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 active ankylosing spondylitis (AS).

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

3. Registration Status
Golimumab was TGA registered on 13 November 2009 for the treatment of ankylosing spondylitis in adult patients.

4. Listing Requested and PBAC's View
The sponsor requested a similar restriction wording to the three current biological disease modifying anti-rheumatic drugs (bDMARD) listings for ankylosing spondylitis (etanercept, adalimumab and infliximab).

For PBAC's view see Recommendation and Reasons.

5. Clinical Place for the Proposed Therapy
The listing of golimumab for active ankylosing spondylitis would provide an alternative bDMARD with once-monthly subcutaneous dosing.

6. Comparator
The submission nominated etanercept, infliximab and adalimumab as comparators for golimumab. Etanercept was additionally nominated as the primary comparator of golimumab in the cost minimisation analysis. The PBAC considered this was appropriate.

7. Clinical Trials
The basis of the submission was an indirect comparison of golimumab versus etanercept, adalimumab and infliximab using evidence derived from one randomised placebo controlled trial of golimumab, and three, two and one randomised placebo controlled trials of etanercept, adalimumab and infliximab respectively in the treatment of AS.

The studies published at the time of the submission were as follows:

Trial ID / First author	Protocol title / Publication title	Publication citation
Golimumab versus placebo		
Inman 2008	Efficacy and safety of golimumab in patients with ankylosing spondylitis: Results of a randomised, double-blind, placebo-controlled, phase III trial.	Inman RD, Davis J, Van Der Heijde D, et al. (2008) Arthritis and Rheumatism 58(11):3402-3412.
Braun 2009	Golimumab, a new, human, TNFA antibody administered subcutaneously every 4 weeks, in	Braun J, van Der Heijde D, Deodhar A, et al.

	ankylosing spondylitis (AS): 104-week efficacy and safety results of the randomized, placebo-controlled GO-RAISE study.	(2009) EULAR 2009 EULAR, Copenhagen, Denmark, June 10-13 2009, Abstract SAT0268
Etanercept versus placebo		
Calin 2004	Outcomes of a multicentre randomised clinical trial of etanercept to treat ankylosing spondylitis.	Calin A, Dijkmans B, Emery P, et al. (2004) Ann Rheum Dis 63:1594-1600.
Dijkmans 2009	Etanercept in the long term treatment of patients with ankylosing spondylitis.	Dijkmans B, Emery P, Hakala M, et al. (2009) Journal of Rheumatology 36(6):1256-1264.
Davis 2003	Recombinant Human Tumor Necrosis Factor Receptor (Etanercept) for treating ankylosing spondylitis.	Davis J, van der Heijde D, Braun J, et al. (2003) Arthritis Rheum 48(11):3230-3236.
Davis 2005	Baseline factors that influence ASAS20 response in patients with ankylosing spondylitis treated with etanercept.	Davis J, van der Heijde D, Dougados M, et al. (2005) Journal of Rheumatology 32(9):1751-1754.
Van Der Heijde 2006	Etanercept 50 mg once weekly is as effective as 25 mg twice weekly in patients with ankylosing spondylitis.	Van der Heijde D, Da Silva J, Dougados M, et al. (2006) Ann Rheum Dis 65:1572-1577.
Braun 2007	Improvement in patient-reported outcomes for patients with ankylosing spondylitis treated with etanercept 50 mg once-weekly, etanercept 25 mg twice weekly and placebo on patient-reported outcomes.	Braun J, McHugh N, Singh A, Wajdula JS, and Sato R. (2007) Rheumatology 46:999-1004.
Adalimumab versus placebo		
Lambert 2007	Adalimumab significantly reduces both spinal and sacroiliac joint inflammation in patients with ankylosing spondylitis.	Lambert R, Salonen D, Rahman P, et al. (2007) Arthritis Rheum 56(12):4005-4014.
Maksymowch 2005	Efficacy of adalimumab in active ankylosing spondylitis (AS)- Results of the Canadian AS study.	Maksymowch W, Rahman P, Keystone E, Wong R and Inman R. (2005b) Arthritis Rheum 52(9):S217.Abstract No.505.
Maksymowch 2008	Beneficial effects of adalimumab on biomarkers reflecting structural damage in patients with ankylosing spondylitis.	Maksymowych WP, Rahman P, Shojania K, et al. (2008). Journal of Rheumatology 35(10):2030-2037.
Van der Heijde 2006	Efficacy and safety of adalimumab in patients with ankylosing spondylitis: Results of a multicenter, randomized, double-blind, placebo-controlled trial.	Van der Heijde D, Kivitz A, Schiff M, et al. (2006) Arthritis Rheum 54(7):2136-2146.
Davis 2007	Health-related quality of life outcomes in patients with active ankylosing spondylitis treated with	Davis J, Revicki D, Van der Heijde D, et al.

