5.22 TOCILIZUMAB 162 mg/0.9 mL injection, 4 x 0.9 mL syringes, Actemra®, Roche Products Pty Limited

1 Purpose of Application

1.1 The minor submission sought to request an Authority Required Listing for a subcutaneous (SC) injection presentation of tocilizumab, for the treatment of severe active rheumatoid arthritis (RA).

2 Requested listing

2.1 The submission sought the same restriction for tocilizumab SC as currently exists for tocilizumab intravenous (IV) injection in severe active RA along with a new grandfathering restriction.

For more detail on PBAC's view, see section 6 "PBAC outcome"

3 Background

3.1 Tocilizumab SC is TGA registered (21/01/2016) for the following indications:

- 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.
- Tocilizumab SC 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, Tocilizumab SC can be given as monotherapy in case of intolerance to MTX or where continued treatment with MTX is inappropriate.

3.2 Tocilizumab SC has not previously been considered by PBAC.

3.3 Tocilizumab solution for IV infusion has previously been considered for severe active RA by the PBAC in July and November 2009, March 2010 and March 2013. The PBAC in July 2009 recommended tocilizumab IV for PBS listing for severe active RA.

3.4 This current submission seeks the PBS listing of a new, SC administered, formulation of tocilizumab.

3.5 This submission nominates etanercept and adalimumab, both delivered in subcutaneous form, as the main comparators and presents a cost-minimisation analysis against these therapies. Based on the previous submission to the July 2011 PBAC for abatacept SC, which was recommended for PBS listing on a cost minimisation basis to etanercept SC.

For more detail on PBAC's view, see section 6 "PBAC outcome"

4 Consideration of evidence

Sponsor hearing

4.1 There was no hearing for this item as it was a minor submission.

Consumer comments

4.2 The PBAC noted that no consumer comments were received for this item.

Clinical trials

4.3 The minor submission presented the results of one pivotal trial, SUMMACTA. The SUMMACTA trial was a randomised, double-blind, parallel group trial of the safety and effect on clinical outcome of tocilizumab SC versus tocilizumab IV, in combination with MTX, in patients with moderate to severe active RA who had an inadequate clinical response to MTX.

The primary objectives of the trial were to compare:

- The efficacy of treatment with 162 mg tocilizumab given SC weekly versus 8 mg/kg tocilizumab given IV every 4 weeks with regard to non-inferiority of the proportion of patients who achieved ACR20 response at Week 24.
- The safety of treatment with 162 mg tocilizumab given SC weekly versus 8 mg/kg tocilizumab given IV every 4 weeks, with regard to AEs and laboratory assessments.

The secondary objectives were to evaluate and compare additional efficacy indicators from the two arms including:

- Long-term safety and efficacy.
- Pharmacokinetics and pharmacodynamics of tocilizumab following SC administration.
- Immunogenicity of tocilizumab following SC administration.
- Effect of IV to SC switch on the safety, efficacy, pharmacokinetics, and pharmacodynamics of tocilizumab.

The minor submission presented one direct randomised clinical trial (see Table 1).

Table 1: Trials and associated reports presented in the submission

Trial ID	Protocol title/ Publication title	Publication citation
Direct randomised trials		
SUMMACTA (WA22762)	SUMMACTA Synopsis (PROTOCOL WA22762). A Randomized, Double-Blind, Parallel Group Study of the Safety and Effect on Clinical Outcome of Tocilizumab SC versus Tocilizumab IV, in Combination with Traditional Disease-Modifying Anti-Rheumatic Drugs (DMARDs), in Patients with Moderate to Severe Active Rheumatoid Arthritis. 2012	Burmester GR, Rubbert-Roth A, Cantagrel A, et al.(2013) Ann Rheum Dis Synopsis of research report 1048410, October 2012

Source: Text, p14 of the submission

4.4 The trial design for the SUMMACTA trial is presented below:

Two-arm, 2-year, randomised, double-blind, double-dummy, active-controlled, parallel-group, multicentre trial:

- Group A: 162 mg of tocilizumab SC weekly and IV placebo q4w for 24 weeks
- Group B: 8 mg/kg of tocilizumab IV q4w and SC placebo qw for 24 weeks

Patients were subsequently re-randomised for the open-label treatment period.

Comparative effectiveness

4.5 Results for the primary endpoint, ACR20 responders (at Week 24) for tocilizumab SC (162 mg fixed dose) and tocilizumab IV (8 mg/kg dose) are shown in Table 2.

