Australian Government
Department of Health
Therapeutic Goods Administration

Australian Public Assessment Report for tocilizumab (rch)

Proprietary Product Name: Actemra

Sponsor: Roche Products Pty Ltd

January 2015

TGA Health Safety Regulation

About the Therapeutic Goods Administration (TGA)

- The Therapeutic Goods Administration (TGA) is part of the Australian Government Department of Health and is responsible for regulating medicines and medical devices.
- The TGA administers the *Therapeutic Goods Act 1989* (the Act), applying a risk management approach designed to ensure therapeutic goods supplied in Australia meet acceptable standards of quality, safety and efficacy (performance), when necessary.
- The work of the TGA is based on applying scientific and clinical expertise to decision-making, to ensure that the benefits to consumers outweigh any risks associated with the use of medicines and medical devices.
- The TGA relies on the public, healthcare professionals and industry to report problems with medicines or medical devices. TGA investigates reports received by it to determine any necessary regulatory action.
- To report a problem with a medicine or medical device, please see the information on the TGA website <http://www.tga.gov.au>.

About AusPARs

- An Australian Public Assessment Record (AusPAR) provides information about the evaluation of a prescription medicine and the considerations that led the TGA to approve or not approve a prescription medicine submission.
- AusPARs are prepared and published by the TGA.
- An AusPAR is prepared for submissions that relate to new chemical entities, generic medicines, major variations, and extensions of indications.
- An AusPAR is a static document, in that it will provide information that relates to a submission at a particular point in time.
- A new AusPAR will be developed to reflect changes to indications and/or major variations to a prescription medicine subject to evaluation by the TGA.

Contents

List of the most common abbreviations used in this AusPAR

Abbreviation	Meaning
ACR	American College of Rheumatology
ACR20	20% improvement in ACR score
ACR50	50% improvement in ACR score
ACR70	70% improvement in ACR score
ADR	Adverse Drug Reaction
AE	Adverse Event
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
AUC	Area Under the Curve (drug concentration-time curve)
CCP	Cyclic citrullinated peptide
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence interval
CMI	Consumer Medicine Information
Cmax	Maximum concentration
CrCL	Creatinine clearance
CRP	C-reactive protein
CSR	Clinical Study Report
CTC	Common Toxicity Criteria
CYP450	Cytochrome P450
DAS28	Disease Activity Score 28
DMARD	Disease Modifying Anti-Rheumatic Drug
EMA	The European Agency for the Evaluation of Medicinal Products
ESR	Erythrocyte sedimentation rate
EULAR	European League Against Rheumatism

Abbreviation	Meaning
FDA	Food and Drug Administration
HAQ	Health Assessment Questionnaire
IL-6	Interleukin-6
IL-6R	Interleukin-6 receptor
IR	inadequate responder
IV	Intravenous
LFT	Liver function test
MTX	Methotrexate
NSAID	Non-steroidal anti-inflammatory drug
PD	Pharmacodynamics
PI	Product Information
pJIA	Polyarticular juvenile idiopathic arthritis
PK	Pharmacokinetics
PMS	Post-Marketing Surveillance
PP	Per protocol
PSUR	Periodic Safety Update Report
PY	Patient-years/person-years
RA	Rheumatoid arthritis
RF	Rheumatoid factor
RMP	Risk Management Plan
RR	Relative risk
SAE	Serious adverse event
SC	Subcutaneous
SJC	Swollen joint count
sJIA	Systemic onset juvenile idiopathic arthritis
SPC	Summary of Product Characteristics

Abbreviation	Meaning
TCZ	Tocilizumab
TEAE	Treatment emergent adverse event
TJC	Tender joint count
TNF	Tumour necrosis factor
Tmax	Time to maximum plasma concentration
ULN	Upper limit of normal
US	United States
VAS	Visual analogue scale
VASP	Physicians global score of disease activity at baseline

Efficacy endpoints and assessments used in clinical trials of tocilizumab:

DAS28

The Disease Activity Score 28 (DAS28) score is a composite score derived using the following formula:

DAS28 = (0.56 * $\sqrt{}$ 28TJC) + (0.28 * $\sqrt{}$ 28SJC) + (0.70 * ln ESR) + (0.014 * GH)

where 28TJC = tender joint count from 28 joints; 28SJC = swollen joint count from 28 joints; ESR = erythrocyte sedimentation rate; GH = patient's global assessment. A DAS28 score of < 2.6 represents one definition of clinical remission. A score of < 3.2 represents low disease activity, and a score of > 5.1 represents high disease activity.

ACR20/ACR50/ACR70 response

The ACR20, ACR50, and ACR70 responses are based on response criteria as defined by the American College of Rheumatology (ACR); an exploratory analysis of ACR90 responses was also performed. ACR responses are based on a core set of outcome measures combined to quantify disease activity (continuous variables), together with definitions of improvement (response variables). An ACR20 response is defined as achievement of at least 20% improvement compared to baseline in both Tender joint count (TJC) and Swollen joint count (SJC), as well as in three out of five of the additional ACR parameters. The endpoints of ACR50 and ACR70 responses reflect a 50% and a 70% improvement from baseline, respectively.

EULAR response

The European League Against Rheumatism (EULAR) response reflects attainment of a lower degree of disease activity combined with an improvement in disease activity from baseline. For example, a good response is defined as an improvement in the DAS28 of more than 1.2 compared with baseline, and attainment of a DAS28 of ≤ 2.6.

ACR/EULAR remission

In 2011, after initiation of the WA19926 study, ACR and EULAR issued a joint agreement with two new definitions for remission for use in clinical trials (Felsom et al. 2011[1]):

- A Boolean-based definition, in which the following must be satisfied at the same visit with no imputation made for missing data: TJC (68) ≤ 1, SJC (66) ≤ 1, Patients Global Assessment of Disease Activity (cm) ≤ 1 and C-reactive protein (CRP) ≤ 1 mg/dL).
- An index-based definition, dependent on the patient achieving a Simplified Disease Activity Index (SDAI) score of ≤ 3.3 (SDAI was defined above as the sum of TJC (28), SJC (28), Patient's Global Assessment of Disease Activity (visual analog scale [VAS], cm), Physician's Global Assessment of Disease Activity (VAS, cm) and CRP (mg/dL).

Clinical disease activity index

The Clinical Disease Activity Index (CDAI) is a continuous measure of RA disease activity. CDAI is defined as the sum of 28TJC, 28SJC, Patient's Global Assessment of Disease Activity (cm), and Physician's Global Assessment of Disease Activity (cm). CDAI scores of >22 are considered indicative of high disease activity, 10.1-22 moderate disease activity, 2.8-10 low disease activity, and < 2.8 remission. CDAI remission is widely used in clinical practice because it is a simplified score and does not include the use of an acute phase reactant (CRP or ESR).

Radiographic assessments

The radiographic assessments in Study WA19926 were the total Sharp score (mTSS), erosion score, and joint space narrowing (JSN) score using the scoring method developed by van der Heijde DM, 2000[2].

Radiographs of hands/wrists and feet were taken at screening, Weeks 24, 52 and 104. For patients who terminated early, hands/wrists and feet radiographs were to be at the time of premature withdrawal. Patients who withdrew from study were asked to return at 24, 52 and 104 weeks for radiographic studies.

HAQ-DI

The Stanford Health Assessment Questionnaire Disability Index (HAQ-DI) is a patient completed questionnaire specific for RA, consisting of a total of 20 questions divided into eight sets of components: dressing/grooming, arising, eating, walking, hygiene, reach, grip, and activity (see WA19926 CSR). The questionnaire was scored based on instructions from the Stanford University Medical Center (Palo Alto, CA; USA).

[1] Felson DT et al. American College of Rheumatology/European League Against Rheumatism provisional definition of remission in rheumatoid arthritis for clinical trials. Arthritis Rheum. 2011;63(3):573-86.
[2] van der Heijde DM. How to read radiographs according to the Sharp/van der Heijde method. *J Rheumatol* 2000;27:261-263.

I. Introduction to product submission

Submission details

Type of submission:	Major variation (extension of indications)
Decision:	Approved
Date of decision:	14 October 2014
Active ingredient:	Tocilizumab (rch)
Product name:	Actemra
Sponsor's name and address:	Roche Products Pty Ltd 4-10 Inman Road Dee Why NSW 2099
Dose form:	Injection concentrated
Strengths:	400 mg/20 mL, 80 mg/4mL, and 200 mg/10 mL
Container:	Vial
Pack sizes:	1 and 4
New approved therapeutic use:	*Rheumatoid Arthritis* *Actemra is indicated for the treatment of moderate to severe active rheumatoid arthritis in adult patients with poor prognostic factors (see Clinical Trials) in combination with MTX in those not previously treated with MTX.*
Route of administration:	Intravenous infusion
Dosage:	Actemra is recommended for IV infusion over 1 h. See approved Product Information at Attachment 1 for *Dosage and Administration*
ARTG numbers:	149402, 149403, 149404

Product background

Tocilizumab (TCZ) is a recombinant, humanised (rch) antihuman, interleukin-6 (IL-6) receptor monoclonal antibody that binds specifically to both soluble and membrane-bound IL-6 receptors, thereby inhibiting IL-6 mediated signalling. Interleukin-6 is a pro-inflammatory, multifunctional cytokine produced by a variety of cell types. Elevated IL-6 levels have been reported in the serum and synovial fluid of patients with rheumatoid arthritis (RA), and IL-6 levels are reported to correlate with disease activity.

Tocilizumab (Actemra) was first registered in Australia in 2009. At the time of the current submission, the approved indications were as follows[3]:

Rheumatoid Arthritis

- *Actemra is indicated 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.*

Actemra has been shown to inhibit the progression of joint damage in adults, as measured by X-ray, when given in combination with methotrexate.

Systemic Juvenile Idiopathic Arthritis

- *Actemra is indicated for the treatment of active systemic juvenile idiopathic arthritis in patients 2 years of age and older. Actemra can be given alone or in combination with methotrexate (MTX).*

This AusPAR describes the application by Roche Products Pty Ltd (the sponsor) to extend the indications for tocilizumab as follows (the proposed amendments are shown in bold font):

Rheumatoid Arthritis

Actemra is indicated for the treatment of moderate to severe active rheumatoid arthritis (RA) in adult patients:

- ***in combination with methotrexate (MTX) in those not previously treated with MTX;***
- *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.*

Actemra has been shown to inhibit the progression of joint damage in adults, as measured by X-ray, when given ***alone or*** *in combination with methotrexate.*

Systemic Juvenile Idiopathic Arthritis

- *Actemra is indicated for the treatment of active systemic juvenile idiopathic arthritis in patients 2 years of age and older. Actemra can be given alone or in combination with methotrexate (MTX).*

The sponsor also proposed amendments to the approved Product Information (PI), including an update to the *Precautions* section. Details of this aspect of the application are beyond the scope of the AusPAR.

[3] In October 2013, the indications for Actemra were further extended via a separate application to include for 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 (MTX). Actemra can be given alone or in combination with MTX.

Regulatory status

The product received initial registration on the Australian Register of Therapeutic Goods (ARTG) on 21 May 2009.

At the time the TGA considered this application, a similar application was under consideration in Canada (submitted December 2013), the European Union (EU; submitted June 2013), New Zealand (submitted October 2013) and Switzerland (submitted July 2013.

Product Information

The approved Product Information (PI) current at the time this AusPAR was prepared can be found as Attachment 1. For the most recent Product Information please refer to the TGA website at <https://www.tga.gov.au/product-information-pi>.

II. Quality findings

There was no requirement for a quality evaluation in a submission of this type.

III. Nonclinical findings

There was no requirement for a nonclinical evaluation in a submission of this type.

IV. Clinical findings

A summary of the clinical findings is presented in this section. Further details of these clinical findings can be found in Attachment 2.

Clinical rationale

Rheumatoid arthritis is a progressive systemic autoimmune disease characterised by inflammation of the synovium leading to irreversible destruction and disability of the joints. The treatment of RA is directed toward the control of synovitis and the prevention of joint injury. Clinical recommendations which support an early aggressive approach to treatment are based upon the observations that joint damage, which may ultimately result in disability, begins early in the course of disease and that the longer active disease persists the less likely the patient is to respond to therapy.

Current therapy consists of anti-inflammatory therapies, including nonsteroidal anti-inflammatory drugs (NSAIDs) and glucocorticoids, to help control symptoms and the disease modifying antirheumatic drugs (DMARDs). In patients with moderately to severely active RA (as defined by at least 5 inflamed joints, elevated acute phase reactants and sometimes early radiographic changes) treatment with a DMARD is recommended. These drugs include methotrexate (MTX) and biologic agents. Most biologic agents for treatment of early RA are tumour necrosis factor (TNF) antagonists. The sponsor states that there is a clinical need for alternative biological agents with different mechanisms of action which can be used in the early RA population. In addition, while MTX is the main DMARD used, some patients may have intolerance or have comorbidities which contraindicate its use. For these reasons TCZ was assessed in combination with MTX and as monotherapy in an early RA population.

Guidance

The following information was provided by the sponsors at the pre-submission stage:

As part of this application the sponsor proposes to revise the existing progression of joint damage claim, as follows: *"Actemra has been shown to inhibit the progression of joint damage in adults, as measured by X-ray, when given alone or in combination with methotrexate."* To support this revision the application includes radiographic data for up to one year of treatment from the WA19926 study. When the study is complete at Week 104, two year radiographic data will also be available. Radiographic data from the previously submitted MRA012JP and the WA17823 studies are also referred to.

The sponsor acknowledges the TGA currently adopts the EMA guideline CPMP/EWP/556/95 Rev 1 *Points to Consider on Clinical Investigation of Medicinal Products other than NSAIDS for Treatment of Rheumatoid Arthritis*, dated December 2003, which includes the following requirement for radiographic data: "For agents which are claimed to prevent structural joint damage, it is currently recommended to demonstrate radiological differences of hands and forefeet on the basis of before/after comparisons taken not less than one year apart ideally for two years using full randomisation and pre-agreed criteria."

