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 Ltd
Date of PBAC Consideration: November 2013

1. Purpose of Application

The submission requested a Section 100 (Highly Specialised Drugs Program) listing for the treatment of active polyarticular course juvenile idiopathic arthritis (JIA) as a single-agent or in combination with methotrexate.

This application was submitted under the TGA/PBAC parallel process. At the time of PBAC consideration the TGA Clinical Evaluation, Delegates' Overview and ACPM outcome were available.

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

The TGA registration of tocilizumab was extended on 11 October 2013 to include the treatment of moderate to severe active polyarticular juvenile idiopathic arthritis in patients 2 years of age and older who have had an inadequate response to or intolerance to methotrexate.

Tocilizumab is also TGA registered for the following indications:

- 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.
- Treatment of active systemic juvenile idiopathic arthritis in a patient two years of age and older. Tocilizumab can be given alone or in combination with methotrexate.

4. Listing Requested and PBAC's View

Listing was requested for the treatment of active polyarticular course JIA in:

1) a patient under 18 years of age; and

2) a patient aged 18 years or older who has a documented history of severe active juvenile idiopathic arthritis with onset prior to the age of 18 years; who meets certain criteria.

The submission also requested that the same interchangeability arrangement between tumour necrosis factor alpha (TNF) inhibitors, repeat prescriptions and assessment of response for adalimumab and etanercept be applied to tocilizumab.

Listing was requested on a cost-minimisation basis on claims of non-inferiority in terms of comparative effectiveness and non-inferiority in terms of comparative safety over etanercept and adalimumab.

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. Polyarticular active course JIA (pJIA) is a subset of JIA.

The submission proposed that the place in therapy of tocilizumab is as an alternative treatment option for patients with pJIA.

6. Comparator

The submission nominated etanercept and adalimumab as comparators. The PBAC accepted the nominated comparators for tocilizumab as being appropriate.

7. Clinical Trials

The submission presented three randomised trials as an indirect comparison of tocilizumab with etanercept and adalimumab; tocilizumab compared to placebo in 188 patients with pJIA (CHERISH); etanercept compared to placebo in 69 patients (Lovell, 2000) and adalimumab compared to placebo in 160 patients (Lovell, 2008).

All three trials included an initial open label phase (16 weeks: tocilizumab, 12 weeks: etanercept, 16 weeks: adalimumab) followed by a double blind phase (24 weeks: tocilizumab, 16 weeks: etanercept, 32 weeks: adalimumab) and open label extension phase.

The published trials and associated reports presented in the submission are shown in the following table:

Trials and associated reports presented in the submission

Trial	Description	Reports
Tocilizumab		
WA19977 (CHERISH)	Phase III, randomised, double-blind, placebo-controlled trial	Clinical Study Report – WA19977: A 24-week Randomised Double-Blind, Placebo Controlled Withdrawal Trial With a 16-week Open-Label Lead-In Phase, and 64-week Open-Label Follow-Up, to Evaluate the Efficacy and Safety of Tocilizumab in Patients with Active Polyarticular Juvenile Idiopathic Arthritis – Research Report No. 1045083 – May 2012
Etanercept		
Lovell et al. (2000)	Randomised, double-blind, placebo-controlled trial	Lovell DJ, Giannini EH, Reiff A R et al. Etanercept in children with polyarticular juvenile rheumatoid arthritis. *N Engl J Med,* 2000;342(11):763-769.
Adalimumab		
Lovell et al. (2008)	Randomised, double-blind, placebo-controlled trial	Lovell DJ, Ruperto N, Goodman S et al. Adalimumab with or without methotrexate in juvenile rheumatoid arthritis. *N Engl J Med,* 2008;359(8):810-820.

The outcome measures in the trials are presented in the table below.

Trial	Primary outcome(s)	Secondary outcome(s)
WA19977 (CHERISH)	Proportion of patients with disease flare during the double-blind period Disease flare defined as a worsening of ≥30% in at least three of the six core components of the JIA ACR and an improvement of ≥30% in no more than one of the core components	Proportion of patients with JIA ACR30, ACR50, ACR70 and ACR90 response at the end of the double-blind period (at 40 weeks)
Etanercept Lovell et al (2000)	Proportion of patients with disease flare during the double-blind period Disease flare defined as worsening of ≥30% in three of the six core component of the JIA ACR and a minimum of two active joints. They also could have improvement of ≥30% in no more than one of the six core components	Proportion of patients with JIA ACR30, ACR50 and ACR70 response at the end of the double-blind period (at 28 weeks)
Adalimumab trial Lovell et al. (2008)	Proportion of patients with disease flare during the double-blind period. Disease flare defined as a worsening of ≥30% in at least three of the six core components of the JIA ACR and an improvement of ≥30% in no more than one of the core components	Proportion of patients with JIA ACR30, ACR50, ACR70 and ACR90 response at the end of the double-blind period (at 48 weeks)

The PBAC considered that the clinically relevant outcome for benefit is the American College of Rheumatology (ACR) 30 response (30% improvement from baseline in at least 3 of 6 response criteria without a worsening of greater than 30% in 1 remaining response variable). The PBAC recalled that it has previously accepted ACR30 response rates as the primary outcome for JIA patients (etanercept, PBAC 2002 and adalimumab, PBAC 2010),

Public Summary Documents (PSDs) were not available at the time of PBAC consideration of etanercept in 2002

The PSD for the March 2010 PBAC consideration of adalimumab is available on the PBS website.

