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 2013

1. Purpose of Application

The submission requested amendment of the NOTE attached for the severe rheumatoid arthritis listings that states which biological disease-modifying anti-rheumatic drugs (bDMARDs) must be used in combination with methotrexate to be PBS subsidised, and specifies which bDMARDs do not necessarily have to be used in combination with methotrexate to be PBS subsidised.

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 its November 2009 meeting the PBAC recommended that tocilizumab monotherapy be listed for the treatment of severe, active rheumatoid arthritis in patients who have failed to demonstrate a response to at least one TNF-alfa antagonist treatment on a cost-minimisation basis compared to etanercept. .

At the March 2010 PBAC meeting, the PBAC recommended amending the recommended restriction for the section 100 (Highly Specialised Drugs Program) listing of tocilizumab as a pharmaceutical benefit to allow first line use for the treatment of severe active rheumatoid arthritis whether when used as monotherapy or in combination with methotrexate.

3. Registration Status

Tocilizumab 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 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.'

Tocilizumab is also registered by the TGA for the following:

- Systematic juvenile idiopathic arthritis in patients 2 years of age and older, alone or in combination with methotrexate.

4. Listing Requested and PBAC's View

The submission did not request a change to the restriction for the use of tocilizumab in rheumatoid arthritis. The requested change is a change to the wording of the NOTE accompanying the restriction only.

For the complete listing, please refer to www.pbs.gov.au

Section 100 Highly Specialised Drugs Program

Requested change to Note (no changes to restriction wording):

'PBS-subsidised abatacept, golimumab, infliximab and rituximab must be used in combination with methotrexate at a dose of at least 7.5 mg weekly. Where a patient has had an inadequate response to DMARDs (including methotrexate) and/or where a patient cannot tolerate 7.5 mg of methotrexate weekly, they are eligible to receive PBS-subsidised tocilizumab. Where a patient cannot tolerate 7.5 mg of methotrexate weekly, they are eligible to receive PBS-subsidised adalimumab, certolizumab pegol, etanercept and tocilizumab.'

5. Clinical Place for the Proposed Therapy

The clinical place for tocilizumab was use in severe active rheumatoid arthritis. Rheumatoid arthritis is an inflammatory disorder, typically featuring a destructive peripheral symmetrical inflammatory arthritis. Tocilizumab is one of six biological disease-modifying anti-rheumatic drugs (bDMARDs) currently listed on the PBS for severe rheumatoid arthritis in adults.

The submission proposes a change to the NOTE which will allow tocilizumab to be used as monotherapy in patients who are not intolerant to MTX.

The submission claimed that the change to the NOTE would allow patients access to tocilizumab monotherapy where continued treatment with MTX is considered inappropriate and not limit access to only MTX-intolerant patients

The PBAC noted that the current PBS listing already permits access to tocilizumab monotherapy. The PBAC considered that the term "inappropriate for MTX" could be subject to wide interpretation by prescribers.

6. Comparator

The submission nominated tocilizumab and methotrexate (MTX) combination therapy as the comparator. The PBAC agreed that this is the appropriate comparator.

7. Clinical Trials

The submission presented three randomised trials comparing tocilizumab with or without placebo and combination tocilizumab with methotrexate or DMARD in 1,174 patients with severe active rheumatoid arthritis.

The ACT-RAY trial is a phase III randomised controlled multicentre double blind trial in patients with moderate to severe active rheumatoid arthritis who have inadequate response to

prior methotrexate. ACT-RAY was designed as a superiority trial, comparing tocilizumab in combination with MTX to tocilizumab monotherapy.

The ACT-STAR is an open label multicentre partly randomised phase III trial to evaluate safety and tolerability and efficacy of tocilizumab monotherapy compared to tocilizumab in combination with another DMARD. Patients could be bDMARD treatment experienced and were eligible if they had poor response or tolerability to the prior treatment; either a) DMARD plus bDMARD b) DMARD monotherapy or c) bDMARD monotherapy. The study randomly assigned patients in a) or b) to receive tocilizumab 4 mg/kg or 8 mg/kg plus DMARD and the group c patients received tocilizumab 8 mg/kg.