However the new draft EMA guideline CPMP/EWP/556/95 Rev 2 *Guideline on clinical investigation of medicinal products other than NSAIDs for the treatment of rheumatoid arthritis*, dated 28 November 2011, has updated this requirement as follows: "Using the existing validated technique to assess radiographic progression, that is, radiographs, measurement after 1 year may be sufficient to confirm efficacy in terms of endpoints relevant to slowing/prevention of structural damage claim. In exceptional cases a measurement after at least 6 months may be sufficient depending on the properties of the test drug; this has to be justified by robustness of the method and convincing clinical data. It is important to demonstrate long-term maintenance of this effect for an additional 12 months".

The sponsor considers sufficient data are provided in this application to address these requirements.

Contents of the clinical dossier

Scope of the clinical dossier

The submission contained the following clinical information:

- One population pharmacokinetics (PK) study (WA17823).
- One Phase III study (WA19926).
- One Phase III extension study (WA18695).
- One Phase IV study (NA25256).
- Literature references.
- Clinical Overview, Summary of Clinical Pharmacology, Summary of Clinical Efficacy, Summary of Clinical Safety, individual study synopses and listing of literature references.

Paediatric data

The submission did not include paediatric data.

Good clinical practice

The studies included in the dossier all included statements that they were conducted in accordance with Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) good clinical practice guidelines as well as local ethical and regulatory requirements.

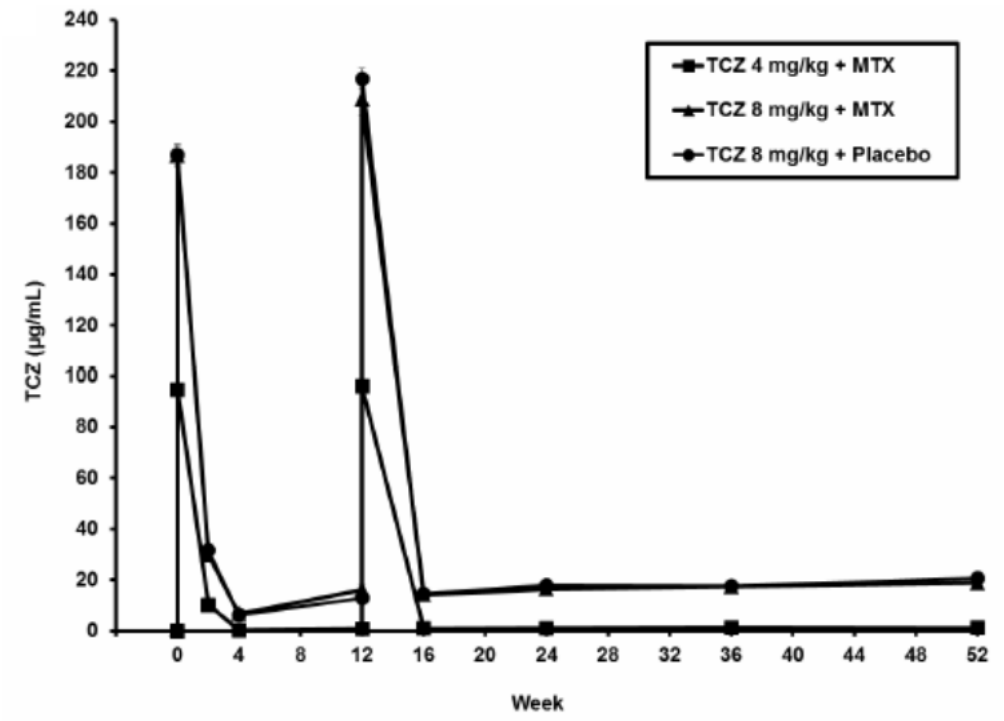
Pharmacokinetics

Studies providing pharmacokinetic data

The dossier included a population PK study report 103077 which was based on samples collected in Study WA17823, a randomised, double-blind, and parallel group study of the safety and prevention of structural joint damage during treatment with TCZ versus placebo, in combination with MTX, in patients with moderate to severe active RA.

Also included was Study WA19926: a Phase III, randomised, double-blind, parallel group study of treatment with TCZ versus placebo, in combination with MTX, in patients with early, moderate to severe active RA. Data were provided to week 52 of treatment. PK analysis found that the mean TCZ pre-dose concentrations levelled from week 16 across the treatment groups (Figure 1).

Figure 1: Mean (SEM) tocilizumab concentrations (µg/mL)



Note: SEMs are not visible for all visits / treatment groups

Steady-state minimum concentration (Cmin) for TCZ in the 4 and 8 mg/kg dose levels were approximately 1 and 17–21 µg/mL, respectively. The maximum concentrations (Cmax) at week 12 were approximately 96 and 209–217 µg/mL at 4 mg/kg and 8 mg/kg TCZ dose levels, respectively. The TCZ PK were comparable between both groups treated with 8 mg/kg TCZ with or without concomitant MTX.

Scatter plots showed no correlation between DAS28 scores at Week 24, or total Sharp score (mTSS) scores at Week 52, and corresponding Cmin values. There was a trend for

increasing proportion of DAS28 responders with increasing quartile(Q) of Cmin from Q1 to Q3 but this did not continue for Q4.

Evaluator's conclusions on pharmacokinetics

The PK data from the 52 week Study WA17823 were adequately described by the reference PK model generated using data from four Phase III 24 week studies. Pharmacokinetics in the early severe RA population were consistent with that observed in RA patients with inadequate response to anti-TNF or other DMARDs.

Pharmacodynamics

Studies providing pharmacodynamic data

The population PK study report 103077 contained data on radiographic findings and TCZ exposure from patients in Study WA17823.

Evaluator's conclusions on pharmacodynamics

The radiograph data from Study WA17823 were presented graphically against categorised TCZ exposure and were suggestive of a possible improvement in modified Sharp score with higher TCZ exposure.

Dosage selection for the pivotal studies

There were no proposed alterations to the current approved dosage regimen of 8 mg/kg given once every 4 weeks as an intravenous (IV) infusion. The maximum dose is 800 mg per infusion. The submitted Trial WA19926 had treatment arms of TCZ 4 mg/kg and 8 mg/kg given by IV infusion every 4 weeks. The primary efficacy analysis was of the 8 mg/kg dose.

Efficacy

Studies providing efficacy data

Pivotal efficacy study of treatment of early RA, MTX naïve patients: Study WA19926

Study WA19926 was Phase III, randomised, double-blind, parallel group study of safety, disease remission, and prevention of structural joint damage during treatment with TCZ as a monotherapy and in combination with MTX, versus MTX, in patients with early, moderate to severe RA. The primary objective was to assess the efficacy of 6 months treatment with TCZ in combination with MTX and TCZ monotherapy versus MTX monotherapy in patients with early, moderate-to severe RA.

Other efficacy studies

The sponsor states that supportive efficacy data for TCZ in an early RA population was provided by Studies WA17824 and MRA012JP. In addition, long term data were available from Study WA17823 and its extension. The studies were summarised in the sponsor's *Summary of Clinical Efficacy*; the clinical study reports were not submitted in this application as they had been included in previous submissions.

Study WA17824 was a Phase III, 24 week, randomised, controlled, non-inferiority study assessing the safety and efficacy of TCZ 8 mg/kg + placebo MTX versus MTX + placebo TCZ in 572 adult patients with active, moderate to severe RA who were MTX naïve or had not

received MTX for 6 months. The primary endpoint was the proportion of patients with ACR20 response at week 24.

Study MRA012JP was a 52 week, unblinded, randomised study of TCZ 8 mg/kg monotherapy compared to conventional DMARD therapy in 306 patients with active RA who had an inadequate response to conventional DMARDs. It was stated that approximately half the patients had an RA duration of ≤ 2 years. The primary endpoint was the mean change in the modified Sharp erosion score at week 52.

Analyses performed across trials (pooled analyses and meta-analyses)

The long term extension (LTE), all-exposure population comprised of data (cut-off date 02 May 2012) pooled from the 5 pivotal RA Phase III Studies: WA17822, WA17823, WA18063, WA17824, and WA18062, the safety Study WP18663, the open label LTE clinical Studies WA18695, WA18696, and 6 month data from the Phase IV TCZ monotherapy Study WA19924. From this pooled population (n = 4171), data were assessed for all patients with ≤ 2 years since their RA diagnosis at the time they received their first dose of TCZ ("LTE early RA subpopulation"). This early RA population consisted of 3165 PY with a mean and median disease duration of 3.93 years and 5.08 years, respectively.

Evaluator's conclusions on clinical efficacy for early RA

The efficacy of TCZ in the early RA, MTX naïve population was based on data from Study WA19926 which included 1162 predominantly female Caucasian patients with RA ≤ 2 years (mean duration 0.4-0.5 years) who were MTX naïve and had moderate to severe disease with a high baseline mean DAS28 (6.6-6.7) but low joint damage (mTSS 5.66-7.72).

The study met its primary endpoint with superior efficacy of TCZ 8 mg/kg + MTX compared to MTX monotherapy demonstrated on DAS28 remission response (DAS < 2.6) at week 24(44.8% versus 15.0%; odds ratio (OR) = 4.77; p<0.0001). Results were maintained to Week 52 and supported by positive results on improvement in ACR20, ACR50 and ACR70 responses and exploratory analyses of EULAR remission. Radiographic joint damage assessment (as measured by the mTSS) found less progression with TCZ 8 mg/kg + MTX than MTX monotherapy and this covered both the erosion score and JSN components. There was also significant improvement in physical function as measured by the HAQ-DI.

The results for the other two groups, TCZ 4 mg/kg + MTX and TCZ 8 mg/kg monotherapy, were generally numerically superior to MTX monotherapy although not statistically significant on the hierarchical testing to control for multiplicity. The exception to this was that TCZ 8 mg monotherapy had a significantly greater DAS28 remission response than MTX monotherapy.

Data from the previously submitted Study WA17824 provided some supportive efficacy evidence for the early RA population treated with TCZ 8 mg/kg monotherapy. The robustness of the data were, however, limited by the fact that it was a post-hoc subgroup analysis. Data from the Japanese Study MRA012JP showed some evidence of TCZ monotherapy efficacy on joint damage reduction. The study however was unblinded and in a different population so results are difficult to extrapolate.

Pooled data from previously submitted studies showed some evidence of maintenance of response however these data may be biased due to the potential withdrawal of poor or non-responders. Therefore, the Week 104 data from the pivotal Study WA19926 needs to be provided for evaluation to better define the longer term efficacy of TCZ in the early RA population.

In relation to the proposed changes to the PI, the data proposed for the *Clinical Trials* section in relation to Study WA19926 are acceptable. The efficacy data from study WA19926 support the proposed indication (amendments shown in bold) of:

> *Actemra is indicated for the treatment of moderate to severe active rheumatoid arthritis (RA) in adult patients:*
>
> ***in combination with methotrexate (MTX) in those not previously treated with MTX;***

The proposal to include the wording in relation to inhibition of joint damage is less clear cut as, while the comparison to the placebo + MTX was statistically significant, the analysis came after the break in the hierarchical testing sequence used to address multiplicity. Consequently, the result cannot be deemed significant. For this reason the evaluator does not support the changes underlined in bold font in the following section of the indication and recommends this information be discussed in the *Clinical Trial* section of the PI noting that there was a numerically superior but not statistically significant result.

> *Actemra has been shown to inhibit the progression of joint damage in adults, as measured by X-ray, when given* ***alone or*** *in combination with methotrexate.*

Other efficacy studies included in the dossier

Study WA18695 was the long term extension for patients completing treatment in Study WA17822. The study was a post-approval commitment from a previous submission to the TGA. It was an open label, single group, international, multicentre study which enrolled 538 patients (86% from an eligible population of 623) who had completed 24 weeks in the primary Study WA17822. The initial patient population were adults with moderate to severe RA with inadequate response to MTX. The study duration was 5 years and it was conducted between August 2005 and May 2012 at 72 sites worldwide. The primary objective was long term safety. Secondary objectives were long term efficacy, reduction in concomitant steroid treatment and effect on biomarkers.

Study NA25256 was a randomised, parallel-group, open-label, multicentre study to evaluate the effects of TCZ on vaccination in 91 subjects with active RA receiving background MTX.

Evaluator's conclusions on other efficacy data

Long term efficacy

Study WA18695 was the 5 year extension study of Study WA17822 and included 538 moderate to severe RA patient with 2461.9 person-years (PY) of exposure. Two thirds of patients completed the 5 years' treatment. At 264 Weeks, 46% of patients had achieved an ACR70 response and 61% DA28 remission. Overall, efficacy results indicated improvement during the first year of treatment and maintenance of response thereafter. Quality of life data were supportive. Ability to reduce or cease oral corticosteroids due to sustained efficacy was, however, infrequent.

> **Evaluator's comment**: The study was open label, uncontrolled and efficacy data are subject to bias from analysis only of subjects continuing in the study who are possibly more likely to be treatment responders. It is acknowledged that a retention rate of 66% is acceptable for a 5 year study.
>
> No efficacy data from this study have been proposed for inclusion in the PI.

Vaccination

Study NA25256 was a randomised, parallel-group, open-label, multicentre study to evaluate the effects of TCZ on vaccination in 91 subjects with active RA receiving

background MTX. A positive immune response (≥ 2 fold or > 1 mg/L increase in the titre concentration of at least 6 anti-pneumococcal antibody serotypes) to Pneumovax 23 valent polysaccharide vaccine was lower in subjects receiving TCZ and MTX compared to MTX alone (60 versus 71%) although the confidence interval (CI) of the difference in response rates crossed zero. Response was lower in older patients 51 to <65 years (56% versus 67%) but the difference between treatment groups remained similar. Immune response to tetanus toxoid was similar between groups (39% versus 42%).

From this study the sponsor has proposed additional information in the PI. Details of these are beyond the scope of the AusPAR.

> **Evaluator's Comment**: The results indicated that only 60% of patients receiving TCZ + MTX can mount an adequate immune response to Pneumovax and that the response is numerically poorer that with MTX alone. The evaluator recommends that it be made clearer to prescribers that, while immunisation is certainly recommended, a substantial proportion of patients may not mount an adequate immune response to vaccination. The proposed sentence [not shown here] should therefore be reworded. Clearly it is desirable that immunisations need to be up to date with vaccination undertaken prior to commencing TCZ.

