PUBLIC SUMMARY DOCUMENT
Product: GOLIMUMAB, injection 50 mg in 0.5 mL, pre-filled syringe, single use pre-filled pen, Simponi®
Sponsor: Schering-Plough Pty Ltd
Date of PBAC Consideration: March 2010

1. Purpose of Application
To request an Authority Required listing for the treatment of adult patients with severe active psoriatic arthritis.

2. Background
This drug has not been considered previously by the PBAC, but was considered for two additional indications at this meeting.

3. Registration Status
Golimumab was TGA registered on 13 November 2009 as: Golimumab, alone or in combination with methotrexate, is indicated for the treatment of active and progressive psoriatic arthritis in adult patients when the response to previous disease-modifying anti-rheumatic drug therapy has been inadequate. Golimumab has also been shown to improve physical function.

4. Listing Requested and PBAC's View
The sponsor requested a similar restriction wording to the three current biological disease modifying anti-rheumatic drug (bDMARD) listings for psoriatic arthritis.

For PBAC's view see Recommendation and Reasons.

5. Clinical Place for the Proposed Therapy
The listing of golimumab for severe active psoriatic arthritis in adults would provide an alternative bDMARD with once-monthly subcutaneous dosing.

6. Comparator
The submission nominated etanercept and adalimumab as the main comparators as they are the most prescribed bDMARDs for psoriatic arthritis in Australia and, like golimumab, are administered subcutaneously. The PBAC considered this was appropriate.

7. Clinical Trials
The submission presented indirect comparisons of golimumab and etanercept and golimumab and adalimumab, using one golimumab trial, two etanercept trials and two adalimumab trials, with a common reference of placebo. All trials included patients with moderate to severe psoriatic arthritis and the key outcomes were American College of Rheumatology (ACR) 20 and 50 response at 12-14 weeks and 24 weeks. A second key outcome was the psoriasis area and severity index (PASI) 75 response for the subgroup of patients with at least 3% of body surface area (BSA) affected with psoriasis.

The studies published at the time of the submissions are as follows:

Trial ID / First author	Protocol title / Publication title	Publication citation
Golimumab		
Kavanaugh A, et	Golimumab, a new human tumor necrosis factor α	Arthritis & Rheumatism

al. 2009	antibody, administered every four weeks as a subcutaneous injection in psoriatic arthritis	2009; 60(4):976−986
Etanercept		
Mease PJ, et al. 2000	Etanercept in the treatment of psoriatic arthritis and psoriasis: a randomised trial.	Lancet 2000; 356:385–390
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
Adalimumab		
Genovese MC, et al. 2007	Safety and efficacy of adalimumab in treatment of patients with psoriatic arthritis who had failed disease modifying antirheumatic drug therapy.	Journal of Rheumatology 2007 34(5):1040-1050. [Erratum appears in J Rheumatol. 2007 34(6):1439]
Mease PJ, et al. 2005	Adalimumab for the treatment of patients with moderately to severely active psoriatic arthritis: results of a double-blind, randomized, placebo-controlled trial.	Arthritis & Rheumatism 2005; 52(10):3279-3289
Gladman DD, et al. 2007a.	Adalimumab improves joint-related and skin-related functional impairment in patients with psoriatic arthritis: patient-reported outcomes of the Adalimumab Effectiveness in Psoriatic Arthritis Trial.	Annals of the Rheumatic Diseases 2007; 66(2):163-168

8. Results of Trials

Based on indirect comparisons, there were no statistically significant differences between golimumab and etanercept or adalimumab for ACR20 and ACR50. The relative risk ratio for golimumab versus etanercept is 1.38 (95% CI: 0.65 to 2.91) and the relative risk ratio for golimumab versus adalimumab is 1.64 (95% CI: 0.78 to 3.45). The submission used the lower bound of the 95% CI around the RR from an indirect comparison of adalimumab and etanercept as an indication of the minimum clinically important (MCID) previously accepted by the PBAC. The RR for adalimumab versus etanercept is 0.84 (0.46 to 1.55). Based on these results, the submission uses a MCID of 0.46. These results, according to the submission, indicate that golimumab meets the non-inferiority criteria (RR = 0.46) for both comparisons. This is reasonable, with the limitation that this claim is based on indirect comparisons and not on head-to-head randomised controlled trials.

Based on indirect comparisons (OR and RR), there were no statistically significant differences between golimumab and etanercept or adalimumab for PASI 75. When meta-regression analyses were used (OR and RR), golimumab was statistically superior to etanercept for PASI 75 at 12 weeks. The PASI 75 results need to be interpreted with caution, because, the PASI 75 score was for the population who had at least 3% BSA affected by psoriasis, and it is not clear whether the trials stratified patients with ≥3% or <3% BSA affected with psoriasis at baseline. Furthermore, there was moderate heterogeneity for the etanercept trials at 12 weeks. The submission performed meta-regression when three trials were available, while this number of trials might be too low to have stability in meta-regression results. The requested restriction does not limit use of golimumab to patients with ≥3% BSA affected with psoriasis.

The submission stated that there were no significant differences between golimumab, etanercept or adalimumab versus placebo in the rate of selected adverse events, except for

a lower number of adverse events for patients treated with adalimumab compared to placebo at 12 weeks. The submission did not provide indirect comparisons of adverse events, except for the incidence of injection site reactions. From trial data up to 24 weeks of treatment, the adverse event profile appears to be similar between golimumab, etanercept and adalimumab. Further information on relative safety was provided by the sponsor during the evaluation process.

For PBAC's view see Recommendation and Reasons.

