Public Summary Document

Product:	Infliximab, powder for intravenous infusion, 100 mg, Remicade®
Sponsor:	Schering-Plough Pty Ltd
Date of PBAC Consideration:	March 2006

1. Purpose of Application

This submission sought an extension of the current Section 100 listing of infliximab to include the treatment of severe, active psoriatic arthritis in patients who meet certain criteria.

2. Background

The PBAC had not previously considered a submission from the sponsor for listing infliximab for severe, active psoriatic arthritis.

3. Registration Status

Infliximab is indicated for the treatment of the signs and symptoms of active psoriatic arthritis in adults where previous response to disease-modifying anti-rheumatic drugs (DMARDS) has been inadequate.

4. Listing Requested and PBAC's View

The submission proposed a public and private hospital authority required restriction similar, but not identical to the PBAC recommended PBS restriction for etanercept for psoriatic arthritis.

The PBAC's view was that the restriction applying to infliximab should align as closely as possible with the recommended restriction for etanercept for the treatment of psoriatic arthritis, taking into account differences in the dosage regimens that apply.

See Recommendations and Reasons for further information.

5. Clinical Place for the Proposed Therapy

The current clinical practice in Australia for treating patients with psoriatic arthritis (PsA) includes disease-modifying antirheumatic drugs (DMARDs), non steroidal anti-inflammatory drugs (NSAIDs), and topical therapies where appropriate (dermal involvement).

Infliximab provides clinicians with extra scope to manage patients with more resistant forms of psoriatic arthritis.

6. Comparator

The submission nominated etanercept as the main comparator. The PBAC agreed this was appropriate.

7. Clinical Trials

The submission presented an indirect comparison of infliximab and etanercept using placebo as the common reference. Two randomised trials comparing infliximab and placebo and two randomised trials comparing etanercept and placebo were included. The full list of published trials at the time of the submission is given below:

Trial/First author	Protocol title	Publication citation
Infliximab trials		
IMPACT I	A 16-week, multi-centre placebo-controlled, double-blind, randomised study of infliximab (n=52) versus placebo (n=52) in patients with active Psoriatic Arthritis (IMPACT).	Antoni C, Kavanaugh A, Kirkham B, Burmester G, Weisman M, Keystone E, Ebner W, Furst D, Wassenberg S, Grunke M, Schneider U, Tutuncu Z, Kalden J, Smolen J. 2002a. The infliximab multinational psoriatic arthritis controlled trial (IMPACT). Arthritis and Rheumatism 46(Suppl 9):S381.
		Antoni CE, Kavanaugh A, Kirkham B, Tutuncu Z, Burmester GR, Schneider U, Furst DE, Molitor J, Keystone E, Gladman D, Manger B, Wassenberg S, Weier R, Wallace DJ, Weisman MH, Kalden JR, Smolen J. 2005. Sustained benefits of infliximab therapy for dermatologic and articular manifestations of psoriatic arthritis: results from the REMICADE multinational psoriatic arthritis controlled trial (IMPACT). Arthritis and Rheumatism 52:1227-36.
IMPACT II	A 24-week, multi-centre, randomized, placebo-controlled double-blind trial of 200 patients with PsA treated with infliximab (n=100) or placebo (n=100).	Antoni C, Krueger GG, De VK, Birbara C, Beutler A, Guzzo C, Zhou B, Dooley LT, Kavanaugh A. 2005. Infliximab improves signs and symptoms of psoriatic arthritis: Results of the IMPACT II trial. Annals of the Rheumatic Diseases 64:1150-7.
Etanercept		
Mease et al, 2000	A double-blind trial in 60 patients with PsA and psoriasis equally randomised to either etanercept 25mg SC twice weekly or placebo for 12 weeks.	Mease PJ, Goffe BS, Metz J, Vanderstoep A, Finck B, Burge DJ. 2000. Etanercept in the treatment of psoriatic arthritis and psoriasis: a randomised trial. Lancet 356:385-90.
		Mease PJ. 2001. Cytokine blockers in psoriatic arthritis. Annals of the Rheumatic Diseases 60:iii37–iii40.
		Girolomoni G, Abeni D. 2001. Anti-tumor necrosis factor α therapy in psoriatic arthritis and psoriasis. Archives of Dermatology 137:784-5.
		Krueger G, Lebwohl M, Gottlieb AB, Mease PJ. 2002. 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 129(suppl 1):S760.
		Mease PJ, Goffe BS, Vanderstoep A. 1999. Enbrel® (etanercept) in patients with psoriatic arthritis and psoriasis. Arthritis and Rheumatism 42(9 suppl):A1835.
Mease et al, 2004a	A randomised, double-blind trial in 205 patients with PsA and psoriasis treated with etanercept 25mg SC twice weekly or placebo for 24 weeks.	Mease PJ, Kivitz AJ, Burch FX, Siegel EL, Cohen SB, Ory P, Salonen D, Rubenstein J, Sharp JT, Tsuji W. 2004a. Etanercept treatment of psoriatic arthritis; safety, efficacy, and effect on disease progression. Arthritis and Rheumatism 50(7):2264–72.
		Goffe B, Gottlieb AB, Lebwhohl M, Randazzo B. 2004. Etanercept therapy results in sustained improvement in skin and joint disease in patients with psoriatic arthritis. Journal of Investigative Dermatology 123(2):A65.
		Gottleib A, Goffe B, Tsuji W, Zitnik R, Burge D. 2003. Etanercept (Enbrel) inhibits radiographic progression in patients with psoriatic arthritis. Journal of Investigative Dermatology 121(1):0402.
		Wanke LA, Mease PJ, Gottlieb AB. 2004. Sustained improvement in functional status and vitality of psoriatic arthritis patients treated with etanercept. Journal of Investigative Dermatology 122(3):A382.

