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: March 2009

1. Purpose of Application

The submission sought an extension to the current Authority required listing to include treatment of severe chronic plaque psoriasis.

2. Background

At the July 2008 meeting, the PBAC rejected the submission for adalimumab for the treatment of severe chronic plaque psoriasis on the grounds of uncertain clinical effectiveness and the resulting uncertain cost-effectiveness of adalimumab when compared with efalizumab.

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.

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 similar to the other biological disease modifying antirheumatic drugs (bDMARDs) for the treatment of severe chronic plaque psoriasis, with initial therapy consisting of 16 weeks of treatment.

5. Clinical Place for the Proposed Therapy

Adalimumab will provide clinicians with an alternative bDMARD therapy for patients suffering with severe chronic plaque psoriasis whose condition is refractory to other systemic treatments or phototherapy.

6. Comparator

The submission nominated efalizumab as the main comparator and infliximab as a secondary comparator. This is as previously advised by the PBAC (See Public Summary Document July 2008).

The PBAC noted the withdrawal of efalizumab from the Australian market due to new safety concerns rather than doubts about the effectiveness of the drug. Given that the submitted cost-effectiveness analysis could not have taken these new safety concerns into account, the PBAC agreed that it still provided a suitable frame of reference against the other biological medicines which remain PBS-listed consistent with the restriction requested for adalimumab.

Of the remaining bDMARDS PBS-listed for chronic plaque psoriasis, the PBAC considered that etanercept would be the more appropriate main comparator due to the similar manner of administration.

For PBAC's view, see Recommendation and Reasons.

7. Clinical Trials

One additional adalimumab trial supplemented the evidence presented in the July 2008 submission.

The basis of the submission was an indirect comparison of initial PASI 75 response employing meta-analyses of four randomised double-blind adalimumab trials and five randomised double-blind efalizumab (main comparator) trials; the four adalimumab trials versus four randomised double-blind infliximab (secondary comparator) trials; with placebo as the common reference for all comparisons. Long-term response was assessed using an unadjusted indirect comparison of active treatment arms of one adalimumab trial and one infliximab trial. No comparison of long-term response of adalimumab and efalizumab was provided.

The additional trial presented, M04-688, was a 24 week randomised trial comparing adalimumab to placebo at doses of 40 mg week 0, 40 mg week 2, then 40mg every fortnight; 80 mg week 0, 40 mg week 1, then 40mg every fortnight; and 80 mg week 0, 80 mg every fortnight.

8. Results of Trials

The key results for initial PASI 75 response, comparing adalimumab versus efalizumab and adalimumab versus infliximab, showed that the proportion of patients with an initial PASI 75 response was statistically significantly greater with adalimumab compared to efalizumab (OR=3.05; 95% CI: 1.77, 5.26; p=0.0001) and statistically significantly lower with adalimumab compared to infliximab (OR=0.26; 95% CI: 0.12, 0.55; p=0.0005).

The submission stated that a comparison of longer-term efficacy between adalimumab and efalizumab could not be made due to lack of efalizumab data and as such only provided a comparison of adalimumab and infliximab for longer-term response. The PBAC noted that there is some long-term data available, in a format similar to that used by the submission for its comparison of adalimumab and infliximab long-term response. However, this trial data did not include a placebo-controlled arm beyond initial 12 week treatment, and therefore an indirect comparison of adalimumab and efalizumab for long-term response was not possible.

The submission based its assessment of long-term response on an unadjusted indirect comparison of one adalimumab trial (REVEAL) and one infliximab trial (EXPRESS). The two trials differed significantly in design, a key difference being that in the adalimumab trial only patients who maintained a PASI 75 response are re-randomised at week 33, whereas in the infliximab trial all placebo-treated patients are crossed-over to infliximab.

The unadjusted indirect comparison presented in the submission included only those patients who were PASI 75 responders at week 12. However, the complex cross-over design of the trials results in a lack of a placebo-controlled arm in both the adalimumab and infliximab trials, such that the submission compared two single arms from each trial.

In the REVEAL trial, the submission determined that there were 423 responders at week 52 who had initial response at week 16 giving a response rate of 72.93% (423/580).

In the EXPRESS trial, patients randomised to placebo were crossed over to infliximab at week 24 and as such, there is no placebo-controlled data available beyond that point. Long-term data is available for patients who achieved PASI 75 at week 10 and maintained that response to week 50. In the EXPRESS trial, 242 of 310 patients were responders at week 10. Of the 242 initial responders, 153 were responders at week 50. There were 17 patients who were not assessed at week 50 and the submission assumed these patients were non-responders, resulting in a response rate 63.22% (153/242).

