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 rheumatoid arthritis who meet certain criteria, in combination with methotrexate.

2. Background

This drug had 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 for use in combination with methotrexate for the treatment of moderate to severely active rheumatoid arthritis in adult patients when the response to disease modifying anti-rheumatic drug (DMARD) therapy, including methotrexate, has been inadequate.

4. Listing Requested and PBAC's View

The sponsor requested a listing based on the current restriction wording for the bDMARDs in rheumatoid arthritis.

For PBAC's view see Recommendation and Reasons.

5. Clinical Place for the Proposed Therapy

The listing of golimumab for severe refractory rheumatoid 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 therapies that most prescribers will replace in practice should golimumab be made available on the PBS and they are the most prescribed bDMARDs on the PBS for rheumatoid arthritis. Golimumab is also most likely to replace treatments administered by subcutaneous injection. The choice of comparators is reasonable for the non-inferiority comparisons as etanercept and adalimumab have the same mode of administration and are the most frequently prescribed bDMARDs in clinical practice. However, listing golimumab would effectively provide another alternative to all other listed bDMARDs and could equally replace intravenously administered agents.

7. Clinical Trials

No direct randomised trials of golimumab compared with either etanercept or adalimumab were identified in the literature search. The submission presented indirect comparisons of golimumab compared with etanercept and adalimumab using data from randomised controlled trials (RCTs) for each drug compared with a common comparator such as placebo, methotrexate or other DMARD therapy. Two golimumab trials, six etanercept trials and eight adalimumab trials were identified for inclusion in the indirect comparisons. In general, the trials recruited subjects who were representative of those for whom PBS listing was sought.

The submission also presented Go-After, a trial of golimumab compared with placebo in patients who had previously discontinued TNF-inhibitors because of a lack of efficacy or other reasons not related to efficacy (intolerance, accessibility issues), although this trial is analysed separately because it is conducted in a different patient population. However, the submission has not sought to undertake a comparison of the results of Go-After with other evidence for use of second-line bDMARDs. Although the sponsor is not requesting second-line bDMARD treatment it is possible that golimumab could be used following failure of other bDMARDs.

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

Trial ID / First author	Protocol title / Publication title	Publication citation
Golimumab		
Kay 2008 (C0524T02)	Golimumab in patients with active rheumatoid arthritis despite treatment with methotrexate: a randomized, double-blind, placebo-controlled, dose-ranging study.	Kay J, 2008. Arthritis & Rheumatism 58(4): 964−975.
Keystone 2009 (Go-Forward)	Golimumab, a human antibody to TNF-α given by monthly subcutaneous injections, in active rheumatoid arthritis despite methotrexate: the Go-Forward Study.	Keystone EC, 2009. Annals of the Rheumatic Diseases 68(6):789−796.
Smolen 2009 (Go-After)	Golimumab in patients with active rheumatoid arthritis after treatment with tumour necrosis factor alpha inhibitors (GO-AFTER study): a multicentre, randomised, double-blind, placebo-controlled, phase III trial.	Smolen JS, Kay J, Doyle MK, et al. 2009. Lancet 374(9685):210-221.
Etanercept		
Combe 2006 (0881A1-309)	Etanercept and sulfasalazine, alone and combined, in patients with active rheumatoid arthritis despite receiving sulfasalazine: a double-blind comparison.	Combe B, Codreanu C, Fiocco U, et al. 2006. Annals of the Rheumatic Diseases 65(10):1357−1362.
Combe 2009	Efficacy, safety, and patient-reported outcomes of combination etanercept and sulfasalazine versus etanercept alone in patients with rheumatoid arthritis: a double-blind randomized two-year study.	Combe B et al 2009. Annals of the Rheumatic Diseases 68(7):1146−1152.
Keystone 2004a (16.0036)	Once-weekly administration of 50 mg etanercept in patients with active rheumatoid arthritis: results of a multicenter, randomized, double-blind, placebo-controlled trial.	Keystone EC, Schiff MH, Kremer JM, et al. 2004a. Arthritis & Rheumatism 50(2):353−363.
Lan 2004 (0881A-100093)	A comparative study of etanercept plus methotrexate and methotrexate alone in Taiwanese patients with active rheumatoid arthritis: a 12-week, double-blind, randomized, placebo-controlled study.	Lan JL, Chou SJ, Chen DY, et al. 2004. Journal of the Formosan Medical Association 103(8):618−263.
Moreland 1999 (16.0009)	Etanercept therapy in rheumatoid arthritis. A randomized, controlled trial.	Moreland LW, Schiff MH, Baumgartner SW, et al. 1999. Annals of Internal Medicine 130(6):478−486.
Mathias 2000	Health-related quality of life and functional status of patients with rheumatoid arthritis randomly assigned to receive etanercept or placebo.	Mathias SD, Colwell HH, Miller DP, et al. 2000. Clinical

