PUBLIC SUMMARY DOCUMENT
Product: Infliximab, powder for IV infusion, 100 mg, Remicade®
Sponsor: Schering-Plough Pty Ltd
Date of PBAC Consideration: July 2008

1. Purpose of Application

The submission sought an extension to the current Section 100 rheumatoid arthritis restriction to allow dose escalation to 5 mg/kg for:

(i) patients who have failed to respond to an initial 3 mg/kg dose (primary non-responders); and

(ii) patients who have responded to treatment at 3 mg/kg but subsequently experienced a disease flare (secondary non-responders).

2. Background

At the September 2002 meeting, the PBAC rejected an application for Section 100 listing of infliximab in adults with rheumatoid arthritis because of uncertain and high cost-effectiveness ratios.

At the March 2003 meeting, the PBAC recommended the Section 100 listing of infliximab for the initial and continuing treatment of adults with severe active rheumatoid arthritis who meet certain criteria on a cost-minimisation basis compared with etanercept, which included the infusion administration costs for infliximab. The equi-effective doses are infliximab 3 mg/kg given over 7.25 infusions and etanercept 25 mg twice weekly for 1 year. Infliximab was listed on 1 November 2003.

At the July 2004 meeting, the PBAC recommended that the Section 100 listing for infliximab for the treatment of rheumatoid arthritis be amended to specify a minimum dose of 7.5 mg weekly for the concomitant methotrexate treatment.

Current Interchangeability Rules

Patients are able to swap to an alternate bDMARD without having to experience a disease flare while they continue to respond to therapy. However, a patient cannot trial and fail, or cease to respond to, the same bDMARD more than once. Once a patient has failed treatment 3 times, they must have a 5-year break before they are eligible to commence the next Treatment Cycle.

3. Registration Status

Infliximab is TGA registered for:

- Rheumatoid arthritis in adults. Reduction of signs and symptoms and prevention of structural joint damage (erosions and joint space narrowing) in combination with methotrexate in: patients with active disease despite treatment with methotrexate; patients with active disease who have not previously received methotrexate. Remicade should be given in combination with methotrexate. Efficacy and safety in RA have been demonstrated only in combination with methotrexate.
- Ankylosing spondylitis
- Psoriatic arthritis
- Psoriasis
- Crohn's disease in adults and in children and adolescents (6 to 17 years)

- Refractory fistulising Crohn's disease
- Ulcerative colitis

4. Listing Requested and PBAC's View

Section 100 (Highly Specialised Drugs Program) Private hospital authority required

Dose escalation:

Patients eligible for treatment with infliximab who do not adequately respond to the initial treatment course can trial one dose escalation of infliximab to 5 mg/kg. Assessment of response is based on the standard criteria for continuing treatment. Response must be measured and submitted to Medicare Australia no later than two weeks prior to the next required dose of infliximab (within 6 weeks of escalated dose).

Continuing treatment:

A patient may qualify to receive up to 24 weeks of continuing treatment at a dose of 5 mg/kg providing they have demonstrated an adequate response to treatment within 6 weeks after dose escalation. Assessment of response is based on the standard criteria for continuing treatment. The patient remains eligible to receive continuing treatment in courses of up to 24 weeks providing they continue to sustain the response.

For PBAC's view, see Recommendation and Reasons.

5. Comparator

The submission nominated etanercept, adalimumab, and rituximab as the comparators.

For PBAC's view, see Recommendation and Reasons.

6. Clinical Trials

The basis of the submission was a sub-group analysis of patients in an uncontrolled single-arm extension of a trial (START), who received dose escalation of infliximab due to primary or secondary failure to respond to infliximab 3 mg/kg. The submission compared infliximab dose escalation with one uncontrolled prospective consecutive case series of etanercept in patients who failed infliximab, and one randomised double blind placebo controlled study of rituximab in patients who were intolerant to or had had inadequate response to TNF antagonists.

The evaluation also presented two additional trials/studies: an open label multi-centre study of the effectiveness of adalimumab in patients who ceased treatment with infliximab and/or etanercept due to lack of efficacy, and an interrogation of the Stockholm TNFα follow-up registry of patients treated with adalimumab as second line therapy after the secondary loss of efficacy of etanercept or infliximab.