Safety

Studies providing evaluable safety data

The sponsor proposed a change of indication of TCZ to include adult patients with severe, active and progressive RA not previously treated with methotrexate. For this purpose the pivotal study was WA19926. In addition, safety data were submitted from the open label extension Study WA18695 in patients with moderate to severe RA and inadequate response to MTX.

Pivotal efficacy Study WA19926 (early RA)

The following safety data were collected:

- General adverse events (AEs), serious adverse events (SAEs) and discontinuations due to AEs.
- AEs of particular interest, including malignancies, myocardial infarction, stoke, elevated lipids, infection, anaphylaxis/serious hypersensitivity[4] and infusion reactions, gastrointestinal perforations, demyelinating disorders, serious bleeding events, thrombocytopaenia, hepatic events and elevated liver enzymes.
- Laboratory tests, including haematology, blood chemistry, serum lipids, liver profile; acute phase reactants (erythrocyte sedimentation rate, ESR).
- Vital signs
- Immunogenicity with anti-TCZ specific blocking and neutralising antibodies in those positive on the screening assay.

Pooled safety data

- Pooled safety data were provided from 3 placebo controlled, Phase III studies (WA17822, WA17823 and WA18063) in patients with inadequate response to DMARDs to allow comparison of safety data to WA19266 (controlled DMARD

[4] Serious hypersensitivity was defined as all SAEs reported during or within 24 h of the injection/ infusion, which were considered by the investigator to be at least remotely treatment-related.

inadequate responder (IR) population). This included treatment to 24 weeks in 2 studies and to 52 weeks in one study.

- Long term extension studies (all-exposure population). This included data from: five pivotal Phase III studies: WA17822, WA17823, WA18063, WA17824 and WA18062, safety Study WP18663; open label LTE clinical Studies WA18695, WA18696, and WA17823 extension, and 6 month data from Phase IV monotherapy Study WA19924. This population included 4171 patients with 16,204.8 PY exposure.
- Two subpopulations: MTX naïve or not received MTX within 6 months (LTE MTX naïve subpopulation) and ≤ 2 years since RA diagnosis (early RA population).
- TCZ monotherapy patients from WA17824 (LTE TCZ monotherapy subgroup).

Other post-marketing data

The sponsor's *Summary of Clinical Efficacy* also included a retrospective epidemiological survey of US health claims using Thomson Reuters MarketScan database. The report was dated 15 April 2013. The study objectives were to estimate the incidence of specific events of interest in early RA patients treated with biologics. Early RA was defined as a new occurrence of RA with follow up restricted to 2 years after RA first diagnosis. The endpoints of interest were acute hepatic events, cardiovascular events, serious infections, serious bleeding event and malignancies.

AE data for deaths, SAEs, AEs leading to withdrawal and of special interest were presented as rates per 100 PY due to differing treatment durations.

Patient exposure

In Study WA19926, there were 282 patients in the placebo + MTX group and 871 in the TCZ (4 and 8 mg) + MTX or TCZ monotherapy groups (Table 1). Data were included up to Week 52 and the mean exposure was similar between groups at 0.87-0.89 years. As mean actual exposure to TCZ was 87-89% of all possible doses, this corresponded to an actual exposure per group of 249-261 PY and a total exposure for the all-TCZ group of 794.9 PY (Table 2).

Table 1: Exposure by treatment group. Study WA19926

Pooled Treatment Group	N	Patient Years Duration	Individual Study Treatment Arms Included
Placebo+MTX	282	254.9	WA19926 placebo+MTX
All-TCZ	871	794.9	WA19926 TCZ 4 and 8 mg/kg
TCZ 4 mg/kg+MTX	289	263.8	WA19926 TCZ 4 mg/kg+MTX
TCZ 8 mg/kg+MTX	290	262.6	WA19926 TCZ 8 mg/kg+MTX
TCZ 8 mg/kg monotherapy	292	268.5	WA19926 TCZ 8 mg/kg+placebo

Table 2: Extent of actual exposure to IV TCZ (or placebo) trial treatment (WA19926 Safety population)

	PLACEBO + MTX (N=282)	TCZ 4 MG/KG + MTX (N=289)	TCZ 8 MG/KG + MTX (N=290)	TCZ 8 MG/KG + PLACEBO (N=292)
Extent of Exposure (years)				
n	282	289	290	292
Mean	0.88	0.88	0.87	0.89
SD	0.254	0.240	0.261	0.237
SEM	0.015	0.014	0.015	0.014
Median	1.00	1.00	1.00	1.00
Min-Max	0.1 - 1.0	0.1 - 1.0	0.1 - 1.0	0.1 - 1.0
Total Patient Years Exposure to IV Treatment	249.2	255.6	253.2	260.6

Extent of exposure = (date of last IV dose within the treatment group + 28 days) minus date of first IV dose within the treatment group + 1 day.
Total patient years exposure is the sum of the exposure to IV across all patients.

Exposure in the controlled DMARD-IR population was 1268.2 PY in the pooled TCZ 4 mg and 8 mg/kg groups. Exposure in the LTE all-exposure population was 16205 PY with 1749 PY and 3165 PY in the MTX naïve and early RA subpopulations, respectively. In study WA19824, the mean duration of TCZ 8 mg/kg monotherapy was 4.9 years with 659 PY exposure.

Safety issues with the potential for major regulatory impact

Liver toxicity

In WA19926, mean alanine transaminase (ALT), aspartate transaminase (AST) and bilirubin were noted to increase across treatment groups with bilirubin remaining within normal range and transaminases increasing more notably. Most increases of AST and ALT were between the upper limit of normal (ULN) to ≤ 3 x ULN however in the TCZ groups the rate of ALT increase to 3 to > 5 x ULN was 3.4%-9.7% and to > 5 x ULN in1.4%-3.1%. The most pronounced effect was in the combination of TCZ 8 mg/kg + MTX. There were however no serious hepatic events. There was one case meeting Hy's Law[5] definition (ALT or AST > 3 x ULN and bilirubin > 2 x ULN) reported in a patient on MTX. Raised transaminases were the major cause of premature termination particularly in the TCZ 8 mg/kg + MTX group and this occurred at a higher rate than reported in the pooled data (6.5% versus 2.5% in the LTE all-exposure population).

ALT increase > 3 x ULN generally occurred on only one occasion and the rate of multiple (≥ 2) elevations (consecutive and non-consecutive), occurred in less frequently: 7.6%, 1.0%, 2.7% and 0.8% of the TCZ 8 mg/kg + MTX, TCZ 8 mg/kg + placebo, TCZ 4 mg/kg + MTX and placebo + MTX groups, respectively. Elevations in AST at multiple time points were less frequent with this occurring in 1.4% of the TCZ 8 mg/kg + MTX group.

While the findings of WA19926 were consistent with presented pooled population data where transaminase increase was also noted, the rate of increased ALT > 3 x ULN in the TCZ 8 mg/kg + MTX group in WA19926 was higher than that reported in the DMARD-IR population TCZ 8 mg/kg + DMARD/MTX (12.8% versus 5.8%). There were no serious hepatic events in the DMARD-IR population and 7 in the LTE data (rate of 0.04 per 100 PY).

Unwanted immunological events

In Study WA19926, immunogenicity testing was conducted at baseline, Week 52 or on study exit. Samples were also collected from patients with infusion reactions. Positivity

[5] Hy's law provides a means to assess a drug's risk of causing serious hepatotoxicity. see for example, Zimmerman HJ. Drug-induced liver disease. *Hepatotoxicity, The adverse effects of drugs and other chemicals on the liver*, 1st edition, New York United-States 1978; and Temple R. Hy's law: predicting serious hepatotoxicity. *Pharmacoepidemiol Drug Safety* 2006; 15:241-243

required antibody detection in the screening and confirmation assays post baseline and negative confirmation assay at baseline. A neutralising assay was performed on samples positive on the confirmation assay. This strategy was reportedly the same as in previous placebo controlled studies with IV TCZ.

In WA19926, the proportion of patients with anti-TCZ antibodies was 1.4%, 1.1% and 2.2% in the TCZ 8 mg/kg + MTX, TCZ 8 mg/kg + placebo, TCZ 4 mg/kg + MTX groups, respectively compared to 3.2% in the placebo + MTX group. The rate of neutralising anti-TCZ antibodies was 1.0%, 1.0% and 1.7% in the respective active groups.

> **Evaluator's comment**: The sponsor reported that the false positive results in the placebo group were consistent with previous studies.

The two patients with anaphylaxis and serious hypersensitivity were not antibody positive. There were 2 of the 19 patients with hypersensitivity AEs who were antibody positive: one with an infusion reaction and one with muscle spasms (who was also antibody positive at baseline). There were 11 patients who were neutralising antibody positive (3 were false positives at baseline) but none were classed as having loss of efficacy or withdrew due to insufficient response to therapy.

> **Evaluator's comment**: There were also an additional three subjects who were neutralising antibody positive with a negative confirmation assay.

In the small number of patients who were anti-TCZ positive (n = 13) there was no reported effect on TCZ concentration reduction.

Data from DMARD-IR studies reported anti-TCZ antibody development in 0 to 3.5% of patients. In the LTE all-exposure population, the reported positivity rate was 1.1% (44/3945) on the confirmation assay. Five of the 44 seropositive patients had an anaphylactic reaction.

Other safety issues

Safety in special populations

There were 7 pregnancies in WA19926 3 in the TCZ 8 mg/kg + MTX group and 4 in the TCZ 8 mg/kg + placebo group. The outcomes were: 2 spontaneous abortions, 2 elective abortions and 3 were ongoing. In the LTE all-exposure population there were 48 reported pregnancies, 44 with known outcome of which 18 had terminations, 10 spontaneous abortions, one a trophoblastic tumour, 14 deliveries at term and 1 premature delivery. Of the live births, 1 died of acute respiratory distress and 1 had left kidney pelviectasis. Some of these women were also taking MTX.

The safety of TCZ monotherapy in early RA patients in WA19266 was compared to the LTE monotherapy subpopulation. The AE rate and AE withdrawal rates were higher however the SAE and death rates were lower in study WA19926 than in the LTE monotherapy population. Comparison of the rates of death and AEs special interest between the two groups shows similarity.

Postmarketing data

Postmarketing data are available since initial market approval in April 2005 in Japan. The estimated cumulative exposure is 184,398 patients. In the last Periodic Safety Update Report (PSUR, April 2013 to October 2012) the most frequently reported events were in the Medical Dictionary for Regulatory Activities (MedDRA) system organ class (SOC) of infections/infestation followed by general disorders and gastrointestinal disorders. The sponsor reported that no new safety signals were identified and no changes to the product labelling were warranted.

Evaluator's conclusions on safety

Early RA population

Study WA19926 assessed the safety of TCZ in 871 early RA patients who were MTX naïve over 52 weeks with 73-76% of these patients receiving all scheduled infusions. The total exposure to TCZ was 794.9 PY.

In general, patients treated with the higher TCZ dose of 8 mg/kg in combination with MTX had a higher rate of AEs, discontinuations due to AEs and death. The SAE rate was however more similar between treatment groups (Table 3) and the number of deaths were low (n = 9) making intergroup comparisons of death rates difficult.

Table 3: Study WA19926 Adverse Events

	No. of Patients (%)			
Type of Events	Placebo +MTX N=282	TCZ 4 mg/kg +MTX N=289	TCZ 8 mg/kg+ MTX N=290	TCZ 8 mg/kg+ placebo N=292
At least one AE	235 (83.3)	256 (88.6)	256 (88.3)	250 (85.6)
Serious AE	24 (8.5)	29 (10.0)	31 (10.7)	25 (8.6)
Deaths	2 (0.7)	4 (1.4)	2 (0.7)	1 (0.3)
AE leading to withdrawal from treatment	21 (7.4)	35 (12.1)	59 (20.3)	34 (11.6)
AE leading to dose modification/interruption	134 (47.5)	153 (52.9)	171 (59.0)	128 (43.8)

AE = adverse event; MTX = methotrexate; TCZ = tocilizumab.

The most frequent AEs were nausea, upper respiratory tract infection (URTI), nasopharyngitis and hepatic transaminase increase. Infection risk remained a major safety issue with higher rates in patients on TCZ in combination with MTX. The serious infections included pneumonia, cellulitis and tuberculosis, and there were 5 fatal cases. Other serious risks were present and included anaphylaxis and hypersensitivity, malignancy, myocardial infarction and serious bleeding. There were no reported cases of gastrointestinal perforation, opportunistic infection or demyelinating disorder in WA19926.

Laboratory parameter changes were consistent with previous studies and included increases in hepatic transaminases and lipids and decreases in neutrophils and platelets. Severe changes were not common and, apart from transaminases, were in line with pooled population data. There were no serious hepatic events in TCZ treated patients (there was one cases meeting Hy's Law definition in the placebo + MTX group). The early RA patients on TCZ, and in particular the combination of TCZ and MTX, were noted to be at a slightly higher risk of raised hepatic transaminases and premature study termination from this AE. The sponsor's rationale was that this was due to more stringent safety withdrawal criteria in relation to raised ALT/AST.

The risk of anti-TCZ antibody formation in the early RA patients was low (1.1-2.2%) and did not appear associated with serious safety issues or loss of efficacy.

Overall, the safety profile of TCZ in the early RA, MTX naïve population of WA19926 was consistent with known data. This group were found to have a slightly higher AE rate and death rate than that reported for pooled populations while the most notable difference was the higher risk of discontinuation due to AEs. When treated with TCZ monotherapy the safety profile of the early RA population appeared in line with that reported from the monotherapy population of other RA trials.

The data from WA19926 was in line with data from the submitted literature review however comparisons are difficult due to possibility of differing definitions of early RA and serious events.

