PUBLIC SUMMARY DOCUMENT
Product: Abatacept, powder for I.V. infusion, 250 mg, Orencia®
Sponsor: Bristol-Myers Squibb Pharmaceuticals
Date of PBAC Consideration: November 2007

1. Purpose of Application

The submission sought a Section 100 (Highly Specialised Drug) listing for the treatment, in combination with methotrexate, of adults with severe active rheumatoid arthritis (RA) who have failed prior disease modifying anti-rheumatic drug (DMARD) therapy.

Highly Specialised Drugs are medicines for the treatment of chronic conditions, which, because of their clinical use or other special features, are restricted to supply to public and private hospitals having access to appropriate specialist facilities.

2. Background

The PBAC had not previously considered this product.

3. Registration Status

Abatacept was TGA registered on 27/9/2007 for the treatment, in combination with methotrexate, of moderate to severe rheumatoid arthritis in adult patients who have had an insufficient response or intolerance to other DMARDs, such as methotrexate (MTX) or tumour necrosis factor (TNF) blocking agents. A reduction in the progression of joint damage and improvement in physical function have been demonstrated during combination treatment with abatacept and methotrexate. Abatacept should not be administered concurrently with other biological DMARDs (eg. TNF inhibitors, rituximab or anakinra).

4. Listing Requested and PBAC's View

(Paraphrased) Section 100 listing (Private hospital authority program)
Initial treatment in combination with methotrexate (MTX) at a dose of at least 7.5 mg weekly, of adults with severe active rheumatoid arthritis who:

1. have received no prior PBS-subsidised treatment with a bDMARD for this condition in this treatment cycle; and
2. have failed to achieve an adequate response to:
    - MTX alone (at least 20 mg weekly); and
    - at least 3 months of treatment with MTX (at least 7.5 mg weekly) in combination with two other non-biological DMARDs; and
    - at least 3 months of treatment with leflunomide alone; or leflunomide in combination with MTX, or cyclosporin.

For PBAC's comments on the requested restriction, see Recommendation and Reasons.

5. Clinical Place for the Proposed Therapy

Abatacept would provide another treatment option for adult patients with severe active rheumatoid arthritis who have failed prior disease modifying anti-rheumatic drug therapy.

6. Comparator

The submission nominated infliximab as the main comparator. This was accepted by the PBAC.

7. Clinical Trials

The submission presented Study 043, a randomised, double-blind, placebo-controlled trial, as the pivotal study. This study compared the change in the primary outcome, disease activity score (DAS28), from baseline at 6 and 12 months in 3 groups:

- abatacept ~10mg/kg[1] on days 1, 15, 29 and then every 28 days (+MTX);
- infliximab 3mg/kg on days 1, 15, 43, 85 and then every 56 days (+MTX), and
- placebo (+MTX). The placebo group was switched to abatacept[1] (+MTX) at 6 months.

The trial enrolled bDMARD naïve patients with active rheumatoid arthritis who had an inadequate response to methotrexate alone. The PBAC noted that the trial was powered for the comparison of abatacept and placebo and was not designed to compare abatacept with infliximab.

The submission presented supportive evidence by indirect comparison of abatacept versus infliximab in bDMARD naïve patients using placebo as a common comparator in Study 102 and ATTRACT. Study 102 was a randomised, double-blind, placebo-controlled trial of abatacept ~10mg/kg[1] on days 1, 15, 29 and then every 28 days (+MTX) or placebo (+MTX) over 12 months in patients with active RA who had been treated with MTX. ATTRACT was a randomised, double-blind, placebo-controlled trial of infliximab 3mg/kg every 8 weeks (+MTX) versus placebo (+MTX) over 30 weeks.

The submission also presented, although not as part of the indirect comparison, Study 029 of abatacept (+MTX) versus placebo (+MTX) in patients who had failed prior anti-TNF therapy.

This submission presented an assessment of the safety and tolerability of abatacept in patients with moderate to severe RA. This included all studies already mentioned above plus Study 031, a randomised, double-blind, placebo-controlled trial, to evaluate the safety and tolerability of abatacept in combination with DMARDs and/or biologics over 12 months.

