PUBLIC SUMMARY DOCUMENT
Product: Tocilizumab, concentrate for injection, 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 2011

1. Purpose of Application

To extend the current S100 (Highly Specialised Drugs Program) Authority Required listing to include treatment by a paediatric rheumatologist or under the supervision of a paediatric treatment centre, of severe active systemic juvenile idiopathic arthritis in a patient under 18 years of age, who meets 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

Tocilizumab had not previously been considered by the PBAC for this indication.

3. Registration Status

As of 4 November 2011, tocilizumab was registered by the TGA for the indications:

- Systemic Juvenile Idiopathic Arthritis: Treatment of active systemic juvenile idiopathic arthritis in patients 2 years of age and older. Tocilizumab can be given alone or in combination with methotrexate.
- Rheumatoid Arthritis: Treatment of moderate to severe active RA in adult patients: in combination with methotrexate or other non-biological 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 or where continued treatment with methotrexate is inappropriate. Tocilizumab has been shown to inhibit the progression of joint damage, as measured by x-ray, when given in combination with methotrexate.

4. Listing Requested and PBAC's View

The proposed amendments to the current PBS restrictions (abbreviated version) for etanercept and adalimumab are highlighted in **BOLD.**

Section 100 - Highly Specialised Drugs Program
Public and Private Hospital Authority required
(Abbreviated version)
Initial 1 (new patient or patient recommencing after a break of more than 12 months)
Initial treatment by a paediatric rheumatologist, or under the supervision of a paediatric rheumatology treatment centre, of a patient under 18 years:

a) who has severe active **systemic** juvenile idiopathic arthritis; AND
b) whose parent or authorised guardian has signed a patient acknowledgement; AND
c) who has not received PBS-subsidised treatment with **tocilizumab** for this condition in the previous 12 months; AND
d) who has demonstrated either:
    i. severe intolerance of, or toxicity due to, methotrexate (see below for definition of severe intolerance and toxicity); or
    ii. failure to achieve an adequate response to 1 of the following treatment regimens:
    in those with polyarticular course disease, oral or parenteral methotrexate at a dose of at least **15 mg** per square metre weekly, alone or in combination with oral or intra-articular corticosteroids

for a minimum of 3 months; or
in those whose disease is characterised by systemic symptoms, an inability to decrease and maintain the dose of corticosteroids below 0.5 mg per kg per day following a minimum of 2 months of therapy.

The following criteria indicate failure to achieve an adequate response and must be demonstrated in all patients at the time of the initial application:

a) in those with polyarticular course disease treated with methotrexate alone or in combination with corticosteroids:
- i. an active joint count of at least 20 active (swollen and tender) joints; OR
- ii. at least 4 active joints from the following list:
  elbow, wrist, knee and/or ankle (assessed as swollen and tender): AND/OR
  shoulder, cervical spine 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).

b) in those whose disease is characterised by systemic symptoms treated with corticosteroids:
- **i. an active joint count of at least 2 active joints; AND**
- **ii. persistent fever >38ºC for at least 5 out of 14 consecutive days; AND/OR**
- **iii. a C-reactive protein (CRP) level and platelet count above the upper limits of normal (ULN)~~;~~.**

A maximum of 16 weeks of treatment will be authorised under this restriction.

Initial 2 (change or re-commencement after a break of less than 12 months)
Initial PBS-subsidised treatment with **tocilizumab** by a paediatric rheumatologist, or under the supervision of a paediatric rheumatology treatment centre, of a patient under 18 years who:
a) has a documented history of severe active **systemic** juvenile idiopathic arthritis; AND
b) in this treatment cycle, has received prior PBS-subsidised treatment with **tocilizumab** for this condition; AND
c) has not failed PBS-subsidised therapy with **tocilizumab** for this condition more than once in the current treatment cycle.

A maximum of 16 weeks of treatment will be authorised under this restriction.

Continuing treatment
Continuing PBS-subsidised treatment with **tocilizumab**, by a rheumatologist or under the supervision of a paediatric rheumatology treatment centre, of a patient:
a) who has a documented history of severe active **systemic** juvenile idiopathic arthritis; AND
b) who has demonstrated an adequate response to treatment with **tocilizumab**; AND
c) whose most recent course of PBS-subsidised bDMARD treatment in this treatment cycle was with **tocilizumab.**

An adequate response to treatment is defined as:

a) in those with polyarticular course disease:
- 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 active joints, from at least 4, by at least 50%:
  elbow, wrist, knee and/or ankle (assessed as swollen and tender); AND/OR
  shoulder, cervical spine 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).

b) in those whose disease is characterised by systemic symptoms:
- **i. absence of fever in the preceding seven days; AND/OR**
- **ii. a 30% reduction in the CRP level and platelet count; AND/OR**
- **iii. a 30% reduction in the dose of corticosteroids.**

A maximum of 24 weeks of treatment will be approved under this restriction.

