

6.10 TOCILIZUMAB, Injection 162 mg/0.9 mL, pre-filled syringe and pen, Actemra[®], Roche Products Pty Ltd

1 Purpose of application

- 1.1 The submission requested a Section 85, Authority Required (in writing) listing for tocilizumab for the treatment of patients with new-onset or relapsed giant cell arteritis (GCA). The PBAC has not previously considered tocilizumab for the treatment of GCA.
- 1.2 The listing was requested on a cost-effectiveness basis compared to standard care, represented by a 52-week corticosteroid tapering regimen.

Table 1: Key components of the clinical issue addressed by the submission

Component	Description
Population	Patients with giant cell arteritis.
Intervention	Tocilizumab 162 mg subcutaneously once weekly for 52 weeks in conjunction with a 26-week corticosteroid tapering regimen.
Comparator	Standard-of-care, represented by a 52-week corticosteroid tapering regimen.
Outcomes	Proportion of patients achieving sustained remission at 52 weeks; time to first flare after achieving remission; proportion of patients experiencing a flare; total cumulative corticosteroid dose over 52 weeks.
Clinical claim	In patients with giant cell arteritis, tocilizumab for 52 weeks in conjunction with a 26-week corticosteroid tapering regimen, is more effective than a 52-week corticosteroid tapering regimen at: achieving a sustained remission; delaying time to first flare following clinical remission; reducing the risk of flare after achieving remission; and reducing the cumulative corticosteroid dose; and non-inferior in terms of safety.

Source: Table 1.1, p.4 of the submission.

2 Requested listing

- 2.1 The listing requested in the submission is outlined below. Suggested additions by the PBAC are in italics and deletions are in strikethrough.

Name, Restriction, Manner of administration and form	Max. Qty packs	Max. Qty units	№.of Rpts	Dispensed Price for Max. Qty	Proprietary Manufacturer	Name and
TOCILIZUMAB						
162 mg/0.9 mL injection, 4 x 0.9 mL pre-filled syringe	1	4	5	\$953.23	Actemra [®]	Roche
162 mg/0.9 mL injection, 4 x 0.9 mL pre-filled pen	1	4	5			

Category / Program	GENERAL – General Schedule (Code GE)
Prescriber type:	<input type="checkbox"/> Dental <input checked="" type="checkbox"/> Medical Practitioners <input type="checkbox"/> Nurse practitioners <input type="checkbox"/> Optometrists <input type="checkbox"/> Midwives
Severity:	Active
Condition:	Giant cell arteritis
PBS Indication:	Active giant cell arteritis

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Treatment phase:	Initial
Restriction Level / Method:	<input checked="" type="checkbox"/> Authority Required - In Writing
Treatment criteria:	<i>Patient must be treated by a specialist or consultant physician rheumatologist, clinical immunologist or neurologist experienced in the treatment management of giant cell arteritis</i>
Clinical criteria:	<p>Patient must have active <i>giant cell arteritis</i> GCA defined as the:</p> <ul style="list-style-type: none"> • presence of clinical signs and symptoms AND ESR \geq 30 mm/hour or CRP \geq 10 mg/L 4 mg/dL within the past 6 weeks; OR • presence of clinical signs and symptoms AND active <i>giant cell arteritis</i> GCA confirmed by positive temporal artery biopsy or imaging within the last 6 weeks <p>AND</p> <p>The treatment must in combination with a tapering course of corticosteroids</p> <p>AND</p> <p>The treatment <i>with this drug for this condition</i> must not exceed a total of 12 months therapy. a lifetime maximum of 52 injections of therapy</p>
Definitions	<p><u><i>Giant cell arteritis</i> GCA diagnosis criteria</u></p> <p><i>Clinical signs and symptoms of active giant cell arteritis must be in the absence of any other identifiable cause and must include:</i></p> <ul style="list-style-type: none"> • Age \geq 50 years • History of ESR \geq 50 mm/hour or CRP \geq 24.5 mg/L at time of diagnosis <p>If historic ESR unavailable, a history of CRP \geq 2.45 mg/dL required.</p> <p>AND at least one of the following:</p> <ul style="list-style-type: none"> • Unequivocal cranial symptoms of giant cell arteritis (new-onset localized headache, scalp tenderness, temporal artery tenderness or decreased pulsation, ischemia-related vision loss, or otherwise unexplained mouth or jaw pain upon mastication); OR • Symptoms of polymyalgia rheumatica, defined as shoulder and/or hip girdle pain associated with inflammatory morning stiffness <p>AND at least one of the following:</p> <ul style="list-style-type: none"> • Temporal artery biopsy revealing features of giant cell arteritis; OR • Evidence of large-vessel vasculitis by MR or CT angiography or PET/CT imaging study

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Administrative Advice	<p>Up to a maximum of 12 months of therapy 52 injections will be reimbursed through the PBS</p> <p>The authority application must be made in writing and must include:</p> <p>(1) a completed authority prescription form;</p> <p>(2) a completed Giant Cell Arteritis - Supporting Information Form; and</p> <p>(3) documentation that the patient has active giant cell arteritis including pathology reports outlining the patient's ESR and CRP levels, or positive temporal artery biopsy or imaging within the last 6 weeks.</p> <p>Any queries concerning the arrangements to prescribe may be directed to the Department of Human Services on 1800 700 270 (hours of operation 8 a.m. to 5 p.m. EST Monday to Friday).</p> <p>Prescribing information (including Authority Application forms and other relevant documentation as applicable) is available on the Department of Human Services website at www.humanservices.gov.au</p> <p>Applications for authority to prescribe should be forwarded to:</p> <p>Department of Human Services Complex Drugs Reply Paid 9826 HOBART TAS 7001</p>
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Category / Program	GENERAL – General Schedule (Code GE)
Prescriber type:	<input type="checkbox"/> Dental <input checked="" type="checkbox"/> Medical Practitioners <input type="checkbox"/> Nurse practitioners <input type="checkbox"/> Optometrists <input type="checkbox"/> Midwives
Severity:	Active
Condition:	Giant cell arteritis
PBS Indication:	Active giant cell arteritis
Treatment phase:	Continuing
Restriction Level / Method:	<input checked="" type="checkbox"/> Authority Required - Telephone
Treatment criteria:	Patient must be treated by a specialist or consultant physician <i>rheumatologist, clinical immunologist or neurologist experienced in the treatment-management of giant cell arteritis</i>
Clinical criteria:	Patient must have previously received PBS-subsidised treatment with this drug <i>for this condition</i> AND The treatment <i>with this drug for this condition</i> must not exceed a total of 12 months therapy. a lifetime maximum of 52 injections of therapy
Administrative Advice	<i>Any queries concerning the arrangements to prescribe may be directed to the Department of Human Services on 1800 700 270 (hours of operation 8 a.m. to 5 p.m. EST Monday to Friday).</i>

2.2 The requested listing was narrower than the TGA indication, as the TGA indication does not restrict tocilizumab to patients with active disease, and does not limit the tocilizumab treatment duration.

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- 2.3 The proposed restriction states that treatment must be in combination with a tapering course of corticosteroids. The restriction does not nominate a particular steroid tapering regimen. In the GiACTA trial, treatment with tocilizumab was in conjunction with a 26-week prednisone tapering regimen. The evaluation and the PBAC considered that it is unclear whether a 26-week corticosteroid tapering regimen, or a longer regimen, would be used in clinical practice with tocilizumab.
- 2.4 The PBAC considered that the initiation restriction should clearly specify that the 'presence of clinical signs and symptoms AND ESR \geq 30 mm/hour *or* CRP \geq 10 mg/L' (i.e. the first clinical criterion defining active GCA) must be satisfied in the prior six weeks, consistent with the GiACTA trial.
- 2.5 The PBAC noted that the requested restriction had proposed that 'active GCA confirmation by positive temporal artery biopsy or imaging' (i.e. part of the second clinical criterion defining active GCA), must have been conducted within the previous six weeks. The PBAC considered that it may not be necessary for the biopsy or imaging to have been conducted in the previous six weeks as this may create a requirement for patients to undergo a second biopsy.
- 2.6 The evaluation, ESC and PBAC noted that tocilizumab may be used fortnightly (rather than weekly) in some patients. The Product Information states that fortnightly treatment (in conjunction with a tapering course of glucocorticoids) may be prescribed based on clinical considerations. The pre-PBAC response (p. 2) stated that clinician feedback suggested that some patients may receive treatment every two weeks once their active disease is under control. Further, the ESC and the PBAC noted that fortnightly use is supported by the GiACTA clinical trial (refer to Section 6).
- 2.7 The initial and continuing restrictions proposed by the submission both stated that the treatment must not exceed a lifetime maximum of 52 injections. However, 52 injections would provide more than 12 months of treatment if tocilizumab is used fortnightly rather than weekly. The ESC and the PBAC considered that a 12 month treatment limitation should be included in the restriction, as the trial data presented was limited to 12 months of therapy with tocilizumab. The PBAC considered there was a risk of use beyond 12 months and considered that a written (initial) and telephone (continuing) authority would be required to mitigate this risk.
- 2.8 The PBAC noted that the proposed restriction did not require patients to experience a particular level of response in order to continue tocilizumab therapy. The PBAC considered that this was appropriate given that, in the trial, patients continued tocilizumab after a flare. The PBAC considered that tocilizumab may continue to have a steroid-sparing effect in these patients.
- 2.9 The PBAC considered that the restriction should specify that the patient must be treated by a rheumatologist, clinical immunologist or neurologist experienced in the management of GCA.