The studies that had been published at the time of submission are as follows:

Trial ID/First Author	Protocol title/ Publication title	Publication citation
Direct randomised trial (pivotal evidence)		
Study 043/ Schiff M	Conference abstract: The efficacy and safety of abatacept or infliximab in RA patients with an inadequate response to MTX: results from a 1-year double-blind, randomized, placebo-controlled trial.	Arthritis Rheum 2006; 54 (suppl): 4117 (abstr).
Supplementary randomised trials		
Study 031 [ASSURE]/ Weinblatt M	Safety of the selective costimulation modulator abatacept in rheumatoid arthritis patients receiving background biologic and non-biologic disease modifying antirheumatic drugs: A one year randomized, placebo-controlled study.	Arthritis Rheum 2006; 54(9):2807-2816.
Weinblatt M	Safety and patient reported outcomes through 2 years of treatment with abatacept in rheumatoid arthritis patients receiving background disease-	ACR 2006; 509: Conference Abstract

[1] Abatacept dose: <60kg = 500mg, 60-100kg = 750mg, >100kg = 1g.

	modifying antirheumatic drugs (DMARDs): the ASSURE Trial.	
Study 029 [ATTAIN]/ Genovese MC et al	Abatacept for rheumatoid arthritis refractory to tumour necrosis factor a inhibition.	NEJM 2005; 353(11):1114-1123.
Study 102 [AIM]/ Kremer JM et al	Effects of abatacept in patients with methotrexate-resistant active rheumatoid arthritis.	Annals of Internal Medicine 2006; 144: 865-876.
ATTRACT/ Maini R et al	Infliximab (chimeric anti-tumour necrosis factor a monoclonal antibody) versus placebo in rheumatoid arthritis patients receiving concomitant methotrexate: a randomised phase III trial.	The Lancet 1999; 354: 1932-1939.

8. Results of Trials

The key results of the trials are summarised in the table below.

Change in disease activity score (DAS28) at 6 months[#]

	Baseline mean (SD)	**Endpoint** mean (SD)	**Change** mean (*SE*)	**Mean difference from placebo** (95% CI)
Study 043 DAS28 primary outcome				
ABA (+MTX), n=156	6.86 (1.01)	4.31 (1.35)	-2.53 (0.12)	-1.04 (-1.42, -0.67)*
INF (+MTX), n=165	6.79 (0.89)	4.55 (1.76)	-2.25 (0.12)	-0.77 (-1.14, -0.39)*
PBO (+MTX), n=110	6.79 (1.02)	5.31 (1.61)	-1.48 (0.15)	
Study 102 DAS28 secondary outcome				
ABA (+MTX), n= 366	6.82 (0.87)	4.34 (1.38)	-2.48 (0.07)	-1.15 (-1.38, -0.91)*
PBO (+MTX), n=*179*	6.84 (0.82)	5.50 (1.35)	-1.33 (0.10)	
Study 029 DAS28 secondary outcome				
ABA (+MTX), n= 182	6.88 (0.99)	4.90 (1.55)	-1.98 (0.10)	-1.27 (-1.62, -0.93)*
PBO (+MTX), n= 98	6.88 (0.92)	6.17 (1.34)	-0.71 (0.14)	

Note: a change in baseline DAS28 score of 1.2 units is considered clinically significant; *p<0.001
[#]Results are from the sponsor's study reports and not the published studies

The primary outcome of change in disease activity score at 6 months obtained from study 043, 102, and 029 indicates that abatacept produced a statistically significant improvement in the disease activity over placebo, although the result for Study 043 did not quite reach the level considered clinically meaningful.

The American College of Rheumatology (ACR) 20 was the primary outcome in supportive studies 102, ATTRACT and 029. ACR 50 was a secondary outcome in these supportive trials. The ACR 20 and ACR 50 response rates at 6 months were secondary outcomes in the pivotal study 043.