The submission requested that additional wording in relation to repeat prescriptions and assessment of response will be equivalent to that included within the current PBS restrictions for etanercept and adalimumab for JIA.

For PBAC's view, see Recommendation and Reasons.

5. Clinical Place for the Proposed Therapy

Juvenile idiopathic arthritis (JIA) is considered the most common rheumatic childhood disease and is characterised by chronic joint pain of unknown cause with symptoms persisting for more than six weeks. Systemic JIA (sJIA) is a subset of JIA that is characterised by the presence of arthritis with intermittent fever and rash (systemic features).

For PBAC's view, see Recommendation and Reasons.

6. Comparator

The submission nominated etanercept and adalimumab as the two comparators to tocilizumab.

For PBAC's view, see Recommendation and Reasons.

7. Clinical Trials

The basis of the submission was an indirect comparison of one randomised controlled trial (TENDER) comparing tocilizumab (8 mg/kg >30 kg, 12 mg/kg ≤30 kg by intra-venous (IV) infusion every 2 weeks) with placebo in patients with sJIA and two randomised controlled trials; (Lovell 2000) comparing etanercept (0.4 mg/kg up to 25 mg sub-cutaneously (SC) twice weekly) with placebo in patients with JIA and (Lovell 2008) comparing adalimumab (24 mg/m^2 SC every 2 weeks) with placebo in patients with JIA.

The PBAC noted that there are differences between the tocilizumab trial and the comparator trials (etanercept and adalimumab) that affect the exchangeability of the trials for an indirect comparison. These include the use of methotrexate disease severity, responder status, study population and study design.

All participants in the TENDER trial had active sJIA. Only 32% of the trial population in the etanercept trial had sJIA. The proportion of patients with sJIA in the adalimumab trial is unknown.

The following trials had been published at the time of submission:

Trial ID / First author	Protocol title / Publication title	Publication citation
Tocilizumab		
TENDER MRA316JP Yokota et al. (2008)	Efficacy and safety of tocilizumab in patients with systemic-onset juvenile idiopathic arthritis: a randomised, double-blind, placebo-controlled, withdrawal phase III trial.	Lancet; 2008,371:998-1006.
Etanercept		
Lovell et al. (2000)	Etanercept in children with polyarticular juvenile rheumatoid arthritis.	N Engl J Med, 2000;342(11):763-769.

Adalimumab		
Lovell et al. (2008)	Adalimumab with or without methotrexate in juvenile rheumatoid arthritis.	N Engl J Med, 2008;359(8):810-820.

8. Results of Trials

The submission presented a primary analysis of the double-blind randomised phase of the TENDER trial with the primary outcome of a JIA American College of Rheumatology (ACR) 30 response (represents a 30% improvement from baseline in at least 3 of 6 response criteria without a worsening of greater than 30% in 1 remaining response variable) and the absence of a fever.

Tocilizumab primary outcome: patients with a JIA ACR30 response and absence of fever

Response rate parameter	Tocilizumab			Placebo (N=37)
	8 mg/kg *(for patients ≥30 kg)* (N=37)	12 mg/kg *(for patients <30 kg)* (N=38)	All (N=75)	
JIA ACR30 and absence of fever				
Responders (%)	28 (75.7%)	36 (94.7%)	64 (85.3%)	9 (24.3%)
95% CI for response rate	61.9, 89.5	87.6, 100.0	77.3, 93.3	10.5, 38.1
Weighted difference (95% CI); p-value			61.5% (44.9, 78.1); <0.0001	

Abbreviations: JIA=juvenile idiopathic arthritis; ACR=American College of Rheumatology; CI=confidence interval; N=number in group

The results indicated that there was a statistically significant improvement in the JIA ACR30 response and absence of fever at 12 weeks with tocilizumab (85.3%) compared with placebo (24.3%).

The submission presented an indirect comparison based on JIA ACR 30, 50, 70 and 90 responses between tocilizumab and both etanercept and adalimumab.