The trials published at the time of submission are listed below:

Trial ID/First Author	Protocol title/publication title	Publication Citation
Infliximab		
START Rahman MU, et al. 2007	Double-blinded infliximab dose escalation in patients with rheumatoid arthritis.	Ann Rheum Dis 66: 1233-1238
Adalimumab		

Bombardieri S,et al. 2007	Effectiveness of adalimumab for rheumatoid arthritis in patients with a history of TNF-antagonist therapy in clinical practice.	Rheumatol 46: 1191–1199
Wick MC, et al. 2005	Adalimumab (Humira) restores clinical response in patients with secondary loss of efficacy from infliximab (Remicade) or etanercept (Enbrel): Results from the STURE registry at Karolinska University Hospital.	Scand J Rheumatol 34: 353–358
Etanercept		
Buch MH, et al. 2007	Therapy of patients with rheumatoid arthritis: outcome of infliximab failures switched to etanercept.	Arth Rheum 57 (3): 448–453
Rituximab		
Cohen SB, et al. 2006	Rituximab for rheumatoid arthritis refractory to anti-tumor necrosis factor therapy: Results of a multicenter, randomized, double-blind, placebo-controlled, phase III trial evaluating primary efficacy and safety at twenty-four weeks.	Arth Rheum 54: 2793–2806

7. Results of Trials

Infliximab versus etanercept

The key outcomes of the submission's main analysis comparing infliximab dose escalation (due to primary or secondary failure to respond to 3 mg/kg) in an uncontrolled subgroup of a single arm of the START trial with the single arm of an uncontrolled prospective consecutive case series of etanercept in patients who failed infliximab (Buch 2007), with no common reference are summarised in the tables below:

ACR20 and ACR50 response rate for infliximab 3mg/kg primary and secondary non-responders treated with infliximab dose escalation or etanercept

Switch to: **Infliximab 3mg/kg**	**Infliximab dose escalation to 4.5mg/kg (START)**		**Etanercept Buch 2007[a]**
	Responders TSJ n/N (%)	**Responders Adjusted to ACR20 n/N (%)[b]**	**Responders ACR20 n/N (%)**
Primary non-responders	21/53 (40) [d]	15/53 (29)	14/34 (41)
Secondary non-responders	30/47 (64) [e]	22/47 (46)	13/38 (34)
Primary + secondary non-responders	51/100 (51)	37/100 (37)	27/72 (38)

ACR, American College of Rheumatology; TSJ, *combined* tender *joint count* and swollen joint count

[a] responders are patients who achieved response after 12 weeks of etanercept therapy

[b] converted from number of TSJ responders using the ratio of ACR20 responders to TSJ responders at week 22

[c] converted using same method as used by submission for adjustment to ACR20. The conversion factor used is 0.4.

[d] responders are the number of patients who received one dose escalation at week 22 and achieved at least a 20% improvement in the combined number of swollen joints and tender joints at week 30

[e] responders are the number of patients who received one dose escalation at week 30 or thereafter and achieved at least 20% improvement in the combined number of swollen joints and tender joints. The submission stated the responders were those who received one dose escalation at week 38, Rahman (2007) p3, specifies that secondary non-responders were those who responded at week 22 but later flared and the START trial response criteria measured response at 8 weeks after the previous dose escalation.

The results showed there was a trend for higher response rates in primary infliximab non-responders who subsequently switched to etanercept compared to escalating the dose of infliximab to 4.5mg/kg.

Infliximab versus adalimumab

The results from the indirect comparison with adalimumab (based on Bombardieri 2007 and Wick 2005) showed that among patients who fail to respond to infliximab initially (primary non-responders), the ACR20 response rate is numerically higher in patients switching to

adalimumab compared with patients increasing their dose of infliximab to 4.5 mg/kg. However, this difference was not statistically significant.

Infliximab versus rituximab

The results from the indirect comparison of infliximab dose escalation with rituximab showed that the ACR20 response rate among primary and secondary infliximab non-responders is numerically higher among patients switching to rituximab compared with patients increasing their dose of infliximab to 4.5 mg/kg. However, this difference was not statistically significant.

The limited available evidence comparing infliximab dose escalation to the comparators demonstrated a trend to increased frequency of serious adverse events and adverse events leading to discontinuation. The rates of overall adverse events were similar (infliximab dose escalation, 85%, etanercept, 81%, rituximab, 88%).

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

8. Clinical Claim

The submission claimed that dose escalation to 4.5 mg/kg infliximab was non-inferior in terms of comparative effectiveness and equivalent in terms of comparative safety compared with etanercept and rituximab in patients who have not responded to initial infliximab 3 mg/kg (primary non-responders) and in patients who have responded to 3 mg/kg and subsequently experienced a flare (secondary non-responders).