- 2.10 The PBAC considered further work was required around the imaging and biopsy requirements for diagnosis of GCA in the proposed restriction to ensure accurate diagnosis of GCA, and that expert input would be required to inform this aspect of the restriction.

For more detail on PBAC's view, see section 7 PBAC outcome.

3 Background

Registration status

- 3.1 The subcutaneous formulation of tocilizumab was registered on the ARTG on 14 November 2017 for the treatment of giant cell arteritis in adult patients.
- 3.2 Tocilizumab is also TGA registered for use in rheumatoid arthritis (intravenous and subcutaneous formulations), polyarticular juvenile idiopathic arthritis (intravenous formulation), and systemic juvenile idiopathic arthritis (intravenous formulation).

4 Population and disease

- 4.1 GCA (formerly known as temporal arteritis or cranial arteritis) is a systemic inflammatory vasculitis of medium- and large-size arteries, occurring almost exclusively in people aged over 50 years. Inflammation associated with GCA typically involves the extracranial branches of the carotid arteries, but may also affect the aorta, aortic arch and its branches.
- 4.2 Typical symptoms of active disease include jaw pain, severe headache, polymyalgia rheumatica (bilateral aching and stiffness of the shoulders and hip-girdle area), visual symptoms (diplopia or visual loss), scalp tenderness, and malaise. Systemic symptoms such as fever, fatigue, and weight loss are also common. Active disease is typically associated with increases in inflammatory biomarkers, including the C-reactive protein (CRP) and the erythrocyte sedimentation rate (ESR).
- 4.3 GCA is treated with high-dose corticosteroid therapy, typically 40 mg to 60 mg per day of oral prednisone/prednisolone. Patients with evolving visual loss or a recent history of transient visual loss receive initial treatment with intravenous methylprednisolone. Corticosteroids produce rapid improvement in systemic symptoms and signs and can prevent visual loss if administered early. Following remission of symptoms and normalisation of inflammatory markers, the dose of corticosteroids is gradually tapered.
- 4.4 Methotrexate may be used in combination with corticosteroid therapy initially, or as a corticosteroid-sparing drug, in patients who require prolonged high-dose corticosteroid therapy or who develop early or severe corticosteroid adverse effects. Cyclosporin and azathioprine are also used in relapsed patients as steroid-sparing agents, though the ESC acknowledged there are limited data available on outcomes with these agents.

- 4.5 The submission positioned tocilizumab as a treatment option for patients with either newly-diagnosed or relapsed GCA.

5 Comparator

- 5.1 The submission nominated standard care, represented by a 52-week tapering course of corticosteroids, as the main comparator. Standard care is the appropriate main comparator. However, treatment guidelines generally recommend treatment with corticosteroids for at least 18 months.
- 5.2 The evaluation considered that methotrexate is a potential secondary comparator. Treatment guidelines suggest that methotrexate may be used in combination with corticosteroid therapy as a corticosteroid-sparing drug in patients who require prolonged high-dose corticosteroid therapy, or for patients who develop early or severe corticosteroid adverse effects.
- 5.3 In addition to methotrexate, the ESC considered that other steroid-sparing agents and immunosuppressive agents that are used in relapsed GCA (such as cyclosporin and azathioprine) may also be appropriate clinical comparators for relapsed patients.
- 5.4 The pre-PBAC response (p. 2) stated that there is limited clinical data for the steroid-sparing agents including methotrexate in GCA, and that these agents are not commonly used.

For more detail on PBAC's view, see section 7 PBAC outcome.

6 Consideration of the evidence

Sponsor hearing

- 6.1 The sponsor requested a hearing for this item. The rheumatologist who presented at the hearing outlined his clinical experience treating patients with GCA including the debilitating nature of the condition, the adverse events of corticosteroids in this population who are predominantly older patients with more comorbidities and higher risk for adverse steroid effects, and the high clinical need for alternative therapies in patients with relapsed or refractory GCA. The rheumatologist outlined that there was no standard corticosteroid regimen used consistently in clinical practice, and there was a tendency to use long courses of corticosteroids out of fear of relapse.

Consumer comments

- 6.2 The PBAC noted and welcomed the input from an individual (1) and health care professionals (8) via the Consumer Comments facility on the PBS website. The comments outlined that GCA is associated with significant disease-related morbidity and treatment-related morbidity from prolonged use of high dose corticosteroids. The comments outlined that tocilizumab can be steroid-sparing which was described as an important patient-relevant outcome.

Clinical trials

6.3 The submission was based on one randomised trial comparing tocilizumab to placebo (GiACTA).

6.4 Details of the GiACTA trial are presented in Table 4.

Table 4: Trials and associated reports presented in the submission

Trial ID	Protocol title/ Publication title	Publication citation
Direct randomised trials		
GiACTA	A Phase III, multicenter, randomized, double-blind, placebo-controlled study to assess the efficacy and safety of tocilizumab in subjects with giant cell arteritis. NCT01791153 Tuckwell K, Collinson N, Dimonaco S et al. Newly diagnosed vs. relapsing giant cell arteritis: Baseline data from the GiACTA trial. Unizony SH, Dasgupta B, Fisheleva E, et al. Design of the Tocilizumab in Giant Cell Arteritis Trial. Collinson N, Tuckwell K, Habeck F et al. Development and implementation of a double-blind corticosteroid-tapering regimen for a clinical trial. Stone J, Tuckwell SD, Klearman M et al. Trial of tocilizumab in giant-cell arteritis.	Clinical study report, October 2016. Seminars in Arthritis and Rheumatism (2017); 46:657-664. International Journal of Rheumatology (2013); 2013: 912562. International Journal of Rheumatology (2015); 2015: 589841. New England Journal of Medicine (2017); 377(4):317-328.

Source: Table 2.4, p.38 of the submission.

6.5 The key features of the GiACTA trial are summarised in the table below.

Table 5: Key features of the included evidence

Trial	N	Design/ duration	Risk of bias	Patient population	Outcomes	Use in modelled evaluation
GiACTA	251	Randomised, double-blind, placebo-controlled multi-centre trial (52 weeks) with 104-week open-label extension.	Low	Patients aged ≥50 years with new-onset or relapsed GCA; evidence of active GCA in the prior 6 weeks.	- Sustained remission at Week 52; - Time to disease flare; - Cumulative prednisone dose; - Health-related quality of life (SF-36 summary scores, Patient's Global Assessment of disease activity, EQ-5D overall score).	No Yes Yes Yes (EQ-5D)

Source: Tables 2.7 to 2.11, pp45-50; Tables 2.14 to 2.15, pp56-58 of the submission.

Abbreviations: CRP, C-reactive protein; EQ-5D, EuroQol five dimension; ESR, erythrocyte sedimentation rate; GCA, giant cell arteritis; SF-36, Short Form-36 questionnaire.

6.6 The GiACTA trial included four treatment arms:

- Tocilizumab 162 mg subcutaneously once a week in conjunction with a 26-week prednisone taper;
- Tocilizumab 162 mg subcutaneously once a fortnight (tocilizumab alternating with placebo once a week) in conjunction with a 26-week prednisone taper;
- Placebo subcutaneously once a week in conjunction with a 26-week prednisone taper;
- Placebo subcutaneously once a week in conjunction with a 52-week prednisone taper.

