PUBLIC SUMMARY DOCUMENT
Product: Adalimumab, injection, 40 mg in 0.8 mL pre-filled syringe, 40 mg in 0.8 mL pre-filled pen, Humira®
Sponsor: Abbott Australasia Pty Ltd
Date of PBAC Consideration: July 2008

1. Purpose of Application

The application sought to extend the current section 85 Authority required listing to include treatment of severe chronic plaque psoriasis.

2. Background

Adalimumab is currently listed on the Pharmaceutical Benefits Scheme (PBS) for the treatment of rheumatoid arthritis, psoriatic arthritis and ankylosing spondylitis and had not previously been considered for treatment of chronic plaque psoriasis.

Adalimumab was recommended for listing for treatment of Crohn disease at the November 2007 Pharmaceutical Benefits Advisory Committee (PBAC) meeting and the listing implemented from 1 August 2008.

3. Registration Status:

Adalimumab was registered 17 April 2008 for the treatment of moderate to severe chronic plaque psoriasis in adult patients who are candidates for systemic therapy or phototherapy.

Adalimumab is also TGA registered for:

- Rheumatoid Arthritis
- Psoriatic Arthritis
- Ankylosing Spondylitis
- Crohn Disease

4. Listing Requested and PBAC's View

The requested listing was identical to that of the current PBS listings for etanercept, efalizumab and infliximab for the treatment of chronic plaque psoriasis.

5. Clinical place for the Proposed Therapy

Psoriasis is a chronic, relapsing inflammatory skin condition of which the plaque type is the most common. Plaque psoriasis is characterized by scaling and inflammation with circular-to-oval red plaques distributed most commonly on the scalp, elbows, knees, and lower back. The inflammation may also affect the fingernails, toenails, soft tissues of the mouth, genitalia, and joints. The inflamed areas cause pain, itching, and discomfort. The extent and duration of the disease is highly variable and can be characterised by acute flare ups and relapses.

Adalimumab is a biological Disease-modifying Antirheumatic Drug (bDMARD). bDMARDS are used to slow down the progression of the disease. Adalimumab will provide clinicians with an alternative bDMARD therapy for patients suffering with severe plaque psoriasis whose condition is refractory to other systemic treatments or phototherapy.

For PBAC's view, see Recommendation and Reasons.

6. Comparator

The submission nominated infliximab as the main comparator and efalizumab as a secondary comparator.

For PBAC's view, see Recommendation and Reasons.

7. Clinical Trials

The submission presented indirect comparisons using meta-analyses of three sets of randomised trials for adalimumab (M02-528, M03-656 REVEAL and M04-716 CHAMPION), infliximab (Chaudhari, Gottlieb, EXPRESS and EXPRESS II) and efalizumab (CLEAR, Gordon, Lebwohl, Leonardi and Papp). Placebo was used as the common comparator.

The following table lists the randomised trials published at the time of the submission.

Trial ID	Protocol title/ Publication title	Publication citation
ADALIMUMAB		
M03-656 (REVEAL) Menter A et al	Adalimumab therapy for moderate to severe psoriasis: a randomized, controlled phase III trial.	Journal of American Academy of Dermatology, 2008; 58(1): 106–115.
Revicki D.A., et al	Impact of adalimumab treatment on patient-reported outcomes: results from a Phase III clinical trial in patients with moderate to severe plaque psoriasis.	Journal of Dermatological Treatment, 2007; 18: 341–350
EFALUZIMAB		
CLEAR Dubertret-L, et al,	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(1): 170-181
Ortonne-Jean-Paul, et al.	Impact of efalizumab on patient-reported outcomes in high-need psoriasis patients: results of the international, randomized, placebo- controlled Phase III Clinical Experience Acquired with efalizumab (CLEAR) trial (NCT00256139).	BMC dermatology, 2005; 5: 13.
Sterry-Wolfram, et al	Clinical Experience Acquired with efalizumab (CLEAR) trial in patients with moderate-to-severe plaque psoriasis: results from extended treatment in an international, Phase III, placebo-controlled trial.	Journal der Deutschen Dermatologischen Gesellschaft - Journal of the German Society of Dermatology: JDDG, 2006; 4(11): 947-56.
Gordon-Kenneth-B., et al, 2003	Efalizumab for patients with moderate to severe plaque psoriasis: a randomized controlled trial.	JAMA : the journal of the American Medical Association, 2003; 290(23): 3073-80
Menter-Alan et al	Efficacy and safety observed during 24 weeks of efalizumab therapy in patients with moderate to severe plaque psoriasis.	Archives of dermatology, 2005; 141(1): 31-8.
Lebwohl-Mark, et al, 2003	A novel targeted T-cell modulator, efalizumab, for plaque psoriasis.	The New England journal of medicine, 2003; 349(21): 2004-13.
Leonardi-Craig-L., et al, 2005	Extended efalizumab therapy improves chronic plaque psoriasis: results from a randomized phase III trial.	Journal of the American Academy of Dermatology, 2005; 52(3 Pt 1): 425-33