The sponsor has proposed two main changes to the AE section of the PI. The first covers the safety profile in the early RA population and is satisfactory:

> *Early rheumatoid arthritis*
>
> *Study VI (WA19926) evaluated 1162 patients with early, moderate to severe RA who were naïve to treatment with both MTX and a biologic agent. The overall safety profile observed in the Actemra treatment groups was consistent with the known safety profile of Actemra (Table).*

The second change (below) covers the higher risk of hepatic transaminase elevation and the evaluator considers this addition adequate:

> *In Study VI, MTX naïve adult patients with moderate to severe, active early RA (mean disease duration ≤ 6 months) experienced more transient elevations in ALT > 3 x ULN compared with the all control population. This was observed in both Actemra treated patients and MTX monotherapy patients.*

The longer term safety of TCZ in the early RA population still needs to be defined. As WA19926 was a 2 year study, the data to 104 weeks should be provided for evaluation as soon as available.

Long term safety in RA with inadequate MTX response

Study WA18695 was a long term extension study of WA17822 (a Phase III, 24 week placebo controlled study in moderate to severe RA) in which 538 patients were treated with 8 mg/kg TCZ every 4 weeks plus stable MTX. The total exposure was 2462 PY with a mean duration of 4.6 years. The retention rate for a 5 year study at 66% was acceptable. Long term treatment with 8 mg/kg TCZ in this trial did not reveal any new safety signals and the safety profile was in line with known data. The frequency of AEs did not increase with time and changes in laboratory parameters were relatively stable after initial changes in the first year of treatment. The withdrawal rate due to AEs was 4.2 per 100 PY.

First round benefit-risk assessment

First round assessment of benefits

The benefits of TCZ in the proposed usage are:

- Efficacy was demonstrated with TCZ 8 mg/kg in combination with MTX showing a superior response compared to MTX monotherapy on DAS28 remission rates after 6 months treatment.
- Efficacy for the TCZ 8 mg/kg + MTX regimen was consistent across other parameters for disease remission including ACR and EULAR criteria.
- Efficacy of TCZ 8 mg/kg + MTX compared to MTX on reduction in joint damage (mTSS).
- Efficacy of TCZ 8 mg/kg monotherapy compared to MTX monotherapy was demonstrated for DAS28 remission but not for other parameters.
- A safety profile which was comparable to other adult RA population data.
- Long term data to 5 years in a moderate to severe RA population found no new safety signals.

First round assessment of risks

The risks of TCZ in the proposed usage are:

- Higher risk of hepatic transaminase elevation in the early RA population, particularly with the 8 mg/kg TCZ dose in combination with MTX. There were however no serious hepatic events in Study WA19926.
- Higher risk of treatment withdrawal in the early RA population treated with TCZ particularly due to hepatic transaminase elevation.
- The known risks of infections, hypersensitivity reactions including anaphylaxis, gastrointestinal perforation, serious bleeding, cardiac events and malignancy. There were no cases of demyelination reported. These risks were in line with data from previous studies in adults with RA.
- The risk of laboratory parameter changes including neutropenia, thrombocytopaenia and lipid elevation. These risks were in line with data from previous studies in adults with RA

First round assessment of benefit-risk balance

The efficacy TCZ in combination with MTX compared to MTX alone was demonstrated in patients with early RA who were MTX naïve. For the 8 mg/kg dose with MTX this was seen across all main efficacy parameters and for TCZ monotherapy the 8 mg/kg dose also was efficacious on DAS28 remission rates. In addition to response of disease remission, TCZ treatment with MTX in this early RA population was found to reduce the progression of joint damage after 52 weeks of treatment. The EMA (2003) guidelines state that *"For agents which are claimed to prevent structural joint damage, it is currently recommended to demonstrate radiological differences of hands and forefeet on the basis of before/after comparisons taken not less than one year apart ideally two years using full randomisation and pre-agreed criteria"*. The more recent draft EMA guideline (2011) states that *"measurement after 1 year may be sufficient to confirm efficacy in terms of endpoints relevant to slowing/prevention of structural damage claim. In exceptional cases a measurement after at least 6 months may be sufficient depending on the properties of the test drug; this has to be justified by robustness of the method and convincing clinical data. It is important to demonstrate long-term maintenance of this effect for an additional 12 months."*

Data from Study WA17823 demonstrated inhibition of radiographic progression at 1 and 2 years in a population with inadequate response to MTX and the current approved indication for TCZ states that *Actemra has been shown to inhibit the progression of joint damage in adults, as measured by X-ray, when given in combination with methotrexate*.

The evaluator agrees that in the early RA population there are consistent findings on joint damage for the combination of TCZ and MTX after 1 year treatment. Data from year two will be needed to demonstrate maintenance of this effect. By contrast, the lack of a significant inhibition of progression of joint damage in TCZ monotherapy group in WA19926 means that only the TCZ and MTX combination should be included in the indication in relation to efficacy on this endpoint.

The safety risks of the combination of TCZ and MTX were slightly higher than MTX alone in the early RA population although this was not an unexpected finding. The main difference was in AEs leading to treatment withdrawal or dose modification/interruption. The safety in the early RA population compared to pooled population data from previous trials also found that in the earlier population the overall AE rate and death rate with TCZ treatment were slightly greater, however the SAE rate and rates of adverse events of special interest were generally in line with pooled data.

The notable difference in the early RA population was the higher rate of raised hepatic transaminases compared to patients who were inadequately responsive of DMARDs. In addition there was a higher rate of premature discontinuation due to AEs. The sponsor proposes that this is due to the patients being MTX naïve and also that there were differing protocol withdrawal criteria in relation to hepatic transaminase increase. Nonetheless these increased risks need to be defined and the proposed PI changes have captured this.

The safety database was adequate in size with nearly 800 PY exposure. Overall, the safety profile in the early RA, MTX naïve population was in line with known data and no new safety signals were observed. The longer term safety of TCZ in the early RA population still needs to be defined and as WA19926 was a 2 year study, the data to 104 weeks should be provided for evaluation as soon as available.

Overall, the efficacy in early RA patients was demonstrated across a number of domains and was in the context of a safety profile in line with current data on RA patients. The increased risk of raised liver enzymes was generally transient, was not associated with serious hepatic events and has been covered in labelling. Therefore, the evaluator finds that the benefit-risk balance of TCZ, given the proposed usage, is favourable subject to the changes recommended below (see *Clinical Questions*) being adopted and the provision of long term safety data.

The long term data submitted in Study WA18695 did not reveal new safety signals and so the current labelling remains adequate.

First round recommendation regarding authorisation

The evaluator recommends approval of the proposed changes to the product information for TCZ IV infusion for the following indication (addition in bold font):

> *Rheumatoid Arthritis*
>
> *Actemra is indicated for the treatment of moderate to severe active rheumatoid arthritis (RA) in adult patients:*
>
> ***in combination with methotrexate (MTX) in those not previously treated with MTX**;*

The proposed change to the indication (below in bold underlined font) in relation to monotherapy efficacy in joint damage reduction is not supported.

> *Actemra has been shown to inhibit the progression of joint damage in adults, as measured by X-ray, when given **alone or** in combination with methotrexate.*

These recommendations are subject to satisfactory responses to the comments on the PI and submission of the 2 year data from Study WA19926.

Details of recommended revisions to the PI other than to the *Indications* are beyond the scope of the AusPAR.

Clinical questions

Product information: indication

The sponsor proposes the following addition (in bold underlined font) to the current indication text:

> *Actemra has been shown to inhibit the progression of joint damage in adults, as measured by X-ray, when given **alone or** in combination with methotrexate.*

Data from Study WA19926 found a numerical reduction in radiographic progression but not a statistically significant one when controlling for multiplicity was conducted in the hierarchical testing sequence. For this reason the evaluator cannot support using the finding in the indication and does not agree with the proposed change. The information has been included in the proposed new paragraph on MTX naïve, early RA in the *Clinical Trial* section of the PI.

Second round evaluation of clinical data submitted in response to questions

Product information: indication

The sponsor agrees to remove the proposed claim and the draft PI has been revised accordingly as follows:

> *Actemra has been shown to inhibit the progression of joint damage in adults, as measured by X-ray, when given in combination with methotrexate.*

This change is acceptable.

Study WA19926

As requested (see *First Round Recommendation Regarding Authorisation* above), the sponsor submitted the Year 2 data (final clinical study report) from Study WA19926.

Full details and the evaluation of this data are in Attachment 2 of this AusPAR.

Second round benefit-risk assessment

Second round assessment of benefits

After review of data submitted following the first round of evaluation, the benefits of TCZ in the proposed usage, in addition to those listed *under First round assessment of benefits* now also include:

- Efficacy of TCZ 8 mg/kg + MTX appears to be maintained after 2 years of treatment. This was consistent across measured parameters. There was, however, no evidence of further improvement in efficacy with longer treatment duration.
- Radiographic data indicated a maintained reduction in joint damage (mTSS) when treated with TCZ 8 mg/kg + MTX.
- No new safety signals were evident in this early RA population when treated with TCZ for two years.

Second round assessment of risks

After review of data submitted following the first round of evaluation, the risks of TCZ remain unchanged from that listed under *First round assessment of risks* above.

Second round assessment of benefit-risk balance

In patients with early moderate to severe RA who are MTX naïve, the data from the final study report of WA19926 indicated that the efficacy achieved after one year of treatment with TCZ was maintained during the second treatment year. While the analysis was exploratory and there was no formal statistical testing, the data were consistent across efficacy endpoints of DAS28, ACR 20/50/70 and HAQ-DI. Consistent with data after year

one of treatment, the efficacy remained greatest with the TCZ 8 mg/kg + MTX treatment regimen. There was, however, no further improvement in efficacy with ongoing treatment.

The impact on joint damage that was noted in year one was found to be maintained during year two. Radiographic data showed that the mean change from baseline in mTSS score remained steady in the second year of treatment in the TCZ 8 mg/kg + MTX group. The effect was less notable in the TCZ 8 mg/kg monotherapy group and, due to the lack of statistically significant result in year one in this group, no formal conclusions can be drawn on the TCZ monotherapy regimen.

Data on the TCZ 4 mg/kg + MTX and placebo + MTX groups are difficult to interpret due to the study design and use of the so-called escape therapy of TCZ 8 mg/kg + MTX in non-responders. For example the high number of subjects with imputated values on radiographic data in these groups (51% of the TCZ 4 mg/kg + MTX group) makes interpretation of results difficult.

The safety database included 682 PY of treatment with TCZ 8 mg/kg + MTX. There were no new safety signals identified and the profile of events was consistent with data from the first treatment year. The rate of AEs was higher with the lower TCZ dose (4 mg/kg + MTX) and there is no clear explanation for this. Laboratory parameter changes remained relatively stable over the second year of treatment. When analysed in 6 monthly intervals, there was also no evidence for an increase in AE rates over time. The highest rates remain in the first 6 months of treatment; nonetheless, the risks of TCZ are ever present after two years of treatment.

Safety in patients switching to TCZ 8 mg/kg + MTX was in line with what would be expected from this higher dose combination and it appears that switching treatment was tolerated.

Overall, in the early RA population after two years treatment, efficacy of TCZ with MTX was maintained and the safety risks were stable indicating little change in the benefit-risk balance for TCZ from that discussed after the first round assessment. The sponsor has also satisfactorily addressed the requested changes to the PI.

Second round recommendation regarding authorisation

After the second round of evaluation, the evaluator recommends approval of the proposed changes (shown in bold font) to the indication for TCZ IV infusion:

> *Rheumatoid Arthritis*
>
> *Actemra is indicated for the treatment of moderate to severe active rheumatoid arthritis (RA) in adult patients:*
>
> ***in combination with methotrexate (MTX) in those not previously treated with MTX**;*

The sponsor has withdrawn the proposed change to the indication in relation to monotherapy efficacy in joint damage reduction.

V. Pharmacovigilance findings

Risk management plan

A number of Risk Management Plans (RMPs) regarding Actemra have been evaluated by the TGA since Actemra was first approved for registration in Australia in May 2009. The sponsor has now submitted the EU-RMP Version: 15.0 (dated May 2013) with Australian

Specific Annex (ASA) Version: 3.0 (dated September 2013) in support of the current application. It is in this context, with consideration of material changes to the most recent previously accepted EU-RMP: Version: 13.0 with an ASA Version: 1.0, as they pertain to the proposed extension of RA indications, that these documents have been reviewed by the TGA Office of Product Review (OPR).

Safety specification

The sponsor provided a summary of ongoing safety concerns in adults and children which are shown at Table 4 and Table 5, respectively.

Table 4: Summary of ongoing safety concerns in adult patients

Category	Safety Concern
Important Identified Risks	Serious infection
	Complications of diverticulitis
	Serious hypersensitivity reactions
Important Potential Risks	Neutropenia and the potential risk of infections
	Thrombocytopenia and the potential risk of bleeding
	Liver enzyme elevations and bilirubin elevations and the potential risk of hepatotoxicity
	Elevated lipid levels and the potential risk of cardiovascular and cerebrovascular events
	Malignancies
	Demyelinating disorders
	Immunogenicity
Important missing information	Elderly
	Paediatric patients
	Effects during pregnancy
	Hepatic impairment
	Renal impairment
	Combination with biologics
Identified and potential interactions including food-drug and drug-drug interactions	CYP450 enzyme normalisation

Table 5: Summary of ongoing safety concerns in paediatric patients

Category	
Important Identified Risks	Serious infection
	Serious hypersensitivity reactions
Important Potential Risks	Skeletal development
	Immunogenicity
	Malignancies
	CYP450 enzyme normalisation
Important missing information	Macrophage Activation Syndrome (MAS) in sJIA patients

Pharmacovigilance plan

The sponsor proposes routine pharmacovigilance activities to monitor all the specified ongoing safety concerns, including guided questionnaires for all the specified important identified and potential risks except for 'Immunogenicity' and 'CYP450 enzyme normalisation').

Furthermore additional pharmacovigilance activities (clinical studies and/or a registry) are also proposed for all the specified ongoing safety concerns, except for the important missing information: 'Hepatic impairment', 'Renal impairment' and 'MAS in sJIA patients'.

Risk minimisation activities

It appears that the sponsor has concluded that routine risk minimisation activities are sufficient for all the specified ongoing safety concerns, except for the important identified risk: 'Serious hypersensitivity reactions' for which additional risk minimisation activities are also proposed.