8. Results of Trials

With regard to comparative effectiveness, the submission presented indirect comparisons based on JIA ACR30 (flare) and ACR30, 50, 70 and 90 responses between tocilizumab and both etanercept and adalimumab.

The results of the indirect comparisons for JIA ACR30 response rate are presented in the tables below.

Indirect Comparison of tocilizumab with or without methotrexate (week 40) and etanercept (week 28) JIA ACR30 response rate

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)
CHERISH	**1.37 (1.08, 1.74)**	61/82 (74.4%)	44/81 (54.3%)			0.59 (0.32, 1.09)
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

Indirect Comparison of tocilizumab with or without methotrexate (week 40) and adalimumab with or without methotrexate (week 48) JIA ACR30 response rate

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)
CHERISH	**1.37 (1.08, 1.74)**	61/82 (74.4%)	44/81 (54.3%)			0.80 (0.51, 1.26)
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 PBAC noted that although both sets of results favoured etanercept and adalimumab relative to tocilizumab, the results indicated that there was no statistically significant difference between tocilizumab and the comparators.

The PBAC also noted that the trial populations of the three trials are different in terms of inflammatory response, prior treatment received and disease severity.

Overall, the PBAC considered that the results of the indirect comparisons for JIA ACR30 were sufficient to support the claim of non-inferiority in terms of comparative effectiveness.

With regard to comparative harms, the PBAC noted that the incidence of adverse events from the CHERISH trial, with no clear difference in the rate of serious adverse events between treatment groups. The most common adverse events were related to infections and infestations followed by musculoskeletal and connective tissue disorders, gastrointestinal disorders, skin and subcutaneous tissue disorders, respiratory, thoracic, and mediastinal disorders, nervous system disorders, and injury, poisoning and procedural complications.

For the double-blind phase, the incidence of adverse events was comparable in the tocilizumab group and the placebo group. There was no statistically significant difference in the incidence of severe adverse events, serious adverse events and treatment-related adverse events compared with placebo.

The submission compared tocilizumab and etanercept and adalimumab in terms of safety. In the etanercept trial, the most common adverse events were injection-site reactions (39% of patients), upper respiratory tract infections (35%), headache (20%), rhinitis (16%), abdominal pain (16%), vomiting (14%), pharyngitis (14%), nausea (12%), gastrointestinal infection (12%), and rash (10%) during the open-label period. During the double-blind period, there were no significant differences in the frequencies of adverse events between patients who received etanercept and those who received placebo. The submission stated that the proportion of patients reporting infusion or injection site reactions appeared higher in the etanercept trial, compared with the proportion of patients experiencing an event in the tocilizumab trial. In both the tocilizumab and etanercept trials, significant decreases in CRP levels from baseline to week 12 were observed in patient groups treated with the active drug.

In the adalimumab trial, a total of 422 events at a rate of 15.5 events per patient-year were reported in patients receiving methotrexate and 447 events at a rate of 15.3 events per patient-year were reported in patients not receiving methotrexate during the open-label period. During the double-blind period, lower rates were reported regardless of methotrexate use. The rate of adverse events was higher in the adalimumab group compared to the placebo group in patients receiving methotrexate. Conversely, the rate of adverse events was lower in the adalimumab group compared to the placebo group in patients not receiving methotrexate. The most frequently reported adverse events were infections and injection-site reactions, however they were considered to be mild to moderate.

The PBAC recalled its findings that tocilizumab had a greater risk of adverse events compared with placebo and a different risk of adverse events compared with etanercept and adalimumab in its consideration of tocilizumab for treatment of sJIA in November 2011.

The PBAC noted the TGA findings that tocilizumab has an acceptable overall safety profile in the pJIA population.

Furthermore, the PBAC noted that the US Food and Drug Administration (FDA) approved tocilizumab for the treatment of pJIA, however there were issues concerning serious side effects. The risk evaluation and mitigation strategy (REMS) document outlines safety information on known and potential risks of: 1) serious infections; 2) gastrointestinal

perforations; 3) demyelinating disorders; 4) immunosuppression and malignancies; and 5) laboratory abnormalities (hepatic transaminases, lipids, neutrophils, and platelets). The FDA medication guide recommends blood tests every 4 to 8 weeks for pJIA during treatment to check for low neutrophil count, low platelet count and an increase in certain liver function tests. The submission had not considered these costs in its cost-minimisation analysis however; these costs were considered and accounted for during the evaluation.

