PUBLIC SUMMARY DOCUMENT
Product: Tocilizumab, solution for I.V. infusion, 80 mg in 4 mL, 200 mg in 10 mL and 400 mg in 20 mL, Actemra®
Sponsor: Roche Products Pty Ltd
Date of PBAC Consideration: July 2009

1. Purpose of Application

To request a Section 100 (Highly Specialised Drugs Program) listing for treatment of severe, active rheumatoid arthritis, in combination with methotrexate or other disease modifying anti-rheumatic drugs (DMARDs).

Highly Specialised Drugs are medicines for the treatment of chronic conditions, which, because of their clinical use or other special features, are restricted to supply to public and private hospitals having access to appropriate specialist facilities

2. Background

This drug had not previously been considered by the PBAC.

3. Registration Status

Tocilizumab (Actemra) was registered by the TGA on 21 May 2009 for the treatment of moderate to severe active rheumatoid arthritis (RA) in adult patients: in combination with methotrexate (MTX) or other non-biological disease-modifying anti-rheumatic drugs (DMARDs) in case of either an inadequate response or intolerance to previous therapy with one or more DMARDs; or as monotherapy in case of intolerance to MTX or where continued treatment with MTX is inappropriate.

4. Listing Requested and PBAC's View

The submission requested a Section 100 (Highly Specialised Drugs Program) listing with a restriction for tocilizumab in combination with methotrexate similar to the current restrictions for other biological DMARD (bDMARD) therapies in rheumatoid arthritis i.e. first line use. Following the ADEC recommendation in April 2009, the sponsor requested an amendment to the listing requested in the major submission, to include use in combination with other non-biological DMARDs.

An abbreviated version of the requested listing is shown below:

Section 100 (Highly Specialised Drugs Program)
Public and Private Hospital Authority Required
Initial treatment would be restricted to use of tocilizumab in combination with methotrexate at a dose of at least 7.5 mg weekly or other non-biological disease-modifying anti-rheumatic drugs (DMARDs), by a rheumatologist or clinical immunologist with expertise in the management of rheumatoid arthritis, of adults who:

1. have severe active rheumatoid arthritis; and
2. have received no prior PBS-subsidised treatment with a bDMARD for this condition in this treatment cycle; and
3. have failed to achieve an adequate response to the following treatments:
   a. methotrexate at a dose of at least 20 mg weekly; and
   b. methotrexate (at a minimum dose of 7.5 mg weekly), in combination with 2 other non-biological disease modifying anti-rheumatic drugs (DMARDs), for a minimum of 3 months; and

a minimum of 3 months' treatment with leflunomide alone; or leflunomide in combination with methotrexate, or cyclosporine.

The submission proposed that the initial treatment authorisation for tocilizumab be limited to provide a maximum of 16 weeks of therapy. Patients would need to demonstrate an adequate response to treatment, using the same criteria that were currently in place for continuing treatment with other bDMARDs in RA, to qualify for this continuing treatment. A maximum of 24 weeks of continuing treatment would be approved under this restriction.

An initial PBS-subsidised treatment restriction for 'grandfather' patients was also requested.

The PBAC agreed that the basis of the restriction wording would be that for rituximab in rheumatoid arthritis, where rituximab is available second-line to those meeting certain criteria and who have not adequately responded to a TNF-alfa antagonist.

5. Clinical place for the proposed therapy

Tocilizumab would provide another treatment option for adult patients with severe active rheumatoid arthritis.

6. Comparator

The submission nominated abatacept and infliximab as the main comparators for the clinical evaluation, and abatacept as the main comparator for the economic evaluation.

The PBAC agreed that the choice of abatacept and inflixmab as the main comparators was appropriate.

7. Clinical Trials

The submission presented indirect comparisons of tocilizumab and abatacept and tocilizumab and infliximab based on three tocilizumab trials, two abatacept trials, two infliximab trials and one trial including both abatacept and infliximab, using placebo + methotrexate as the common comparator. All trials included patients with moderate to severe rheumatoid arthritis (RA) and the key outcomes assessed were ACR response (a measure of treatment response in rheumatoid arthritis, proposed by the American College of Rheumatology) and DAS28 response (Disease Activity Score involving 28 joints – another measure of the activity of RA) at six months.

The mean methotrexate dose used in the trials was 15 mg weekly, which was lower than the methotrexate dose stipulated by the PBS eligibility criteria for prior therapy, which was for a methotrexate dose of at least 20 mg weekly.

