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 Limited
Date of PBAC Consideration: November 2009

1. Purpose of Application

The submission sought an extension to the section 100 (Highly Specialised Drug) listing recommended at the July 2009 PBAC meeting to include the initial and continuing treatment, as monotherapy, of patients with severe active rheumatoid arthritis who meet certain criteria.

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

At the July 2009 meeting, the PBAC recommended that tocilizumab solution for infusion be listed as a section 100 (Highly Specialised Drug) 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. The equi-effective doses are 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.

3. Registration Status

Tocilizumab was registered on 15 May 2009 for the treatment of moderate to severe active rheumatoid arthritis (RA) in adult patients:

- in combination with methotrexate or 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 methotrexate (MTX) or where continued treatment with MTX is inappropriate.

4. Listing Requested and PBAC's View

The submission requested a listing similar to that for adalimumab and etanercept, which are listed for first-line use as either combination therapy or monotherapy. A listing for tocilizumab was requested in section 100 similar to infliximab and abatacept (which are also administered intravenously).

(Abbreviated Version)

Public and Private Hospital Authority Required
Initial Treatment:
Application for initial PBS-subsidised treatment with tocilizumab, 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:
i. methotrexate at a dose of at least 20 mg weekly; and
ii. 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

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

A maximum of 16 weeks of treatment will be authorised under this restriction. At the time of the authority application, medical practitioners should request the appropriate quantity of vials, based on the weight of the patient, to provide sufficient for a single infusion. Up to a maximum of 3 repeats may be authorised.

Continuing Treatment:
Continuing PBS-subsidised treatment with tocilizumab, by a rheumatologist or clinical immunologist with expertise in the management of RA, of adults:
(1) who have a documented history of severe active RA; and
(2) who have demonstrated an adequate response to treatment with tocilizumab; and
(3) whose most recent course of PBS-subsidised bDMARD treatment in this treatment cycle was with tocilizumab.'

An adequate response to treatment is defined as:
An erythrocyte sedimentation rate (ESR) no greater than 25 mm per hour or a C-reactive protein (CRP) level no greater than 15 mg per L or either marker reduced by at least 20% from baseline;
AND either of the following:
i. a reduction in the total active (swollen and tender) joint count by at least 50% from baseline, where baseline is at least 20 active joints; or
ii. a reduction in the number of the following major active joints, from at least 4, by at least 50%:
- elbow, wrist, knee and/or ankle (assessed as swollen and tender); and/or
- shoulder and/or hip (assessed as pain in passive movement and restriction of passive movement, where pain and limitation of movement are due to active disease and not irreversible damage such as joint destruction or bony overgrowth).

A maximum of 24 weeks of treatment will be authorised under this restriction. At the time of the authority application, medical practitioners should request the appropriate quantity of vials, based on the weight of the patient, to provide sufficient for a single infusion. Up to a maximum of 5 repeats may be authorised.

Grandfather Patients
Initial PBS-subsidised supply for continuing treatment with tocilizumab, ~~in combination with methotrexate at a dose of at least 7.5 mg weekly,~~ by a rheumatologist or clinical immunologist with expertise in the management of RA, of an adult who:
(1) has a documented history of severe active RA; and
(2) was receiving treatment with tocilizumab prior to 4 November 2009; and
(3) has demonstrated a response as specified in the criteria for continuing PBS-subsidised treatment with tocilizumab.

For PBAC's view see Recommendation and Reasons.

5. Clinical Place for the Proposed Therapy

Rheumatoid arthritis is an inflammatory disorder, typically featuring a combination of peripheral symmetrical inflammatory arthritis and a number of well-described extra-articular symptoms. It is associated with significant morbidity, disability and mortality.

Tocilizumab would provide another treatment option for adult patients with severe active rheumatoid arthritis which can be used in combination with methotrexate or alone if the patient cannot tolerate methotrexate.

6. Comparator

Appropriately, the submission nominated etanercept 50 mg per week via subcutaneous injection as the main comparator. Adalimumab and etanercept are the only two bDMARDS currently listed for monotherapy for RA in the event of methotrexate (MTX) intolerance.

Etanercept was chosen on the basis of comparable trial patient populations and outcome measures to the tocilizumab trials.

7. Clinical Trials

The submission presented an adjusted indirect comparison of tocilizumab and etanercept via a meta-analysis of four randomised trials comparing tocilizumab with MTX/DMARD and three randomised trials comparing etanercept with MTX/DMARD in patients with severe rheumatoid arthritis. A long-term non-comparative study of tocilizumab in Japan (MRA009JP) was also included in the Extended Assessment of Comparative Harms.