The CHARISMA trial is a 16 week phase II double blind randomised 7 arm study comparing different doses of tocilizumab monotherapy, and tocilizumab in combination with MTX compared to MTX only in people with inadequate response to MTX.

The table below details the published trials presented in the submission.

Trial ID/ First author	**Protocol title/ Publication title**	**Publication citation**
ACT-RAY (MA21488)	Statistics Report; week 24 interim analysis – Randomized placebo-controlled study to evaluate the safety and efficacy of adding tocilizumab (TCZ) to methotrexate (MTX) versus switching to TCZ (placebo-controlled), with possible addition of other disease-modifying antirheumatic drugs (DMARDs), in patients with active rheumatoid arthritis who have inadequately responded to prior MTX treatment.	Statistics report: July 2011.
	Protocol for MA21488: Randomized placebo-controlled study to evaluate the safety and efficacy of adding tocilizumab (TCZ) to methotrexate (MTX) versus switching to TCZ (placebo-controlled), with possible addition of other disease-modifying anti-rheumatic drugs (DMARDs), in patients with active rheumatoid arthritis who have inadequately responded to prior MTX treatment.	Protocol:MA21488 Dec 2010
	Dougados M, Kissel K, Sheeran T et al. Adding tocilizumab or switching to tocilizumab monotherapy in methotrexate inadequate responders: 24-week symptomatic and structural results of a 2-year randomised controlled strategy trial in rheumatoid arthritis (ACT-RAY).	*Annals of the Rheumatic Diseases* 2012. Published online as 10.1136/ annrheumdis-2011-201282.

ACT-STAR (ML22533B)	Clinical Study Report – ML 22533B: An open-label, randomized study to evaluate the safety, tolerability and efficacy of tocilizumab (TCZ) monotherapy or TCZ in combination with non-biologic DMARDs in patients with active rheumatoid arthritis who have an inadequate response to current non-biologic or biologic DMARDs.	Research Report No. 1043045. October 2011.
	Weinblatt ME, Kremer ME, Cush, JM et al. Efficacy and safety of tocilizumab as monotherapy or in combination with nonbiologic disease-modifying antirheumatic drugs: A 24-week randomized study in a United States population.	*Arthritis and Rheumatism* 2011;63(10):SUPPL. 1. October 2011.
CHARISMA	Clinical Study Report – LRO 301: A double-blind, randomised, parallel group, dose ranging study of the safety, tolerability, pharmacokinetics and efficacy of repeat doses of MRA given alone or in combination with methotrexate in patients with rheumatoid arthritis.	June 2004.
	Maini RN, Taylor PC, Szechinski J et al. Double-blind randomized 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* 2006;54(9):2817-2829.

The eligible PBS population are those who are able to tolerate MTX as prior therapy but seek to discontinue MTX in conjunction with a bDMARD (i.e. tocilizumab monotherapy).

The PBAC noted that the sponsor's pre-subcommittee response (PSCR) presented new trial results from the TEMPO1 trial comparing etanercept with and without MTX and the ADACTA trial comparing tocilizumab monotherapy with adalimumab monotherapy. These trials were not presented in the submission and were therefore not included in the initial evaluation.

8. Results of Trials

The ACT-RAY trial was considered to provide results with a low risk of bias and that can be generalised to the current PBS population as the study population had prior treatment with MTX, albeit for a slightly shorter time than that required by the current PBS restriction. The PBAC considered it to provide a robust basis for assessing the submission's claims.

The PBAC noted a significant risk of bias in the ACT-STAR trial due to a lack of random allocation to the tocilizumab monotherapy arm, the open-label design of the trial, incomplete outcome data, and the fact that as a safety trial the efficacy outcomes were secondary outcomes.