The results for the indirect comparison of tocilizumab with or without methotrexate (week 24) and etanercept (week 28) JIA ACR30 response rate are shown in the table below:

Trial ID	Treatment effect RR (95% CI)	Tocilizumab n with event/N (%)	Placebo n with event/N (%)	Etanercept n with event/N (%)	Treatment effect RR (95% CI)	Indirect estimate of effect Indirect RR (95%CI)
TENDER	3.89 (2.20, 6.88)	106/112 (94.6%)	9/37 (24.3%)			1.68 (0.76, 3.75)
Lovell 2000			9/26 (34.6%)	20/25 (80.0%)	2.31 (1.32, 4.06)	

Abbreviations: CI=confidence interval; n=number with event; N=number in group; RR=relative risk

The results for the indirect comparison of tocilizumab with or without methotrexate (week 48) and adalimumab with or without methotrexate (week 48) JIA ACR30 response rate are shown in the following table:

Trial ID	Treatment effect RR (95% CI)	Tocilizumab n with event/N (%)	Placebo n with event/N (%)	Adalimumab n with event/N (%)	Treatment effect RR (95% CI)	Indirect estimate of effect Indirect RR (95%CI)
TENDER	3.34 (1.88, 5.94)	91/112 (81.3%)	9/37 (24.3%)			1.96 (0.98, 3.92)
Lovell 2008			23/65 (35.4%)	41/68 (60.3%)	1.70 (1.16, 2.49)	

Abbreviations: CI=confidence interval; n=number with event; N=number in group; RR=relative risk

The relative risk for tocilizumab versus etanercept is 1.68 (95%CI: 0.76, 3.75) for Paediatric ACR30 (PedACR30) and the relative risk for tocilizumab versus adalimumab is 1.96 (95% CI: 0.98, 3.92) for Paediatric ACR30 (PedACR30). These results indicate that there is no statistically significant difference between tocilizumab and the comparators.

However, the percentage of patients achieving a JIA ACR 30, 50, 70 or 90 response in the placebo (common reference) group differed between the three trials, and the common reference groups were completely different between the trials. In the etanercept and adalimumab trials, the placebo group only included patients who had initially responded to treatment with the active drug. In the tocilizumab trial, the placebo group had received no initial prior treatment.

For PBAC's view on these results, see Recommendation and Reasons.

Overall, the incidence of adverse events was higher in the tocilizumab group compared with the placebo group (88.0% and 62.2%, respectively). The most common adverse events were related to infections and infestations, mainly upper respiratory tract infection (13.3%) and nasopharyngitis (10.7%). The submission stated that there was no statistically significant difference in the incidence of infections and infestations with tocilizumab compared with placebo.

The submission stated that no new additional adverse events or safety concerns were identified from the additional data sources included in the extended assessment of comparative safety for tocilizumab, etanercept and adalimumab.

For PBAC's view, see Recommendation and Reasons.

9. Clinical Claim

The submission described tocilizumab as non-inferior in terms of comparative effectiveness and non-inferior in terms of comparative safety over etanercept and adalimumab.

The PBAC accepted the submission's claim of non-inferiority of tocilizumab in terms of comparative effectiveness over etanercept and adalimumab. The PBAC considered that tocilizumab has a greater risk of adverse events compared with placebo and a different risk of adverse events compared with etanercept and adalimumab.

10. Economic Analysis

The submission presented a cost minimisation analysis.

The equi-effective doses are, tocilizumab: <30 kg 12 mg/kg and ≥30 kg 8 mg/kg administered by 60 minute IV infusion every 2 weeks compared with etanercept: 0.4 mg/kg up to 25mg SC twice weekly, estimated using the weight distribution from the TENDER trial.

For PBAC's view, see Recommendation and Reasons.

11. Estimated PBS Usage and Financial Implications

The likely number of patients treated was estimated by the submission to be less than 10,000 over the first 5 years. The estimate was uncertain.

The submission estimated there would be net financial savings to the PBS.

12. Recommendation and Reasons

The PBAC recommended listing tocilizumab on the PBS in the Section 100 (Highly Specialised Drugs Program) as a Public and Private Hospital Authority Required benefit on a cost minimisation basis compared with etanercept and adalimumab. The equi-effective doses estimated using the weight distribution from the TENDER trial are, tocilizumab: <30kg 12mg/kg and ≥30kg 8mg/kg administered by 60 minute IV infusion every 2 weeks compared with etanercept: 0.4mg/kg up to 25mg SC twice weekly and adalimumab 24 mg/m^2 SC every two weeks (Lovell 2008 trial).