The key trials published at the time of submission are shown in the table below:

Trial ID / First author	Protocol title / Publication title	Publication citation
Tocilizumab vs Placebo+MTX or DMARD		
AMBITION Jones G, et al. (2009).	Comparison of tocilizumab monotherapy versus methotrexate monotherapy in patients with moderate to severe rheumatoid arthritis: The AMBITION study.	Annals of Rheumatic Diseases Online First, Published on 17 March 2009 as 10.1136/ard.2008.105197
CHARISMA Maini RN, et al. (2006).	Double-blind randomised controlled clinical trial of the interleukin-6 receptor antagonist, tocilizumab, in European patients with rheumatoid arthritis who had an incomplete response to methotrexate.	Arthritis and Rheumatism 54 (9): 2817-2829
SAMURAI Nishimoto N, et al. (2007).	Study of active controlled monotherapy used for rheumatoid arthritis, an IL-6 inhibitor (SAMURAI): evidence of clinical and radiographic benefit from an X-ray reader-blinded randomised controlled trial of tocilizumab.	Annals of Rheumatic Diseases 66 (9): 1162-1167
SATORI Nishimoto N, et al. (2009).	Study of active controlled tocilizumab monotherapy for rheumatoid arthritis patients with an inadequate response to methotrexate (SATORI): Significant reduction in disease activity and serum vascular endothelial growth factor by IL-6 receptor inhibition therapy.	Modern Rheumatology 19 (1): 12-19
Etanercept vs Placebo+MTX or DMARD		
TEMPO Klareskog L, et al. (2004).	Therapeutic effect of the combination of etanercept and methotrexate compared with each treatment alone in patients with rheumatoid arthritis: double-blind randomised controlled trial.	Lancet 363 (9410): 675-681
van der Heijde D, et al. (2006a).	Patient reported outcomes in a trial of combination therapy with etanercept and methotrexate for rheumatoid arthritis: the TEMPO trial.	Annals of Rheumatic Diseases 65 (3): 328-334
van der Heijde D, et al. (2006).	Comparison of etanercept and methotrexate, alone and combined, in the treatment of rheumatoid arthritis: two-year clinical and radiographic results from the TEMPO study, a double-blind, randomised trial.	Arthritis and Rheumatism 54 (4): 1063-1074
van der Heijde D, et al. (2007).	Disease remission and sustained halting of radiographic progression with combination etanercept and methotrexate in patients with rheumatoid arthritis.	Arthritis and Rheumatism 56 (12): 3928-3939

ERA		
Bathon JM, et al. (2000).	A comparison of etanercept and methotrexate in patients with early rheumatoid arthritis.	New England Journal of Medicine 343 (22): 1586-1593
Genovese MC, et al. (2002).	Etanercept versus methotrexate in patients with early rheumatoid arthritis: two-year radiographic and clinical outcomes.	Arthritis and Rheumatism 46 (6): 1443-1450
Kosinski M, et al. (2002).	Health-related quality of life in early rheumatoid arthritis: impact of disease and treatment response.	The American Journal of Managed Care 8 (3): 231-240
Other Studies		
Combe et al. (2006) (Etanercept 309 Study)	Etanercept and sulfasalazine, alone and combined, in patients with active rheumatoid arthritis despite receiving sulfasalazine: a double- blind comparison.	Annals of Rheumatic Diseases 65 (10): 1357-1362

MTX=methotrexate; DMARD=disease-modifying anti-rheumatic drug

8. Results of Trials

The submission presented an indirect comparison of tocilizumab and etanercept for American College of Rheumatology (ACR)20, ACR50 and ACR70 outcomes. The results are presented in following table.

Summary of results of the indirect comparison

	Tocilizumab vs MTX/Dmard RR (95% CI)	**Etanercept vs MTX/Dmard RR (95% CI)**	**Tocilizumab vs Etanercept RR (95% CI)**
ACR20	1.92 (1.29, 2.86)	1.29 (0.92, 1.80)	1.49 (0.88, 2.51)
ACR50	2.28 (1.20, 4.33)	1.39 (0.89, 2.16)	1.64 (0.75, 3.58)
ACR70	2.55 (1.22, 5.32)	1.50 (0.83, 2.72)	1.70 (0.66, 4.38)

CI = confidence interval, RR = relative risk

The PBAC noted the adjusted indirect comparison of tocilizumab and etanercept via a meta-analysis of four randomised trials comparing tocilizumab with MTX/DMARD and three randomised trials comparing etanercept with MTX/DMARD in patients with severe rheumatoid arthritis for ACR20, ACR50, and ACR70 outcomes demonstrated no significant differences in outcomes between tocilizumab and etanercept.