Routine risk minimisation activities will comprise labelling, including PK data, precautionary statements, instructions for use and notification of drug interactions and/or undesirable effects for all the specified ongoing safety concerns.

Additional risk minimisation activities for the important identified risk: 'Serious hypersensitivity reactions' attempt to minimise the risk associated with management of possible hypersensitivity reactions occurring during or after an infusion outside of the hospital setting. Infusions in the centres are administered by dedicated nurses qualified for this purpose. All nurses receive appropriate and extensive training and attend mandatory refreshers on an annual basis. All nurses hold current cardiopulmonary resuscitation (CPR) certification.

Reconciliation of issues outlined in the RMP report

Table 6 summarises the OPR's first round evaluation of the RMP, the sponsor's responses to issues raised by the OPR and the OPR's evaluation of the sponsor's responses.

Table 6: Reconciliation of issues outlined in the RMP report

Recommendation in RMP evaluation report	Sponsor's response	OPR evaluator's comment
Now that the application to extend the indications for use in active polyarticular juvenile idiopathic arthritis patients aged 2 years and older has been approved the ASA should be updated accordingly.	The sponsor has provided an updated ASA (version 3.1), including information on the indication for use in active polyarticular juvenile idiopathic arthritis patients aged 2 years and older. At the same time the sponsor has updated the ASA format in line with that recommended in TGA RMP Questions and Answers document version 1.3, October 2012 and made other changes to the ASA as detailed within the document's "Change history of RMPs submitted to TGA" table.	This is generally acceptable. However, the sponsor of its own volition has removed the Table: 'Australian Risk Management Plan' of the ASA Version 3.0 and replaced it with a 'Risk Minimisation Activities (RMinA)' section. The former provided a detailed comparison of Australian and EU labelling. However the latter, in regard to routine risk minimisation, only applies the statement: "Information in Australian PI is essentially similar to EU-SPC." to almost all of the ongoing safety concerns. This is unsatisfactory and the sponsor should reinstate the detailed comparison of Australian and EU labelling in a revised ASA before this application is approved.
It appears the sponsor has not provided any justification for the removal of the important potential risk: 'Viral reactivation' and the important missing information: 'Increased mortality in the Japanese PMS compared to clinical study population' and 'Vaccinations' as ongoing safety concerns. The sponsor should now provide compelling justification for these deletions or consider reinstating these ongoing safety concerns.	The sponsor has provided justification for the deletion of these previously accepted ongoing safety concerns.	This is acceptable.

Recommendation in RMP evaluation report	Sponsor's response	OPR evaluator's comment
For completeness the Table: 'Summary of Ongoing Safety Concerns in Paediatric Patients' of the EU-RMP should include 'MAS in sJIA patients' as important missing information to be consistent with the Table: 'Summary of Ongoing Safety Concerns in Paediatric Patients' of the EU-RMP when this document is next updated.	The sponsor commits to correcting this inconsistency with the next update to the RMP.	This is acceptable.
The Table: 'Australian Risk Management Plan' of the ASA appears to makes erroneous EU-RMP table references for the proposed EU pharmacovigilance activities, which are in fact captured in Table: 'Safety concerns and overview of planned pharmacovigilance actions for All Patients' of the EU-RMP. The Table also does not appear to indicate whether such pharmacovigilance activities are also proposed and/or are relevant for Australia. The sponsor should correct such deficiencies in a revised ASA.	The sponsor has provided a revised version of the ASA. The cross-reference to the Table has been included as requested. The ASA indicates which pharmacovigilance activities are relevant for Australia.	This is acceptable.
The studies referenced in the pharmacovigilance plan will generate safety data that will simply support the known safety profile of the medicine, while others will generate data that will provoke applications to amend the Australian registration details. To this end it is suggested that the sponsor	The sponsor has provided a revised 'Studies referenced in the RMP' section of the ASA, which references the EU-RMP v15.0 Table On-Going and Planned Studies in the Post-Authorisation Pharmacovigilance Development Plan. This section does not include anticipated dates for their	This is not entirely satisfactory, as data from Studies NP25737 and MA21488 have been stated as being available as of the third quarter (Q3) 2013 and Q4 2013 respectively. Consequently it is reiterated that the anticipated dates for the submission in Australia of studies referenced in the

Recommendation in RMP evaluation report	Sponsor's response	OPR evaluator's comment
should provide an attachment to the ASA setting out all the forthcoming studies and the anticipated dates for their submission in Australia.	submission in Australia, but rather refers to the EU-RMP table for estimated timelines for data availability. The sponsor states that following availability of data from these studies, the results will be assessed and if deemed necessary, the company Core Data Sheet (CDS) will be updated. Any relevant safety updates to the company CDS, will result in applications to amend the PI.	pharmacovigilance plan should be included in this section of a revised ASA before this application is approved.
The 'RMP submission history table' of the ASA should state that the guided questionnaires erroneously associated with the important missing information: 'Effects during pregnancy' and 'Hepatic Impairment' have now been removed in the ASA Version: 3.0.	In the revised ASA provided, the '*Change history of RMPs submitted to TGA'* tables notes that Guided Questionnaires erroneously associated with the Important Missing information 'Effects during pregnancy' and 'Hepatic Impairment' in ASA v1.0 have been removed from the ASA.	This is acceptable.
The sponsor should provide an update on the status of the unnamed paediatric patient registry and provide an assurance that if it is still not yet initiated at least a draft protocol will be submitted to the TGA for review once it becomes available.	A draft protocol for the pJIA paediatric patient registry is now available and has been provided in Annex 5 of the updated ASA. The protocol has been submitted to EMA and FDA for review and therefore is considered a draft.	This is acceptable.
The sponsor's handling of the potential for medication errors with Actemra using routine pharmacovigilance and risk minimisation activities remains acceptable. However the ASA should refer to not just to Section 7.4.1 of the	The revised ASA cross-references EU-RMP sections 7.4.1 Potential for medication errors involving the IV formulation and 7.4.2.1-6 SVI.4.4. Reports of medication errors with the marketed product(s) which appropriately	This is acceptable.

Recommendation in RMP evaluation report	Sponsor's response	OPR evaluator's comment
EU-RMP, but also to Sections 7.4.2.1-6 of the EU-RMP in regard to the potential for medication errors with Actemra.	describes the potential for medication errors in Australia.	
The proposed Australian risk minimisation activities remain the same as previously accepted for Actemra. At this time they continue to be acceptable.	The sponsor acknowledges this comment.	n/a
In regard to the proposed routine risk minimisation activities, the draft PI document is considered satisfactory.	The sponsor acknowledges this comment.	n/a
In regard to the proposed routine risk minimisation activities, the draft Consumer Medicine Information (CMI) is considered satisfactory.	The sponsor acknowledges this comment.	n/a

In addition, the sponsor provided an updated ASA Version: 3.1 (dated March 2014).

Outstanding issues

Issues in relation to the RMP

Outstanding issues are detailed in Table 6 above, against numbers 1 and 5.

Comments on the safety specification of the RMP

Clinical evaluation report

The clinical evaluator concluded that:' the Safety Specifications identified by the sponsor in the RMP are consistent with the adverse event/safety profile from the clinical trial data' and: 'Analysis of the 104 week data from Study WA19926 did not reveal any new safety issues to be included in the Safety Specifications of the RMP'.

Recommendation to the delegate

The European Risk Management Plan Version 15.0 (dated May 2013), with an Australian Specific Annex (ASA) Version: 3.1 (dated March 2014) to be revised to the satisfaction of the TGA, must be implemented.

VI. Overall conclusion and risk/benefit assessment

The submission was summarised in the following Delegate's overview and recommendations:

Background

Tocilizumab is a recombinant, humanised, anti-human IL-6 receptor monoclonal antibody of the immunoglobulin IgG1 subclass. It is composed of two heterodimers, each of which consists of a heavy and light polypeptide chain. The four polypeptide chains are linked intra- and inter-molecularly by disulphide bonds.

Tocilizumab binds specifically to both soluble and membrane-bound IL-6 receptors, inhibiting IL-6 mediated signalling. IL-6 is a pro-inflammatory multifunctional cytokine produced by a variety of cell types. Elevated levels of IL-6 have been reported in the serum and synovial fluid of patients with RA, and levels are thought to correlate with disease activity.

Actemra was first approved in Australia in May 2009 for the treatment of moderate to severe active RA in adult patients. In October 2010 the indication was extended to include inhibition of the progression of joint damage, as measured by X-ray, when given in combination with methotrexate. In October 2011 the indication was extended to include systemic onset juvenile idiopathic arthritis (sJIA) in patients 2 years of age and older, and in October 2013 it was further extended to include polyarticular juvenile idiopathic arthritis in patients 2 years of age and older.

In August 2010, a fatal case of anaphylaxis after Actemra administration was notified to the TGA. This resulted in a safety-related update of the Actemra PI, communication with healthcare professionals and the development of a safety protocol for administration of the drug in dedicated infusion clinics (ACTiv program), based on advice received by the sponsor from medical organisations with an interest in the emergency management of anaphylaxis. However it was a specific condition of registration attached to the Delegate's approval of the sJIA indication that administration of TCZ for the paediatric indication *"should take place in a hospital with immediate access to medical personnel, at least until there is adequate demonstration of safety of administration in sufficiently large number of children"*.

In December 2011 the sponsor notified the TGA of a second case of anaphylaxis with a fatal outcome. This resulted in a further safety update and additional communication with healthy professionals by the sponsor.

In June 2014, the sponsor has issued a safety related request to add a warning about Stevens Johnston syndrome to the PI for TCZ.

Quality

There was no requirement for a quality evaluation in a submission of this type.

Nonclinical

There was no requirement for a nonclinical evaluation in a submission of this type.

Clinical

The clinical dossier provided to support the proposed extension of indications included the following data:

- One population PK study using data from Study WA17823, evaluated in a previous submission
- One Phase III study (WA19926) that also provided PK and PD data
- One Phase III extension study (WA18695)
- One Phase IV study (NA25256)
- Integrated summaries of efficacy and safety

The TGA adopted guidance of most relevance to this submission is CPMP/EWP/556/95 Rev 1 dated December 2003 *Point to Consider on Clinical Investigation of Medicinal Products Other than NSAIDS for Treatment of Rheumatoid Arthritis*, adopted in 2007.

The sponsor did not propose any changes to the dosage or dosage administration instructions.

Pharmacology

Study WA17823 was a randomised, double-blind, parallel group safety of the safety and prevention of structural joint damage during treatment with TCZ versus placebo in combination with MTX in patients with moderate to severe active RA with an inadequate response to MTX, conducted over 52 weeks. A population PK report analysed data from 3336 samples from 841 patients. The model was based on data from four Phase III studies of 24 months duration each. Using a Bayesian analysis, the two-compartment disposition model with parallel first-order and Michaelis-Menten elimination kinetics adequately described the data from study WA17823.

A graphical analysis of the radiographic scores comparing the area under the concentration-time curve (AUC) of responders (mTSS ≤ baseline at 52 weeks) indicated a slower progression of the erosion score component of the mTSS when TCZ exposure increased in patients with a moderate to high exposure (cumulative TCZ AUC > 240 $x10^3$ µg.h/mL), compared to placebo. There was no difference in JSN score.

Study WA19926 was a Phase III, multinational, multicentre, randomised, double-blind, parallel group study of disease remission, prevention of structural joint damage and safety during treatment with TCZ as a monotherapy and in combination with MTX versus MTX alone in 1162 MTX naïve adult patients with moderate to severe RA of ≤ 2 years duration conducted over 52 weeks of therapy. Steady state Cmin concentrations were approximately 1 µg/mL from week 16 for TCZ 4 mg/kg + MTX and approximately 17-21 µg/mL for the TCZ dosage groups. The week 12 Cmax was 95.9 µg/mL in the TCZ 4 mg/kg group and 209–217 µg/mL in the TCZ 8 mg/kg groups. The PK profile of TCZ was similar in 13 patients with anti-TCZ antibodies following initiation of treatment. There was no clear correlation between DAS28, mTSS score and TCZ PK profiles.

Efficacy

Study WA19926: This was a Phase III, multinational, multicentre, randomised, double-blind, parallel group superiority study of disease remission, prevention of structural joint damage and safety during treatment with TCZ 8 mg/kg as a monotherapy, TCZ 4 mg/kg or 8 mg/kg combination with MTX, or MTX alone in 1162 MTX naïve adult patients with moderate to severe RA of ≤ 2 years duration, conducted over 104 weeks. The included patients had a DAS > 3.2, a swollen joint count ≥ 4 and tender joint count ≥ 6, an ESR ≥ 28 mm/h or a CRP ≥ 10 mg/L, and were rheumatoid factor (RF) or anti-cyclic citrullinated peptide (CCP) antibody positive or, if not antibody positive, had radiological evidence of RA. NSAIDS and corticosteroids (< 10 mg/day prednisolone or equivalent) were permitted but not previous treatment with other biological agents. The patients were Caucasian (76-79%), female (75–80%), with a mean age of 49–51 years (range

18-84 years), and a mean RA duration of 0.4–0.5 years. DMARDS had not been used in 76-82%. They had a high baseline mean DAS28 (6.6-6.7) but low joint damage (mTSS 5.66–7.72). The study had 80% power to detect a 10% difference between DAS28 remission rates of the TCZ 8 mg/kg + MTX versus placebo + MTX, and a 98% power to detect a mean difference of 2.17 DAS28 units between the TCZ + MTX group and the placebo + MTX group.

