PUBLIC SUMMARY DOCUMENT

Product: Leflunomide, tablet 10 mg, 20 mg, Arava®/Arabloc®; pack of 3 tablets leflunomide 100 mg and 30 tablets leflunomide 20 mg, 1, Arava®

Sponsor: sanofi-aventis australia pty ltd

Date of PBAC Consideration: March 2007

1. Purpose of Application

To extend the Authority required listing to include the treatment of active psoriatic arthritis.

2. Background

Leflunomide was recommended for the treatment of severe active rheumatoid arthritis in patients for whom other disease modifying anti-rheumatic drugs (including methotrexate) are inappropriate and/or ineffective by the PBAC at its September 1999 meeting and listed on the PBS 1 February 2000.

3. Registration Status

Leflunomide is registered for the treatment of active rheumatoid arthritis and active psoriatic arthritis. Leflunomide is not registered for the treatment of psoriasis that is not associated with manifestations of arthritic disease.

4. Listing Requested and PBAC's View

Authority required
Initiation by consultant physicians for the treatment of active psoriatic arthritis in patients for whom other disease modifying anti-rheumatic drugs (including methotrexate) are inappropriate or ineffective;

Ongoing leflunomide therapy for active psoriatic arthritis in patients for whom other disease modifying anti-rheumatic drugs (including methotrexate) are inappropriate and/or ineffective.

See Recommendation and Reasons for PBAC's view.

5. Clinical Place for the Proposed Therapy

Leflunomide would provide patients with active psoriatic arthritis access to an alternative treatment when other disease modifying anti-rheumatic drugs are inappropriate and/or ineffective.

6. Comparator

Placebo was nominated as the appropriate comparator. The PBAC considered that a trial of leflunomide before resorting to treatment with biological DMARDs would be

clinically logical and appropriate, and would reflect the approach taken in the PBS listing of leflunomide in the treatment of rheumatoid arthritis.

7. Clinical trials

One randomised trial Treatment of Psoriatic Arthritis Study (TOPAS trial) comparing leflunomide, initially 100 mg for 3 days and then 20 mg daily, with placebo in patients with Psoriatic Arthritis (PsA) over 24 weeks and two trials (reported by Mease et al, 2000 and Mease et al, 2004) comparing etanercept and placebo in patients with PsA were presented. The trial reported by Mease et al, 2000 was conducted over 12 weeks in 60 patients in the US. The trial reported by Mease et al, 2004 was conducted over 24 weeks in 205 patients in the US.

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

'Trials comparing leflunomide and placebo' (TOPAS)		
Trial/First author	**Protocol title/Publication title**	**Publication citation**
Kaltwasser JP et al	Efficacy and safety of leflunomide in the treatment of psoriatic arthritis and psoriasis: a multinational, double-blind, randomized, placebo-controlled clinical trial.	Arthritis and Rheumatism. 2004; 50: 1939-1950
Nash P et al	Leflunomide improves psoriasis in patients with psoriatic arthritis: an in-depth analysis of data from the TOPAS study.	Dermatology. 2006; 212(3):238-49
'Trials comparing etanercept and placebo'		
Mease PJ et al, 2000	Etanercept in the treatment of psoriatic arthritis and psoriasis: a randomised trial.	Lancet. 2000; 356: 385–390
Mease PJ, 2001	Cytokine blockers in psoriatic arthritis.	Annals of the Rheumatic Diseases. 2001; 60: iii37-iii40
Girolomoni G et al.	Anti-tumor necrosis factor α therapy in psoriatic arthritis and psoriasis.	Archives of Dermatology. 2001; 137: 784–785
Krueger G et al	Etanercept improves psoriasis in patients with psoriatic arthritis: results of a phase 3 multi-center clinical trial. 20th World Congress of Dermatology, Paris, France.	Annales de Dermatologie et de Venereologie. 2002 ; 129 (supplement 1): S760
Mease PJ et al, 1999	Enbrel® (etanercept) in patients with psoriatic arthritis and psoriasis.	Arthritis and Rheumatism 1999; 42 (supplement 9): A1835
Mease PJ et al, 2004	Etanercept treatment of psoriatic arthritis; safety, efficacy, and effect on disease progression.	Arthritis and Rheumatism 2004; 50(7): 2264-2272
Goffe B et al	Etanercept therapy results in sustained improvement in skin and joint disease in patients with psoriatic arthritis.	Journal of Investigative Dermatology 2004; 123(2): A65
Mease PJ et al, 2006	Continued inhibition of radiographic progression in patients with psoriatic arthritis following 2 years of treatment with etanercept.	Journal of Rheumatology 33(4): 712– 721