The PBAC noted incomplete outcome data from the CHARISMA trial (16.7% missing data) with no detail on the analysis.

The sponsor claimed that the results of the TEMPO1 and ADACTA trials, not provided in the submission but in the PSCR, demonstrate that tocilizumab is the bDMARD of choice for bDMARD monotherapy. The PBAC considered that this claim was different from the stated purpose of the submission, and that these trials were therefore not relevant to its considerations.

The submission presented outcomes as ACR50 (a composite outcome for a 50% improvement in American College of Rheumatology (ACR) score) and Disease activity score for 28 joints (DAS28) less than 2.6. The PBAC has previously acknowledged ACR50 as the preferred clinically relevant outcome in this therapeutic area. The PBAC also considered DAS28 to be a common and relevant outcome for rheumatoid arthritis.

The table below presents the results of ACR response rates at 24 weeks across the direct randomised trials:

Trial ID	TCZ[1] n/N (%)	TCZ + MTX/DMARD n/N (%)	RD (95% CI)	RR (95% CI)	NNT/NNH (95% CI)
ACR20					
ACT-RAY	195/276 (70.7%)	199/277 (71.8%)	−1.19% (−8.73%, 6.36%)	0.98 (0.89, 1.09)	NNH 84 (NE)
ACT-STAR	78/135 (58.7%)	178/312 (57.1%)	0.7% (−9.3%, 10.7%)	1.01 (0.85, 1.20)	NNT 138 (NE)
CHARISMA [2]	32/51 (62.7%)	36/49 (73.5%)	−10.7% (−28.9%, 7.4%)	0.85 (0.65, 1.12)	NNH 9 (NE)
ACR50					
ACT-RAY	113/276 (40.9%)	125/277 (45.1%)	−4.2% (−12.4%, 4.1%)	0.91 (0.75, 1.10)	NNH 24 (NE)
ACT-STAR	40/135 (29.6%)	97/312 (31.1%)	−1.5% (−10.7%, 7.8%)	0.95 (0.70, 1.30)	NNH 68 (NE)
CHARISMA [2]	21/51 (41.2%)	26/49 (53.1%)	−11.9% (−31.3%, 7.6%)	0.78 (0.51, 1.18)	NNH 8 (NE)
ACR70					
ACT-RAY	71/276 (25.7%)	69/277 (24.9%)	0.8% (−6.4%, 8.1%)	1.03 (0.78, 1.38)	NNT 123 (NE)
ACT-STAR	12/135 (7.4%)	37/312 (10.3%)	−3.0% (−9.0%, 3.0%)	0.75 (0.40, 1.40)	NNH 34 (NE)
CHARISMA [2]	8/51 (15.7%)	18/49 (36.7%)	**−21.1% (−37.8%, −4.3%)**	**0.43 (0.21, 0.89)**	**NNH 5 (3, 23)**
DAS28 < 2.6					
ACT-RAY	96/276 (34.8%)	112/277 (40.4%)	-5.7% (-13.7%, 2.4%)	0.86 (0.69, 1.07)	NNH 18 (NE)
ACT-STAR	25/126 (19.8%)	76/302 (25.2%)	-5.3% (-13.8%, 3.2%)	0.79 (0.53, 1.18)	NNH 19 (NE)
CHARISMA [2]	9/51 (17%)	17/49 (34%)	**-17.1% (-34.0%, -0.1%)**	0.51 (0.25, 1.03)	**NNH 6 (3, 1000)**

ACR = American College of Rheumatology, CI = confidence interval; DMARD = disease-modifying anti-rheumatic drug; MTX = methotrexate; TCZ = tocilizumab; NE = non-evaluable; NNH = number needed to harm; NNT = number needed to treat; RD = risk difference; RR = relative risk;
bolded = significant

1. The ACT-RAY monotherapy TCZ arm included Placebo.
2. CHARISMA results are at 16 weeks.

The results show that tocilizumab monotherapy and tocilizumab combination therapy with MTX or DMARD are not statistically significantly different for ACR improvements or DAS28 remission rates.