Trial ID	Protocol title/ Publication title	Publication citation
Papp-Kim-A et al, 2006	Safety of efalizumab in adults with chronic moderate to severe plaque psoriasis: a phase IIIb, randomized, controlled trial.	International journal of dermatology, 2006; 45(5): 605-14
INFLIXIMAB		
Chaudhari-U et al, 2001	Efficacy and safety of infliximab monotherapy for plaque-type psoriasis: a randomised trial.	Lancet; 2001; 357(9271): 1842-7
Gottlieb-Alice-B et al	Infliximab monotherapy provides rapid and sustained benefit for plaque-type psoriasis.	Journal of the American Academy of Dermatology; 2003a; 48(6): 829-35
Gottlieb-A-B et al	Pharmacodynamic and pharmacokinetic response to anti-tumor necrosis factor-(alpha) monoclonal antibody (Remicade) treatment of moderate to severe psoriasis vulgaris.	Journal of the American Academy of Dermatology; 2003b; 48(1): 68-75
Gottlieb-Alice-B et al, 2004	Infliximab induction therapy for patients with severe plaque-type psoriasis: a randomized, double-blind, placebo-controlled trial.	Journal of the American Academy of Dermatology; 2004; 51(4):534-42
Feldman-S-R et al	Infliximab treatment results in significant improvement in the quality of life of patients with severe psoriasis: a double-blind placebo- controlled trial.	The British journal of dermatology; 2005; 152(5): 954-60
EXPRESS Reich-Kristian et al	Infliximab induction and maintenance therapy for moderate-to-severe psoriasis: a phase III, multicentre, double-blind trial.	Lancet; 2005; 366(9494): 1367-74
Reich-K et al	Improvement in quality of life with infliximab induction and maintenance therapy in patients with moderate-to-severe psoriasis: a randomized controlled trial.	The British journal of dermatology; 2006; 154(6): 1161-8
Reich-Kristian et al	Infliximab treatment improves productivity among patients with moderate-to-severe psoriasis.	European journal of dermatology; 2007; 17(5): 381-386
EXPRESS II Menter-Alan et al	A randomized comparison of continuous vs. intermittent infliximab maintenance regimens over 1 year in the treatment of moderate-to-severe plaque psoriasis.	Journal of the American Academy of Dermatology; 2007; 56(1): 31.e1-15
Leonardi C et al	Infliximab for the treatment of moderate to severe psoriasis: response to re-treatment.	Abstract P2888. American Academy of Dermatology 64th Annual Meeting March 3-7, 2006, J Am Acad Dermatol; 54: AB220

8. Results of Trials

Adalimumab vs. infliximab – 12 weeks

The submission presented a pooled odds ratio indirect comparison suggesting adalimumab was inferior to infliximab in achieving a PASI 75 at week 12. However, an indirect analysis conducted during the evaluation of the pooled relative risk suggested adalimumab was non-inferior to infliximab in achieving a PASI 75 at week 12.