Details of the published trials presented are shown in the following table.

Trial ID	Protocol title/ Publication title	Publication citation
Direct randomised trials		
Tocilizumab		
WA17822 (OPTION)	Smolen JS, Beaulieu A, Rubbert-Roth A et al. Effect of interleukin-6 receptor inhibition with tocilizumab in patients with RA (OPTION study): a double-blind, placebo-controlled, randomised trial.	*Lancet 2008; 371(9617):987-997.*

WA17823 (LITHE)	Kremer JM, Fleischmann RM, Halland A-M et al. (2008). Tocilizumab inhibits structural joint damage in rheumatoid arthritis patients with an inadequate response to methotrexate: The LITHE study. L11.	*American College of Rheumatology* abstract/presentation number
WA18063 (TOWARD)	Genovese M, McKay J, Nasonov E et al. (2008). Interleukin-6 receptor inhibition with tocilizumab reduces disease activity in rheumatoid arthritis with inadequate response to disease-modifying antirheumatic drugs.	*Arthritis and Rheumatism* 58 (10): 2968-2980.
Abatacept		
AIM	Kremer J, Genant H, Moreland L et al. (2006). Effects of abatacept in patients with methotrexate-resistant active rheumatoid arthritis. Russell A, Wallenstein G, Li T et al. (2007). Abatacept improves both the physical and mental health of patients with rheumatoid arthritis who have inadequate response to methotrexate treatment. Li T, Gignac M, Wells G et al. (2008). Decreased external home help use with improved clinical status in rheumatoid arthritis: An exploratory analysis of the Abatacept in Inadequate Responders to Methotrexate (AIM) trial.	*Annals of Internal Medicine* 144: 865-876. *Annals of the Rheumatic Diseases* 66: 189-194. *Clinical Therapeutics* 30 (4): 734-748.
Kremer et al. 2003	Kremer J, Westhovens R, Leon M et al. (2003). Treatment of rheumatoid arthritis by selective inhibition of T-cell activation with fusion protein CTLA4Ig. Kremer J, Dougados M, Emery P et al. (2005). Treatment of rheumatoid arthritis with the selective costimulation modulator abatacept. Emery P, Kosinski M, Li T et al. (2006). Treatment of rheumatoid arthritis patients with abatacept and methotrexate significantly improved health-related quality of life. Weisman M, Durez P, Hallegua D et al. (2006). Reduction of inflammatory biomarker response by abatacept in treatment of rheumatoid arthritis.	*New England Journal of Medicine* 349: 1907-1915. *Arthritis and Rheumatism* 52 (8): 2263-2271. *Journal of Rheumatology* 33 (4): 681-689. *Journal of Rheumatology* 33 (11): 2162-2166.
Infliximab		
ATTRACT	Maini R, St Clair E, Breedveld F et al. (1999). Infliximab (chimeric anti-tumour necrosis factor alpha monoclonal antibody) versus placebo in rheumatoid arthritis patients receiving concomitant methotrexate: a randomised phase III trial. Lipsky P, van der Heijde D, St Clair E et al. (2000). Infliximab and methotrexate in the treatment of rheumatoid arthritis. Maini RN, Breedveld FC, Kalden JR et al. (2004). Sustained improvement over two years in physical function, structural damage, and signs and symptoms among patients with rheumatoid arthritis treated with infliximab and methotrexate. *Arthritis and Rheumatism* 50: 1051-65.	*Lancet* 354: 1932-1939. *New England Journal of Medicine* 343: 1594-1602.

	Smolen J, Han C, Bala M et al. (2005). Evidence of radiographic benefit of treatment with infliximab plus methotrexate in rheumatoid arthritis patients who had no clinical improvement: a detailed subanalysis of data from the anti-tumor necrosis factor trial in rheumatoid arthritis with concomitant therapy study.	*Arthritis and Rheumatism* 52 (4): 1020-30.
	Breedveld F, Han C, Bala M et al. (2005). Association between baseline radiographic damage and improvement in physical function after treatment of patients with rheumatoid arthritis.	*Annals of the Rheumatic Diseases* 64 (1): 52-5.
	St Clair E, Wagner C, Fasanmade A et al. (2002). The relationship of serum infliximab concentrations to clinical improvement in rheumatoid arthritis: results from ATTRACT, a multicenter, randomized, double-blind, placebo-controlled trial.	*Arthritis and Rheumatism* 46 (6): 1451-1459.
START	Westhovens R, Yocum D, Han J et al. (2006). The safety of infliximab, combined with background treatments, among patients with rheumatoid arthritis and various comorbidities.	*Arthritis and Rheumatism* 54: 1075-1086.
Abatacept and infliximab		
ATTEST	Schiff M, Keiserman M, Codding C et al. (2008). Efficacy and safety of abatacept or infliximab versus placebo in ATTEST: a phase III, multicenter, randomized, double-blind, placebo-controlled study in patients with rheumatoid arthritis and an inadequate response to methotrexate.	*Annals of the Rheumatic Diseases*, published on November 29, 2007 as 10.1136/ard.2007.080002.