The primary efficacy endpoint was the rate of DAS28 remission, defined as < 2.6, at Week 24 based on an intent-to-treat (ITT) population. The rates of this endpoint for each of the treatment arms were as follows:

- 15%, placebo + MTX
- 31.9%, TCZ 4 mg/kg + MTX
- 44.8%, TCZ 8 mg/kg + MTX ($p < 0.0001$ versus placebo + MTX, OR 4.8 [95% CI: 3.2, 7.1])
- 38.7%, placebo + TCZ 8 mg/kg

Secondary efficacy endpoints were statistically significant for the comparison of TCZ 8 mg/kg + MTX versus placebo + MTX for the following variables: DAS < 2.6, ACR20, ACR50, ACR 70, HAQ-DI at Week 24 and 52 (see Table 7). The comparison between TCZ 8 mg monotherapy and placebo + MTX groups also reached significance for DAS28 < 2.6 at Week 24. DAS remission responses at Week 52 occurred in 19.5%, 34.0%, 49.0% and 39.4% of the placebo + MTX, TCZ 4 mg/kg + MTX, TCZ 8 mg/kg + MTX, and TCZ 8 mg/kg + placebo groups, respectively. The majority of the difference from baseline occurred in the first 16-24 weeks of therapy, and the mean effect was maintained until Week 104.

Radiographic assessments were performed at baseline and Week 52. The mean change from baseline to Week 52 in the mTSS was 0.08 in the TCZ 8 mg/kg + MTX and 1.14 in the placebo + MTX groups ($p = 0.0001$). The mean change from baseline to Week 52 in the modified Sharp erosion score (mSES) was lower in the TCZ 8 mg/kg + MTX than placebo + MTX group (0.05 versus 0.63, $p = 0.0006$). The mean change from baseline in JSN was also lower with TCZ 8 mg + MTX (0.03 versus 0.51) but was not statistically significant due to the hierarchical chain of statistical testing. The reduction in joint damage in the TCZ 8 mg/kg monotherapy group was less than the TCZ 8 mg/kg + MTX group and was not statistically significant in the hierarchical testing sequence. Between Week 52 and Week 104, the mTSS had increased by 0.06/0.32/0.68/0.89 in the TCZ 8 mg/kg + MTX, TCZ 8 mg/kg + placebo, TCZ 4 mg/kg + MTX, and placebo + MTX groups, respectively.

Table 7: Study WA19926. Overview of efficacy outcomes

Efficacy Parameter	Placebo + MTX n=287	TCZ 4 mg/kg + MTX n=288	TCZ 8 mg/kg + MTX n=290	TCZ 8 mg/kg + Placebo n=292
Primary Endpoint				
DAS28 (No. [%] of Patients)				
DAS28 Remission at Week 24	43 (15.0)	92 (31.9) [a]	130 (44.8) [b]	113 (38.7) [b]
Secondary And Exploratory Endpoints				
DAS28 (No. [%] of Patients)				
DAS28 Remission at Week 52	56 (19.5)	98 (34.0) [c]	142 (49.0) [b]	115 (39.4) [d]
EULAR Response (good or moderate) at Week 24	211 (73.5)	242 (84.0)	248 (85.5)	254 (87.0) [b]
DAS 28/ACR Core Parameters at Week 24 (adjusted mean change from baseline)				
SJC 28	-6.1	-7.3 [c]	-7.8 [c]	-7.4 [c]
TJC 28	-8.4	-10.3 [c]	-10.2 [c]	-9.8 [c]
SJC 66	-8.0	-9.4 [c]	-10.3 [c]	-9.2 [c]
TJC 68	-13.7	-15.6 [c]	-16.5 [b]	-15.2
Patients GA VAS	-31.7	-35.9 [c]	-36.8 [c]	-31.1
Physician GA VAS	-37.1	-40.3 [b]	-42.1 [b]	-38.7
Global Pain Score VAS	-29.5	-33.4 [c]	-33.9 [c]	-29.4
HAQ-DI	-0.61	-0.71 [a]	-0.78 [b]	-0.65
CRP	-1.668	-1.674	-2.350 [d]	-2.307 [d]
ESR	-21.7	-33.8 [c]	-44.0 [c]	-42.3 [c]
ACR Endpoints (No. [%] of Patients)				
ACR20 at Week 24	187 (65.2)	212 (73.6) [a]	216 (74.5) [b]	205 (70.2)
ACR50 at Week 24	124 (43.2)	138 (47.9)	165 (56.9) [b]	139 (47.6)
ACR70 at Week 24	73 (25.4)	100(34.7) [a]	112 (38.6) [b]	88 (30.1)
ACR 20 at Week 52	164 (57.1)	181(62.8) [b]	195 (67.2)	184 (63.0)
ACR50 at Week 52	117 (40.8)	151(52.4) [a]	162 (55.9) [b]	144 (49.3) [a]
ACR70 at Week 52	83 (28.9)	107 (37.2) [a]	125 (43.1) [b]	105 (36.0)
Major Clinical Response at Week 52	47 (16)	64 (22)	91 (31) [a]	83 (22)
Other Remission Endpoint (No. [%] of Patients)				
ACR/EULAR Boolean Remission at Week 24	25 (10.0)	43 (16.7) [c]	47 (18.4) [c]	38 (14.2)
CDAI Remission at Week 24	38 (13.2)	64 (22.2) [c]	71 (24.5) [c]	60 (20.5) [c]
Radiographic Endpoints				
Mean Change From Baseline in:				
mTSS at Week 52	1.14	0.42 [a]	0.08 [b]	0.26 [a]
Modified Sharp Erosion Score at Week 52	0.63	0.25 [a]	0.05 [b]	0.15 [a]
Modified Sharp JSN Score at Week 52	0.51	0.17 [a]	0.03 [a]	0.11 [a]
Proportion of Patients with no Progression in:				
mTSS at Week 52	194 (73)	211 (79)	226 (83) [b]	226 (82) [c]
HAQ-DI (No. [%] of Patients)				
HAQ-DI Improvement ≥ 0.3 units from baseline at Week 24 [d]	148 (69.2)	185 (81.5)	186 (81.6)	170 (73.9)

a: $p < 0.05$; however this comparison occurred after the break in hierarchical ordered testing sequence; b: $p < 0.05$; c: $p < 0.05$; however endpoint is exploratory so not adjusted for multiple comparisons; d: Exploratory endpoint of categorical change from baseline in HAQ-DI was not formally tested.
Note: All comparisons are versus placebo + MTX. Secondary endpoints are not presented in the sequential order in which they were tested and the n for different analyses varies. For categorical endpoints (such as ARC20/50/70 and EULAR response) withdrawn patients were classified as non-responders following withdrawal. For radiographic and all other endpoints, assessments prior to

withdrawal were included and all data measured following early withdrawal from the study were excluded.

At the end of 52 weeks 95/290 (33%) of the patients taking TCZ 4 mg/kg + MTX and 142/289 (49%) of the patients taking placebo + MTX were switched to TCZ 8 mg/kg + MTX because their DAS28 was > 3.2 ('escape therapy'). The remainder of patients continued on the same medication. Blinding was maintained for patients and site staff. All endpoints in the second year of the study were exploratory. Overall the responses to therapy achieved at Week 52 were maintained at Week 104. About 22-25% of patients with DAS28 remission at Week 52 shifted to being a non-responder by Week 104 and a similar rate of patients shifted from non-response at Week 52 to response at Week 104. DAS28 remission at Week 104 was achieved in 30.4% and 51.4% of the escape therapy patients in the TCZ 4 mg/kg + MTX and placebo + MTX groups.

Study WA17824 was a Phase III, 24 week randomised controlled non-inferiority study assessing the safety and efficacy of TCZ 8 mg/kg + placebo versus MTX + placebo in 572 adult patients with active moderate to severe RA that were MTX naïve or had not received MTX for 6 months. The patients were predominantly female (81%), White (71.5%) with a mean age of approximately 50 years. The primary endpoint was the proportion of patients with ACR20 response at Week 24 and had previously been evaluated by the TGA. A post-hoc analysis of the subgroup of 241 patients (116 TCZ, 125 MTX) with RA of ≤ 2 years duration at baseline showed a weighted difference of 22.4% (95% CI: 10.0, 34.7) in the proportion of patients with DAS remissions at Week 24. Similar responses were seen on ACR20, ACR50, ACR70 and HAD-QI in this analysis compared with the secondary endpoints in study WA19926. The ACR/EULAR remission responses were similar to an exploratory endpoint in study WA19926.

Study MRA012JP: This open-label, randomised trial of TCZ 8 mg/kg monotherapy compared to conventional DMARD therapy in 306 patients with active RA and an inadequate response to conventional DMARDS had a median duration of RA of 2.0 years and a mean baseline mTSS 28.3 in the TCZ 8 mg/kg group. The inhibition of mTSS, mSES and modified JSN score was 62% inhibition.

Study WA18695: This study was a long term extension study of WA17822 (a Phase III, 24 week, placebo controlled study in moderate to severe RA). This Phase III open label, single group, multinational, multicentre 5 year extension of the 24 week, Phase III, randomised, controlled Trial WA17822 to assess the long term safety of 8 mg/kg TCZ in 538 patients with at total exposure of 2461.9 PY and a median of 5.37 (range 0.2–6.4 years). The study population was mostly female (82%) and White (72%) with a mean age of 50.8 years. At 264 weeks 46% of the patients had achieved an ACR70 response and 61% had a DAS28 remission. Quality of life data was supportive but sufficient disease control allowed the reduction or cessation of oral corticosteroids in 10 or 20% of patients respectively.

Study NA2526: This was a US based, randomised, parallel-group, open-label, multicentre study to evaluate the effects of 8 mg/kg TCZ on vaccination with Pneumovax 23-valent polysaccharide vaccine and adsorbed tetanus toxoid vaccine in 91 adult patients aged < 65 years receiving background MTX for RA of > 6 months duration. The patients were not taking other DMARDs and were permitted maintenance doses of corticosteroids. The patients had not received pneumococcal vaccination in at least 3 years and tetanus toxoid vaccine in least 5 years. Anti-pneumococcal and anti-tetanus antibody titres were measured 5 weeks post vaccination.

The primary efficacy endpoint was the proportion of responders (defined as ≥ 2 fold increase in serum antibody titre or an increase of > 1mg/L from baseline) with ≥ 6 of 12 anti-pneumococcal antibody serotypes.

The primary efficacy results were:

- 60% response, TCZ 8 mg/kg + MTX (n = 54)

- 70.8% response, MTX only (n = 27)
- Difference -10.8% (95% CI: -33.7%, 12.0%)

Patients aged 51-< 65 years responded less well to vaccination (56.3% TCZ + MTX versus 66.7% MTX alone). The MTX only group produced a response to more serotypes than the TCZ group. The response to the tetanus toxoid vaccine in the TCZ + MTX group was 42.0% versus 39.1% in MTX alone (difference -2.9% 95% CI -21.4%, 27.1%). A post hoc analysis found no impact from corticosteroid use or duration of treatment for RA. The sample size was small in this study.

Pooled efficacy data: Pooled efficacy data from 5 studies showed 449 patients with early RA (treatment duration ≤ 2 years) receiving TCZ treatment at Week 264 showed 35.4% maintained DAS28 remission for 48 consecutive weeks, 26.9% for 96 consecutive weeks, 19.8% for 144 consecutive weeks and 15.8% for 192 consecutive weeks.

Safety

The safety profile was similar to that seen in previous studies of TCZ with RA. There were no new safety signals detected in the patient population with early RA.

Study WA18695: This was a Phase III, open label, single group, multinational, multicentre 5 year extension of the 24 week, Phase III, randomised, controlled Trial WA17822, to assess the long term safety of TCZ 8 mg/kg in 538 patients with at total exposure of 2461.9 PY and a median individual exposure of 5.37 (range 0.2–6.4 years). The study population was mostly female (82%) and White (72%) with a mean age of 50.8 years. Overall the AE rate was 275.7 per 100 PY, higher in the first 12 months (393.8 per 100 PY) then relatively constant over the subsequent 5 years. Observed changes in laboratory parameters were relatively stable after initial changes in the first year of treatment. There were 10 deaths (0.41 events per 100 PY). Serious AEs occurred at a rate of 13.85/100 PY, mostly infections (3.63/100 PY), neoplasms (1.3/100 PY) and gastrointestinal disorders (1.26/100 PY). The same types of AEs as well as elevated transaminases led to withdrawal. The most frequent AEs were from the infections/infestations SOC (84.2 per 100 PY). The frequency of SAEs and AEs did not increase with time.

In the pivotal Study WA19926, 1,012 patients received at least one dose of TCZ. The total duration of exposure to MTX 8 mg/kg + MTX drug was 682 years and 380.1, 481.1 and 331.7 for TCZ 4 mg/kg + MTX, TCZ 8 mg/kg + placebo and placebo + MTX, respectively. The mean duration of exposure was 1.29 years. Adverse events were frequent (83.3%-88.6%). The rates of AEs were 434.1/100 PY, 444.3/100 PY, 394.1/100 PY and 367.9 AEs per 100 PY in the TCZ 8 mg/kg + MTX, TCZ 4 mg/kg + MTX, TCZ 8 mg/kg + placebo and placebo + MTX groups, respectively. Adverse events followed a similar profile to that reported in the first treatment year. On switching to escape therapy there was no increase in AE rates. In the all-exposure population, AE rates in the early RA and MTX naïve subpopulations were also lower that those found in Study WA19926 (288 and 272 versus 434 events per 100 PY). The events rates in TCZ monotherapy were higher in WA19926 than WA17824 LTE (394 versus 254 per 100 PY).The highest AE rate was in the infection/infestation SOC followed by the gastrointestinal disorders and investigations.

There were 14 deaths were reported in Study WA19926. The rate was highest in the TCZ 4 mg/kg + MTX group compared to the other groups (1.27 per 100 PY versus 0.56-0.60 per 100 PY). Infections, particularly pneumonia were involved in 6 of the 9 cases and 3 patients were aged over 80 years. The death rate in WA19926, all TCZ and placebo + MTX groups was higher than in the other pooled populations including the early RA subpopulation (all TCZ, 0.88 versus 0.54 for early RA subpopulation). In the all-exposure LTE population, the most frequent cause of death was infections followed by cardiac disorders and malignancies. The death rate in the TCZ monotherapy group of WA19926

was lower than in the monotherapy group in WA17824 (0.37 versus 0.76). There was no pattern of aetiology in the deaths. The reported mortality rates with TCZ in the literature were between 0.3 and 0.83 events per 100 PY. The rate of SAEs was higher in TCZ groups than the placebo + MTX group (11.6-14.7 versus 9.1 SAEs per 100 PY). The most frequent SAEs were infections. The rate of SAEs increased on escape therapy.