		Therapeutics 22(1):128−139.
Klareskog 2004 TEMPO (0881A1-308-EU/AU) Van der Heijde 2005	Therapeutic effect of the combination of etanercept and methotrexate compared with each treatment alone in patients with rheumatoid arthritis: double-blind randomised controlled trial. Comparison of different definitions to classify remission and sustained remission: 1 year TEMPO results.	Klareskog L, van der Heijde D, de Jager JP, et al. 2004. Lancet 363(9410):675−681. Van der Heijde D, Klareskog L, Boers M, et al. 2005. Annals of the Rheumatic Diseases 64(11):1582−1587.
Weinblatt 1999	A trial of etanercept, a recombinant tumor necrosis factor receptor:Fc fusion protein, in patients with rheumatoid arthritis receiving methotrexate.	Weinblatt ME, Kremer JM, Bankhurst AD, et al. 1999. New England Journal of Medicine 340(4):253−259.
Adalimumab		
Miyasaka 2008 (CHANGE)	Clinical investigation in highly disease-affected rheumatoid arthritis patients in Japan with adalimumab applying standard and general evaluation: The CHANGE study.	Miyasaka N, The CHANGE Study Investigators. 2008. Modern Rheumatology 18(3):252−262.
Chen 2009	Randomized, double-blind, placebo-controlled, comparative study of human anti-TNF antibody adalimumab in combination with methotrexate and methotrexate alone in Taiwanese patients with active rheumatoid arthritis.	Chen DY, Chou SJ, Hsieh TY, et al. 2009. Journal of the Formosan Medical Association 108(4):310−319.
Van de Putte 2003 (DE007)	Efficacy and safety of the fully human anti-tumour necrosis factor alpha monoclonal antibody adalimumab (D2E7) in DMARD refractory patients with rheumatoid arthritis: a 12 week, phase II study.	Van de Putte LB, Rau R, Breedveld FC, et al. 2003. Annals of the Rheumatic Diseases 62(12):1168−1177.
Weinblatt 2003 (DE009/Armada)	Adalimumab, a fully human anti-tumor necrosis factor alpha monoclonal antibody, for the treatment of rheumatoid arthritis in patients taking concomitant methotrexate: The ARMADA trial.	Weinblatt ME, Keystone EC, Furst DE, et al. 2003. Arthritis and Rheumatism 48(1):35−45.
Van der Putte 2004 (DE011)	Efficacy and safety of adalimumab as monotherapy in patients with rheumatoid arthritis for whom previous disease modifying antirheumatic drug treatment has failed.	Van de Putte BA, Atkins C, Malaise M, et al. 2004. Annals of the Rheumatic Diseases 63(5):508−516.
Keystone 2004b (DE019)	Radiographic, clinical, and functional outcomes of treatment with adalimumab (a human anti-tumor necrosis factor monoclonal antibody) in patients with active rheumatoid arthritis receiving concomitant methotrexate therapy: a randomized, placebo-controlled, 52-week trial.	Keystone EC, Kavanaugh AF, Sharp JT, et al. 2004b. Arthritis & Rheumatism 50(5):1400−1411.
Furst 2003 (DE031)	Adalimumab, a fully human anti tumor necrosis factor-alpha monoclonal antibody, and concomitant standard antirheumatic therapy for the treatment of rheumatoid arthritis: results of STAR (Safety Trial of Adalimumab in Rheumatoid Arthritis.	Furst DE, Schiff MH, Fleischmann RM, et al. 2003. Journal of Rheumatology 30(12):2563−2571.
Kim 2007	A randomized, double-blind, placebo-controlled, phase III study of the human anti-tumor necrosis factor antibody adalimumab administered as subcutaneous injections in Korean rheumatoid arthritis patients treated with methotrexate.	Kim HY, Lee SK, Song YW, et al. 2007. APLAR Journal of Rheumatology 10(1):9-16. Erratum: APLAR

		Journal of Rheumatology 10(2):166.

8. Results of Trials

The submission conducted indirect comparisons based on meta-analyses of American College of Rheumatology (ACR) 20 and ACR50 outcomes for each drug at short (8-16 weeks) and medium-term time points (24 weeks). The table below shows the relative risks of achieving an ACR20 or ACR50 response with golimumab compared with etanercept or adalimumab at short (8-16 weeks) and medium-term (24 week) time-points.

The following table presents the results of the indirect comparisons of golimumab with etanercept and adalimumab for ACR20 and ACR50 response at short and medium-term time-points

Outcome	Golimumab versus etanercept RR (95% CI)	Golimumab versus adalimumab RR (95% CI)
Short-term (8-16 weeks)		
ACR20	0.82 (0.51, 1.33)	0.67 (0.47, 0.95)
ACR50	0.96 (0.38, 2.46)	1.07 (0.59, 1.96)
Medium-term (24 weeks)		
ACR20	0.87 (0.33, 2.25)	0.98 (0.64, 1.51)
ACR50	0.69 (0.21, 2.22)	0.83 (0.46, 1.47)

Abbreviations: RR=relative risk.