The PBAC were concerned that dose escalation of infliximab appeared to be inferior to switching to an alternate bDMARD in primary non-responders.

For PBAC's view, see Recommendation and Reasons.

9. Economic Analysis

The submission presented a cost minimisation analysis. The submission estimated the equi-effective doses as infliximab 5 mg/kg for 6.75 infusions over one year (based on infusions every 8 weeks over 54 weeks) and etanercept 25 mg twice per week for over one year.

For PBAC's view, see Recommendation and Reasons.

10. Estimated PBS Usage and Financial Implications

The submission estimated the financial cost per year to the PBS minus any savings in use of other drugs to be less than $10 million in Year 5. The PBAC considered this was likely to be an underestimate.

11. Recommendation and Reasons

The PBAC noted that the clinical evidence in the START trial suggests that some patients who do not respond to 3 mg/kg infliximab will respond to 4.5 mg/kg infliximab. However the PBAC considered that the clinical benefit was uncertain because of the very small number of patients in the trial who represent the population who would be eligible for infliximab through the PBS. Furthermore, the PBAC considered that the quality of the evidence presented in the submission was not sufficient to support the recommendation that infliximab dose escalation to 4.5 mg/kg is non-inferior to etanercept or rituximab in primary or

secondary non-responders to infliximab 3 mg/kg. The submission's main analysis compared infliximab dose escalation in an uncontrolled subgroup of a single arm of the START trial with the single arm of an uncontrolled study of etanercept in patients who failed infliximab (Buch 2007), with no common reference. The submission also presented an indirect comparison of the single arm of the START trial with a randomised placebo controlled trial of rituximab in patients who are intolerant to or have had an inadequate response to TNF antagonists (Cohen 2006), with placebo as the common comparator. The PBAC considered that the indirect comparison with adalimumab, based on Bombardieri 2007 and Wick 2005, was also relevant despite the submission excluding these studies as the definition of non-response was not provided. The PBAC noted that the exclusion of these trials is inconsistent with the submission's inclusion of Buch 2007 and Cohen 2006 which also do not define non-response criteria.

Notwithstanding limitations of the comparisons presented in the submission, the PBAC were concerned that dose escalation of infliximab appeared to be inferior to switching to an alternate bDMARD in primary non-responders. The PBAC noted that the evidence was stronger for secondary non-responders treated with a higher dose of infliximab, but considered that there is uncertainty as to whether a response to the higher dose of infliximab would be maintained over time.

The PBAC considered that if dose escalation to 5 mg/kg infliximab were to be recommended, that it would be reasonable to allow an initial treatment period at the higher dose sufficient for completion of two infusions prior to assessment of response. The submission suggests assessment at 6 weeks, therefore patients would only have had one infusion at the higher dose. The Committee noted the submission's request that dose escalation of infliximab be counted as one trial of a bDMARD within a treatment cycle, but considered that this request needed further examination in the context of a broader review of PBS subsidised bDMARDs.

The PBAC sought clinical opinion during the Hearing, which suggested that clinicians would prefer the option of initiating patients on the 5 mg/kg dose rather than commencing on 3 mg/kg and increasing to 5 mg/kg if there was no response. The PBAC noted that 5 mg/kg is the dose of infliximab used for all other approved indications including Crohn disease, ankylosing spondylitis, and psoriasis. However, the PBAC recognised that the current TGA indication for infliximab in rheumatoid arthritis stipulates that patients initiate on a dose of 3 mg/kg and increase in increments of 1.5 mg/kg to a maximum of 7.5 mg/kg.

Despite clinical and anecdotal evidence that a proportion of patients do not respond to infliximab 3 mg/kg, Medicare Australia provided data to the PBAC that indicated that the vast majority of all patients commenced on PBS infliximab continue on with treatment. Therefore the clinical need for the availability of infliximab dose escalation in the PBS population is somewhat uncertain.

The PBAC acknowledged that for a proportion of patients the availability of a bDMARD that can be administered as an infusion is preferable to subcutaneous administration, but considered that abatacept and rituximab offer alternative intravenous treatments in this group of patients.

The PBAC therefore rejected the application on the basis of uncertain clinical effectiveness and consequently uncertainty in establishing cost-minimisation against existing therapies.

Recommendation
Reject

12. 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.

13. Sponsor's Comment

The sponsor chose not to comment.