ACR 20 and ACR 50 response rates at 6 months

Study	ACR	ABA n/N (%)	INF n/N (%)	PBO n/N (%)	RR (95% CI)		
					ABA vs INF	ABA vs PBO	INF vs PBO
Study 043	ACR 20	104/156 (66.7)	98/165 (59.4)	46/110 (41.8)	1.12 (0.95, 1.33)	1.59 (1.25, 2.04)	
	ACR 50	63/156 (40.4)	61/165 (37.0)	22/110 (20.0)	1.09 (0.83, 1.44)	2.02 (1.33, 3.07)	
Study 102	ACR 20	288/424 (67.9)		85/214 (39.7)		1.71 (1.43, 2.04)	
	ACR 50	169/424 (39.9)		36/214 (16.8)		2.37 (1.72, 3.26)	
ATTRACT	ACR 20		43/86 (50)	18/88 (20)			2.44 (*1.54*, 3.88)
	ACR 50		22/83 (27)	4/84 (5)			5.57 (2.01, 15.46)
Study 029	ACR 20	129/256 (50.4)		26/133 (19.5)		2.58 (1.79, 3.72)	
	ACR 50	52/256 (20.3)		5/133 (3.8)		5.40 (2.21, 13.2)	

In the pivotal trial, 043, there were no statistically significant differences between the proportion of patients taking abatacept or infliximab who were classified as ACR 20 or 50 responders at 6 months (ARC 20, relativity risk of 1.12 (0.95, 1.33); ARC50, relativity risk of 1.09 (0.83, 1.44).

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

The PBAC noted headache, urinary tract infection and dyspepsia occurred to a greater extent in patients taking abatacept compared to placebo in the 12-month safety Study 031. In the pivotal efficacy Study 043 there was little difference in the incidence of adverse events for patients taking abatacept compared to infliximab. Long term safety data of abatacept in rheumatoid arthritis are not yet available.

9. Clinical Claim

The submission claimed that abatacept is non-inferior to infliximab in terms of comparative effectiveness and safety.

For the PBAC's view of this claim, see Recommendation and Reasons.

10. Economic Analysis

The submission presented a cost-minimisation analysis of abatacept versus infliximab.
The equi-effective doses in the context of cost-minimisation were claimed to be abatacept ~10mg/kg administered on days 1, 15, 29 and then every 28 days, is equivalent to infliximab 3mg/kg administered on days 1, 15, 43 and then every 56 days.

11. Estimated PBS Usage and Financial Implications

The likely number of prescription vials per year was estimated to be less than 50,000 vials in Year 5. The PBAC considered that the extent of substitution of abatacept for other biologics was uncertain. The overall market was not expected to grow more rapidly as a result of listing abatacept. There are no financial implications for government.

12. Recommendation and Reasons

The PBAC recommended the listing of abatacept on the PBS for the treatment, in combination with methotrexate, of adults with severe active rheumatoid arthritis (RA) who have failed prior DMARD therapy on a cost-minimisation basis compared with infliximab in the treatment of rheumatoid arthritis. The PBAC recommended that the equi-effective doses were abatacept 10mg/kg administered on days 1, 15, 29 and then every 28 days, and infliximab 3mg/kg administered on days 1, 15, 43 and then every 56 days.

However, the PBAC was concerned that there was some uncertainty as the pivotal trial (043), using disease activity score (DAS28) response, was not powered to demonstrate non-inferiority of abatacept and infliximab, and also considered the indirect comparison between each drug involving placebo as the common reference added to the uncertainty.

The PBAC considered that Study 029 which included patients who had failed a prior tumour necrosis factor (TNF) inhibitor, may not have included a high proportion of patients who had active biologic failures.

The PBAC also considered that the extent of substitution of abatacept for other biologics was uncertain. There was also uncertainty regarding the long-term safety of abatacept as only one 12 month safety study (031) was provided.

The PBAC recommended that the interchangeability criteria be the same as for the other currently listed TNF alpha antagonists for rheumatoid arthritis, as the listing is on a cost-minimisation basis. Therefore, within the same Treatment Cycle, a patient cannot trial and fail, or cease to respond to, the same PBS-subsidised bDMARD more than once. Once a patient has either failed or ceased to respond to treatment 3 times, they are deemed to have completed a Treatment Cycle and they must have a minimum 5 year break.

The final PBS restriction will be available at pbs.gov.au from the date of listing.

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 chose not to comment.