- 6.7 The GiACTA trial recruited patients with either new-onset or relapsed disease. Patients were screened up to 6 weeks prior to the baseline randomisation visit. During screening, patients received corticosteroids for the treatment of GCA at the discretion of the investigator. At the end of the screening period, patients were required to be on a prednisone dose of between 20 mg and 60 mg per day. Patients switched to the sponsor-provided prednisone and commenced an open-label, protocol-defined tapering schedule, with a weekly reduction in prednisone dose based on dose increments of 60 mg, 50 mg, 40 mg, 35 mg, 30 mg, 25 mg and 20 mg. Once patients completed a week of 20 mg prednisone, they entered a blinded tapering phase in which either a short or long tapering schedule was followed.
- 6.8 Patients in the tocilizumab weekly, tocilizumab fortnightly, and placebo plus 26-week taper groups were treated with a shorter prednisone tapering regimen, with a total prednisone duration of up to 26-weeks. Patients in the placebo plus 52-week taper arm were treated with prednisone for up to 52 weeks.
- 6.9 The evaluation, the ESC and the PBAC considered that the prednisone dosing in the trial may not be representative of clinical practice, as clinical guidelines recommend tapering following resolution of symptoms and normalisation of inflammatory markers, while in the trial tapering of the prednisone dose may have been commenced prior to achieving disease remission in some patients. Further, the total duration of the prednisone taper was shorter than recommended in clinical guidelines. Treatment in the placebo plus 52-week taper group was for a maximum of 52 weeks; however, clinical guidelines generally recommend treatment with prednisone for at least 12 to 18 months. While acknowledging that treatment guidelines for GCA are limited and poorly evidence based, the ESC and the PBAC considered that the steroid tapering regimens used in the trial were not representative of clinical practice.
- 6.10 The Pre-Sub-Committee Response (PSCR, acknowledged that there are limitations in applying the GiACTA study to clinical practice where patients are generally treated according to their individual circumstances.
- 6.11 The PBAC noted that patients who required initial treatment with IV methylprednisolone were excluded from the GiACTA trial. This is likely to have had the effect of excluding more severe presentations of GCA and hence the effect of tocilizumab in this subgroup is uncertain.
- 6.12 The primary outcome of the GiACTA trial was the proportion of tocilizumab-treated patients in sustained remission at Week 52 versus placebo plus a 26-week prednisone taper. Remission was defined as the absence of flare and normalisation of the CRP <10mg/L). Sustained remission was defined as the absence of flare following induction of remission within 12 weeks of randomisation and maintained from week 12 up to the 52-week timepoint. Flare was determined by the investigator and defined as the recurrence of signs or symptoms of GCA and/or an ESR ≥ 30 mm/hr attributable to GCA.

- 6.13 Patients were considered non-responders if they did not achieve remission within 12 weeks of baseline, experienced a flare, had elevated CRP values at two consecutive study visits from Week 12 onwards, received escape therapy, did not adhere to the prednisone taper regimen, withdrew from the study prior to Week 52, or if remission status could not be determined at Week 52.
- 6.14 The clinical claim in the submission was based on a comparison of tocilizumab plus 26-week prednisone tapering regimen to placebo plus a 52-week prednisone tapering regimen.

Comparative effectiveness

- 6.15 Table 6 presents the results for the proportion of patients in sustained remission at Week 52 in the GiACTA trial.

Table 6: Proportion of patients in sustained remission at Week 52

	PBO + 26-week taper (N=50)	PBO + 52-week taper (N=51)	TCZ weekly + 26-week taper (N=100)	TCZ fortnightly + 26-week taper (N=49)
Responders, n (%)	7 (14.0)	9 (17.6)	56 (56.0)	26 (53.1)
Difference in response rates (99.5% CI)				
vs. PBO + 26-week prednisone taper (primary outcome)			42.0 (18.0, 66.0)	39.1 (12.5, 65.7)
vs. PBO + 52-week prednisone taper (key secondary outcome)			38.4 (17.9, 58.8)	35.4 (10.4, 60.4)

Source: Table 2.19, p.61 of the submission.

Abbreviations: CI, confidence interval; PBO, placebo; TCZ, tocilizumab.

- 6.16 Treatment with tocilizumab once weekly in conjunction with a 26-week prednisone taper was associated with a statistically significant increase in response rates compared to placebo plus a 26-week prednisone taper, or placebo plus 52-week prednisone taper. The ESC and the PBAC noted that treatment with fortnightly tocilizumab was also associated with a statistically significant increase compared to placebo in combination with 26-week or 52-week prednisone tapering regimens. However, it is unclear whether the direct biologic effects of tocilizumab on CRP and ESR levels may have led to an overestimation of the response to treatment with tocilizumab, given that CRP and ESR were included as part of the disease response criteria.
- 6.17 The PBAC noted that 17.6% of patients experienced remission with a 52 week corticosteroid taper without the addition of tocilizumab. The PBAC also noted that 38.4% (95% CI: 17.9%, 58.8%) more patients responded with tocilizumab weekly compared to a 52 week corticosteroid taper.
- 6.18 Table 7 presents the results for the time to first GCA disease flare at Week 52.

Table 7: Time to first giant cell arteritis disease flare at Week 52

	PBO + 26-week taper (N=50)	PBO + 52-week taper (N=51)	TCZ weekly + 26-week taper (N=100)	TCZ fortnightly + 26-week taper (N=49)
Patient with event, n (%)	34 (68)	25 (49)	23 (23)	13 (27)
Median time-to-event, days (range)	165 (1-365)	295 (1-362)	NE (1-367)	NE (1-364)
Hazard ratio (99% CI)				
vs. PBO + 26-week taper	-	-	0.23 (0.11, 0.46)	0.28 (0.12, 0.66)
vs. PBO + 52-week taper	-	-	0.39 (0.18, 0.82)	0.48 (0.20, 1.16)

Source: Table 2.21, p.62 of the submission.

Abbreviations: CI, confidence interval; NE, not estimable; PBO, placebo; TCZ, tocilizumab.

- 6.19 Tocilizumab weekly plus a 26-week prednisone taper was associated with a 61% reduction in risk of first flare compared with placebo plus a 52-week prednisone taper. Tocilizumab fortnightly plus a 26-week prednisone taper was associated with a 72% reduction in risk of first flare compared with placebo plus a 26-week prednisone taper; however, the risk of first flare with tocilizumab fortnightly compared with placebo plus a 52-week prednisone taper was associated with a non-statistically significant 52% reduction in risk of first flare.
- 6.20 At the time of the GiACTA interim analysis, the duration of follow-up in the open-label extension (Part 2) ranged from 48 to 84 weeks. Of the 45 patients who met the primary endpoint in Part 1 of the study, flares were observed in 18 patients: 1/5 (20%) in the placebo plus 26-week taper group, 1/5 (20%) in the placebo plus 52-week group, 8/24 (33%) in the tocilizumab weekly group, and 8/11 (73%) in the tocilizumab fortnightly group. The remaining 27 (60%) patients remained in remission throughout available follow-up. The PBAC considered that the large number of flares in the post-treatment period, especially among patients who had been treated fortnightly, suggests that tocilizumab may suppress rather than prevent relapse. It also suggests that treatment (with tocilizumab and/or corticosteroids) may be required beyond 12 months in some patients, though the ESC and PBAC noted that no data had been provided regarding the efficacy of tocilizumab beyond 12 months.
- 6.21 The PBAC also noted another study of tocilizumab in patients with GCA for which long-term follow-up data were available (Adler 2016, Villiger 2016).^{1,2} This was a randomised, double-blind, placebo controlled study, albeit using a different dosing regimen to that requested for PBS-listing (tocilizumab was administered as an 8mg intravenous infusion every 4 weeks for 52 weeks), and based on fewer patient numbers (n = 30). This study found that 55% (11/20) of patients treated with tocilizumab relapsed after a 52 week treatment course. The median time to relapse was 5 months (range 2-14 months). The study authors concluded that “clinical and

¹ Adler S, et al. Termination of Tocilizumab-Treatment in Giant Cell Arteritis: Follow-up of Patients after the RCT (ClinicalTrials.gov registration number: NCT01450137). ACR/ARHP Annual Meeting 2016, Abstract number: 867, date of first publication: September 28, 2016. <https://acrabstracts.org/abstract/termination-of-tocilizumab-treatment-in-giant-cell-arteritis-follow-up-of-patients-after-the-rct-clinicaltrials-gov-registration-number-nct01450137/>. Accessed November 25, 2018