8. Results of Trials

The results of an indirect comparison, using Bayesian techniques, was presented in the submission, which showed that there was no statistically significant difference between the benefits of infliximab over placebo and the benefits of etanercept over placebo. This was supported by a standard frequentist analysis conducted during the evaluation.

Results (ACR 50) of the comparative randomised trials

Trial	**Infliximab** n/N (%)	**Placebo** n/N (%)	**Etanercept** n/N (%)	**Risk Difference (RD) (95% CI)**
IMPACT I	24/52 (46.2)	0/52 (0.0)		**0.46 (0.32, 0.60)**
IMPACT II	36/100 (36.0)	3/100 (3.0)		**0.33 (0.23, 0.43)**
Pooled	**60/152 (39.5)**	**3/152 (2.0)**		**0.38 (0.29, 0.46)**
Mease et al, 2000		1/30 (3.3)	15/30 (50.0)	**0.47 (0.28, 0.66)**
Mease et al, 2004		4/104 (3.8)	38/101 (37.6)	**0.34 (0.24, 0.44)**
Pooled		**5/134 (3.7)**	**53/131 (40.5)**	**0.37 (0.28, 0.46)**

9. Clinical Claim

The submission claimed that infliximab was no worse than the main comparator, etanercept, in terms of effectiveness and toxicity. The PBAC accepted this claim for infliximab when used for the treatment of psoriatic arthritis.

10. Economic Analysis

The submission presented a preliminary economic evaluation (trial-based) which was a cost-minimisation analysis for infliximab against etanercept.

The costs for administration of infliximab assumed in the current submission were substantially lower than those estimated in the submission to the March 2003 PBAC requesting listing of infliximab for rheumatoid arthritis.

The submission inferred that infliximab 5mg/kg given over 6.5 infusions and etanercept 25mg twice weekly for 1 year were equi-effective. However the PBAC noted that the recommended dosage schedule for infliximab in PsA is the same as that in rheumatoid arthritis (RA).

For PBAC's view of this analysis, see Recommendations and Reasons.

11. Estimated PBS Usage and Financial Implications

The submission estimated the financial impact on the PBS of infliximab for severe, acute psoriatic arthritis, assuming it was the only product on the market, to be between $10 – 30 million up to Year 3. The submission noted that the above financial estimates would not be valid if infliximab shared the psoriatic arthritis market with etanercept.

12. Recommendation and Reasons

The PBAC recommended listing on a cost-minimisation basis concluding that the indirect comparison showed that infliximab is no worse than etanercept in terms of effectiveness and safety when used for the treatment of psoriatic arthritis. In calculating the cost of infliximab, the PBAC agreed the equi-effective dose is infliximab 5 mg/kg given for 7.25 infusions in total, compared with etanercept 25 mg twice a week given for one year. The PBAC agreed the use of Australian data on weight distributions in the cost calculations to be appropriate. However, the PBAC did not accept the reduced administration costs for infliximab claimed in this submission compared to those used for the listing of infliximab in rheumatoid arthritis. The PBAC considered that the true costs would lie somewhere in between these two figures and asked that the Department investigate this matter further.

The PBAC considered that it would be appropriate for interchangeability arrangements, similar to the current arrangements for the biological DMARDs in the treatment of rheumatoid arthritis and ankylosing spondylitis, to also apply to the bDMARDs for the treatment of psoriatic arthritis at the time more than one bDMARD is PBS listed for this condition. The PBAC considered that a 5 year exclusion period for each bDMARD included in the interchangeability arrangements, following failure to demonstrate a response as defined in the continuation restriction, would be appropriate.

The PBAC requested that the sponsor provide the PBAC with data, as it becomes available, relating to the cost-effectiveness of using infliximab following failure to demonstrate a response to a previously administered bDMARD for the treatment of psoriatic arthritis.

The PBS restriction will be posted on the PBAC outcomes website when finalised.

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.