The submission also included results of a *published* trial assessing the use of tocilizumab following failure of other bDMARDs:
Emery P, Keystone E, Tony HP et al. (2008). IL-6 receptor inhibition with tocilizumab improves treatment outcomes in patients with rheumatoid arthritis refractory to anti-tumor necrosis factor biologicals: results from a 24-week multicentre randomised placebo-controlled trial. *Annals of the Rheumatic Diseases* 67: 1516-1523

8. Results of Trials

The primary efficacy endpoint for the tocilizumab studies was a comparison of the proportion of patients in each treatment with an ACR20 response at week 24.

The following table provides the results of the indirect comparisons of tocilizumab and abatacept and infliximab for proportion of patients achieving ACR response and DAS28 response at six months.

Results of the indirect comparisons of tocilizumab and abatacept and tocilizumab and infliximab for ACR response and DAS28 response at 6 months

Outcome	Tocilizumab versus abatacept RR (95% CI)	Tocilizumab versus infliximab RR (95% CI)
ACR response		
ACR20	1.35 (1.14, 1.61)	1.16 (0.79, 1.69)
ACR50	1.62 (1.19, 2.20)	1.33 (0.75, 2.35)
ACR70	2.31 (1.13, 4.71)	2.48 (1.38, 4.45)
DAS28 response		
DAS remission (DAS28 <2.6)	3.34 (1.70, 6.54)	4.76 (2.19, 10.36
Low disease activity (DAS28 ≤3.2)	3.54 (2.29, 5.49)	3.60 (1.84, 7.06)

RR=relative risk.

The results of the indirect comparisons showed that tocilizumab had a statistically significant advantage over abatacept for all ACR outcomes and DAS remission and low disease activity. Tocilizumab also demonstrated a statistically significant advantage compared to infliximab in proportion of patients achieving ACR70 response as well as DAS remission and low disease activity. The submission removed the ATTEST trial (comparing abatacept and infliximab) from all analyses due to heterogeneity. When the ATTEST trial was excluded the advantage remained for tocilizumab, except for ACR70 versus both abatacept and infliximab, as no statistically significant differences were observed.

There was a statistically significant advantage for tocilizumab, abatacept and infliximab versus placebo + methotrexate across all trials in achievement of greater than or equal to 0.3 point decrease in Health Assessment Questionnaire Disability Index (HAQ-DI) score. There were a greater proportion of patients achieving a HAQ-DI decrease for abatacept and infliximab compared to tocilizumab (e.g. proportions ranged from 58.3 % to 63.7 % for abatacept compared to 36.2 % to 54.4 % for tocilizumab). The pre-sub-committee response noted that although a numerical comparison of the HAQ scores shows higher absolute improvements for abatacept and infliximab, compared with tocilizumab, this difference does not take into account the HAQ scores in the common reference MTX arms of the studies. The incremental improvement in HAQ scores for tocilizumab compared with MTX is similar to the incremental improvement in HAQ scores for abatacept. In addition, the incremental improvement in HAQ scores for tocilizumab compared with MTX was greater than the incremental improvement in HAQ scores for infliximab. The pre-sub-committee response also provided an indirect comparison of HAQ scores, which demonstrated a statistically significant advantage for tocilizumab compared to both abatacept and infliximab with respect to achieving at least a 0.22 to 0.3 point decrease from baseline at week 24.