	adalimumab: results from a randomised study.	(2007) Arthritis Rheum 57(6):1050–1057.
Revicki 2008	Adalimumab reduces pain, fatigue, and stiffness in patients with ankylosing spondylitis: Results from the adalimumab trial evaluating long-term safety and efficacy for ankylosing spondylitis (ATLAS).	Revicki DA, Luo MP, Wordsworth P, et al. (2008) Journal of Rheumatology 35:1346-1353.
Van der Heijde 2009	Adalimumab effectiveness for the treatment of ankylosing spondylitis is maintained for up to 2 years: long-term results from the ATLAS trial.	Van der Heijde D, Schiff MH, Sieper J, et al. (2009) Annals of the Rheumatic Diseases 68(6):922-929.
Infliximab versus placebo		
Braun 2006	Major reduction in spinal inflammation in patients with ankylosing spondylitis after treatment with infliximab: Results of a multicenter, randomized, double-blind, placebo-controlled magnetic resonance imaging study.	Braun J, Landewe R, Hermann KGA, et al. (2006) Arthritis and Rheumatism 54:1646-1652.
Braun 2008	Efficacy and safety of infliximab in patients with ankylosing spondylitis over a two-year period.	Braun J, Deodhar A, Dijkmans B, et al. (2008) Arthritis and Rheumatism 59(9): 1270-1278.
Van Der Heijde 2005	Efficacy and safety of infliximab in patients with ankylosing spondylitis: Results of a randomized, placebo-controlled trial (ASSERT).	D, Dijkmans B, Geusens P, et al. (2005) Arthritis and Rheumatism 52:582-591.
Van Der Heijde 2006	Infliximab improves productivity and reduces workday loss in patients with ankylosing spondylitis: Results from a randomized, placebo-controlled trial.	Van Der Heijde D, Han C, DeVlam K, et al. (2006) Arthritis Care and Research 55:569-574.

8. Results of Trials

The submission presented results of indirect comparisons of golimumab versus individual trials of etanercept, adalimumab and infliximab, as well as meta-analysed results from all trials using placebo as common comparator. The following outcomes were indirectly compared:

- Proportion of patients achieving a 20% response in the ankylosing spondylitis assessment score (ASAS20) response at Week 12. This was a primary outcome for all trials except GO RAISE and ASSERT, for which it was a secondary outcome. The primary outcomes in GO RAISE and ASSERT were proportion of patients achieving ASAS20 at Week 14 and 24, respectively.
- Proportion of patients achieving a 50% improvement in the Bath ankylosing spondylitis activity index (BASDAI) at Week 12/14
- Change from baseline in the Short Form-36 questionnaire (SF-36) at Week 14

The main indirect comparison was the proportions of patients achieving an ASAS20 response at Week 12. All trials demonstrated that statistically more patients treated with each bDMARD achieved an ASAS20 response compared to patients treated with placebo.