The PBAC noted that JIA is a heterogeneous disease in which inflammatory arthritis may involve many or a few joints plus fever. It has a complex disease classification and may run a variable course including a polycyclic course characterised by flare-ups in systemic activity (sJIA). Systemic JIA is an uncommon, serious and potential crippling disease associated with a notable morbidity risk. The PBAC agreed with the advice of the Paediatric Medicines Advisory Committee (PMAG) that there was a high clinical need for tocilizumab for use in the treatment of children who currently have very limited effective PBS-subsidised treatment options for sJIA.

The PBAC agreed that the comparators etanercept and adalimumab are appropriate for patients with polyarticular joint involvement. The PBAC considered that tocilizumab would be used as an alternative to etanercept and adalimumab in this population group. However, etanercept and adalimumab are not currently TGA-approved or PBS-listed for use in sJIA. The PBAC therefore agreed that separate systemic JIA (sJIA) and polyarticular JIA (PaJIA) listings are appropriate. The PBAC noted that that finalisation of the restriction wording will require input from the Department, relevant sponsors, Medicare PMAG and specialist paediatric rheumatologists regarding interchangeability criteria and appropriate criteria for use in patients with systemic JIA.

The PBAC noted that no head-to-head studies comparing tocilizumab with the two TNF-alpha inhibitors (bDMARDs) in paediatric sJIA patients are available. The basis of the submission was an indirect comparison of the TENDER randomised controlled trial (RCT) of tocilizumab (8 or 12mg per kg intravenously every two weeks) versus placebo in patients with sJIA, a RCT (Lovell 2000) of etanercept (0.4 mg per kg up to 25 mg SC twice weekly) versus placebo in patients with JIA and sJIA, and a third RCT (Lovell 2008) comparing adalimumab (24 mg/m^2 second weekly) versus placebo in patients with JIA based on the common comparator placebo. The indirect comparison was based on the ACR30 response rates with placebo as the common reference.

The PBAC noted that the comparative effectiveness of tocilizumab is difficult to assess in the absence of head-to-head data. The results of the placebo-controlled RCTs, taken separately, suggest that tocilizumab has similar effectiveness to the comparators. However, the study designs are different and patients enrolled in the trials are different and not wholly representative of those for whom listing is sought and the validity of the combined indirect comparison is therefore questionable.

The PBAC noted that the comparative safety of tocilizumab is difficult to assess in the absence of head-to head trial data and this limits the conclusions that may be drawn from the available evidence. The PBAC noted however that tocilizumab has a greater risk of adverse events compared with placebo, and reported side effects included increased risk of infection and elevated lipid levels. In addition, infusion and anaphylactic reactions can occur. The PBAC acknowledged the unknown risks associated with the use of biologic agents in children. The PBAC noted that as a PBS-subsidised HSD, tocilizumab will be managed by specialist physicians and be supplied through public and private hospitals that have appropriate specialist facilities. The PBAC agreed that this is appropriate as the long-term safety profile of tocilizumab in sJIA is being established.

The PBAC also noted the TGA recommendation that infusion of tocilizumab for this indication should take place in a hospital until there is adequate demonstration of safety of administration in sufficiently large numbers of children. The PBAC considered that paediatric patients receiving tocilizumab will most likely be treated in a public rather than a private hospital setting given the requirement for intravenous administration and that short stay admission into hospital may be needed. The PBAC further noted that the process of administering intravenous infusions for children may be difficult and the submission's estimated MBS administration cost for intravenous infusions is underestimated. The full costs will vary greatly for a small child compared to an adolescent, as a small child will require closer monitoring and supervision and possibly sedation and anaesthesia for the insertion of the IV cannula. The PBAC also noted that an admitted patient (inpatient) would not be eligible for PBS-subsidisation under Section 100 HSD funding arrangements.

The PBAC accepted the submission's claim of non-inferiority of tocilizumab in terms of comparative effectiveness over etanercept and adalimumab. The PBAC considered that tocilizumab has a greater risk of adverse events compared with placebo and a different risk of adverse events compared with etanercept and adalimumab.

The PBAC requested that when available, the sponsor provide the PBAC with the outcomes of the European-based double-blind CHARISMA RCT trial that is investigating the safety and efficacy of repeat infusions of tocilizumab alone and in combination with methotrexate for the treatment of rheumatoid arthritis.

Recommendation:
TOCILIZUMAB, concentrate for injection, 80 mg in 4 mL, 200 mg in 10 mL and 400 mg in 20 mL

Extend the current restriction to include:

Restriction: **To be finalised**

Section 100 Highly Specialised Drugs Program
Public and Private Hospital Authority Required

Maximum qty: 1 (all strengths)
Rpt: Nil

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 had no further comment.