The responders from REVEAL and EXPRESS were then compared to provide an assessment of long-term response. The table below provides the results of the unadjusted indirect comparison presented.

Unadjusted indirect comparison of adalimumab and infliximab – initial PASI 75 response maintained at week 52

Treatment	Initial PASI 75 responders with response at week 52	OR (95% CI)	RR (95% CI)	RD (95% CI)
Adalimumab	423/580 (72.93%) [a]	**1.57 (1.14, 2.16)**	**1.15 (1.04, 1.29)**	**0.10 (0.03, 0.17)**
Infliximab	153/242 (63.22%)			

[a] chi square test p=0.0056

The PBAC noted that while a greater proportion of adalimumab patients maintained response at week 52, the design of the trials and the methodology used to generate this outcome leads to some uncertainty. The submission's unadjusted indirect comparison, in which arms of different trials are compared and randomisation is lost, is an approach recommended against in the literature (Gartlehner and Moore 2008) and considered no more valid than a comparison based on observational studies (Sutton et al., 2008). In addition, the response rate for the adalimumab arm (72.93%) includes patients who were re-randomised to placebo (almost half the total group), and it was assumed they would have the same response rate as those re-randomised to adalimumab.

The submission also presented an indirect comparison of week 24 and week 52 response comparing adalimumab and infliximab. However, as noted by the submission, these analyses did not control or allow for the PBS stopping rule (ie patients who do not respond to initial treatment are included) and as such were not directly applicable to the conditions under which adalimumab will be used under PBS listing.

The submission provided indirect comparisons of any adverse events, serious adverse events and discontinuations due to adverse events, with results indicating statistically significant advantages for adalimumab compared to efalizumab and compared to infliximab. The submission did not provide comparisons of treatment-related adverse events, even though data appropriate for analysis was available, nor did the submission provide an assessment of long-term safety.

The submission presented additional data addressing rebound following efalizumab treatment and the incidence of positive antibodies to infliximab that was not presented in the July 2008 submission. The submission calculated a probability of rebound of 18% in non-responders to

efalizumab. However the study from which this data was sourced reports that rebound also occurred in 11% of patients treated with placebo. Rebound was defined as PASI 125% of baseline or new, generalised pustular, erythrodermic or more inflammatory psoriasis occurring within 3 months of discontinuation of treatment. Rebound criteria may be fulfilled by variations in severity of psoriasis as part of natural history of disease and may be unrelated to treatment withdrawal.

For PBAC's comments, see Recommendation and Reasons.

9. Clinical Claim

The submission made the following claims regarding the comparison with efalizumab:

- adalimumab is superior in terms of comparative effectiveness for initial treatment response and superior in terms of comparative safety during the initial treatment period;
- although long-term data for efalizumab was not available, since the initial treatment response with adalimumab was well-maintained, the superiority of adalimumab over efalizumab can also be expected to be maintained.

The PBAC agreed that, based on the adjusted indirect comparison provided in the submission, adalimumab is more effective than efalizumab following the initial treatment period. However, as no comparisons of long-term response versus efalizumab were made by the submission, there was no basis to assume that the superiority over efalizumab would be maintained.

In regard to comparative safety, the PBAC considered that it may be more appropriate to consider that adalimumab and efalizumab are similar in terms of safety.

The submission made the following claims in regard to the comparison with infliximab:

- adalimumab is inferior to infliximab in terms of comparative effectiveness for initial treatment response and superior in terms of comparative safety during the initial treatment;
- adalimumab is superior in terms of maintaining response over one year of treatment and is non-inferior to infliximab after one year of treatment according to PBS listing criteria.

The PBAC agreed that, based on the adjusted indirect comparison provided in the submission, adalimumab is less effective than infliximab following the initial treatment period. However, the PBAC did not accept the claim that adalimumab is more effective than infliximab in terms of maintaining long-term response and initial safety due to uncertainty regarding the use of a comparison of the results of single-arm studies of adalimumab and infliximab.

10. Economic Analysis

The submission presented a cost-effectiveness analysis comparing adalimumab and efalizumab, as well as a cost-minimisation analysis comparing adalimumab and infliximab.

For the cost-effectiveness analysis, a stepped economic evaluation was used, culminating in a cost-utility analysis comparing adalimumab and efalizumab. The type of model used was a Markov cohort model with ten health states running for a duration of five years.