² Villiger P, et al. Tocilizumab for induction and maintenance of remission in giant cell arteritis: a phase 2, randomised, double-blind, placebo-controlled trial. *Lancet*. 2016;387:1921-27

serologic remission in response to tocilizumab for 52 weeks does not result in relapse-free survival after termination of treatment. Although IL-6 blockade using tocilizumab controls clinical disease, it may not control pathogenesis in all cases. The fact that 45% of patients remained in lasting remission may help to design treatment protocols to determine appropriate maintenance dosage regimens of tocilizumab after achievement of remission”.²

6.22 Table 8 presents the results for cumulative prednisone dose at Week 52.

Table 8: Results for cumulative prednisone dose at Week 52

	PBO + 26-week taper (N=50)	PBO + 52-week taper (N=50)	TCZ weekly + 26-week taper (N=100)	TCZ fortnightly + 26-week taper (N=49)
Median cumulative prednisone dose, mg (range)	3296 (2729, 4023)	3817 (2817, 4425)	1862 (1582, 1942)	1862 (1568, 2239)
p value				
vs. PBO + 26-week taper	-	-	<0.0001	0.0003
vs. PBO + 52-week taper	-	-	<0.0001	<0.0001

Source: Table 2.22, p.64 of the submission.

Abbreviations: PBO, placebo; TCZ, tocilizumab.

6.23 Treatment with tocilizumab (weekly and fortnightly) was associated with a statistically significantly lower median cumulative prednisone dose at Week 52 compared to the placebo plus 26-week and placebo plus 52-week prednisone taper groups.

6.24 Treatment with tocilizumab (weekly or fortnightly) was associated with larger improvements in the Patient’s Global Assessment assessed by visual analogue scale compared to the placebo plus 26-week and placebo plus 52-week prednisone taper groups. The differences between the tocilizumab fortnightly and placebo plus 26-week and 52-week prednisone taper arms were statistically significant. These results are shown in the table below. Note that lower scores indicate less severe disease activity.

Table 9: Results for change from baseline to Week 52 in Patient's Global VAS Assessment

	PBO + 26 wk (N=50)	PBO + 52 wk (N=51)	TCZ QW + 26 wk (N=100)	TCZ Q2W + 26 wk (N=49)
n	34	42	88	46
Least Square Means	-3.4	-7.2	-19.0	-25.3
Differences in Least Square Means				
vs PBO + 26 wk (99% CI)			-15.6 (-34.3, 3.1)	-21.9 (-42.4, -1.4)
P-value			p = 0.0312	p = 0.0059
vs PBO + 52 wk (99% CI)			-11.8 (-27.2, 3.6)	-18.2 (-35.8, -0.5)
P-value			p = 0.0476	p = 0.0081

Source: Table 31, p. 130, GIACTA CSR

Abbreviations: CI, confidence interval; PBO, placebo; TCZ, tocilizumab.

Notes: Repeated measures model used for analysis included the following covariates and interactions: treatment, starting prednisone dose (<=30mg/day, >30mg/day), visit, treatment-by-visit interaction, starting dose-by-visit interaction, baseline score and baseline score-by-visit interaction. n represents patients included in the model.

6.25 There were no statistically significant differences between the tocilizumab groups and the placebo groups for the change from baseline in the SF-36 mental component

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score. A statistically significant difference between groups was observed in the tocilizumab weekly group compared to the placebo plus 52-week prednisone taper group for the SF-36 physical component score.

Table 10: Change from Baseline to Week 52 in SF-36 Mental and Physical Component Score

Change from baseline at Week 52	PBO + 26 wk (n=50)	PBO + 52 wk (n=51)	TCZ QW + 26 wk (n=100)	TCZ Q2W + 26 wk (n=49)
n (respondents)	33	41	85	46
Mental Component Score differences in least square means (99% CI)				
Least Square Means (LSM)	6.67	2.84	7.28	6.12
vs PBO + 26 wk (99% CI)			0.61 (-5.86, 7.07)	-0.56 (-7.64, 6.53)
P-value			p = 0.8067	p = 0.8374
vs PBO + 52 wk (99% CI)			4.44 (-0.69, 9.56)	3.27 (-2.59, 9.14)
P-value			p = 0.0252	p = 0.1468
Physical Component Score				
Least Square Means (LSM)	-0.28	-1.49	4.10	2.76
vs PBO + 26 wk (99% CI)			4.38 (-1.58, 10.34)	3.04 (-3.43, 9.51)
P-value			p = 0.0570	p = 0.2218
vs PBO + 52 wk (99% CI)			5.59 (0.86, 10.32)	4.25 (-1.14, 9.64)
P-value			p = 0.0024	p = 0.0412

Source: Table 32, p. 131, GfACTA CSR

Abbreviations: CI, confidence interval; PBO, placebo; TCZ, tocilizumab.

Notes: Repeated measures model used for analysis included the following covariates and interactions: treatment, starting prednisone dose (<=30mg/day, >30mg/day), visit, treatment-by-visit interaction, starting dose-by-visit interaction, baseline score and baseline score-by-visit interaction. No imputation of missing PCS and MCS has been performed. Post-escape SF-36 data will be set to missing. n represents patients included in the model.

6.26 As shown in the table below, there were no notable changes in mean overall EQ-5D scores for any of the included treatment groups.

Table 11: Results for change from baseline in EQ-5D overall scores

	PBO + 26-week taper (N=50)	PBO + 52-week taper (N=51)	TCZ weekly + 26- week taper (N=100)	TCZ fortnightly + 26-week taper (N=49)
Baseline				
Number of patients	50	59	99	49
Mean overall score (SD)	0.74 (0.219)	0.66 (0.264)	0.74 (0.207)	0.74 (0.218)
Week 24				
Number of patients	22	29	77	37
Mean overall score (SD)	0.68 (0.303)	0.79 (0.211)	0.75 (0.237)	0.77 (0.172)
Mean change from baseline (SD)	-0.01 (0.325)	0.05 (0.136)	0.00 (0.264)	-0.01 (0.213)
Week 52				
Number of patients	11	17	60	26
Mean overall score (SD)	0.77 (0.272)	0.78 (0.165)	0.86 (0.131)	0.83 (0.132)
Mean change from baseline (SD)	0.07 (0.293)	-0.02 (0.159)	0.10 (0.198)	0.05 (0.215)

Source: Table 2.21, p.62 of the submission.

Abbreviations: PBO, placebo; SD, standard deviation; TCZ, tocilizumab.

Notes: assessments were also conducted at Weeks 12, 36 and 48. These are not reported in the table above for brevity.

Comparative harms

6.27 Table 12 presents a summary of the adverse events reported in the GiACTA trial.

Table 12: Summary of adverse events for the GiACTA trial

	PBO + 26-week taper (N=50)	PBO + 52-week taper (N=51)	TCZ weekly + 26-week taper (N=100)	TCZ fortnightly + 26-week taper (N=49)
Serious AE, n (%)	11 (22.0)	13 (25.5)	15 (15.0)	7 (14.3)
Treatment related AE, n (%)	32 (64.0)	27 (52.9)	68 (68.0)	36 (73.5)
-Tocilizumab/placebo	21 (42.0)	18 (35.3)	52 (52.0)	26 (53.1)
-Prednisone	31 (62.0)	25 (49.0)	50 (50.0)	30 (61.2)
Discontinuation due to AE, n (%)	6 (12.0)	0	11 (11.0)	6 (12.2)
AE leading to death, n (%)	0	0	0	0
Any AE, n (%)	48 (96.0)	47 (92.2)	98 (98.0)	47 (95.9)
• Headache	16 (32.0)	12 (23.5)	27 (27.0)	10 (20.4)
• Nasopharyngitis	99 (18.0)	13 (25.5)	29 (29.0)	12 (24.5)
• Peripheral oedema	8 (16.0)	6 (11.8)	16 (16.0)	12 (24.5)
• Arthralgia	11 (22.0)	8 (15.7)	13 (13.0)	8 (16.3)
• Back pain	7 (14.0)	10 (19.6)	14 (14.0)	7 (14.3)
• Dizziness	6 (12.0)	8 (15.7)	6 (6.0)	10 (20.4)
• Diarrhoea	8 (16.0)	5 (9.8)	12 (12.0)	3 (6.1)

Source: Table 2.29, p.71; Table 2.30, p.72 of the submission; Table 34, p.143 of the GiACTA clinical study report.