The submission also provided the results of a trial in which patients who had failed treatment with one or more TNF inhibitors were randomised to treatment with tocilizumab + methotrexate or placebo + methotrexate. A comparison of this trial with the three other trials in the first-line setting indicated that the proportion of patients with an ACR response was lower in second-line treatment compared to first-line therapy. For example, 28.8 % of patients in the trial achieved an ACR50 response, whereas in the pivotal trials the proportion achieving ACR response ranged from 32.2 % to 43.9 %. The proportion of placebo-treated responders was also lower in Emery et al. 2008. Therefore, overall the incremental improvement in efficacy associated with use of tocilizumab in the second-line setting is consistent with the incremental improvement in efficacy in the first-line setting.

The pre-sub-committee response provided an indirect comparison in second-line settings between tocilizumab and abatacept which suggested that, with the exception of ACR20, there were no statistically significant differences for ACR50, ACR70, DAS outcomes or HAQ between the two drugs.

With respect to the requested listing for use in combination with DMARDs other than methotrexate, the submission stated that the use of DMARDs other than methotrexate in combination with tocilizumab did not modify the treatment effect (i.e. in terms of adverse events and measures of efficacy) associated with tocilizumab.

The submission noted that despite the differences in the regimens for tocilizumab in combination with methotrexate and other DMARDs used in Trials WA17822, WA17823 and WA18063, the findings in terms of the absolute risk differences and relative risks were similar for the ACR50 response rates and for the DAS28 scores. In trials WA17822 and 17823, all patients were using methotrexate. In trial WA18063, 75.8 % of patients used methotrexate and only a small proportion of patients used tocilizumab in combination with another DMARD.

The submission referred to a test for interaction analysis presented in the major submission, reporting that the results of this test found that the choice of background DMARD did not influence the treatment effect associated with tocilizumab.

Tocilizumab appeared to be associated with a lower incidence of upper respiratory tract infection, headache, nausea and fatigue than abatacept and infliximab. Tocilizumab was also associated with a lower incidence of infection than infliximab, but higher than abatacept and also a higher incidence of musculoskeletal and connective tissue disorders than abatacept. However, the results of the indirect comparison presented in the pre-subcommittee response indicated no statistically significant difference in any of the adverse events known to be associated with bDMARDs at 24 weeks.

On the basis of the evidence presented regarding extended assessment of comparative harms the submission concluded that no additional adverse events or safety concerns had been identified. During evaluation it was identified the submission did not adequately address a number of issues, including a greater rate of occurrence of infusion reactions and infection based on long-term data; more than doubling of incidence of malignancy in the long-term data compared to trial data; impact of lipid parameters, particularly in terms of need for additional treatment; and deaths reported (n=15) in a post-marketing surveillance study of Japanese patients.

The pre-sub-committee response argued that these long term safety outcomes had already been assessed by the TGA. Infection rates did not increase beyond the rates in the six month safety population, infusion reactions were uncommon and there was no data to suggest an increased risk of malignancy

Increases in mean fasting lipid level were observed in all tocilizumab groups at 6 months, however only mean triglyceride levels rose above the normal range. Elevations in lipid levels appeared to stabilise in the long term safety population and only 139 of 2,439 patients receiving tocilizumab (5.7 %) commenced lipid lowering therapy. However, the PI stated that ‘approximately 24 % of patients receiving tocilizumab in clinical trials experienced sustained elevations in total cholesterol greater than 6.2 mmol/L (240 mg/dL), with 15 % experiencing a sustained increase in LDL greater than or equal to 4.1 mmol/L (160 mg/dL). Elevations in lipid parameters responded to treatment with lipid-lowering agents.’

Based on the results of a pooled meta-analysis of the ACR20, ACR50 and ACR70 response rates for trials WA18063, WA17822 and WA17823 presented in the major submission, which found no significant differences in the overall incidence of adverse events, the submission considered that the safety profile of different DMARDs used in combination with tocilizumab was similar.

9. Clinical Claim

The submission claimed that tocilizumab was no worse than abatacept and infliximab in terms of comparative efficacy and safety.

For PBAC's views see Recommendation and Reasons.

10. Economic Analysis

The submission presented a cost-minimisation analysis using abatacept as the comparator.

The equi-effective doses were tocilizumab 8 mg/kg administered on days 1 and 29 and then every 28 days, and abatacept at approximately 10 mg/kg administered on days 1, 15, 29 and then every 28 days.

The results of the cost-minimisation analyses presented by the submission across a number of timepoints showed the cost of tocilizumab was less than that for abatacept. However, following one year of treatment when both drugs were administered every four weeks the cost difference was negligible.

11. Estimated PBS Usage and Financial Implications:

The likely number of patients per year was less than 1000 patients in Year 5 of listing. The financial cost per year to the PBS was less than $10 million.