Table 2: Summary of data for the primary outcome of SUMMACTA

Efficacy	162 mg SC qw+MTX (N=558)	8 mg/kg IV q4w+MTX (N=537)	Weighted difference (95% CI)
Primary endpoint at week 24 (PP) Percentage of ACR20 responders	69.4%	73.4%	−4.0(−9.2, 1.2)
Sensitivity analysis (ITT) Percentage of ACR20 responders	n=631 67.7%	n=631 70.2%	−2.7 (−7.6, 2.2)

Source: Submission page 15

Abbreviations: ACR=American College of Rheumatology; CI=confidence intervals; ITT=intent to treat; IV=intravenous; MTX=methotrexate; PP=per protocol; SC=subcutaneous.

4.6 The submission concluded that tocilizumab SC was non-inferior to tocilizumab IV. The ACR20 response at Week 24 using a non-inferiority margin of −12%. The percentages of patients who achieved an ACR20 response for tocilizumab SC and tocilizumab IV were 69.4% and 73.4%, respectively.

4.7 Analysis of the secondary endpoints of ACR50 responders, ACR70 responders, disease activity score (DAS remission), decrease in HAQ-DI, and withdrawal for lack of therapeutic response is presented below (Table 3).

Table 3: Summary of data for the secondary outcomes of SUMMACTA

Efficacy	162 mg SC qw+MTX (N=558)	8 mg/kg IV q4w+MTX (N=537)	Weighted difference (95% CI)
Secondary endpoints at week 24			
ACR50 responders, n (%)	262 (47.0)	261 (48.6)	−1.8 (−7.5, 4.0)
ACR70 responders, n (%)	134 (24.0)	150 (27.9)	−3.8 (−9.0, 1.3)
DAS remission (< 2.6) n (%)	198 (38.4)	184 (36.9)	0.9 (−5.0, 6.8)
Decrease in HAQ-DI ≥ (0.3) n (%)	336 (65.2)	337 (67.4)	−2.3 (−8.1, 3.4)
Withdrawal due to lack of therapeutic response n (%)	[redacted]	[redacted]	[redacted]

Source: Submission page 15

Abbreviations: ACR=American College of Rheumatology; CI=confidence intervals, DAS=disease activity score; HAQ-DI-Health Assessment Questionnaire-Disability Index; ITT=intent to treat; IV=intravenous; MTX=methotrexate; PP=per protocol; SC=subcutaneous

4.8 The submission stated all secondary outcomes supported the hypothesis that the tocilizumab SC regimen was non-inferior to the tocilizumab IV regimen. Similar improvements in quality of life endpoints (HAQ-DI score and SF-36) between baseline and Week 24 were also observed in both treatment arms.

4.9 As this was a minor submission, the results have not been independently evaluated.

Comparative harms

4.10 Comparisons of adverse events between tocilizumab SC and tocilizumab IV are shown in Table 4.

Table 4 Summary of SUMMACTA safety results

Safety	162 mg SC qw+MTX (N=631)	8 mg/kg IV q4w+MTX (N=631)
Any AE	481 (76.2%)	486 (77.0%)
Serious AEs	29 (4.6%)	33 (5.2%)
Deaths	0 (0.0%)	1 (<1%)
Withdrawal due to AE	30 (4.8%)	41 (6.5%)
AEs leading to dose modification or interruption	172 (27.3%)	170 (26.9%)

Source: Submission page 16

Abbreviations: AE=Adverse Event; IV=intravenous; MTX=methotrexate; SC=subcutaneous.

4.11 There was no significant difference in the type or frequency of adverse events across the two treatment arms. The incidence of any adverse events was also comparable across both arms (77.0% in the IV arm versus 76.2% in the SC arm).

4.12 As this was a minor submission, the results have not been independently evaluated.

Clinical claim

4.13 The submission claimed non-inferior comparative effectiveness and non-inferior

comparative safety of tocilizumab SC (162 mg fixed dose) compared with tocilizumab IV (8 mg/kg dose).

For more detail on PBAC's view, see section 6 "PBAC outcome"

5 Pricing considerations

5.1 This submission presents cost-minimisation analyses are based on the current PBS prices for etanercept and adalimumab for an equivalent treatment period. The submission claimed that the listing of tocilizumab SC will be cost neutral to the PBS.

5.2 At the price proposed in the submission, the negligible increase in net cost to Commonwealth Government was due to differences in patient co-payments and preferential cannibalisation of adalimumab by tocilizumab SC (see Table 5 below). No increase in MBS costs was predicted due to similarity of administration to etanercept and adalimumab.