Abbreviations: AE, adverse event; PBO, placebo; TCA, tocilizumab.

6.28 Most patients in each arm experienced at least one adverse event. There were numerically higher serious adverse events in the placebo arms compared to the tocilizumab arms.

6.29 Treatment-related adverse events related to tocilizumab/placebo were higher in the tocilizumab groups compared to the placebo groups. The most commonly reported treatment related adverse events in the tocilizumab weekly group were nasopharyngitis, cystitis, upper respiratory tract infection, bronchitis, herpes zoster, rhinitis and fungal skin infection.

Benefits and harms

6.30 On the basis of the evidence presented in the submission, for every 100 patients treated with weekly tocilizumab in conjunction with a 26-week prednisone taper compared to placebo in conjunction with a 52-week prednisone taper:

- Approximately 38 additional patients would achieve a sustained remission from Week 12 to Week 52;
- Approximately 26 fewer patients would experience a disease flare by Week 52.
- There were no notable differences in adverse events.

6.31 The ESC and the PBAC noted that the benefits and harms were similar if based on fortnightly tocilizumab rather than weekly tocilizumab. That is, on the basis of the evidence presented in the submission, for every 100 patients treated with fortnightly tocilizumab in conjunction with a 26-week prednisone taper compared to placebo in conjunction with a 52-week prednisone taper:

- Approximately 35 additional patients would achieve a sustained remission from Week 12 to Week 52;
 - Approximately 22 fewer patients would experience a disease flare by Week 52.
 - There were no notable differences in adverse events.
- 6.32 However, the ESC and PBAC also noted that, based on preliminary data, there appeared to be a higher risk of flares after ceasing tocilizumab treatment (weekly or fortnightly) than after corticosteroids alone.

Interpretation of clinical evidence

- 6.33 The submission described tocilizumab 162 mg subcutaneously once weekly in conjunction with a 26-week tapering course of corticosteroids as superior at 52 weeks in terms of effectiveness, and non-inferior in terms of safety compared to a 52-week tapering course of corticosteroids.
- 6.34 The evaluation, the ESC and the PBAC considered that the therapeutic conclusion presented in the submission was adequately supported during the 52 week randomised trial period. However, the following issues were noted:
- The durability of the treatment effect with tocilizumab in the post-treatment period (beyond 52 weeks) is unclear, due to limited long-term follow-up data. Preliminary data from the open label extension of the GiACTA trial suggests that the relapse rate may be higher in the tocilizumab arms when tocilizumab treatment has ceased after 12 months, especially when tocilizumab has been used fortnightly. Hence, treatment beyond 52 weeks may be required. However, the role of tocilizumab beyond 12 months has not been established.
 - The magnitude of the clinical benefit associated with tocilizumab was unclear, as direct biologic effects of tocilizumab on CRP and ESR levels may have led to an overestimation of the response to treatment with tocilizumab.
 - The prednisone dosing in the trial may not be representative of clinical practice, as tapering of the prednisone dose was commenced prior to achieving remission in some patients, and the duration of the prednisone taper was shorter than recommended in clinical guidelines. The ESC acknowledged that treatment guidelines for GCA are limited and poorly evidence based, but considered that the placebo plus 52-week prednisone taper arm of the GiACTA trial was not an adequate proxy for standard care.
- 6.35 Further, the PBAC considered that the patients included in the GiACTA trial may not be representative of the PBS population because:
- a high proportion (around 60%) of patients in the GiACTA trial had symptoms of polymyalgia rheumatica (with concomitant GCA) at baseline;
 - a low proportion (<1% of patients) of patients in the GiACTA trial had ischaemic optic neuropathy at baseline;

- the baseline ESR of patients in the GiACTA trial (mean 24 mm/hr) was likely lower than would be expected in the PBS population;
 - the GiACTA trial excluded patients who had received intravenous methylprednisolone (at a dose > 100 mg daily) in the previous six weeks. The PBAC considered that this may have excluded patients with more severe disease at baseline; and
 - approximately 53% of participants had relapsing GCA at baseline (versus 47% with newly diagnosed GCA). It was unclear whether this was representative of the PBS population likely to use tocilizumab.
- 6.36 The ESC and the PBAC considered that the clinical need for tocilizumab is highest in patients with relapsed/refractory GCA, while the need is lower in patients who are adequately controlled on corticosteroids. As such, the ESC considered that it may be more appropriate to limit tocilizumab to a subgroup of the GCA population, such as patients who have relapsed whilst on tapering corticosteroids. The pre-PBAC response (p.2) stated that tocilizumab may also be appropriate in a proportion of newly-diagnosed patients, including those who have received a high cumulative corticosteroid dose for other conditions or who are at risk of adverse events (e.g. patients with osteoporosis, diabetes, infections) or patients with multiple comorbidities. The pre-PBAC response further stated that this group of patients is hard to define as GCA patients often have a high risk of steroid complications due to their age and comorbidities.
- 6.37 Notwithstanding the limitations noted above, the PBAC considered that the claim of superior comparative efficacy at 52 weeks was adequately supported by the data for the comparison of tocilizumab (weekly or fortnightly) plus a 26 week tapering course of corticosteroids versus a 52-week tapering course of corticosteroids.
- 6.38 The PBAC considered that the claim of non-inferior safety was adequately supported by the data.

Economic analysis

- 6.39 The submission presented a modelled economic evaluation of once-weekly tocilizumab used in combination with a 26 week corticosteroid taper compared to placebo used in combination with a 52 week corticosteroid taper for the treatment of GCA. The economic evaluation was based on a direct randomised trial (GiACTA) with additional modelled data.

Table 13: Key components of the modelled economic evaluation

Component	Description
Type of analysis	Cost-utility analysis
Outcomes	Quality adjusted life years
Time horizon	30 years (lifetime)
Methods used to generate results	Semi-Markov cohort model
Treatments	Tocilizumab once weekly with 26 week corticosteroid taper; placebo with 52 week corticosteroid taper
Health states	The model includes four core health states (primary remission on corticosteroids; primary remission off corticosteroids; subsequent remission on corticosteroids; death), one temporary health state (disease flare) and two quasi-states (GCA complications; corticosteroid complications)
Cycle length	Weekly
Transition probability	<p>Transition probabilities for flares (time to first flare in first year, time to first flare in later years) were derived from the GiACTA trial. The risk of subsequent flare was estimated based on published epidemiological data (Labarca 2016) calibrated with data from the GiACTA trial.</p> <p>Transition probabilities for GCA complications (vision loss, stroke) were estimated based on a UK HTA assessment of diagnostic procedures for GCA (Luqmani 2016).</p> <p>The estimated cumulative corticosteroid dose was derived from the GiACTA trial and a retrospective analysis of GCA patients from a US health insurance claims database (MarketScan 2016). The cumulative corticosteroid dose was used to inform transition probabilities for corticosteroid complications (infection, fracture, osteoporosis, diabetes) which were estimated based on case-control analyses of GCA patients from the UK Clinical Practice Research Datalink (Wilson 2017a, Wilson 2017b).</p> <p>Transition probabilities for all-cause death were based on Australian life tables. Transition probabilities for stroke death were based on the Luqmani 2016 publication.</p>
Discount rate	5% for costs and outcomes
Software	Microsoft Excel

Source: 3.2 (p 86) of the submission

- 6.40 All patients start in the primary remission on corticosteroids health state (though the ESC noted there may have been patients in the clinical trial who were not in remission on commencement of the trial period). Patients in the tocilizumab arm continue in this health state until flare, death or the end of the 26 week tapering period. Patients in the placebo arm continue in this health state until flare, death or the end of the 52 week tapering period. Patients who did not flare during the tapering period then transition to the primary remission off corticosteroid health state until flare or death. Patients experiencing flare enter a temporary disease flare health state before transitioning to a subsequent remission on corticosteroids health state. Patients in the subsequent remission state remain on corticosteroids until death and may continue to experience multiple disease flares.
- 6.41 The complications associated with GCA and corticosteroid therapy were implemented as quasi-health states allowing patients to be in multiple health states at the same time. Patients could experience GCA complications in any cycle in which they also experienced flare. Patients could experience corticosteroid complications in any cycle in which their cumulative corticosteroid dose exceeded the nominated risk thresholds for adverse events.

