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: AbbVie Pty Ltd
Date of PBAC Consideration: March 2013

1. Purpose of Application

The submission requested extension of the current Authority required listing to include treatment of an adult patient with moderate to severe chronic plaque psoriasis, defined by a Psoriasis Area and Severity Index (PASI) or Dermatology Life Quality Index (DLQI) greater than 10 and PASI less than or equal to 15, who have failed to achieve an adequate response to at least two non-biologic therapies.

2. Background

The PBAC had not previously considered adalimumab for moderate to severe chronic plaque psoriasis.

3. Registration Status

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

4. Listing Requested and PBAC's View

Authority required

Treatment of moderate whole-body chronic plaque psoriasis in patients with PASI or Dermatology Life Quality Index (DLQI) >10 but PASI ≤15 who have failed 2 prior systemic therapies.

Response to treatment would be measured by a PASI 75 reduction.

The PBAC noted the advice in the submission's Pre-Sub-Committee Response (PSCR) that the sponsor consented to the evaluator's recommendation of a listing for moderate to severe disease consistent with the current listing for severe disease, with patients being required to have failed to respond to treatment with 3 of 4 prior therapies, and assessment of disease severity on PASI alone.

5. Clinical Place for the Proposed Therapy

Patients with moderate chronic plaque psoriasis are currently treated with phototherapy, methotrexate, acitretin or cyclosporine. Patients with an inadequate response to these treatments are recommended to cycle between treatments until an adequate response is achieved.

Adalimumab will provide clinicians with a biological therapy for patients suffering with moderate chronic plaque psoriasis whose condition is refractory to phototherapy or non-biological systemic treatments.

6. Comparator

The sponsor nominated placebo for no treatment as the comparator.

The PBAC considered that this was the appropriate comparator for the revised population of patients who have failed 3 prior therapies.

7. Clinical Trials

The submission presented a meta-analysis of two randomised trials (M02-528 and REVEAL) comparing adalimumab 40 mg dosed every other week (eow) with placebo in 1,309 patients with moderate or severe plaque psoriasis, and a *post-hoc* subgroup of 468 patients with moderate plaque psoriasis only.

Details of the trials and associated reports presented in the submission are in the table below.

Trial ID/ First author	Protocol title/ Publication title	Publication citation
Direct randomised trials		
M02-528 Gordon et al	Clinical response to adalimumab treatment in patients with moderate to severe psoriasis: Double-blind, randomized controlled trial and open-label extension study	*J Am Acad Dermatol*, 2006; 55(4):598-606.
Shikiar et al	The validity and responsiveness of three quality of life measures in the assessment of psoriasis patients: results of a phase II study.	*Health Qual Life Outcomes,* 2006; 4:71.
Shikiar et al	Adalimumab treatment is associated with improvement in health-related quality of life in psoriasis: Patient-reported outcomes from a Phase II randomized controlled trial.	*J Dermatol Treat,* 2007; 18(1):25-31.
M03-656 (REVEAL) Menter et al	Adalimumab therapy for moderate to severe psoriasis: A randomized, controlled phase III trial	*J Am Acad Dermatol*, 2008; 58(1):106-15
Menter et al	Efficacy and safety of adalimumab are consistent across weight quartiles in patients with moderate to severe psoriasis: Subanalysis of REVEAL	*J Am Acad Dermatol,* 2009; 60(3):AB173
Menter et al	Efficacy and safety of adalimumab across subgroups of patients with moderate to severe psoriasis	*J Am Acad Dermatol,* 2010; 63(3):448-56
Kimball et al	Efficacy and safety of adalimumab among patients with moderate to severe psoriasis with comorbidities: Subanalysis of results from a randomized, double-blind, placebo-controlled, phase III trial	*Am J Clin Dermatol,* 2011; 12(1):51-62
Leonardi et al	Efficacy of adalimumab is consistent across body weight in patients with moderate to severe psoriasis: Subanalysis of REVEAL	*J Am Acad Dermatol*, 2011; 64(2):AB158
Gordon et al	Effect of weight and body mass index on the onset of adalimumab efficacy: Subanalysis of REVEAL	*J Am Acad Dermatol,* 2012; 66(4):AB191
Gordon et al	Efficacy and safety of adalimumab in patients with psoriasis treated continuously for over 3 years	*J Eur Acad Dermatol Venereol,* 2010;24:28
Gordon et al	Efficacy and safety in patients with psoriasis treated continuously with adalimumab for	*J Am Acad Dermatol,* 2010; 62(3):AB140

