyses were undertaken by the submission for this input, which was not considered appropriate by

the PBAC. Study 2390/2391 suggested that the attrition rate after 3 months on maintenance with efalizumab is approximately 19%. This would indicate that a higher rate of attrition after each 24 weeks than the 12.2 % assumed in the submission would be more appropriate. A higher attrition rate would result in a higher incremental cost-effectiveness ratio than calculated in the submission.

The incremental cost per extra QALY gained estimated in the submission fell in the range of $15,000 - $45,000.

For PBAC's view, see Recommendation and Reasons.

11. Estimated PBS Usage and Financial Implications

The submission estimated the likely number of patients per year to be less than 10,000 in Year 4. The PBAC considered this to be uncertain.

The financial cost per year to the PBS was estimated by the submission to be less than $10 million in Year 4. The PBAC considered that this may be an overestimate as the submission did not consider the substitution away from other bDMARDs.

12. Recommendation and Reasons

The PBAC recommended extending the current listing for chronic plaque psoriasis to extend the initial treatment phase from 12 to 24 weeks for patients who achieve a PASI over 50 and less than 75 at 12 weeks. These patients would be eligible for the extended treatment, but the fact that they have not achieved a response of PASI 75 in the first 12 weeks will count as one of the 3 treatment failures allowed before a 5-year break in PBS-subsidised biological agent therapy must commence, after which they are eligible to begin another cycle. Therefore if continuing patients fail to achieve a response of a PASI 75 at 24 weeks they will be eligible to only to commence one more treatment if they had received no prior biological agents.

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 efalizumab treatment.

The PBAC noted data received from Medicare Australia suggesting that, even excluding patients who received 24 weeks of efalizumab under the previous interchangeability rules, 75 % of patients respond at 12 weeks. The PBAC were aware that the sponsor had not had a chance to review this data.

The studies presented added uncertainty to the analysis, as the trial data do not correlate with the Medicare Australia data which indicates that in practise the responder rate is much higher than in the trials. The PBAC described the relapse rate used for infliximab and etanercept as uncertain. The ideal trial comparison would be data which includes efalizumab non-responders.

The PBAC noted that the model was robust and provided an appropriate comparison. The model however was sensitive to the attrition rate. The PBAC noted the sensitivity analyses in the ESC Advice, an attrition rate of 35 % producing an ICER in the range of $45,000 - $75,000 per QALY and an attrition rate of 20 % producing an ICER in the range of $15,000 -

$45,000 per QALY, but higher than that estimated in the submission. The PBAC thought increasing the attrition rate to 35 % was likely to be an overestimate and 20 % was considered to be more reasonable.

Recommendation

EFALIZUMAB, injection set containing 4 vials powder for injection 125 mg and 4 pre-filled syringes diluent 1.3 mL

Restriction:	The full restriction will be available on the PBS website at www.pbs.gov.au from the date of listing.
Maximum quantity:	1
Number of repeats:	6

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.