The PBAC considered that the comparative safety of tocilizumab was difficult to assess in the absence of head-to-head trial data and this limited the conclusions that may be drawn from the evidence. The PBAC noted, however, that tocilizumab has a greater risk of adverse events (infections, GI disorders etc.) compared with placebo and that the lipid profile changes are concerning although no associated increase in cardiovascular risk has been described.

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 or 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 based on the indirect comparison of tocilizumab and etanercept using placebo as a common comparator. The submission stated that a cost-minimisation basis based on a comparison of tocilizumab and adalimumab was not conducted as adalimumab has been shown to be equi-effective and of equivalent cost to etanercept. The PBAC considered this was appropriate.

The PBAC accepted the estimated equi-effective doses as tocilizumab 8 mg/kg for bodyweight 30 kg or more and 10 mg/kg for bodyweight less than 30 kg every 4 weeks and etanercept 0.4 mg/kg up to a maximum of 25 mg twice weekly. These were the dose regimens specified in the draft Product Information (PI) and used in the clinical trials.

The submission compared the total costs of tocilizumab with the total costs of etanercept therapy, and extrapolated the conclusions to the comparison of tocilizumab and adalimumab. The equi-effective dose of adalimumab was 20 mg for bodyweight of 15 kg to less than 30 kg, and 40 mg for bodyweight of 30 kg or more fortnightly. The PBAC considered this approach was appropriate, given the previous acceptance of the equi-effectiveness and equivalent costs of etanercept and adalimumab.

The PBAC agreed that monitoring costs of tocilizumab treatment particularly the frequency of blood tests (as per FDA medication guide conducted every 4-8 weeks) and co-administered medications (e.g. methotrexate) should be included in the total costs of treatment with tocilizumab.

11. Estimated PBS Usage and Financial Implications

The submission estimated that a total of less than 1,000 patients would be treated with tocilizumab over the first 5 years of listing, with estimated total net savings to the PBS of less than $10 million.

The PBAC noted that the submission's assumption of the prescriptions per year implied 100% adherence to the treatment regimen and considered this was unlikely to be realised. Therefore the PBAC considered that the proposed savings may be overestimated in the submission. In addition the additional costs associated with testing and drug treatment associated with adverse effects of tocilizumab had not been considered and would also result in an overestimate of savings to the PBS/RPBS.

12. Recommendation and Reasons

The PBAC recommended listing of tocilizumab on the PBS in the Section 100 (Highly Specialised Drugs Program) as a Public and Private Hospital Authority Required benefit for the treatment of active polyarticular course juvenile idiopathic arthritis (JIA) as a single-agent or in combination with methotrexate, on a cost-minimisation basis compared with etanercept and adalimumab. The equi-effective doses estimated are:

- tocilizumab: 10 mg/kg of body weight for patients less than 30 kg and 8 mg/kg for patients more than 30 kg, IV administration every 4 weeks, 16 week cycles compared with
- adalimumab: 20 mg for patients with body weight between 15 kg to less than 30 kg and 40 mg for patients with body weight 30 kg or more fortnightly as a SC injection, 16 week cycles compared with
- etanercept: 0.4 mg/kg up to 25 mg sub-cutaneously twice weekly 0.4 mg/kg (up to a maximum of 25 mg) twice weekly, subcutaneously, 16 week cycles.

The PBAC agreed that the comparators etanercept and adalimumab are appropriate for patients with active polyarticular course juvenile idiopathic arthritis (JIA).

The PBAC considered that, in terms of comparative benefit, although the results of the indirect comparison for JIA ACR30 both favoured etanercept and adalimumab relative to tocilizumab, the difference was not statistically significant.

However, in terms of comparative safety, the PBAC considered that the comparative safety of tocilizumab was difficult to assess in the absence of head-to-head trial data and this limited the conclusions that may be drawn from the evidence. The PBAC considered that the adverse events monitoring costs (as per the FDA medication guide recommends blood tests every 4 to 8 weeks for pJIA during treatment to check for low neutrophil count, low platelet count and an increase in certain liver function tests) should be considered in the cost-minimisation analysis.

As in its November 2011 consideration of tocilizumab for systemic JIA, the PBAC considered that paediatric patients receiving tocilizumab will most likely be treated in public rather than 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 patients may be difficult and the full costs will vary greatly for a small child compared to an adolescent as a small child will requires 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 considered that tocilizumab remains unsuitable for inclusion in the list of PBS medicines for prescribing by nurse practitioners.

The Safety Net 20 Day Rule should not apply.

In accordance with subsection 101 3BA of the National Health Act 1953, the PBAC advised the Minister that it is of the opinion that, on the basis of the material available to its November 2013 meeting, tocilizumab concentrate for injection should not be treated as interchangeable on an individual patient basis with any other drug(s) or medicinal preparation(s).

Outcome:
Recommended

The recommended restriction will be available on the PBS website once listing occurs.

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

Roche is pleased that a treatment with another mechanism of action will be available for children with pJIA.