The PBAC noted in the CHARISMA trial that the ACR70 and DAS28 improvement results favoured tocilizumab/MTX combination therapy. The PBAC viewed these results with caution, noting the 16-week end-point for this trial as opposed to the 24-weeks for the other two trials.

In ACT-RAY and CHARISMA, improvements in ACR20, ACR50 and DAS remission were numerically better in the tocilizumab combination therapy arms than tocilizumab monotherapy, albeit not statistically significantly different.

Overall, the PBAC considered that tocilizumab monotherapy is non-inferior to tocilizumab with MTX.

With regard to comparative harms, the major harms associated with tocilizumab use are infections and infestations. In addition to serious infections, a systematic review of tocilizumab safety reported an increased frequency of neutropenia, thrombocytopenia, hyperlipidaemia and elevations of transaminase levels observed with tocilizumab compared with placebo (Navarro-Millán I et al. 2012).

Tocilizumab is associated with increased liver enzymes (ALT levels) and hypercholesterolemia that are not recorded by other first-line bDMARDs. For MTX, the most common adverse events reported include ulcerative stomatitis, leukopenia, nausea and abdominal symptoms. Others reported are malaise, undue fatigue, chills and fever, headaches, dizziness, drowsiness, tinnitus, blurred vision, eye discomfort and decreased resistance to infection (MTX PI, 29th March 2010). The occurrence and severity of these adverse events are believed to be dose and frequency related.

The majority of patients in the trials experienced at least one adverse event but only a small proportion of patients had serious adverse events. Some patients suffered serious infections, according to MedDRA baskets by Roche Pharmaceutical Department, which does not take into account System Organ Class criteria.

Dose interruptions were common mostly due to adverse events. The ACT-RAY trial indicated a protective effect of tocilizumab monotherapy for dose interruptions, high liver enzymes (alanine and aspartate aminotransferase levels) but also significantly worse low platelets. No new safety concerns relating to tocilizumab were revealed in the three trials. The low incidence of serious adverse events was consistent with a recent systematic review on tocilizumab safety (Navarro-Millán I et al. 2012). Overall, the evidence shows mixed results for specific and general adverse events and abnormal laboratory parameters. A more appropriate claim may be no worse safety profile.

In the latest Periodic Safety Update Report period (Oct 2011 to Apr 2012), the most frequently reported serious adverse events were infections and infestations, gastrointestinal disorders and general disorders and administration site conditions. The submission claims no

change to current safety information is warranted at this time. The PBAC considered this reasonable.

9. Clinical Claim

The submission described tocilizumab monotherapy as no worse than tocilizumab combination therapy in terms of comparative effectiveness and better or no worse than tocilizumab combination therapy in terms of comparative safety.

The PBAC considered it reasonable on the evidence presented to accept that tocilizumab monotherapy is non-inferior to tocilizumab with MTX.

The PBAC considered that although there are no statistically significant differences in outcomes between patients treated with tocilizumab with MTX compared to tocilizumab without MTX, patients who can tolerate MTX appear to consistently achieve better outcomes than patients using tocilizumab monotherapy. The PBAC noted emerging views that the effect of MTX in this combination may be to suppress the development of tocilizumab antibodies, thereby preserving the clinical effectiveness of tocilizumab.

10. Economic Analysis

The submission presented a cost-minimisation analysis based on non-inferiority for ACR response outcomes.

The submission considered 8 mg/kg IV tocilizumab monotherapy every four weeks to be equi-effective to 8 mg/kg IV tocilizumab every four weeks with 15 mg MTX weekly. The submission assumed a MTX dose of 15 mg weekly based on the average dose of MTX in the ACT-RAY clinical trial (15.3 mg).

The submission presented a 'fit-for-purpose' evaluation and included only the drug acquisition costs for MTX, intended to represent the cost-savings of tocilizumab monotherapy.