The results of the indirect comparison of adalimumab versus infliximab (PASI 75 at week 12) using odds ratios and relative risks are summarised in the following table:

Adalimumab vs. placebo Pooled treatment effect (95% CI)	Infliximab vs. placebo Pooled treatment effect (95% CI)	Indirect estimate of effect (95% CI)
OR 31.93 (18.79, 54.24)	OR 118.57 (60.39, 232.83)	0.2692 (0.11, 0.63)
RR 9.64 (4.36, 21.28)*	RR 17.40 (6.41, 47.19)*	0.5540 (0.15, 1.98)*

* Analyses conducted during the evaluation

Adalimumab vs. efalizumab – 12 weeks

Similarly, the submission presented a pooled odds ratio indirect comparison suggesting adalimumab was superior to efalizumab in achieving a PASI 75 at week 12. However, an indirect analysis conducted during the evaluation using the pooled relative risks indicated that adalimumab was not superior to efalizumab but rather adalimumab was non-inferior to efalizumab in achieving a PASI 75 at week 12.

The results of the indirect comparison of adalimumab versus efalizumab (PASI 75 at week 12) using odds ratios and relative risks are summarised in the following table:

Adalimumab vs. placebo Pooled treatment effect (95% CI)	Efalizumab vs. placebo Pooled treatment effect (95% CI)	Indirect estimate of effect (95% CI)
OR 31.93 (18.79, 54.24)	OR 9.96 (6.60, 15.02)	3.2068 (1.64, 6.27)
RR 9.64 (4.36, 21.28)*	RR 7.34 (5.23, 10.30)*	1.31 (0.55, 3.11)*

* Analyses conducted during the evaluation

The PBAC considered that the pooled odds ratio was a more relevant measure for the indirect comparison in the submission.

When analyses are conducted using relative risks, there were no statistically significant differences in effect size between adalimumab and either infliximab or efalizumab. In each case the confidence interval around the indirect estimate of effect was quite wide.

Adalimumab vs. infliximab – 52 and 50 weeks

The submission also presented an indirect comparison of two trials (REVEAL and EXPRESS) using odds ratios, suggesting adalimumab was non-inferior to infliximab in achieving a PASI 75 at 52 weeks. The conclusion was similar using an indirect comparison using relative risks.

The results of the indirect comparison of adalimumab versus infliximab (PASI 75 at week 52) are summarised in the following table:

Adalimumab vs. placebo Treatment effect (95% CI)	Infliximab vs. placebo Treatment effect (95% CI)	Indirect estimate of effect (95% CI)
OR 16.45 (9.74, 27.78)	OR 25.50 (7.87, 82.67)	0.6452 (0.18, 2.34)
RR 9.47 (5.98, 14.99)*	RR 13.05 (4.28, 39.78)*	0.7257 (0.22, 2.42)*

* Analyses conducted during the evaluation

The 52-week data presented in the submission were difficult to interpret because of the complex cross-over design of these trials, in combination with the interruption and re-randomisation of the treatment and placebo arms in each case.

Both adalimumab and infliximab treatment arms showed a decrease in response over time. The limited data available suggested there may be a smaller loss of response over time with adalimumab compared with infliximab. Given the complexity of the two study designs, definitive conclusions are not possible.

A table summarising the of results of the indirect comparison of adalimumab to infliximab of patients maintaining a PASI 75 response at 52 and 50 weeks respectively – Odds Ratios (OR) is shown below:

	Adalimumab			**Infliximab**			**Indirect estimate of effect (95% CI)**
Trial ID	**OR (95% CI)**	**ADA n/N (%)**	**Placebo n/N (%)**	**Placebo n/N (%)**	**INF n/N (%)**	**OR (95% CI)**	
REVEAL 52 weeks	16.45 (9.74, 27.78)	113/250 (45.2%)	19/398 (4.8%)	-	-	-	
EXPRESS 50 weeks	-	-	-	3/77 (3.9%)	153/301 (50.8%)	25.50 (7.87, 82.67)	
Treatment effect[a]	16.45 (9.74, 27.78)					25.50 (7.87, 82.67)	0.6452 (0.18, 2.34) p=0.505

Abbreviations: ADA = Adalimumab; INF = Infliximab
[a] pooled using the random effects model

An indirect comparison of treatment effect suggested no statistically significant difference between adalimumab and infliximab at 52 weeks. However, the confidence interval around the indirect estimate of effect was wide.