- 6.42 The ESC and the PBAC noted that the model extrapolated 12 months of randomised trial data to a 30 year time horizon. The submission estimated the time to first flare beyond 12 months (i.e. after the 12 month randomised trial period) for both treatment arms based on a parametric (Weibull) function using data from the tocilizumab treatment arm. This resulted in an ongoing treatment effect being assumed for the 30-year modelled time horizon. The ESC and the PBAC considered that it was not reasonable to assume that tocilizumab administered over a limited duration (1 year) will be associated with benefits over such a long term period, based on the trial data presented. This was particularly an issue given that the limited data available on patient outcomes after treatment discontinuation indicated a large number of flares in the post-treatment period. The ESC considered that the model more reasonably would have included a convergence of the treatment effects, and noted that the model is highly sensitive to the assumed duration of benefit.
- 6.43 The model assumes that patients who experience a flare remain on corticosteroids until death. The PSCR argued that disease flare is a transient health state, but further stated that the model applies the corticosteroid use as a weighted average dose to the entire cohort alive irrespective of their health state (resulting in an average dose of <1 mg per day for some patients). The ESC noted that the model applied a disutility of -0.07 to all patients receiving corticosteroids regardless of dose or incidence of complications. As such, patients who experience a flare continue to accrue a constant disutility from corticosteroid use until death, despite receiving an average dose <1 mg per day. The ESC and PBAC considered that these assumptions were not plausible.
- 6.44 The ESC and the PBAC considered that a 30 year time horizon (as used in the base case) was not realistic given that the submission indicated that the mean age at diagnosis in Australia is estimated to be 73-78 years. Further, the ESC and PBAC considered that a 30 year time horizon introduces high levels of uncertainty as data on the use of tocilizumab beyond 12 months are limited.
- 6.45 Key drivers of the economic model are summarised in the table below.

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Table 14: Key drivers of the model

Description	Method/Value	Impact
Extrapolation of treatment benefit	<p>The submission estimated the time to first flare in the first year of the model using a Weibull survival function for tocilizumab and an exponential survival function for placebo based on observed data from the GiACTA trial.</p> <p>The submission estimated the time to first flare in subsequent years for both treatment arms based on a Weibull function using data from the tocilizumab treatment arm. It may not be appropriate to base extrapolations on the tocilizumab treatment arm as the risk of flare while on treatment (first year) may not reflect the risk of flare while off-treatment (subsequent years).</p> <p>The extrapolated time to first flare suggested long-term treatment benefits of tocilizumab after treatment discontinuation which was not adequately supported by available clinical data.</p>	High, favours tocilizumab
Duration of corticosteroid exposure	<p>The submission estimated corticosteroid exposure during the primary remission period based on the taper protocol from the GiACTA trial.</p> <p>The submission assumed that patients in the subsequent remission state would remain on corticosteroids until death. The estimated cumulative dose during this period was based on a post-hoc analysis of the GiACTA trial and a sponsor-commissioned retrospective analysis of GCA patients from a US health insurance claims database (MarketScan 2016).</p> <p>The structure of the economic model did not allow patients to discontinue corticosteroid therapy after they experience a flare. This was inconsistent with treatment guidelines and available utilisation estimates which indicate that many patients will be able to cease corticosteroid therapy. This also resulted in implausible situations in the model in which patients were exposed to corticosteroid doses < 1 mg per day as the estimated cumulative dose was distributed across the extended treatment duration in the model.</p>	High, favours tocilizumab
Disutility associated with corticosteroids	<p>The submission estimated disutility values for corticosteroid complications based on a published decision analytic model on the management of temporal arteritis (Niederkoehr 2005). The publication synthesized disutility values for corticosteroids complications based on various published sources. The publication also assumed a base disutility (- 0.03) for corticosteroid treatment to represent common steroid-related events (doctor visits, weight gain, excessive body hair, moon face etc). There was substantial uncertainty associated with the data sources, method of calculation and assumptions used to derive utility estimates.</p> <p>The submission applied the disutility of corticosteroids as a temporary loss in every week the patient received corticosteroid treatment.</p> <p>The application of a corticosteroid disutility to patients receiving doses < 1 mg per day did not appear reasonable.</p> <p>The disutility associated with corticosteroids was not linked to the incidence of corticosteroid complications in the model and therefore the economic evaluation may not accurately reflect the treatment burden associated with corticosteroids.</p>	High, favours tocilizumab

Source: Constructed during the evaluation

6.46 The results of the modelled economic evaluation presented in the submission are summarised below.

Table 15: Results of the modelled economic evaluation (from the submission)

Component	Tocilizumab (short taper)	Placebo (longer taper)	Increment
Costs	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]
QALYs	[REDACTED]	[REDACTED]	[REDACTED]
Incremental cost per QALY gained			\$ [REDACTED]

Source: Table 3.30 (p 122) of the submission

The redacted table shows an ICER in the range of \$45,000/QALY – \$75,000/QALY.

6.47 The ESC considered that there were a number of errors and logical inconsistencies in the economic model, only some of which were acknowledged in the PSCR. Errors directly affected a number of variables/outputs including QALY loss due to flare, flare dosing, corticosteroid dosing (during initial remission), disease management costs, cumulative incidence of stroke and stroke cost.

6.48 Correcting three of these issues - flare misapplication, disease management costs and cumulative corticosteroid dose in primary remission for the placebo arm - increased the ICER from \$45,000/QALY – \$75,000/QALY to \$45,000/QALY – \$75,000/QALY (Table 16). The pre-PBAC response claimed that the impact of some of the errors had been overstated and that correcting these three errors increased the ICER to \$45,000/QALY – \$75,000/QALY. The evaluation and the pre-PBAC response used different approaches to correct the application of the four-week disutility for flares; the approach used in the pre-PBAC response was unable to be validated.

6.49 The PBAC noted that there were additional errors or logical inconsistencies in the economic model which were not addressed in the pre-PBAC response including that the proportion of patients with major stroke was not adjusted for the proportion with fatal stroke, and the cost of stroke was negative due to adjustments to incorporate memory.

6.50 Overall, the evaluation, the ESC and the PBAC considered that the cost-effectiveness estimate was not reliable given the errors and logical inconsistencies identified in the model, the issues relating to the duration of corticosteroid exposure and associated disutility values and costs, and the uncertain durability of the treatment effect. The ESC and the PBAC noted that the economic model did not assess fortnightly administration of tocilizumab, and noted this would likely improve the cost-effectiveness of tocilizumab.

6.51 The results of the sensitivity analyses indicated that the model was most sensitive to the assumptions of long term benefit, method of extrapolation, time horizon, corticosteroid disutility values and calculation errors (summarised below).

Table 16: Results of sensitivity analyses (based on the tocilizumab price presented in the submission)

Analyses	Incremental cost	Incremental QALY	ICER
Base case presented in the submission	\$ [redacted]	[redacted]	\$ [redacted]
Time horizon (30 years)			
20 year time horizon	\$ [redacted]	[redacted]	\$ [redacted]
10 year time horizon	\$ [redacted]	[redacted]	\$ [redacted]
5 year time horizon	\$ [redacted]	[redacted]	\$ [redacted]
Treatment benefit (no convergence of flare risk in the model)			
Convergence at 5 years	\$ [redacted]	[redacted]	\$ [redacted]
Convergence at 2 years	\$ [redacted]	[redacted]	\$ [redacted]
Time to first flare extrapolation (first year tocilizumab: Weibull, placebo: exponential; subsequent year both treatments: Weibull based on tocilizumab data)			
Exponential curve for tocilizumab for whole model	\$ [redacted]	[redacted]	\$ [redacted]
Gamma curve for tocilizumab for whole model	\$ [redacted]	[redacted]	\$ [redacted]
Log-logistic curve for tocilizumab for whole model	\$ [redacted]	[redacted]	\$ [redacted]
Utility values (corticosteroid treatment: -0.07)			
Decrease disutility for corticosteroid treatment to -0.04	\$ [redacted]	[redacted]	\$ [redacted]
Decrease disutility for corticosteroid treatment to -0.03	\$ [redacted]	[redacted]	\$ [redacted]
Calculation errors			
Correcting four week flare misapplication	\$ [redacted]	[redacted]	\$ [redacted]
Correcting cost of disease management (26 weeks of 'on corticosteroid' costs applied instead of 52 weeks)	\$ [redacted]	[redacted]	\$ [redacted]
Correcting cumulative corticosteroid dose on primary remission in placebo arm (26 weeks applied instead of 52 weeks)	\$ [redacted]	[redacted]	\$ [redacted]
Correcting 3 of the identified errors: Correcting flare misapplication; disease management costs; and cumulative corticosteroid dose in primary remission for placebo arm.	\$ [redacted]	[redacted]	\$ [redacted]
Pre-PBAC responses' approach to correcting the 3 errors outlined in the row above			\$ [redacted]
Pre-PBAC responses' approach to correcting the 3 errors outlined in the row above plus [redacted]% lower price			\$ [redacted]

Source: Table 3.31 (p 122), Table 3.32 (p 123) and Table 3.34 (p 124), tornado diagram (p 124) of the submission; additional analyses conducted during the evaluation based on the Economic Evaluation Excel workbook

Abbreviations: ICER, incremental cost effectiveness ratio; QALY, quality-adjusted life year

Italicised analyses were conducted during the evaluation

Note: Convergence derived from year 1, assuming the convergence curve did not exceed the tocilizumab time to first flare curve.