The submission reported the cost-savings per year per patient for receiving tocilizumab monotherapy without methotrexate. This does not take into account other DMARDs that may be used concurrently with tocilizumab monotherapy.

11. Estimated PBS Usage and Financial Implications

The submission estimated that the number of additional patients to receive tocilizumab monotherapy is less than 10,000 in Year 5.
The submission assumed only new patients eligible for bDMARDs should be included in the figures for proposed tocilizumab monotherapy; however the method of derivation of the estimates was unclear and could not be verified. The PBAC considered it possible that switching would occur in patients currently receiving bDMARD combination therapy, potentially underestimating patients on tocilizumab monotherapy.

The PBAC considered it possible for the market share for tocilizumab to increase if prescribers infer from the revised note that this product has some advantage over other

bDMARDs that can be used as monotherapy. The PBAC considered that no evidence was presented to support any benefit of tocilizumab over the alternative bDMARDs.

The submission estimated total net cost savings to the PBS of less than $10 million over the first 5 years on the basis of a reduction in the need to prescribe MTX, and because tocilizumab is less expensive than other bDMARDs. As bDMARD monotherapy is already available to patients, the PBAC considered that the savings predicted from the reduction in MTX prescriptions would be unlikely to be realised.

The submission projected a net cost to State and Federal budgets for the cost of administration of tocilizumab monotherapy. The submission claimed that these costs be offset by the Sponsor's community-based ACTiv Infusion Program. These cost offsets could not be verified during evaluation, therefore the PBAC considered the cost offsets unreliable.

The financial implications are to be further verified.

12. Recommendation and Reasons

The PBAC rejected the sponsor's suggested change to the NOTE.

The PBAC considered that although the sponsor had presented clinical evidence establishing the non-inferiority of tocilizumab monotherapy to tocilizumab with MTX, the current PBS restriction already permits the use of tocilizumab monotherapy; however, it is limited to where the patient has a contraindication or intolerance to MTX.

The PBAC considered that the sponsor's stated intent to allow access to patients considered "inappropriate for MTX" could lead to wider than anticipated interpretations of "inappropriate". The risk of unpredictable utilisation patterns driven by such interpretations was noted by the PBAC.

Notwithstanding the sponsor's claim regarding prescriber confusion regarding the intent of the NOTE, the sponsor was not able to establish that such confusion was indeed occurring.

The PBAC did not accept the sponsor's claim that the suggested change to the NOTE would result in savings to the Commonwealth, noting that the current restriction already permits the use of tocilizumab as monotherapy.

The PBAC considered that were the NOTE to be amended as suggested, it may lead prescribers to infer that tocilizumab monotherapy has a clinical advantage over the other PBS-subsidised bDMARDs which can also be used as monotherapy (adalimumab, certolizumab pegol and etanercept). The PBAC did not consider that the evidence in the submission supported such a conclusion.

The PBAC considered that the intention of the listing was adequately captured by the text of the restriction. The PBAC further considered that as medical practitioners prescribing bDMARDs for rheumatoid arthritis are specialists with significant experience with this class of drugs, the section of the NOTE highlighted by the sponsor added little value to the restriction wording.

The PBAC therefore recommended that the following section of the NOTE be deleted:

> 'PBS-subsidised abatacept, golimumab, infliximab and rituximab must be used in combination with methotrexate at a dose of at least 7.5 mg weekly. Where a patient cannot tolerate 7.5 mg of methotrexate weekly, they are eligible to receive PBS-subsidised adalimumab, certolizumab pegol, etanercept and tocilizumab.'

Recommended listing

Deletion of the portion of the NOTE and reformatting of the restriction 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 is pleased that the PBAC accepted that tocilizumab monotherapy is non-inferior to tocilizumab with methotrexate, and welcomes the removal of the NOTE in the restriction to increase the clarity for the prescriber in the appropriate use of monotherapy. The sponsor is considering a submission assessing the clinical benefit of tocilizumab monotherapy over other bDMARD monotherapy, based on the ADACTA trial data.