The table below shows the proportion of subjects maintaining a PASI 75 response at various time points in REVEAL:

Period A	**Proportion of adalimumab patients achieving a PASI 75 response n/N (%)**	
Week 12[a]	551/814 (67.7)	
Week 16[b]	578/814 (70.9)	
Period B[c]	**Proportion of week 16 PASI 75 responders on adalimumab maintaining a PASI 75 response n/N (%)**	
Week 24	538/580 (92.8)	
Week 33	490/580 (84.5)	
Period C[d]	**Proportion of week 33 PASI 75 responders maintaining a PASI 75 response**	
	Adalimumab n/N (%)	**Placebo n/N (%)**
Week 36	234/250 (93.6)	220/240 (91.7)
Week 40	215/250 (86.0)	186/240 (77.5)
Week 44	214/250 (85.6)	158/240 (65.8)
Week 48	208/250 (83.2)	135/240 (56.3)
Week 52	198/250 (79.2)	102/240 (42.5)

NB: missing values imputed as non-responders. [a, b, c, d]Source: REVEAL.

A table of the proportion of infliximab patients who were PASI 75 responders at week 10 and who maintained a PASI 75 response at week 24 and week 50 is shown below:

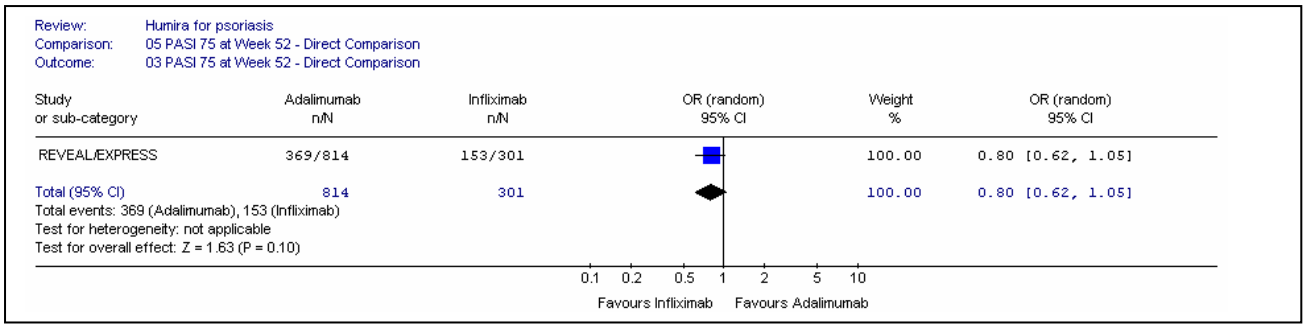
Trial duration	Proportion of infliximab patients achieving a PASI 75 response n/N (%)
Week 10	**242/301 (80.4)**
	Proportion of week 10 responders on infliximab maintaining a PASI 75 response n/N (%)
Week 24 Intention to treat Evaluable patients **Week 50** Intention to treat Evaluable patients	 203/242 (83.9) 203/229 (88.6) 153/242 (63.2) 153/225 (68.0)

Alternative analyses

The results using evaluable patient populations for both adalimumab and infliximab showed that infliximab was superior at 52 weeks (OR = 0.39, CI 0.27, 0.56). The results using the ITT population for both adalimumab and infliximab numerically favoured infliximab, but were not statistically significant (OR = 0.80, CI 0.62, 1.05).

The results of the Odds Ratios for the various therapies versus placebo at 52 weeks are summarised in the following figure.

The results of the Odds Ratio for adalimumab versus infliximab – 52 weeks, ITT (adalimumab 814 patients; infliximab 301 patients) is shown in the figure below:



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

The use of pooled odds ratios in preference to pooled relative risks impacted significantly on the results of the indirect comparison of adalimumab and infliximab.

A table summarising the results of the indirect comparison of adalimumab versus infliximab adverse events – Odds Ratios (OR) is shown below:

Adalimumab vs. placebo Pooled treatment effect (95% CI)	Infliximab vs. placebo Pooled treatment effect (95% CI)	Indirect estimate of effect (95% CI)
OR 1.09 (0.74, 1.59)	OR 1.82 (1.37, 2.42)	0.5983 (0.37, 0.96)

* Analyses conducted during the evaluation

As safety was assessed at different time points, the results of the comparative safety analyses should be interpreted cautiously. The safety results are for 'any' adverse event, which includes mild to severe. This makes the comparison difficult to interpret.

