

PUBLIC SUMMARY DOCUMENT

Product: Adalimumab, injection, 40 mg in 0.8 mL pre-filled syringe, Humira®

Sponsor: Abbott Australasia Pty Ltd

Date of PBAC Consideration: November 2006

1. Purpose of Application

The submission requested an extension to the current PBS Authority Required listing for adalimumab to include the treatment of ankylosing spondylitis.

2. Background

The PBAC had not previously considered a submission from the sponsor for the listing of adalimumab for ankylosing spondylitis.

3. Registration Status

Adalimumab is registered for the following indications:

Rheumatoid arthritis: Reducing signs and symptoms, as well as inhibiting the progression of structural damage in adult patients with moderate to severely active rheumatoid arthritis. This includes the treatment of patients with recently diagnosed moderate to severely active disease who have not received methotrexate. Humira can be used alone or in combination with methotrexate.

Psoriatic arthritis: Treatment of signs and symptoms of moderate to severely active psoriatic arthritis in patients where response to previous DMARDs has been inadequate. Humira is not indicated for the treatment of psoriasis that is not associated with manifestations of arthritic disease.

Ankylosing spondylitis: For reducing signs and symptoms in patients with active ankylosing spondylitis.

4. Listing Requested and PBAC's View

The submission proposed listing adalimumab for the treatment of adults with ankylosing spondylitis who have had an inadequate response to conventional therapy.

See Recommendation and Reasons for PBAC's view.

5. Clinical Place for the Proposed Therapy

Ankylosing spondylitis (AS) is a disease characterised by inflammation of multiple joint structures, frequently resulting in fusion of the bones and having an affinity for the backbone and skull. Most people develop some disabilities due to spinal problems, but can lead normal productive lives. However, in others, the condition is more progressive, leading to severe deformity.

Adalimumab, as a tumour necrosis factor (TNF) antagonist drug, represents an alternative treatment option for ankylosing spondylitis to the currently available biological Disease Modifying AntiRheumatic Drugs (bDMARDS).

6. Comparator

The submission nominated etanercept as the main comparator. The PBAC accepted this as appropriate, however noted that infliximab is also an appropriate comparator.

7. Clinical Trials

The basis of the submission was an indirect comparison of adalimumab and etanercept using placebo as a common reference.

The submission presented six clinical studies as the key clinical evidence as follows:

- Studies M03-606 (2003) and M03-607, adalimumab versus placebo;
- Brandt et al (2003), Calin et al (2004), Davis et al (2003) and Gorman et al (2002), etanercept versus placebo.

These trials had been published at the time of submission, as follows:

Trial/First author	Protocol title	Publication citation
Etanercept trials		
Gorman et al. (2002)	Treatment of ankylosing spondylitis by inhibition of tumor necrosis factor alpha	N Engl J Med 346(18): 1349-56
Davis et al (2005)	Reduction in health related quality of life in patients with ankylosing spondylitis and improvements with etanercept therapy.	Arthritis Care and Research 53 (4):494-501
Maksymowych et al (2005)	Etanercept exerts beneficial effects on articular cartilage biomarkers of degradation and turnover in patients with ankylosing spondylitis.	Journal of Rheumatol 32(10):1911-1917.
Wanders et al, (2004)	Responsiveness and discriminative capacity of the assessments in ankylosing spondylitis disease-controlling antirheumatic therapy core set and other outcome measures in a trial of etanercept in ankylosing spondylitis.	Arthritis & Rheumatism 51(1): 1-8.
Davis et al. (2003)	Recombinant human tumor necrosis factor receptor (etanercept) for treating ankylosing spondylitis: a randomized, controlled trial.	Arthritis Rheum 48(11): 3230-6
Davis et al (2005)	Baseline factors that influenced ASAS 20 response in patients with ankylosing spondylitis treated with etanercept.	Journal of Rheumatol 32(9):1751-1754.
Baraliakos et al (2005)	Magnetic resonance imaging examinations of the spine in patients with ankylosing spondylitis before and after therapy with the tumor necrosis factor (alfa) receptor fusion protein etanercept.	Arthritis & Rheumatism 52(4):1216-1223.
Brandt et al.	Six-month results of a double-blind,	Arthritis Rheum 48(6): 1667-75

Trial/First author	Protocol title	Publication citation
(2003)	placebo-controlled trial of etanercept treatment in patients with active ankylosing spondylitis.	
Rudwaleit et al (2004)	Prediction of a major clinical response (BASDAI 50) to tumour necrosis factor α blockers in ankylosing spondylitis.	Annals of the Rheumatic Diseases 63(6):665-670
Calin et al. (2004)	Outcomes of a multicentre randomised clinical trial of etanercept to treat ankylosing spondylitis.	Ann Rheum Dis 63(12): 1594-600

The adalimumab trials, M03-606 and M03-607, had not been published at the time of the submission.

8. Results of Trials

In the majority of the trials, both the adalimumab and etanercept treatments were associated with statistically significantly higher proportions of patients achieving an ASAS 20 (Assessment in Ankylosing Spondylitis response with at least a 20% improvement) at 12 weeks (at 6 weeks in case of the trial reported by Brandt et al, 2003) compared to placebo. The only exception is the M03-606 trial, where the difference in the proportion of patients achieving an ASAS 20 response between the adalimumab and placebo arms did not reach the level of statistical significance.

The submission presented a pooled analysis of injection site reaction rates for adalimumab versus placebo trials and for etanercept versus placebo trials. The difference in incidence of injection site reactions for the active treatment versus placebo was significant in both comparisons.

9. Clinical Claim

The submission claimed that adalimumab is no worse than etanercept in terms of clinical effectiveness and suggested that, compared with etanercept, treatment with adalimumab was associated with a reduced likelihood of injection site reactions.

10. Economic Analysis

A preliminary economic evaluation was presented using a cost-minimisation approach.

A modelled economic evaluation was not presented.

11. Estimated PBS Usage and Financial Implications

The submission estimated that in Year 3 the likely number of packs dispensed would be < 10,000.

It was claimed that there would be no net financial implications for the PBS as a consequence of listing adalimumab. However, there were uncertainties with respect to the rate of growth of the TNF-alpha antagonist market for AS.

12. Recommendation and Reasons

The PBAC recommended extending the authority required listing to include the treatment of ankylosing spondylitis on a cost minimisation basis with etanercept. The equi-effective doses are adalimumab 40 mg every fortnight and etanercept 25 mg twice weekly. Although the Committee had concerns that infliximab was also an appropriate comparator, it was reassured by its own numerical comparison of the results of clinical studies in ankylosing spondylitis with all three drugs which showed similar placebo and active response rates.

The PBAC further recommended that the interchangeability rules for the biological Disease Modifying AntiRheumatic Drugs (bDMARDs) PBS-subsidised for ankylosing spondylitis be extended to include adalimumab and that, consistent with the interchangeability rules for rheumatoid arthritis and psoriatic arthritis, patients be permitted to trial three bDMARDs.

The PBAC recommended the 20 day safety net rule should apply.

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 has no comment.