Trial ID/ First author	Protocol title/ Publication title	Publication citation
	approximately 3 years	
Gordon et al	Long-term efficacy and safety of adalimumab in patients with moderate to severe psoriasis treated continuously over 3 years: Results from an open-label extension study for patients from REVEAL	*J Am Acad Dermatol,* 2012; 66(2):241-51.
Poulin et al	Psoriasis patients required to discontinue adalimumab therapy have worsening in their quality of life out of proportion to worsening in the objective signs of disease: Subanalysis of REVEAL	*J Am Acad Dermatol,* 2012; 66(4):AB201
Papp et al	Long-term outcomes of interruption and retreatment vs. continuous therapy with adalimumab for psoriasis: Subanalysis of REVEAL and the open-label extension study	*J Eur Acad Dermatol Venereol.,2012*
Strober et al	Impact of sustained robust response on patient-reported outcomes for adalimumab-treated patients with moderate to severe psoriasis: Subanalysis of REVEAL	*J Am Acad Dermatol*, 2012; 66(4):AB194

The primary outcome measure in the trials was the proportion of subjects achieving at least a PASI 75 response (75% improvement from baseline in PASI score) at week 12.

The submission presented a comparison of the 'moderate' patient subgroup versus the full ITT (moderate-severe) trial populations.

A further trial (CHAMPION) was considered during the evaluation to have been inappropriately excluded from the submission.

Details of the studies are presented in the table below.

Trial ID/ First author	Protocol title/ Publication title	Publication citation
M04-716 (CHAMPION) Saurat et al	Efficacy and safety results from the randomized controlled comparative study of adalimumab vs. methotrexate vs. placebo in patients with psoriasis (CHAMPION)	*Br J Dermatol* , 2008;158(3):558-66.
Revicki 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	*J Dermatol Treat* , 2007;18(6):341-50.
Revicki et al	Impact of adalimumab treatment on health-related quality of life and other patient-reported outcomes: Results from a 16-week randomized controlled trial in patients with moderate to severe plaque psoriasis	*Br J Dermatol, 2008;* 158(3):549-57.
Revicki et al	Adalimumab improves health-related quality of life in patients with moderate to severe plaque psoriasis compared with the United States general population norms: results from a randomized, controlled Phase III study	*Health Qual Life Outcomes*, 2008; 6:75.

Trial ID/ First author	Protocol title/ Publication title	Publication citation
Reich et al	Risk-benefit analysis of adalimumab versus methotrexate and placebo for the treatment of moderate to severe psoriasis: Comparison of adverse event-free remission days in the CHAMPION trial	*J Am Acad Dermatol*, 2009; 60(3):AB178.
Reich et al	Risk-benefit analysis of adalimumab versus methotrexate and placebo for the treatment of moderate to severe psoriasis: Comparison of adverse event-free response days in the CHAMPION trial	*J Invest Dermatol, 2009;* 129:S26.
Reich et al	Benefit-risk analysis of adalimumab versus methotrexate and placebo in the treatment of moderate to severe psoriasis: Comparison of adverse event-free response days in the CHAMPION trial	*J Am Acad Dermatol, 2010;* 63(6):1011-8.
Saurat et al	Adalimumab response is consistent across subgroups of patients with moderate to severe psoriasis: Subanalysis of the CHAMPION study	*J Am Acad Dermatol, 2010;* 62(3):AB124.
Navarini et al	Adalimumab treatment for moderate to severe psoriasis substantially improves PASI scores as analyzed by body region and individual PASI component: Sub-analysis from the CHAMPION study	*J Invest Dermatol*, 2012;132:S85.

8. Results of Trials

The submission presented results for PASI 75 response at week 12 and 16 in the ITT populations and the moderate subgroup of patients across the direct randomised trials. Consistent with the full ITT (moderate to severe) population, the moderate subgroup demonstrated that a statistically significantly greater proportion of patients achieved a PASI 75 response when treated with adalimumab compared with placebo.

The submission stated that the short and long-term safety of adalimumab was accepted by the PBAC in its consideration for 'severe' plaque psoriasis in March 2009, based on safety evidence in the full ITT population. Given that there are no substantial differences between the demographic characteristics of patients with moderate disease and the full ITT populations, the same data as provided in the March 2009 submission were presented in the current submission.

In REVEAL, the largest of the trials presented, the incidence of any adverse event was significantly higher in patients treated with adalimumab compared with placebo (62.2% vs 55.5%), driven mainly by infectious adverse events (28.9% vs 22.4%, respectively, particularly upper respiratory tract infections (7.2% vs 3.5%, respectively). Injection site reactions were also common across all patients.

Adverse events identified across the adalimumab trial program for all indications and post marketing surveillance included serious infections, opportunistic infections, tuberculosis and malignancies. The submission presented long-term safety analysis report by Leonardi et al (2011) which is consistent with the known safety profile of adalimumab.

For PBAC's view, see Recommendation and Reasons.

9. Clinical Claim

The submission described adalimumab as superior in terms of comparative effectiveness and (marginally) inferior in terms of comparative safety compared to placebo. The PBAC considered that the clinical claim was adequately supported by the data presented.

10. Economic Analysis

The submission presented a cost utility analysis based on the claim of superior efficacy versus standard-care (placebo). Adverse events were not included in the model.