The submission claimed that the ACR results show no significant difference in efficacy between golimumab and etanercept and adalimumab, with the exception of the ACR20 result at 12 weeks for golimumab and adalimumab. The submission refers to the confidence interval for the meta-regression, the sensitivity analysis excluding DE007 and the calculation of the relative risk of harm (RRH) to demonstrate that these analyses show no significant difference for ACR20 at 12 weeks. The results of the indirect comparisons indicate that golimumab is non-inferior to adalimumab and etanercept in terms of efficacy, and is associated with a lower risk of injection site reactions. The submission stated that because the lower confidence limits of ACR20 relative risk at 12 weeks do not fall below the calculated MCID of 0.40, golimumab meets the criterion for non-inferiority. All patients in the golimumab trials were treated concomitantly with methotrexate.

For the safety analysis, the submission detailed the adverse effects that occurred in the RCTs and 52 week follow-up data where available. The submission provided a reasonable interpretation of the comparative occurrence for each event type across the three treatments, but no indirect analysis was undertaken to compare the likelihood of adverse effects with golimumab to etanercept or adalimumab, with the exception of the analysis for injection site reactions. The results indicate that injection site reactions occur significantly more with etanercept than golimumab. The lower rate of injection site reactions is likely to be related to the reduced administration burden of golimumab (once every four weeks) compared with etanercept (once or twice weekly). The submission's claim that golimumab is non-inferior to etanercept and adalimumab for safety outcomes was not well supported. However further information was provided by the sponsor during the evaluation process.

Information available for the long-term safety of golimumab in rheumatoid arthritis is limited to the 52-week follow-up from the clinical trials. However, from this information, no additional safety concerns related to golimumab treatment have been identified. The submission did not provide any assessment of long-term harms of golimumab compared with its comparators, etanercept and adalimumab.

For PBAC's view see Recommendation and Reasons.

9. Clinical Claim

The submission claimed that golimumab is non-inferior to both etanercept and adalimumab in terms of comparative efficacy and safety. The PBAC accepted that the results of the indirect comparisons indicate that golimumab is non-inferior to adalimumab and etanercept in terms of efficacy in the treatment of rheumatoid arthritis, however that there is uncertainty due to the limitations of indirect comparisons rather than head-to-head randomised controlled trials.

10. Economic Analysis

The submission presented a cost-minimisation analysis based on the claim of non-inferiority of golimumab to adalimumab and etanercept. The submission calculated the cost of one year of golimumab treatment to be equivalent to the weighted yearly cost of the comparator treatments, including the costs of bDMARD treatments, concomitant treatments and administration.

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 etanercerpt 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.

11. Estimated PBS Usage and Financial Implications

The submission cost-minimised golimumab to exactly the cost of its comparator treatments, including the cost of methotrexate and administration costs (with the additional cost of golimumab in the submission compared to adalimumab and etanercept 50 mg coming from inclusion of etanercept 25 mg in the weighted average yearly comparator cost). The likely number of packs dispensed per year was between 10,000 and 50,000 per year in Year 5 while the net financial cost per year to the PBS was < $10 million in Year 5.

12. Recommendation and Reasons

The PBAC recommended the listing of golimumab on the PBS as an authority required PBS listing in combination with methotrexate for the treatment of adult patients with severe active rheumatoid 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 (C0524T02, GO FORWARD and GO AFTER trials) compared with etanercept and adalimumab using data from randomised controlled trials for each drug compared with common comparators including placebo, methotrexate or other DMARD therapy. The PBAC noted there were no significant differences in the primary outcome of the American College of Rheumatology (ACR) 20 response at 8-16 and 24 weeks, with the exception of the ACR 20 result at 12 weeks for golimumab versus adalimumab. The PBAC also noted that there were no significant differences in the secondary outcome of ACR 50 between golimumab and etanercept and adalimumab. The PBAC accepted that the results of the indirect comparisons indicate that golimumab is non-inferior to adalimumab and etanercept in terms of efficacy in the treatment of rheumatoid 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 rheumatoid arthritis with the adverse event profile appearing similar in the trial data and 52 week follow-up data where available. The PBAC noted that injection site reactions appear less common with golimumab than etanercept based on the indirect analysis in the submission for this adverse event. The PBAC also noted that the Pre-Sub-Committee Response 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 trials presented in the submission.

The PBAC considered that the listing of golimumab on the PBS for the treatment of rheumatoid arthritis would be subject to the price reduction of 25 – 30 % required for all bDMARDs listed on the PBS for the treatment of rheumatoid arthritis resulting from the cost effectiveness review, as recommended at the December 2009 PBAC Special Meeting.

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 frequently injection dosing schedule compared to the other bDMARDs on the PBS for the treatment of severe active rheumatoid 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 rheumatoid 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 also recommended that the recent restriction changes for bDMARDs for the treatment of rheumatoid arthritis recommended at the December 2009 PBAC Special Meeting would also apply to golimumab's listing. These include revised eligibility criteria and a maximum of five bDMARDs in a lifetime.

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 (rheumatoid 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.