12. Recommendation and Reasons

The PBAC recommended that tocilizumab solution for infusion 80 mg in 4 mL, 200 mg in 10 mL and 400 mg in 20 mL be listed for the treatment of severe, active rheumatoid arthritis in combination with methotrexate in patients who have failed to demonstrate a response to at least one TNF-alfa antagonist treatment on a cost-minimisation basis compared to abatacept. In the context of cost-minimisation the equi-effective doses were tocilizumab 8 mg/kg administered on days 1 and 29 and then every 28 days and abatacept 10 mg/kg administered on days 1, 15, 29 and then every 28 days.

The PBAC agreed that the basis of the restriction wording would be that for rituximab in rheumatoid arthritis, where rituximab was available second-line to those meeting certain criteria and who had not adequately responded to a TNF-alfa antagonist.

The PBAC agreed that the choice of abatacept and infliximab as the main comparators was appropriate.

The PBAC considered that tocilizumab was no worse that abatacept and infliximab in terms of comparative efficacy. The results of the indirect comparisons showed that tocilizumab had a statistically significant advantage over abatacept for all ACR outcomes, and DAS (Disease Activity Score) remission and low disease activity. Tocilizumab also demonstrated a statistically significant advantage compared to infliximab in proportion of patients achieving ACR70 response as well as DAS remission and low disease activity. There was a statistically significant advantage for tocilizumab, abatacept and infliximab versus placebo plus methotrexate across all trials in achievement of greater than or equal to 0.3 point decrease in Health Assessment Questionnaire Disability Index (HAQ-DI) score. The Pre-Sub-Committee response provided an indirect comparison of HAQ scores, which demonstrated a statistically significant advantage for tocilizumab compared to both abatacept and infliximab with respect to achieving at least a 0.22 to 0.3 point decrease from baseline at week 24.

The PBAC noted that results of a *published* trial in patients who had failed treatment with one or more TNF inhibitors (Emery et al. 2008), a comparison with use in the first-line setting indicated that the proportion of patients with an ACR response was lower in the second-line setting compared to first-line therapy

The PBAC was concerned with respect to comparative safety, in particular long-term safety. Tocilizumab was associated with a higher incidence of infection than abatacept, more than doubling of incidence of malignancy in the long-term data compared to trial data, sustained elevations in total cholesterol requiring additional treatment, and recently, 15 deaths had been reported in a post-marketing surveillance study of Japanese patients.

The PBAC noted that tocilizumab belonged to a new class of biological DMARDS, being an interleukin-6 monoclonal antibody with a place in the treatment of severe active rheumatoid arthritis.

Therefore, given the toxicity concerns of the increased risks of infection and raised lipid profile the PBAC considered that a second-line listing on a cost-minimisation basis with abatacept appropriate.

The PBAC noted listing was also requested for the treatment of severe active rheumatoid arthritis with tocilizumab in combination with a non-biological DMARD.

The PBAC noted in the pivotal trial WA18063 (published as Genovese et al, 2008) in support of the extension, 75.8 % of patients in the tocilizumab plus DMARD arm received methotrexate, and only a relatively small proportion of patients in this arm were treated with other DMARDs.

The submission claimed that the results of an interaction analysis demonstrated that the choice of background DMARD did not alter the treatment effect associated with tocilizumab. However, the PBAC questioned the validity of this analysis due to the small proportion of patients who used non-MTX DMARDs.

Further, the plausibility that, for example, hydroxychloroquine was equivalent to leflunomide was clinically questionable.

The PBAC considered there was uncertainty associated with the costings for the use of DMARDs in combination with tociliziumab. The submission claimed, based on the Genovese study and Chan and Tett et al (2006) that the majority of use will be in methotrexate, however the Chan and Tett data suggested that a substantial proportion (43 %) of DMARDs other than methotrexate were used in combination with tocilizumab.

The PBAC decided not accept listing in combination with other DMARDs on the basis of uncertain equivalent efficacy of tocilizumab in combination with non-MTX DMARDs and the uncertain costs of non-MTX DMARDs in the cost minimisation equation.

Recommendation

TOCILIZUMAB, solution for IV infusion, 80 mg in 4 mL, 200 mg in 10 mL and 400 mg in 20 mL

Restriction: Section 100 (Highly Specialised Drugs Program)
Public and private hospital authority required

To be 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 further comment.