Table 5: Overall net cost to Commonwealth Health budget of listing tocilizumab SC

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
Overall net cost to the PBS	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]
Overall net cost to the RPBS	−$0.19	−$0.37	−$0.64	−$0.90	−$0.95	−$0.99
Overall net cost to Medicare Australia	$0.00	$0.00	$0.00	$0.00	$0.00	$0.00
Overall net cost for MBS	$0.00	$0.00	$0.00	$0.00	$0.00	$0.00
Overall Net cost to Commonwealth Government Health Budget of listing Drug	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]

Source: submission page 19

The redacted table above shows that at year 6, the net cost to PBS would be negligible.

5.3 As this was a minor submission, the financial estimates have not been independently evaluated.

For more detail on PBAC's view, see section 6 "PBAC outcome"

6 PBAC Outcome

6.1 The PBAC recommended the Authority Required listing of tocilizumab, delivered by a subcutaneous (SC) injection, for the treatment of severe active rheumatoid arthritis (RA) on a cost minimisation basis to the biological disease modifying antirheumatic drugs (bDMARDS). The PBAC agreed with the submission that it was reasonable to assume that tocilizumab SC is equi-effective to all currently PBS-listed bDMARDs for this indication.

6.2 Based on the trial evidence provided in the submission, the equi-effective doses were tocilizumab 162 mg in 0.9 mL administered subcutaneously weekly and tocilizumab 8 mg/kg administered intravenously on day 1 and day 29 and then every 28 day later.

6.3 The PBAC considered that a general schedule listing is consistent with other PBS-listed bDMARDS that are delivered via the subcutaneous route. The PBAC noted the request for grandfather clause to allow patients who have received tocilizumab SC outside the PBS to continue to access the treatment on the PBS. The potential size of the patient population was provided in the submission.

6.4 The PBAC considered that the outcomes of the SUMMACTA trial supported a clinical claim that tocilizumab SC was non-inferior in terms of comparative effectiveness and comparative safety to tocilizumab IV. The PBAC noted that the submission stated that in demonstrating non-inferiority of tocilizumab SC to an existing bDMARD (ie IV tocilizumab) it is possible to infer that tocilizumab SC is non-inferior to all other PBS-listed bDMARDs. The PBAC agreed that there is this inference from the consideration of other bDMARDs for severe active rheumatoid arthritis by the PBAC. The PBAC noted that in recommending tocilizumab IV, abatacept and infliximab were considered to be appropriate as the main comparators when tocilizumab was used with methotrexate and etanercept to be appropriate as the main comparators when tocilizumab was used in monotherapy.

6.5 The PBAC noted the submission's cost-minimisation analysis of tocilizumab SC versus etanercept and adalimumab for an equivalent treatment period. The PBAC considered that all bDMARDs were appropriate comparators, noting that infliximab was the lowest cost comparator. Based on the evidence presented in the submission, the PBAC was not satisfied that tocilizumab SC provides a significant improvement in efficacy or reduction of toxicity over infliximab. Therefore, there was no basis for tocilizumab to have a cost advantage over infliximab for an equivalent treatment period.

6.6 The PBAC noted that there will be flow on changes to the listing of all bDMARDs following the listing of subcutaneous version of tocilizumab (SC) to the listing of all bDMARDs.

6.7 The PBAC advised that tocilizumab SC is not suitable for prescribing by nurse practitioners.

6.8 The Early Supply Rule should apply to the continuing treatment phase listing as it currently applies to other bDMARDs preparation on the general schedule.

6.9 The PBAC advised that tocilizumab SC should be treated as interchangeable on an individual patient basis with the currently listed bDMARDs for this indication: abatacept, adalimumab, certolizumab pegol, etanercept, golimumab, infliximab, rituximab, tocilizumab and tofacitinib.

6.10 The submission is not eligible for an Independent Review, because the PBAC has made a positive recommendation.

Outcome:
Recommended

7 Recommended listing

7.1 Add new item:
Restriction to be finalised.

8 Context for Decision

The PBAC helps decide whether and, if so, how medicines should be subsidised in Australia. It considers submissions in this context. A PBAC decision not to recommend listing or not to recommend changing a listing does not represent a final PBAC view about the merits of the medicine. A company can resubmit to the PBAC or seek independent review of the PBAC decision.

9 Sponsor's Comment

Roche welcomes a positive recommendation for tocilizumab SC. However, there is a clear distinction between the patient populations that will be prescribed tocilizumab SC, and as such different comparators to tocilizumab are appropriate for these patient groups. Roche does not believe that the PBAC's choice of comparator for tocilizumab (infliximab, as the lowest cost bDMARD) is aligned with clinical practice, previous PBAC decisions regarding the bDMARDs in rheumatoid arthritis, nor the existing or in-development versions of the PBAC guidelines.

Roche is committed to working with the PBAC to achieve a PBS listing for tocilizumab SC in patients with severe active RA at the earliest opportunity.