9. Clinical Claim

The submission described golimumab as non-inferior in terms of comparative effectiveness and non-inferior in terms of comparative safety over etanercept and adalimumab. Based on the supporting data, this description is reasonable for the claim in terms of comparative effectiveness, with the limitation that this non-inferiority claim is based on indirect comparisons, which are at risk of a number of sources of bias. The submission did not present an indirect comparison of adverse events between golimumab and its comparators, except for injection site reactions.

10. Economic Analysis

The submission presented a cost-minimisation analysis using etanercept and adalimumab as comparators. The equi-effective doses are estimated as golimumab 50 mg once per month and etanercept 50 mg once per week or 25 mg twice per week and adalimumab 40 mg every other week. In relation to the weighting of golimumab's price to the bDMARD comparators, the PBAC considered that etanercept at a dose of 25 mg twice weekly should not be included in the weighting, as the PBAC considered that patients on this dose of etanercept would not switch to golimumab. The PBAC hence considered that in the comparison with etanercept, the price of golimumab should be based against the 50 mg weekly dose only. The PBAC also considered that the pricing of golimumab should be based on administration once every four weeks as this is consistent with the dosing schedule used in the trial presented in the submission (GO REVEAL study).

For PBAC's view see Recommendation and Reasons.

11. Estimated PBS Usage and Financial Implications

The likely number of patients per year was < 10,000 and the net financial cost per year to the PBS was < $10 million in Year 5. The main areas of uncertainty are the market growth of subcutaneous bDMARDs for the use of psoriatic arthritis and the market share of golimumab.

12. Recommendation and Reasons

The PBAC recommended the listing of golimumab on the PBS as an authority required PBS listing for the treatment of adult patients with severe active psoriatic arthritis on a cost minimisation basis with adalimumab and etanercept. The equi-effective doses are golimumab 50 mg every 4 weeks, adalimumab 40 mg every 2 weeks and 50 mg etanercept weekly.

The submission presented indirect comparisons of golimumab (GO REVEAL study) with etanercept and adalimumab with a common reference of placebo. The PBAC noted that there were no significant differences in the key outcomes of the American College of Rheumatology (ACR) 20 response and 50 response at 12-14 weeks and 24 weeks. For

ACR20 at 12-14 weeks, the relative risk for golimumab versus etanercept was 1.38 (95% CI: 0.65 to 2.91) and the relative risk for golimumab versus adalimumab was 1.64 (95% CI: 0.78 to 3.45). The PBAC also noted that for the second key outcome of the psoriasis area and severity index (PASI) 75 response there were no statistically significant differences between golimumab and etanercept or adalimumab. The PBAC considered these results supported the claim of non-inferior efficacy of golimumab to entanercept or adalimumab in the treatment of psoriatic arthritis, however that there is uncertainty due to the limitations of indirect comparisons rather than head-to-head randomised controlled trials.

The PBAC considered the safety of golimumab appeared similar to etanercept and adalimumab in the treatment of psoriatic arthritis with the adverse event profile appearing similar in the trial data for up to 24 weeks of treatment. The PBAC also noted that the Pre-Sub-Committee Response for the submission for golimumab in the treatment of rheumatoid arthritis (item 5.6) presented results of a pooled analysis of week 52 data from rheumatoid arthritis and psoriatic arthritis trials, as well as week 104 data from a trial in ankylosing spondylitis, which showed no difference between placebo and 50 mg golimumab in the rates of serious infections, malignancies or deaths.

The PBAC considered there were uncertainties in the financial estimates presented in the submission due to uncertainties in the proportions of patients switching to golimumab from other currently listed bDMARDs and in the cost offsets claimed. The PBAC noted that a higher price was requested for golimumab than the weighted comparator bDMARDs based on the costs of administration for golimumab being lower than for other bDMARDs. The PBAC considered the cost-offset incorporated in the cost-minimisation analysis of 10 % of patients requiring assistance with subcutaneous administration of bDMARD treatment involving a visit to a doctor uncertain, but accepted 10 % was a reasonable estimation.

In relation to the weighting of golimumab's price to the bDMARD comparators, the PBAC considered that etanercept at a dose of 25 mg twice weekly should not be included in the weighting, as the PBAC considered that patients on this dose of etanercept would not switch to golimumab. The PBAC hence considered that in the comparison with etanercept, the price of golimumab should be based against the 50 mg weekly dose only.

The PBAC also considered that the pricing of golimumab should be based on administration once every four weeks as this is consistent with the dosing schedule used in the trial presented in the submission (GO REVEAL study). The PBAC considered there was some uncertainty in the utilisation of golimumab. The PBAC considered there could be changes in market-share favouring golimumab due to the less frequent injection dosing schedule compared to the other bDMARDs on the PBS for the treatment of severe active psoriatic arthritis.

The PBAC noted the patient support program outlined by the sponsor in its Pre-PBAC response and was concerned about the privacy implication of patients providing their telephone, mobile phone or email details for phone, text or email reminders of when their next injection is due. The PBAC assumed that this aspect of the patient support program would be an opt-in scenario so as to not infringe on patient privacy.

The PBAC recommended that golimumab be listed with the same restriction as for the other bDMARDs on the PBS for the treatment of severe active psoriatic arthritis and that the restrictions and associated notes for these bDMARDs will need to be updated to include golimumab at the time of golimumab's listing.

The PBAC recommended that the Safety Net 20 day rule should apply.

Recommendation:
GOLIMUMAB, injection 50 mg in 0.5 mL, pre-filled syringe and single use pre-filled pen

Restriction:	Authority Required (psoriatic arthritis) complex restriction - to be finalised
Maximum quantity:	1
Repeats:	3 (initial treatment)
Repeats:	5 (continuing treatment)

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 thanks the PEB and the PBAC for their evaluations and wishes to clarify that the patient support program is optional and administered by a third party so as to not infringe on patient privacy.