For further PBAC comments, see Recommendation and Reasons.

The submission presented a meta-analysis of serious adverse events. Tocilizumab demonstrated significantly increased cholesterol in particular LDL and triglyceride levels were elevated and also had a trend to increases in ALT/AST and bilirubin levels as compared to the reference arm. There was also a slight trend to higher incidence of infusion reactions.

The results of the indirect comparisons indicated no differences between tocilizumab and etanercept for infections, infusion reactions and neoplasms, while there are statistically significant differences for ALT and AST increases.

Data presented by the submission on long term follow up trials and Periodic Update Safety Reports (PSUR) found the same types of adverse events at comparable levels to the six month trial data. Tocilizumab and etanercept display somewhat different safety profiles however the evidence presented by the submission supports the claim that tocilizumab is no worse than etanercept on the grounds of safety.

For PBAC's comments, see Recommendation and Reasons.

9. Clinical Claim

The submission described tocilizumab as no worse than etanercept in terms of efficacy and safety.

The PBAC accepted that tocilizumab is no worse than etanercept in terms of efficacy, however the adverse event profile remained of concern.

10. Economic Analysis

The submission presented a cost minimisation analysis. The equi-effective doses were estimated as tocilizumab 8 mg/kg every four weeks and etanercept 50 mg weekly. This was consistent with the product information for etanercept and the proposed product information for tocilizumab and with the doses used in the randomised trials.

The submission determined that tocilizumab is cost saving compared with etanercept, in patients with severe active RA who cannot tolerate MTX. In addition, the submission asserted that total treatment costs for both tocilizumab and etanercept will both be lower in subsequent years because fewer specialist visits are required to assess response than in the first year.

11. Estimated PBS Usage and Financial Implications

The likely number of patients per year was estimated to be less than 10,000 in Year 5.

The financial savings per year to the PBS was estimated to be less than $10 million in Year 5. This estimate was considered uncertain as costs overall to the health care system are increased by the mode of administration (IV versus the SC route of the comparator).

12. Recommendation and Reasons

The PBAC recommended that tocilizumab be listed as monotherapy for the treatment of severe active rheumatoid arthritis in patients who have failed to demonstrate a response to a TNF-alfa antagonist treatment on a cost-minimisation basis compared to etanercept. The equi-effective doses are tocilizumab 8 mg/kg every four weeks and etanercept 50 mg weekly, and the PBS costings would take into account administration and preparation costs associated with tocilizumab due to the different mode of administration.

The PBAC recalled that at the July 2009 meeting tocilizumab had been recommended for listing when in combination with methotrexate for the same patient group, second line for those who have failed to demonstrate a response to a TNF-alfa antagonist.

The PBAC noted the adjusted indirect comparison of tocilizumab and etanercept via a meta-analysis of four randomised trials comparing tocilizumab with MTX/DMARD and three randomised trials comparing etanercept with MTX/DMARD in patients with severe rheumatoid arthritis for ACR20, ACR50, and ACR70 outcomes demonstrated no significant differences in outcomes between tocilizumab and etanercept.

The applicability of the trials to the Australian PBS population was of concern as the meta-analysis included two tocilizumab trials (SAMURAI and SATORI) which were performed in Japan with different maximum doses of methotrexate (8 mg). The Pre-Sub-Committee

response provided the results of an indirect comparison of ACR50 response rates between the tocilizumab studies, AMBITION and CHARISMA, and the etanercept study, TEMPO. This comparison excluding the Japanese trials did not alter the conclusion that tocilizumab is no worse than etanercept in terms of efficacy, (RR 1.33, 95%CI: 0.99, 1.80).

With respect to the adverse event profile of tocilizumab, the PBAC remained concerned. At the July 2009 meeting, the PBAC noted 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. To date, the follow-up in trials was considered too short to adequately assess the long-term toxicity risks.

Therefore, the PBAC considered that at this time the place of tocilizumab, both as combination therapy with methotrexate, and as monotherapy, was second line to TNF-alfa antagonists.

Recommendation:
TOCILIZUMAB, solution for I.V. infusion, 80 mg in 4 mL, 200 mg in 10 mL and 400 mg in 20 mL

Restriction: Section 100 (Highly Specialised Drugs Program)
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.