8. Results of Trials

Results of the TOPAS trial

Variable	OR (leflunomide vs placebo) (95% CI)	Leflunomide n/N (%)	Placebo n/N (%)
PsARC	3.40 (1.20, 5.80)	56/95 (58.9%)	27/91 (29.7%)
ACR20	2.06 (1.09, 3.89)	29/95 (30.5%)	16/91 (17.6%)
% change from baseline in HAQ score	*14%*	*18%* (0.19/1.08)	4% (0.05/1.14)

Leflunomide resulted in a statistically significant increase in: (i) proportion of Psoriatic Arthritis Response Criteria (PsARC) responders; (ii) proportion of American College of Rheumatology (ACR) 20 responders; and (iii) improvement in the Health Assessment Questionnaire (HAQ) from baseline compared to placebo.

9. Clinical Claim

The submission described leflunomide as having significant advantages in effectiveness over placebo but having more toxicity.

10. Economic Analysis

A series of preliminary economic evaluations comparing leflunomide and placebo was presented. The trial-based incremental cost per extra health outcome gained (extra PsARC responder and ACR 20 responder) was estimated to be < $15,000.

A modelled economic evaluation comparing leflunomide and placebo in the management of PsA over a 5 year time horizon was presented. The base case modelled incremental discounted cost per extra discounted Quality Adjusted Life Year (QALY) gained over 5 years was estimated to be < $15,000.

11. Estimated PBS Usage and Financial Implications:

The submission estimated that the likely number of patients on leflunomide would be 10,000 – 50,000 per year in Year 4. A net financial saving to the PBS was estimated to be > $100 million in Year 4 of listing. The extent of this cost saving was sensitive to the extent to which leflunomide will be used as a substitute for bDMARDs.

12. Recommendation and Reasons

The PBAC noted that the restriction requested by the sponsor did not match the evidence provided in the submission and that fifty per cent of the patients enrolled in TOPAS had not received prior DMARD treatment. The PBAC also noted concerns about the economic model. Despite these concerns, the Committee considered that a trial of leflunomide before resorting to treatment with biological DMARDs would be clinically logical and appropriate, and would reflect the approach taken in the PBS listing of leflunomide in the treatment of rheumatoid arthritis.

PBS subsidy of leflunomide would provide a further treatment option for psoriatic arthritis and could result in patients either delaying treatment with a bDMARD or not requiring treatment with the bDMARDs at all. Leflunomide treatment could also be useful for those patients who do not meet the criteria for treatment with the bDMARDs.

The PBAC recommended listing of leflunomide in psoriatic arthritis on a cost-effectiveness basis compared to placebo for patients who have not responded to DMARD treatment and on the basis of clinical need.

The PBAC requested the secretariat to consult with the sponsors for the PBS listed bDMARDs regarding any change to the current listings of the bDMARDs in psoriatic arthritis to add leflunomide to the list of prior therapies that must be tried before patients can access bDMARD treatment.

Recommendation

LEFLUNOMIDE, tablet 10 mg, 20 mg,

Add the following to the restriction:

CAUTION:

Leflunomide is a category X drug and must not be given to pregnant women. Pregnancy should be avoided for two years after cessation of therapy, unless special wash-out procedures are carried out.

Authority required

Initial treatment of severe active psoriatic arthritis where other disease modifying anti-rheumatic drugs (including methotrexate) are ineffective and/or inappropriate. Treatment must be initiated by a physician.

Maximum Quantity: 1 (Pack containing 3 x 100 mg tablets and 30 x 20 mg tablets)
Repeats: 0

Note:

No applications for increased maximum quantities and/or repeats will be authorised.

Authority required

Severe active psoriatic arthritis where other disease modifying anti-rheumatic drugs (including methotrexate) are ineffective and/or inappropriate. Treatment must be initiated by a physician.

Maximum Quantity: 30 (10 and 20 mg tablets only)
Repeats: 5

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

Sanofi-aventis, welcomes the PBAC's decision to include leflunomide on the PBS for the treatment of active psoriatic arthritis.