A stepped economic evaluation using a decision analytic Markov model to estimate the incremental cost-effectiveness of adalimumab compared to standard care (placebo) in patients with moderate plaque psoriasis was presented. The model had two health states: PASI ≥75 response; or PASI <75 non-response.

Two publications providing utility weights for patients with psoriasis were identified in the literature (Schmitt et al, 2008; Zug et al, 1995). Due to the lack of appropriately defined health states in Zug, the Schmitt study was considered most appropriate by the sponsor. The incremental cost per extra QALY gained was $15,000-$ 45,000 based on the PASI 75 response rate at week 12 from the trials, extrapolated to 10 years with an assumed annual discontinuation rate of 20% and applying utility weights from Schmitt et al (2008).

The utility values reported by Schmitt et al (2008) are equivalent (with the exception of the population used to elicit them) to the utilities previously accepted as representing patients with severe plaque psoriasis. The PBAC considered that given the severity of the condition is less in patients with moderate psoriasis compared with severe psoriasis, the utility for non-response is likely to be different.

Results of sensitivity analyses indicated that the model was highly sensitive to the utility weight applied in the health states. The reliability of the ICER derived in the base case was thus dependent on acceptance that the baseline utility is the same for moderate and severe patients and that the incremental utility gain from being a PASI 75 non-responder to responder would be the same for patients with moderate and severe disease.

For PBAC's view, see Recommendation and Reasons.

11. Estimated PBS Usage and Financial Implications

The net cost per year to the PBS was estimated in the submission to be less than $10 million in Year 5. The revised net cost per year to the PBS calculated by the evaluators during the evaluation was estimated to be between $10-30 million in Year 5.

For PBAC's view, see Recommendation and Reasons.

12. Recommendation and Reasons

The PBAC rejected the submission requesting extension to the current listing for adalimumab to include patients with moderate plaque psoriasis on the basis of highly uncertain cost-effectiveness.

With the sponsor consenting to the evaluator's recommendation of a restriction consistent with the current listing for severe disease with respect to disease severity being assessed by PASI alone, and failure of three prior therapies, the PBAC agreed that placebo was the appropriate comparator.

The PBAC accepted that the clinical data presented in the submission supported the effectiveness of adalimumab in the requested population, but there remained some uncertainty with regard to the effect size given that the analysis of the "moderate" group was a post hoc subgroup analysis and the previous therapies were not necessarily consistent with the requested indication of 3 of 4 prior failed therapies.

With regard to safety, the PBAC was particularly concerned with the use of adalimumab (and monoclonal antibodies in general) in larger patient populations to treat milder forms of disease, albeit with high health distress, insofar as it increases exposure of patients to the adverse effects associated with use of these agents, particularly infection and malignancy.

The PBAC did not consider the utility values from Schmitt et al (2008) to be appropriate. The PBAC noted that these utilities are equivalent (with the exception of the population used to elicit them) to the utilities previously accepted as representing patients with severe plaque psoriasis. The PBAC considered it was unlikely that baseline utility is the same for moderate and severe patients and that the incremental utility gain from being a PASI 75 non-responder to responder would be the same for patients with moderate and severe disease. The utility weights compromised the reliability of the cost-utility analysis and the resultant ICER was considered uncertain.

The PBAC noted that incremental utility gains applied in other economic evaluations associated with treatment response with a biological therapy in psoriasis, range from approximately 0.2 to 0.3 in moderate to severe psoriasis for PASI 75 response. The PBAC recalled that it had previously accepted an incremental gain in utility for severe psoriasis of between 0.26 and 0.30. The PBAC considered the submission's incremental utility gain of 0.37 applied in the base case for moderate psoriasis to be excessive and unrealistic.

The PBAC noted the results of sensitivity analyses showed the ICER to be sensitive to the utility weights used, with the ICER increasing to be between $105,000 – $200,000 pre QALY, using utility values for responder and non-reponder based on 'Psoriasis A' and 'Psoriasis B' from Zug (1995). The PBAC accepted that it was difficult to determine what the appropriate utility gain should be for moderate psoriasis.

The PBAC noted that the patient estimates provided in the pre-submission committee response were considerably lower than estimates revised during the evaluation. The PBAC considered that the submission's estimates of both the number of patients treated and thus the cost to the PBS were highly uncertain.

The PBAC considered that there was a risk that adalimumab would be used in a proportion of patients with mild disease (i.e., PASI < 10), since determination of a PASI score is to some extent subjective. Furthermore, the PBAC noted that a proportion of patients with moderate psoriasis might be currently receiving PBS subsidised adalimumab under the severe disease restriction. The PBAC requested a review of the use of adalimumab in patients with moderate disease.

The PBAC noted that the submission is eligible for an Independent Review.

The PBAC noted the consumer comments received in relation to the submission.

Recommendation:
Rejected

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

AbbVie is disappointed with the PBAC decision and will be considering its position regarding any future course of action.