Discontinuations due to AEs were higher in the TCZ groups than in the placebo + MTX group (9.9-12.0 versus 6.5 AEs per 100 PY) and highest in the TCZ 8 mg/kg + MTX group (20% versus 7.4–12.1%). Rates of withdrawal decreased in the 'non-escape' patients in the second year of therapy and were 7%, 10%, 9% and 3% of the TCZ 8 mg/kg + MTX, TCZ 8 mg/kg + placebo, TCZ 4 mg/kg + MTZ and placebo + MTX groups, respectively. Dose modifications and interruptions due to AEs were more common in the TCZ+ MTX groups than in the placebo + MTX or TCZ 8 mg/kg + placebo groups. The most common AEs leading to discontinuations were infections, increased transaminases and gastrointestinal disorders.

Infections: In the safety study the rate of infections was relatively constant over each year of the 5 year time period (87-93 per 100 PY years 1 to 4 and 72 per 100 PY at > 4 years). The serious infection rate was 3.6 per 100 PY with the most frequent being pneumonia (2 cases were fatal). Opportunistic infections occurred at a rate of 0.2 per 100 PY and tuberculosis at 0.3 events per 100 PY. In the pivotal study the rates of infections were 3.8/100 PY in the TCZ 8 mg/kg + MTX group and 4.2 in the TCZ 4 mg/kg + MTX group compared with 2.4 in the MTX + placebo group. The most common infections were URTI, nasopharyngitis and urinary tract infection. Serious infections were more common in the TCZ groups (3.6 per 100 PY versus 2.4 per 100 PY in the placebo + MTX group), and were mostly pneumonia and cellulitis.

Liver function tests: The rates of shift from normal at baseline to > ULN to ≤ 3 x ULN in ALT were 48.6%, 35.6% 39.1% and 36.9% in the TCZ 8 mg/kg + MTX, TCZ 8 mg/kg + placebo, TCZ 4 mg/kg + MTX and placebo + MTX groups, respectively, and for > 3 x ULN in 12.8% of TCZ 8 mg/kg + MTX group. There were no Grade 4 cases and 3.4–3.5% were Grade 3 in the TCZ + MTX groups. From Weeks 52–104 mean ALT, AST and bilirubin levels were steady. The rate of ALT > 3 x ULN was higher than reported in previous studies (for example, TCZ 8 mg/kg + DMARD/MTX (5.8%) in the DMARD-IR population in previous TCZ studies). In the safety study the mean ALT and AST increased by Week 2 then remain relatively stable at the ULN. Most of the shifts were within the range of > ULN to 3 x ULN. No cases met Hy's Law definition. There were 8 patients withdrawn for liver enzyme changes with 6 of these occurring in the first 12 months of treatment.

Haematological changes: In the pivotal study, the mean neutrophil count decreased by Week 8 and remained relatively stable through the rest of the study. Neutropenia was most frequent with TCZ 8 mg/kg doses. Common toxicity criteria (CTC) Grade 3 neutropenia was reported in 3.4%, 2.7%, 0.4%, and 0.7% in the TCZ 8 mg/kg + MTX, TCZ 8 mg/kg +placebo, TCZ 4 mg/kg + MTX and placebo + MTX groups, respectively; and Grade 4 occurred in 1 patient in the TCZ 8 mg/kg + placebo group. Approximately 5% of patients had CTC Grade 3 neutropenia in the safety study and the long term exposure population; < 1% had CTC Grade 4. In the pivotal study thrombocytopenia occurred in 9%, 9.2%, 7.3%, and 2.5% of the TCZ 8 mg/kg + MTX, TCZ 8 mg/kg + placebo, TCZ 4 mg/kg + MTX, and placebo + MTX groups, respectively. The decrease occurred in the first 4-8 weeks of therapy and the mean platelet count remained stable thereafter. This pattern was also seen in the safety study. CTC Grades 3 and 4 thrombocytopenia occurred in < 1% of patients in the safety and pivotal studies. Serious bleeding events rate was 0.5 per 100 PY in the safety study: one case was fatal (haemorrhagic stroke), 2 led to discontinuation (rectal haemorrhage, melaena) and 5 to dose modification.

Hypersensitivity: In the pivotal study, hypersensitivity events were seen in all groups: 17.6%, 15.4%, 20.4%, and 13.8% for TCZ 8 mg/kg + MTX, TCZ 8 mg/kg + placebo, TCZ

4 mg/kg + MTX, and placebo + MTX groups, respectively. The five serious hypersensitivity cases all occurred in the first year, including the two cases of anaphylaxis. Rates were consistent with pooled safety data. There were no cases of anaphylaxis in the safety study.

Immunogenicity: In the pivotal study anti-TCZ antibody development occurred in 1.4%, 1.0%, 3.5%, and 3.6% of the TCZ 8 mg/kg + MTX, TCZ 8 mg/kg + placebo, TCZ 4 mg/kg + MTX, and placebo + MTX groups, respectively. None of the 9 subjects with neutralising anti-TCZ antibodies was withdrawn for lack of treatment efficacy. Anti-TCZ immunoglobulin IgG antibody positivity did not predict hypersensitivity events but one patient with severe hypersensitivity (urticaria) was positive for IgE.

Malignancies: The 13 malignancy cases occurring in the first year of WA19926 were evenly spread across the treatment arms. In the second year of the study the eight malignancy cases (basal cell carcinoma (BCC), small cell lung cancer, two endometrial cancers, two squamous cell carcinomas (SCC), prostate cancer, and metastatic cancer with undetermined primary) all occurred in TCZ treated patients. The rate of malignancy and serious malignancy was consistent with the pooled safety data. The most frequent malignancies were breast, lung/bronchus and non-melanoma skin cancer.

Clinical evaluator's recommendation

The clinical evaluator has recommended approval for TCZ for the extension of indication to include *'in combination with methotrexate (MTX) in those not previously treated with MTX'*. The sponsor has withdrawn its proposal to change the monotherapy efficacy in joint damage reduction claim.

Risk management plan

The TGA OPR has accepted the EU Risk Management Plan for Actemra (tocilizumab), Version 15.0, dated May 2013 with Australian Specific Annexe, Version 3.1, dated March 2014.

The following were outstanding matters and should be followed up with OPR and in the response to the Delegate's Overview:

- The anticipated dates for the availability of data from studies NP25737 and MA21488 should be included in the pharmacovigilance plan if not already completed
- A detailed comparison of the Australian PI and the European Summary of Product Characteristics (SPC) should be reinstated in the ASA.

Risk-benefit analysis

Delegate's considerations

The primary issue with this submission is as follows:

The safety concerns with increased adverse events including elevations of transaminases observed early in therapy with the combination of TCZ and MTX compared with previous clinical trial experience with the combination of TCZ and MTX.

Efficacy

The superiority of TCZ 8 mg/kg + MTX versus MTX + placebo based on DAS remission at 24 weeks was demonstrated. This was supported by superiority of TCZ 8 mg/kg + MTX versus placebo + MTX across other parameters for disease remission, and this was sustained over a further year of treatment. There was an apparent induction of remission when non-responding patients with active disease from the MTX monotherapy group had

TCZ 8 mg/kg added. Radiological progression as measured by the mTSS was slowed in both the erosion and JSN components of the score. This effect was seen after 1 and 2 years of treatment. Supportive evidence of clinical efficacy was provided in addition to the pivotal clinical trial, and supportive evidence was provided for the reduction of erosion but not JSN.

The antibody responses mounted by patients to pneumococcal and tetanus toxoid vaccines while taking either TCZ 8 mg/kg or MTX were comparable.

Safety and RMP

Tocilizumab had an adequate duration of exposure, although some of the experience is not with concomitant MTX. The previously identified risks of infection, including tuberculosis, gastrointestinal perforation, hypersensitivity, elevation of transaminases, haematological abnormalities, elevated lipids and cardiovascular risk were observed in the early RA population in similar proportions to those seen in previous studies. However, an increased mortality, although not SAEs, more discontinuations secondary to AEs and a higher proportion of patients with elevated transaminases were seen. Most of the increased AEs appeared to occur early in treatment. The sponsor would be requested to comment on this issue.

An acceptable RMP has been provided.

Data deficiencies

There are some apparent discrepancies in the number of responders and the numbers of some AEs reported in the interim and final study reports for WA19926. The sponsor would be asked to make comment.

Proposed action

The Delegate was not in a position to say, at this time, that the application to amend the indication for tocilizumab (Actemra) should not be approved.

Conditions of registration

The following were proposed as conditions of registration:

- The implementation in Australia of the EU Risk Management Plan for Actemra (tocilizumab), version 15.0, date May 2014, with the Australian Specific annex (ASA), version 3, dated March 2014.
- The following studies must be submitted to the TGA, as soon as possible after completion, for evaluation as a Category 1 submission:
  - The final study report for the randomised controlled trial to rule out a moderate increase in the risk of serious cardiovascular events with TCZ (WA25204).
  - The Study NP25747, a PK and safety study of TCZ in patients less than 2 years old with active sJIA.

Request for ACPM advice

The Delegate proposed to seek general advice on this application from the Advisory Committee on Prescription Medicines (ACPM) and to request the committee provide advice on the following specific issues:

1. The following questions relate to the evidence supporting the proposal to extend the indication to include treatment of moderate to severe active rheumatoid arthritis in adult patients in combination with methotrexate (MTX) in those not previously treated with MTX:

a. Does the committee consider the population of patients with early RA, for whom the benefits and risks of the combination of TCZ 8 mg/kg and MTX is favourable, has been adequately characterised in the studies provided in the submission?

b. Does the committee consider that there should be modification of the indication to better define the population that will benefit from early therapy with TCZ and MTX?

c. If the extension of indication is approved does the committee consider the risks in the patients with early RA have been adequately described in the PI?

2. Is the committee satisfied that the immune responses to Pneumovax 23 and adsorbed tetanus toxoid vaccines in patients taking TCZ + MTX compared with those taking MTX alone are sufficient to be considered effective?

Questions for the sponsor:

The Delegate requested the sponsor address the following in its response to the Delegate's Overview

1. Please provide an update to the AEs experienced by patients in the ACTiv program. Please include the following:
   - The total number of patients exposed on the program, plus the exposure expressed in PY,
   - All reports of anaphylaxis or serious hypersensitivity events,
   - All SAEs in patient on the program, and
   - The number of discontinuations from the program, a brief summary of the reasons for discontinuation, and, if possible, and their disposition (for example, return to hospital based care, discontinued therapy with TCZ).
2. Please address all the outstanding RMP matters as discussed above under *Risk Management Plan*, or provide an assurance that this has been done.
3. Please explain the power calculation for Study NA25256.
4. The following questions relate to Study WA19926:
   a. In the pivotal Study WA19926, the rate of deaths, SAEs and discontinuations were greater in the TCZ groups compared with the MTX/placebo groups. The rates of these events were higher in WA19926 than comparable studies. Please provide an explanation of these differences.

   b. Cardiovascular deaths were noted in Study WA19926, as was an increase in serum lipids over time. Please provide an analysis of the cardiovascular deaths according to baseline lipids at study entry, lipid lowering medications if any, and lipid profile during the study.

   c. In Study WA19926 there are differences between the DAS remission rates reported at the end of the Week 52 in the report provided in this submission and the rates reported in the final study report. This also impacts the results for neutralising antibodies. This affects all the key secondary endpoint results for 52 weeks in the proposed to be tabulated in draft PI. It is presumed that these differences occurred because of imputation methods for missing data. Please provide a detailed account of the methods used to arrive at a different set of Week 52 results to provide assurance there are no data integrity issues such as transcription or optical data transfer issues. Please indicate if these data handling processes have been conducted on the data to 24 Weeks. If so, please provide a

re-analysis to demonstrate the impact on the primary efficacy analysis and the key secondary efficacy outcomes.

d. Elevation of ALT > 3 x ULN in Study WA19926 in the TCZ 8 mg/kg + MTX group (12.8%) was greater than that reported for the in the TCZ 8 mg/kg + DMARD/MTX group (5.8%) in DMARD-IR from previous studies. Please provide an explanation of the difference observed between the two studies. Please indicate whether the elevated liver enzymes returned to normal on TCZ withdrawal or dose modification.

5. Please provide an update to the submission under evaluation by the EMA. Please provide a brief summary of the issues raised by the European rapporteurs and the sponsor's responses.
6. Please provide a list of all ongoing or planned clinical studies involving TCZ together with their planned dates of completion.

Remaining questions related to revisions to the PI. Details of these are beyond the scope of the AusPAR.

Response from sponsor

Sponsor comment on the delegate's request for ACPM advice (Delegate's overview)

The sponsor considers that the benefit-risk profile for Actemra for this application is positive and therefore should be approved.

The pivotal Study WA19926 enrolled a patient population with moderate to severe active early RA of ≤ 2 years duration. To be eligible for the study patients must have had clinical evidence of early moderate to severe RA as characterized by DAS28 > 3.2, a minimum of 4 and 6 swollen and tender joints respectively, elevated ESR or CRP, and must have been positive for RF or anti-CCP antibodies. Patients without positive RF or anti-CCP tests must have had radiographic evidence of at least 1 erosion of the hands, wrists or feet. This is an enriched population of patients with poor prognosis who will benefit from early aggressive treatment.

Sponsor responses to the questions for the sponsor raised by the delegate

Response to delegate's question 1.

ACTiv is an Infusion Management Program for Actemra (TCZ) offering a coordinated approach to infusion services making Actemra treatment easier for the health care professional and the patient.

From 2009, the total number of anaphylaxis or serious hypersensitivity events experienced in patients on the program is 12 and the total number of SAEs experienced in patients on the program is 1307.

From the commencement of the ACTiv program in 2009, 26% of patients have permanently discontinued TCZ under the ACTiv program, the average length of treatment before cessation was 9 months. This is comparable with the average rate of discontinuations of all biological treatments for RA and discontinuation rates for Actemra seen in other treatment settings[6,7].