The redacted table shows ICERs in the range \$15,000/QALY – \$45,000/QALY to \$105,000/QALY – \$200,000/QALY.

6.52 The submission based the proposed DPMQ for tocilizumab on the PBS price in rheumatoid arthritis, and noted that this price may be subject to an upcoming statutory reduction due to the introduction of a new formulation of tocilizumab. The submission stated that the new price, once known, would also apply to the GCA indication. The pre-PBAC response stated that, at the time the pre-PBAC response was prepared, the sponsor was anticipating there would be a [redacted]% reduction to the tocilizumab price in rheumatoid arthritis. The pre-PBAC response stated that this lower price would reduce the ICER from \$45,000/QALY – \$75,000/QALY (with the errors corrected, per the second-last row of Table 16) to \$45,000/QALY – \$75,000/QALY.

6.53 The pre-PBAC response also stated that, with the █% price reduction, a supportive trial-based cost effectiveness analysis resulted in an incremental cost of \$15,000 - \$45,000 per 52-week corticosteroid-free sustained remission responder.

Drug cost/patient/year

6.54 The estimated drug cost for tocilizumab per patient per year was \$12,392 (based on █ scripts using the DPMQ \$953.23 for 4 x 162 mg weekly injections). The PBAC noted this would reduce to \$9,926 per patient per year with the █% price reduction offered in the pre-PBAC response (which would result in a DPMQ of \$763.55). These costs were based on weekly administration of tocilizumab.

6.55 Tocilizumab should be used with concomitant corticosteroids with a cost per year of approximately \$184 (based on a 26-week taper with a cumulative dose of 2,632 mg and an average cost per mg of \$0.07 using June 2018 DPMQ for prednisone).

6.56 The estimated drug cost for corticosteroid per patient per year was approximately \$276 (based on a 52-week taper with a cumulative dose of 3,945 mg and an average cost per mg of \$0.07 using June 2018 DPMQ for prednisone).

Estimated PBS usage & financial implications

6.57 This submission was considered by DUSC.

6.58 The submission used an epidemiological approach to estimate the utilisation and financial implications associated with the PBS listing of tocilizumab for GCA. The submission took account of newly diagnosed (incident) patients and a pool of patients diagnosed over the previous 5 years experiencing disease relapse (prevalent patients). The net cost to the PBS/RPBS, as estimated in the submission, is shown in Table 17.

Table 17: Estimated utilisation and cost to the PBS of listing tocilizumab for GCA – estimated in the submission

	Year 1 (2019)	Year 2 (2020)	Year 3 (2021)	Year 4 (2022)	Year 5 (2023)	Year 6 (2024)
Prevalent GCA patients	█	█	█	█	█	█
Incident GCA patients	█	█	█	█	█	█
Total GCA patients	█	█	█	█	█	█
Patients treated with tocilizumab (█%)	█	█	█	█	█	█
Tocilizumab scripts (█ scripts per patient)	█	█	█	█	█	█
Cost of tocilizumab scripts (\$953.23 per script)	\$█	\$█	\$█	\$█	\$█	\$█
Patient copayments (\$20.41 per script)	\$█	\$█	\$█	\$█	\$█	\$█
Net cost to PBS/RPBS	\$█	\$█	\$█	\$█	\$█	\$█
Drug monitoring (6.5 tests per patient; \$17.70 per test)	\$█	\$█	\$█	\$█	\$█	\$█
Net cost to government	\$█	\$█	\$█	\$█	\$█	\$█

Source: Table 4.6 (p 138), Table 4.8 (p 139), Table 4.9 (p 140), Table 4.13 (p 142), Table 4.14 (p 143) of the submission
 Abbreviations: GCA, giant cell arteritis; PBS, Pharmaceutical Benefits Scheme; RPBS, Repatriation Pharmaceutical Benefits Scheme.

The redacted table shows that at Year 6, the estimated number of patients was less than 10,000 per year.

- 6.59 The submission estimated that the net cost to the PBS/RPBS for tocilizumab would be \$20 – \$30 million in Year 1 decreasing to \$10 – \$20 million in Year 6, with a cumulative total cost of \$60 – \$ 100 million in the first 6 years of listing.
- 6.60 The submission estimated that the incidence of GCA was 12.73 per 100,000 persons aged ≥50 years, based on a retrospective analysis of 363 consecutive patients who underwent temporal artery biopsy at a New Zealand (NZ) hospital (Abdul-Rahman et al., 2011). The submission stated that the incidence of GCA in NZ was chosen because NZ has a similar population demographic to Australia. However, the DUSC commented that the NZ population is genetically different to the Australian population, and there is a higher number of north European and Scottish descendants in NZ, who have a higher incidence of GCA.
- 6.61 DUSC noted the submission presented an Australian publication which reported the incidence of GCA in Australia as 3.2 per 100,000 persons >50 years of age (Dunstan 2014). DUSC noted this study was based on a South Australian cohort with biopsy-proven GCA. DUSC considered that the incidence of GCA may be higher in Australia than reported in Dunstan, as Dunstan only reported biopsy proven GCA while the proposed PBS restriction includes temporal artery biopsy or evidence of large-vessel vasculitis by angiography or imaging study. DUSC considered that, given the differences between the Australian and NZ populations, the Australian data provided a more appropriate (albeit conservative) estimate to inform the base case. Overall, DUSC considered the true incidence in Australia is likely higher than 3.2 per 100,000 persons aged >50 years, but lower than 12.73 per 100,000 persons aged ≥50 years.
- 6.62 The other main issues identified by DUSC were:
- Prevalent patients were underestimated as the submission did not account for patients diagnosed more than 5 years ago. However, the mean age of diagnosis in the Labarca study was 75 years old, and therefore the number of prevalent patients is likely to be small compared to the incident population.
 - Patients are likely to trial tocilizumab as there are no other treatments available for GCA. However, it is unlikely uptake will be ■■■% due to potential side effects which are more likely in older patients.
 - The trial-based drug use of 85% should be the base case compliance rate.
- 6.63 Overall, DUSC considered the estimates presented in the submission were overestimated.
- 6.64 The pre-PBAC response revised the financial estimates to incorporate DUSC’s advice that the compliance rate should be 85% (based on usage in the trial), and to reduce the price of tocilizumab (based on the tocilizumab price in rheumatoid arthritis likely being reduced by ■■■%). These revisions reduced the net cost to the PBS/RPBS from \$60 – \$100 million to \$60 – \$100 million in the first 6 years of listing.

- 6.65 The pre-PBAC response also acknowledged that the incidence of GCA is uncertain and conducted a sensitivity analysis which used an incidence rate [REDACTED] that reported in Dunstan (resulting in an incidence of [REDACTED] per 100,000 persons aged >50 years). This value was chosen because the submission stated, “Discussion with Roche’s advisory board supported the incidence being considered low and consensus was that a more realistic estimate was to [REDACTED] the incidence reported by Dunstan.” The PBAC noted that this resulted in a net cost to the PBS/RPBS of \$30 – \$60 million in the first 6 years of listing.
- 6.66 The PBAC considered that there is potential for use outside the proposed restriction to treat polymyalgia rheumatica (i.e. without concomitant GCA) and other types of vasculitis.

Financial management – risk sharing arrangements

- 6.67 The submission stated that the sponsor is willing to consider a risk share arrangement (RSA) to reduce the uncertainty associated with budget impact estimates.
- 6.68 The ESC considered that an RSA would be required to manage the uncertain patient population.