9. Clinical Claim

The submission claimed that:

(i) Adalimumab was inferior to infliximab in terms of short term effectiveness (12 weeks).
Adalimumab was non-inferior in terms of long-term comparative effectiveness (52 weeks).
Adalimumab was potentially superior to infliximab in terms of short-term comparative safety and non-inferior to infliximab in terms of long-term comparative safety.

The PBAC agreed that the pooled odds ratio indirect comparison suggests adalimumab is inferior to infliximab in achieving a PASI 75 at week 12.

However, the Committee was not satisfied that adalimumab is non-inferior to infliximab in terms of long-term effectiveness (at 52 weeks).

(ii) Adalimumab was superior to efalizumab in terms of short-term effectiveness and non-inferior in terms of short-term comparative safety.

The PBAC was unable to reach a firm conclusion on the relativity of adalimumab against efalizumab on the basis of the data presented.

For PBAC's view, see Recommendation and Reasons.

10. Economic Analysis

The submission presented a cost minimisation analysis. The equi-effective doses were estimated as adalimumab 40 mg subcutaneous injection (1 unit) and infliximab 148 mg intravenous injection (1.48 units).

11. Estimated PBS Usage and Financial Implication:

The submission estimated a financial cost/year to the PBS of in the range of $10 – 30 million in year 5.

Recommendations and Reasons:

The PBAC did not accept the submission's nomination of infliximab as the primary comparator and efalizumab as a secondary comparator, noting that efalizumab has the highest market share in this condition and that infliximab's listing for psoriasis become effective only on 1 December 2007. This makes efalizumab the product most likely to be substituted by adalimumab should it be recommended for PBS listing. The PBAC however, agreed that a comparison with infliximab remains useful, particularly if the sponsor of adalimumab will continue to seek PBS listing on a cost-effectiveness basis against efalizumab, in which case a comparison against infliximab would be an appropriate second step in determining the relativities of all three agents in the treatment of severe chronic plaque psoriasis.

The Committee agreed with the submission that in comparing the biological agents in the treatment of chronic plaque psoriasis it is important to consider both the short term

effectiveness (at around 12 weeks) and the durability of response thereafter. This is because the PBS subsidy of these agents is currently limited to those patients who achieve a PASI 75 response after 12 – 16 weeks of treatment and thereafter to patients who maintain this response at each 6 monthly assessment point.

The PBAC was unable to reach a firm conclusion on the relativity of adalimumab against efalizumab on the basis of the data presented. Although the pooled odds ratio of the indirect comparison presented suggests adalimumab is superior to efalizumab in achieving a PASI 75 after 12 weeks of treatment, no data were presented on the longer term comparative durability of response to these two agents, making an overall assessment of relative effectiveness impossible. Additionally, even if it were accepted that adalimumab is superior to efalizumab in terms of effectiveness no data were presented on the cost-effectiveness of using adalimumab instead of efalizumab.

The PBAC agreed with the sponsor that the pooled odds ratio indirect comparison suggests adalimumab is inferior to infliximab in achieving a PASI 75 at week 12. The Committee however found the claim that adalimumab is non-inferior to infliximab at 52 weeks more difficult to interpret. This was partly because of the complex cross-over design of the trials used in this comparison, and additionally because PBAC considered the most relevant comparison to be one in which the durability of response in responders at week 12 (or thereabouts) is assessed, rather than overall response from the beginning to the end of treatment as presented by the submission, as under the conditions of PBS subsidy only those patients who respond at week 12 are eligible for continuing treatment. The Committee noted that the EXPRESS trial reported that 68% of patients (153/225) who had achieved a PASI 75 at week 10 maintained this response to week 50.

Taking into account both the results of short term comparison and the uncertainty around the longer term comparison, the Committee was not satisfied that adalimumab is non-inferior to infliximab.

Overall however, the PBAC rejected the submission on the grounds of uncertain clinical effectiveness and the resulting uncertain cost-effectiveness of adalimumab when compared with efalizumab.

Recommendation
Reject

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 is working with the PBAC to obtain PBS listing for Humira in chronic plaque psoriasis.