[6] Stand Vet al Discontinuation of biologic therapy in rheumatoid arthritis (RA): Analysis from the Consortium of Rheumatology Researchers of North America (CORONA) database. *Ann Rheum Dis* 2013;72(suppl3):71.
[7] Tovor Beltram JV et al. ACT-LIFE Study: patterns of tocilizumab use and dosing among patients with rheumatoid arthritis in the clinical practice. *Ann Rhuem Dis* 2013;72(suppl3):456.

Response to delegate's question 2.

All outstanding matters have been addressed in the updated Australian Specific Annex v3.2 (July 2014) to the EU-RMP v15.0 and a copy provided to the OPR on 14 July 2014.

Response to delegate's question 3.

The sample size for Study NA25256 was based on practical considerations of a reasonable sized population and statistical considerations based on the accuracy of the estimate of the proportion of responders. No power calculation was performed as no formal statistical hypothesis testing was.

Response to delegate's question 4a.

In the DMARD-IR population, the rate of deaths was slightly lower than in the WA19926 population but 95% CIs were wide and overlapping. In the pivotal study WA19926, there were 9 patient deaths reported at Week 52, and 14 deaths at Week 104. Twelve deaths were reported in TCZ treated patients compared to two deaths in placebo + MTX-treated patients. The underlying causes of death were variable across treatment groups with no particular clustering of types of events over time.

Overall the rate of deaths at Week 104 per 100 PY in the TCZ groups was similar to that seen in the placebo + MTX group with the exception of the TCZ 4 mg/kg + MTX group which had a numerically higher rate of deaths compared with the placebo + MTX group (TCZ 4 mg/kg + MTX: 1.27 [95% CI; 0.41, 2.96]; TCZ 8 mg/kg + MTX: 0.56 [95% CI; 0.15, 1.43]; TCZ 8 mg/kg + placebo: 0.60 [95% CI; 0.12, 1.75]; placebo + MTX: 0.59 [95% CI; 0.07, 2.13] deaths per 100 PY). However, the 95% CIs were wide and overlapping and 3 of the 5 deaths reported in the 4 mg/kg + MTX group occurred in patients over the age of 80. The majority of deaths in the study were considered to be unrelated to TCZ treatment.

The rate of SAEs was numerically higher in the TCZ groups than in the placebo + MTX groups at both Week 52 and Week 104 of Study WA19926, with 95% CIs overlapping (TCZ 4 mg/kg + MTX 14.7 [95% CI; 11.2, 19.0], TCZ 8 mg/kg + MTX 11.6 [95% CI; 9.2, 14.3] and TCZ 8 mg/kg + placebo 13.3 [95% CI; 10.3, 16.9] versus placebo + MTX 9.1 [95% CI; 6.2, 13.0] SAEs per 100 PY at Week 104). The SAEs reported during the study were consistent with the known safety profile of TCZ, with infections and infestations being the SOC with the highest rate of events per 100 PY. Patients in the TCZ 4 mg/kg + MTX had the highest rate of SAEs but it is worth noting that these patients were marginally older than patients in the other treatment groups (mean: 51.2 versus 49.5-49.9 years) and had a higher number of concurrent diseases at baseline. The rates of events in WA19926 were broadly similar to those observed in the DMARD-IR study populations, with overlapping 95% CIs.

An increase in discontinuations due to safety reasons was observed with increased intensity of RA treatment from placebo + MTX, through TCZ 4 mg/kg + MTX, TCZ 8 mg/kg monotherapy, up to TCZ 8 mg/kg + MTX. This increase appears to be driven mainly by elevations in hepatic enzymes, since the number of discontinuations for safety reasons other than increased transaminases is consistent between the arms. A risk mitigation strategy against hepatic changes required patients with an ALT/AST elevation > 5 x ULN to be withdrawn from the study, and for patients with an elevation > 3 x ULN to be withdrawn if elevations continued despite reduction of MTX below 7.5 mg/week or interruption of TCZ for more than 3 consecutive doses.

Response to delegate's question 4b.

Listings of baseline lipids, lipid profile during the study, and lipid lowering medications for deaths due to cardiovascular reasons were provided. One patient in the TCZ 4 mg/kg + MTX group died as a result of arteriosclerosis. The patient was not taking any lipid lowering medication and did not have any elevated lipid parameters during the study. A patient in the 8 mg/kg TCZ + placebo group died as a result of congestive cardiac failure. The patient had elevated triglycerides at baseline and throughout the study despite taking

simvastatin prior to and during the study. These data suggest that the cardiovascular deaths that occurred during the study were not as a result of any TCZ induced increase in lipids.

Response to delegate's question 4c.

Standard data handling methods for collection, transfer and imputation of data, were applied to both the Week 52 datacut and the final Week 104 datacut Therefore Roche provides the assurance that there are no data integrity issues. Week 24 data was analysed at the primary analysis datacut at Week 52 and also applied the standard data handling rules. Differences in the data between Week 52 and Week 104 datacuts are expected due to ongoing cleaning of the open database throughout the study. Pre-defined sensitivity analyses were also carried out on the primary endpoint to ensure the integrity of the data and the robustness of the imputation method used.

Differences in DAS remission rates reported in the Week 52 study report and the final study report (Week 104 results) are due to missing data at the time of the Week 52 analysis. This was an ongoing study at the time of the primary analysis and therefore changes could be made to the database after the primary analysis was carried out. The discrepancy is due to 27 patients missing an ESR result at Week 52 in the original analysis, which resulted in no DAS28 score being calculated, and the imputation of "nonresponder" for remission status for these patients. All 27 missing ESR scores were available at the time of the final analysis, resulting in 15 patients being classed as not in DAS remission and 12 patients being classed as in DAS remission.

Similar data discrepancies due to performing analysis on a live database resulted in small variations in the results of all secondary endpoints. The one exception to this is the radiographic scores which saw greater differences in the data between the Week 52 and Week 104 analyses. Extensive investigation of the data indicated that this was due to the fact that two independent campaigns of X-ray readings were used. No differences in imputation methods were employed.

The final clinical study report (CSR) reported that 3 patients reported in the primary CSR as having developed neutralising anti-TCZ antibodies are no longer considered to have done so as they had positive confirmation assay results at baseline. One additional patient had a positive neutralising result at Week 104, therefore resulting in an overall difference of 2 patients.

Response to delegate's question 4d.

Both MTX and TCZ have known risks of causing elevations in hepatic enzymes (including ALT) which are addressed in the PI. In clinical trials with TCZ, transient or intermittent mild to moderate elevations in ALT were commonly reported with TCZ treatment without progression to hepatic injury. An increased frequency of these elevations was observed when potentially hepatotoxic drugs (such as MTX) were used in combination with TCZ. Since patients in WA19926 were MTX naïve when entering the study and placed on a rapid titration of MTX to a maximum of 20 mg/week, elevations of ALT were expected to be greater than those observed in the DMARD-IR population, especially in the TCZ treatment arms.

Of 47 patients in the WA19926 TCZ 8 mg/kg + MTX treatment group with elevations of ALT > 3 x ULN, 34 patients returned to normal, with 24 patients not having any modification in TCZ dose. The median time from last elevation ALT > 3 x ULN to normalisation for these 34 patients was 33 days. Of the 13 patients whose ALT levels did not return to normal, 8 stopped TCZ treatment while 5 had no TCZ dose modification.

Response to delegate's question 5.

Information on the status of the submission in the EU was provided as requested.

Response to delegate's question 6.

An overview of all ongoing and planned clinical studies involving TCZ and the planned dates of completion was provided as requested.

Remaining responses relate to revisions to the PI. Details of these are beyond the scope of the AusPAR.

Advisory committee considerations

The ACPM, having considered the evaluations and the Delegate's overview, as well as the sponsor's response to these documents, advised the following:

The submission seeks to register an extension of indications for a currently registered product.

The ACPM, taking into account the submitted evidence of efficacy, safety and quality, considered Actemra solution for IV infusion containing 80 mg, 200 mg, 400 mg as 20 mg/mL of TCZ to have an overall positive benefit–risk profile for the amended indication as follows:

> *Actemra is indicated for the treatment of moderate to severe active rheumatoid arthritis (RA)* ***with poor prognostic factors*** *(see Clinical Trials) in adult patients in combination with methotrexate (MTX) in those not previously treated with MTX;*
>
> *Actemra has been shown to inhibit the progression of joint damage in adults, as measured by X-ray, when given in combination with methotrexate.*

In making this recommendation the ACPM considered this indication better reflected the inclusion criteria of the population in the trial submitted who had poor prognostic factors defined as those who were positive for either RF or anti-CCP antibodies (Abs) at screening or if negative for RF and anti-CCP, and had one or more erosions of the hands wrists or feet at screening.

Proposed conditions of registration

The ACPM agreed with the Delegate on the proposed conditions of registration.

Proposed Product Information (PI)/Consumer Medicine Information (CMI) amendments

The ACPM agreed with the Delegate to the proposed amendments to the PI and CMI and specifically advised on the inclusion of the following:

- The *Clinical Trials* section of the PI should include the percentage by which the transaminases are increased.
- Amendment of the statement in the *Precautions* section regarding vaccinations to In a randomised open-label study, adult RA patients treated with Actemra plus MTX had a comparable effective response to both the 23-valent pneumococcal polysaccharide (PPV) and tetanus toxoid (TTV) vaccines to the response seen in patients receiving MTX only (60% versus 71% for PPV; 42% versus 39% for TTV, respectively).
- A statement in the relevant sections of the CMI should state that Steven-Johnson syndrome is a rare side effect and its symptoms should be grouped together under the heading 'Stevens-Johnson syndrome' to assist identification.

Specific advice

The ACPM advised the following in response to the specific delegate's questions on this submission:

1. The following questions relate to the evidence supporting the proposal to extend the indication to include treatment of moderate to severe active RA in adult patients in combination with methotrexate (MTX) in those not previously treated with MTX:

    a. Does the committee consider the population of patients with early RA, for whom the benefits and risks of the combination of TCZ 8 mg/kg and MTX is favourable, has been adequately characterised in the studies provided in the submission?

The ACPM considered that the population of patients was adequately characterised in the studies. The DAS28 score of more than 3.2 was indicative of patients with moderate to severe activity of disease and included patients with poor prognosis with a high risk of erosive changes who would deteriorate rapidly if left untreated but would benefit from early treatment.

    b. Does the committee consider that there should be modification of the indication to better define the population that will benefit from early therapy with TCZ and MTX?

The ACPM noted the population enrolled in the pivotal trial (WA19926) included patients with progressive disease and poor prognostic factors. The ACPM noted the indication proposed by the CHMP of the EMA but considered that the inclusion of 'poor prognostic factors' was a more practical way of defining the population, was consistent with the characteristics of the trial population, and with the current classification of rheumatoid arthritis disease severity.

The ACPM therefore considered that the indication should be amended to *moderate to severe rheumatoid arthritis with poor prognostic factors (see Clinical Trials)*.

    c. If the extension of indication is approved does the committee consider the risks in the patients with early RA have been adequately described in the PI?

The ACPM considered that the risks in patients with early RA have been adequately described in the PI. The ACPM recommended that the percentage increase in transaminases be included in the PI for further clarification to indicate percentage risk.

2. Is the committee satisfied that the immune responses to Pneumovax 23 and adsorbed tetanus toxoid vaccines in patients taking TCZ + MTX compared with those taking MTX alone are sufficient to be considered effective?

The ACPM considered that the vaccine study was too small and not sufficiently powered to detect a difference in response in those patients receiving methotrexate alone versus those receiving methotrexate plus TCZ. The ACPM considered that the 10% difference in effect was not statistically significant. The ACPM advised an alternative statement for the *Precautions* section of the PI.

The ACPM advised that the implementation by the sponsor of the recommendations outlined above to the satisfaction of the TGA, in addition to the evidence of efficacy and safety provided would support the safe and effective use of this product.

Outcome

Based on a review of quality, safety and efficacy, TGA approved the registration of Actemra injection concentrate containing tocilizumab (rch) for the new indication:

> ***Rheumatoid Arthritis***
>
> *Actemra is indicated for the treatment of moderate to severe active rheumatoid arthritis in adult patients with poor prognostic factors (see Clinical Trials) in combination with MTX in those not previously treated with MTX.*

The full indications are now:

Rheumatoid Arthritis

Actemra is indicated 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.

Actemra is indicated for the treatment of moderate to severe active rheumatoid arthritis in adult patients with poor prognostic factors (see Clinical Trials) in combination with MTX in those not previously treated with MTX.

In the two groups of patients above, Actemra can be given as monotherapy in case of intolerance to MTX or where continued treatment with MTX is inappropriate.

Actemra has been shown to inhibit the progression of joint damage in adults, as measured by X-ray, when given in combination with methotrexate.

Polyarticular Juvenile Idiopathic Arthritis

Actemra is indicated for 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 (MTX). Actemra can be given alone or in combination with MTX.

Systemic Juvenile Idiopathic Arthritis

Actemra is indicated for the treatment of active systemic juvenile idiopathic arthritis in patients 2 years of age and older. Actemra can be given alone or in combination with methotrexate (MTX).

Specific conditions of registration applying to these goods

- The Actemra tocilizumab (rch) EU Risk Management Plan (RMP), version 15.0, dated May 2013, with Australian Specific Annexe (ASA) version 3.2, dated July 2014 included with submission PM-2013-02398-1-3, and any subsequent revisions, as agreed with the TGA will be implemented in Australia.
- The final clinical study reports of the following studies must be submitted to the TGA as soon as possible after completion, for evaluation as a Category 1 submission or Category 1 submissions:
  - That for the randomised controlled trial, WA25204, to determine whether or not there is a moderate increase in the risk of serious cardiovascular events with tocilizumab
  - That for the Study NP25747, a pharmacokinetic and safety study of tocilizumab in patients less than 2 years old with active sJIA.

Attachment 1. Product Information

The Product Information approved for Actemra at the time this AusPAR was published is at Attachment 1. For the most recent Product Information please refer to the TGA website at <https://www.tga.gov.au/product-information-pi>.

Attachment 2. Extract from the Clinical Evaluation Report

Therapeutic Goods Administration

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