7 PBAC Outcome

- 7.1 The PBAC deferred making a decision regarding the listing tocilizumab for the treatment of giant cell arteritis (GCA). The PBAC noted the trial data showed that tocilizumab (weekly or fortnightly) was associated with a statistically significant increase in response rates compared with placebo plus a 52-week prednisone taper, and considered this was an important clinical benefit in this condition. The PBAC considered that tocilizumab treatment for GCA was likely to be cost-effective given: the [REDACTED]% price reduction offered in the pre-PBAC response; that a proportion of patients could be treated fortnightly (rather than weekly); and that tocilizumab treatment would be limited to 12 months in line with trial evidence. The PBAC deferred making a decision to seek further information regarding the restriction and for the financial caps to be revised to account for fortnightly dosing.
- 7.2 In deciding to defer, the PBAC considered there was a high unmet clinical need for effective treatments for GCA particularly given the adverse events associated with corticosteroids in this population who are often older patients with comorbidities, and the limited treatment options available.
- 7.3 The PBAC considered that the clinical need for tocilizumab is highest in patients with relapsed or refractory GCA, rather than newly diagnosed patients or those who are adequately controlled on corticosteroids. While the PBAC considered that it may be appropriate to limit tocilizumab to those patients who are likely to benefit the most, the PBAC considered that it would be difficult to confine use to such a population through a PBS restriction. This was because the population may be difficult to define and there would be a high risk of leakage.

- 7.4 The PBAC considered that, based on the data presented, there was limited difference in efficacy between weekly versus fortnightly dosing of tocilizumab. The PBAC noted the pre-PBAC response stated that clinician feedback suggested that some patients may receive treatment every two weeks once their active disease is under control. In addition, the PBAC considered that fortnightly administration (for 12 months) may also be an appropriate alternative to weekly administration for newly diagnosed patients, with weekly administration reserved for patients with relapsed GCA or who experience flares on fortnightly tocilizumab. The PBAC also considered that fortnightly administration may be preferred in patients who cannot self-administer the subcutaneous injection. However, the PBAC acknowledged that there was limited evidence to support this algorithm, and clinical judgement would also be required as to whether weekly versus fortnightly dosing would be preferred for a particular patient.
- 7.5 The PBAC noted that the submission had requested a lifetime total of 52 injections of tocilizumab, which would allow tocilizumab to be used beyond 12 months if administered fortnightly. The PBAC considered that the PBS restriction should specify that tocilizumab treatment is limited to 12 months in line with the trial evidence.
- 7.6 The PBAC considered that the restriction would require further work with expert advice around the imaging and biopsy requirements for diagnosis of GCA.
- 7.7 The PBAC noted that the submission had nominated standard of care, represented by a 52 week tapering course of corticosteroids, as the comparator. The PBAC considered that, in clinical practice, a longer corticosteroid tapering regimen may be used, and that other steroid-sparing agents and immunosuppressive agents (such as methotrexate, cyclosporin and azathioprine) may also be relevant comparators in relapsed patients. However, overall, the PBAC considered that the comparator nominated by the submission was reasonable.
- 7.8 The PBAC considered that the magnitude of the benefit of tocilizumab in GCA was uncertain given the following issues with the clinical evidence:
- the trial was relatively short (12 months) despite the long term nature of GCA.
 - the corticosteroid tapering regimens used in the GiACTA trial (in all arms) were shorter than recommended in treatment guidelines. The PBAC noted that tocilizumab was used in conjunction with a 6 month corticosteroid tapering regimen in the trial. The PBAC considered that tocilizumab may be used in conjunction with longer corticosteroid regimens in clinical practice, which may reduce some of its corticosteroid-sparing effects.
 - the direct biologic effects of tocilizumab on CRP and ESR may have led to an overestimation of the response to treatment with tocilizumab, given that CRP and ESR were included as part of the disease response criteria.
 - The GiACTA trial may not be representative of the PBS population as patients in the trial had high baseline rates of polymyalgia rheumatica symptoms, low rates of ischaemic optic neuropathy, and low ESR levels at baseline. Further, the trial excluded patients who had received intravenous methylprednisolone

(at a dose > 100 mg daily) in the previous six weeks, which the PBAC considered may have excluded patients with more severe disease.

- 7.9 The PBAC noted the trial data showed that tocilizumab (weekly or fortnightly) was associated with a statistically significant increase in response rates compared with placebo plus a 52-week prednisone taper. The PBAC considered this was an important clinical benefit in this condition. Overall, the PBAC considered that the claim of superior comparative efficacy at 52 weeks was adequately supported by the data for the comparison of tocilizumab (weekly or fortnightly) plus a 26 week tapering course of corticosteroids versus a 52 week tapering course of corticosteroids.
- 7.10 The PBAC noted that, based on the limited longer-term data available, there were high rates of relapse in patients who initially responded to 12 months of tocilizumab treatment. The open-label extension of the GiACTA trial found that, of patients who were in remission after 12 months of treatment, flares were subsequently observed in 8/24 (33%) of the tocilizumab weekly group, and 8/11 (73%) of the tocilizumab fortnightly group. The PBAC noted that similar rates of relapse (11/20 (55%)) were observed in a Phase 2 study of tocilizumab in GCA (albeit a different dose of tocilizumab was used) (Adler 2016). The PBAC considered that the large number of flares in the post-treatment period suggests that tocilizumab may suppress rather than prevent relapse. The PBAC considered that it would be important for the sponsor to ensure there are Quality Use of Medicines initiatives to help manage the expectations of clinicians and patients.
- 7.11 The PBAC considered that the claim of non-inferior safety was adequately supported by the data.
- 7.12 The pre-PBAC response estimated that the cost per QALY gained was \$45,000 – \$75,000 following correction of three of the errors identified during the evaluation and incorporation of the tocilizumab price reduction. The PBAC also noted the ESC considered that the cost-effectiveness estimate was not reliable given the errors and logical inconsistencies identified in the model, and the issues relating to the duration of corticosteroid exposure and associated disutility values and costs. The PBAC considered a key uncertainty for estimating the cost-effectiveness of tocilizumab was the assumed duration of benefit and noted there was a lack of reliable long-term clinical data to inform this. The PBAC noted that the pre-PBAC response had provided a trial-based analysis which resulted in a cost of \$15,000 - \$45,000 per 52-week corticosteroid-free sustained remission responder (with the ■% price reduction included), and considered this, together with the modelled analysis, supported that tocilizumab was likely to be cost-effective for the treatment of GCA.
- 7.13 In relation to the financial estimates, the PBAC noted DUSC's concerns regarding the assumed incidence of GCA, uptake and compliance, and the underestimate of prevalent patients. DUSC considered the true incidence in Australia is likely higher than 3.2 per 100,000 persons aged >50 years (based on a South Australian cohort with biopsy-proven GCA; Dunstan), but lower than 12.73 per 100,000 persons aged ≥50 years (as

assumed in the submission based on a New Zealand retrospective analysis of consecutive patients who underwent temporal artery biopsy). The pre-PBAC response conducted a sensitivity analysis which used an incidence rate [REDACTED] that reported in Dunstan (resulting in an incidence of [REDACTED] per 100,000 persons aged >50 years). The PBAC considered this lower incidence should inform the caps for the RSA. The PBAC considered the caps should also be informed by a compliance rate of 85% (as per DUSC's advice and included in the pre-PBAC response), a reduced uptake rate and a proportion of patients who could be treated with fortnightly dosing.

- 7.14 The PBAC considered that there is potential for use outside the proposed restriction to treat polymyalgia rheumatica (i.e. without concomitant GCA) and other types of vasculitis, particularly where patients with these conditions failed to achieve remission with corticosteroids or experienced flare despite corticosteroid therapy.
- 7.15 The PBAC considered that an RSA with a 100% rebate above the caps would be required given the uncertain GCA incidence rate and the potential for use outside the proposed restriction.
- 7.16 The PBAC considered that the outstanding issues that would need to be addressed in a minor resubmission were:
- the financial estimates should be updated to account for the proportion of patients who could use fortnightly dosing;
 - an RSA proposal with hard caps should be provided; and
 - expert advice around the imaging and biopsy requirements for diagnosis of GCA in the restriction.

Outcome:

Deferred

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 is committed to addressing the outstanding matters raised by PBAC to bring tocilizumab to patients with GCA at the earliest opportunity.