The submission also presented a cost-minimisation analysis comparing adalimumab and the secondary comparator infliximab.

For PBAC's view, see Recommendation and Reasons.

11. Estimated PBS Usage and Financial Implications

The submission estimated the likely number of initiating and continuing courses/year to be less than 10,000 in year 5.

The submission estimated financial savings/year to the PBS (excluding co-payments) to be less than $10 million in year 5. This differed considerably from the July 2008 submission.

12. Recommendation and Reasons

The PBAC recommended listing adalimumab on the PBS for the treatment of severe chronic plaque psoriasis on a cost-minimisation basis with efalizumab or etanercept at TGA-recommended steady state continuous doses (ie adalimumab 40 mg fortnightly and efalizumab 1 mg weekly and etanercept 50 mg weekly are equi-effective). The PBAC agreed that the listing of adalimumab on the PBS for this condition would offer an alternative therapy for subcutaneous use.

The PBAC noted that there were some difficulties with interpreting the cost-effectiveness analysis comparing adalimumab with efalizumab due to withdrawal of efalizumab from the Australian market. The PBAC acknowledged that efalizumab was the comparator requested in the July 2008 Minutes. The withdrawal of efalizumab had been due to new safety concerns rather than doubts about the effectiveness of the drug. Given that the submitted cost-effectiveness analysis could not have taken these new safety concerns into account, the PBAC agreed that it provided a suitable frame of reference against the other biological medicines which remain PBS-listed consistent with the restriction requested for adalimumab.

The PBAC noted that, without efalizumab listed on the PBS, there would only be two such drugs listed: infliximab, which is given by intravenous administration and etanercept, given subcutaneously. Of these, the PBAC considered that etanercept would be the more appropriate main comparator due to the similar manner of administration.

The PBAC agreed that, based on the adjusted indirect comparison provided in the submission, adalimumab is more effective than efalizumab following the initial treatment period. However, as no comparisons of long-term response versus efalizumab were made by the re-submission, there was no basis to assume that the superiority over efalizumab would be maintained. On the basis of single-arm studies of the various options which have been assessed for the requested restriction, the maintenance of response appears to vary, but there are no randomised trial results from which a direct or indirect comparison can be made. The PBAC therefore concluded that the re-submission had not convincingly demonstrated that adalimumab is more effective than efalizumab overall.

The PBAC therefore did not accept the claim of cost-effectiveness over efalizumab as a basis for recommending the listing of adalimumab as requested. It concluded that a cost-minimisation basis would be more appropriate. In this regard, the parallel PBAC recommendation for continuous etanercept on a cost-minimisation basis with efalizumab is relevant because etanercept is not being removed from the Australian market.

The PBAC also rejected the cost-minimisation analysis comparing adalimumab with infliximab, the secondary and less relevant comparator, due to clinical uncertainty.

The PBAC agreed that, based on the adjusted indirect comparison provided in the submission, adalimumab is less effective than infliximab following the initial treatment period. However, the PBAC did not accept the claim that adalimumab is more effective than infliximab in terms of maintaining long-term response and initial safety due to uncertainty regarding the use of a comparison of the results of single-arm studies of adalimumab and infliximab. The PBAC considered that there were insufficient data on long-term comparative effectiveness and noted that the design of the single-arm follow-ups of the two trials providing such longer-term data differ widely. For example, a key difference is that, in the follow-up study from the adalimumab trial (REVEAL), only patients who maintained a PASI 75 response are re-randomised at week 33, whereas in follow-up study from the infliximab trial (EXPRESS), all placebo-treated patients are crossed over to infliximab).

In regard to comparative safety, the re-submission did not provide analyses of drug-related adverse events. In addition, there were no differences in the proportion of patients with serious adverse events or those who discontinued treatment due to an adverse event. Thus, the PBAC considered that it may be more appropriate to consider that adalimumab and infliximab are similar in terms of safety.

The PBAC considered that the therapeutic relativity of 1.6983 between adalimumab and infliximab calculated in the cost-minimisation analysis may not be accurate, given that the greater number of infliximab vials used was due largely to the use of a patient sample with greater weight, and noted that these data were also used to determine the proportion continuing treatment.

The PBAC considered that the financial implications estimates presented by the re-submission did not reflect the actual impact of the listing of adalimumab, given that the re-submission's estimates of effectiveness influenced the calculation of estimated financial implications but are not strongly supported. In addition, the re-submission did not address the possibility that PBS listing for adalimumab may increase the market size.

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

The sponsor is pleased that patients will benefit from this positive result.