No significant difference in the proportion of patients achieving an ASAS20 response was observed between golimumab and any of the three currently listed bDMARDs or between golimumab and the pooled estimate of all bDMARDs (RR (95% CI): 0.991(0.639, 1.537)). The lower bound of the 95% CI did not cross the submission's nominated non-inferiority margin (0.43) for any comparison. This was the basis of the submission's claim that golimumab is non-inferior, or no worse in clinical efficacy, to etanercept, adalimumab or infliximab.

In general, with the exception of injection site reactions, there appeared to be no substantial differences in toxicity between golimumab, etanercept, adalimumab and infliximab. The proportion of subjects experiencing adverse events (AEs) in the study drug treatment group was similar for all included trials (84.8% in the golimumab 50 mg group in GO RAISE versus 71% to 88.7% for the three comparator bDMARDs). The most frequently reported AEs across all included trials were respiratory tract infections, nasopharyngitis, fatigue and headache. Approximately 3.6% of subjects in the golimumab 50 mg group experienced serious adverse events (SAEs), which was comparable with the rate of SAEs in the etanercept, adalimumab and infliximab trials. There were low numbers of withdrawals due to AEs for patients taking any of the bDMARDs and no deaths occurred in any of the included trials. The ESC noted that the lower rate of injection site reactions with golimumab compared to etanercept could be at least partly attributed to the lower number of golimumab injections patients receive.

For PBAC's view see Recommendation and Reasons.

9. Clinical Claim

The submission describes golimumab as non-inferior in terms of comparative effectiveness and equivalent in terms of comparative safety over etanercept, adalimumab and infliximab. The equi-effective dose is golimumab 50mg monthly to etanercept 25mg twice weekly or 50mg weekly. However, the PBAC considered that patients on etanercept at a dose of 25 mg twice weekly would not switch to golimumab and that in the comparison with etanercept, the price of golimumab should be based against the 50 mg weekly dose only.

10. Economic Analysis

The submission presented a cost minimisation analysis. The equi-effective doses are estimated as golimumab 50mg once per month to etanercept 50 mg once per week or 25 mg twice per week. The correct approach assumes equivalent total annual treatment costs (including administration) for etanercept and golimumab, then subtracts the annual cost of administration associated with golimumab from the total cost to give the drug cost per year, and divides this value by 12 to calculate the DPMQ.

For PBAC's view see Recommendation and Reasons.

11. Estimated PBS Usage and Financial Implications

The likely number of packs dispensed per year accounting for market share was < 10,000 in Year 5 of listing. The financial cost per year to the PBS was < $10 million in Year 5. 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 active ankylosing spondylitis.

12. Recommendation and Reasons

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

The submission presented indirect comparisons of golimumab versus individual trials of etanercept, adalimumab and infliximab, as well as meta-analysed results from all trials using placebo as the common comparator. The PBAC noted there was no significant difference in the proportion of patients achieving an assessment in ankylosing spondylitis (ASAS) 20 response at 12 weeks in the indirect comparison of golimumab (GO RAISE study) versus all bDMARDs (etanercept, adalimumab and infliximab) via placebo. The PBAC considered this supported the claim of non-inferior efficacy of golimumab to these bDMARDs in the treatment of active ankylosing spondylitis, however that there is uncertainty in the results of the indirect analysis due to differences between the trials, including differences identified in the clinical characteristics of patients across the four sets of trials. The relative risk (RR) for golimumab versus etanercept, adalimumab and infliximab were 1.090 (0.689, 1.725), 0.983 (0.528, 1.831) and 0.782 (0.451, 1.356), respectively. For all bDMARDs the RR was 0.991 (0.639, 1.537).

The PBAC considered the safety of golimumab appeared similar to etanercept, adalimumab and infliximab in the treatment of active ankylosing spondylitis, with the proportion of subjects experiencing adverse events in the study drug treatment groups similar in the trials for golimumab and the three comparator bDMARDs. The PBAC noted that the safety data to 104 weeks treatment with golimumab did not identify further safety concerns to those known to be associated with the bDMARDs.

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 RAISE 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 active ankylosing spondylitis. 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 active ankylosing spondylitis 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 (ankylosing spondylitis) 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.