

5.14 SARILUMAB, Injection, 150 mg in 1.14 mL pre-filled syringe, 200 mg in 1.14 mL pre-filled syringe, Kevzara[®], Sanofi-Aventis Australia Pty Limited

1 Purpose of Application

- 1.1 The submission requested an Authority Required listing for sarilumab (SAR) for the treatment of severe rheumatoid arthritis (RA) of patients meeting certain criteria. This is the first submission of SAR for RA considered by the PBAC.
- 1.2 The basis for the requested listing was a cost-minimisation analysis to tocilizumab (TCZ) subcutaneous (SC) formulation, which is a pharmacological analogue. There are two TCZ formulations listed on the PBS: an intravenous (IV) injection since 2010, and a SC injection since 2016.

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

Component	Description
Population	Adults with severe RA and an inadequate response to cDMARDs
Intervention	SAR 200mg SC q2w; dose modification (interruption and temporary dose reduction to 150mg q2w) recommended for management of neutropenia, thrombocytopenia and elevated liver enzymes.
Comparator	TCZ SC 162mg qw; dose modification (interruption and temporary dose frequency reduction to 162mg q2w) recommended for management of neutropenia, thrombocytopenia and elevated liver enzymes. The submission did not nominate TCZ IV 8mg/kg q4w as a relevant comparator (dose reduction to 4mg/kg q4w for adverse events), but included in the clinical claim given the clinical evidence for TCZ was primarily for the IV formulation.
Outcomes	ACR response (20%, 50%, 70%), at Week 12 and 24. In its consideration of past submissions for RA, the PBAC had accepted that an ACR50 response was a reasonable treatment target, and is consistent with the PBS response criteria. Given response to initial treatment is assessed after 12 weeks under the proposed listing, ACR50 at Week 12 is the most relevant outcome.
Clinical claim	In severe RA, SAR is non-inferior in terms of efficacy and safety versus TCZ. The majority of the evidence presented in the submission compared SAR 200mg q2w and TCZ IV 8mg/kg q4w at Week 24. The PBAC has previously accepted that TCZ SC 162mg qw is equivalent to TCZ IV 8mg/kg q4w. The evidence presented also supported non-inferiority across the reduced dose regimens (SAR 150mg q2w, TCZ IV 4mg/kg q4w, and TCZ SC 162mg q2w).

Abbreviations: cDMARDs=conventional disease-modifying anti-rheumatic drugs; SAR=sarilumab; TCZ=tocilizumab; SC=subcutaneous; IV=intravenous; ACR=American College of Rheumatology; qw=every week; q2w=every second week; q4w=every four weeks; Source: Table 1.1, p2 of the submission.

2 Requested listing

- 2.1 The Sponsor requested PBS listing of SAR 200mg and 150mg formulations, as a prefilled syringe and auto-injector. The listing of the 200mg formulation provides for initial (16 weeks) and continuing (24 weeks) treatment; the listing of the 150mg formulation provides for continuing (maximum duration undefined) treatment for patients with adverse events requiring temporary dose reduction.

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Name, Restriction, Manner of administration and form	Max. Qty (packs)	Max. Qty (units)	No. of Rpts	Dispensed Price for Max. Qty	Proprietary Name and Manufacturer
<u>Initial treatment 1 or 2, balance of supply</u>					
SARILUMAB, prefilled syringe, 200mg	1	2	3	\$ [REDACTED] ^a	
SARILUMAB, auto-injector, 200mg	1	2	3	\$ [REDACTED] ^a	
<u>Continuing treatment, balance of supply</u>					
SARILUMAB, prefilled syringe, 200mg	1	2	5	\$ [REDACTED] ^a	Kevzara® Sanofi-Aventis
SARILUMAB, auto-injector, 200mg	1	2	5	\$ [REDACTED] ^a	
SARILUMAB, prefilled syringe, 150mg	1	2	0	\$ [REDACTED] ^a	
SARILUMAB, auto-injector, 150mg	1	2	0	\$ [REDACTED] ^a	
<u>Grandfathered patients</u>					
SARILUMAB, prefilled syringe, 200mg	1	2	5	\$ [REDACTED] ^a	
SARILUMAB, auto-injector, 200mg	1	2	5	\$ [REDACTED] ^a	

Category	General Schedule (Section 85)
PBS indication:	Severe active rheumatoid arthritis
SAR 200mg formulation	
Restriction:	Authority Required - In Writing
Treatment phase:	Initial treatment – Initial 1 (new patient or patient recommencing after a break of >24 months)
Clinical criteria:	<ul style="list-style-type: none"> • Patient must have severe active rheumatoid arthritis, AND • Patient must have received no PBS-subsidised treatment with a biological disease anti-rheumatic drug (bDMARD) for the condition in the previous 12 months, AND • Patient must not have failed previous PBS-subsidised treatment with sarilumab for this condition, and not have already failed, or ceased to respond to, PBS-subsidised bDMARD treatment for this condition 5 times, AND • Patient must have failed, in the 24 months immediately prior to the date of application, to achieve an adequate response to a trial of at least 6 months of intensive treatment with disease modifying anti-rheumatic drugs (DMARDs); AND • Patients must not receive more than 16 weeks of treatment under this restriction.
Treatment phase:	Continuing treatment
Clinical criteria:	<ul style="list-style-type: none"> • Patient must have a history of severe active rheumatoid arthritis, AND • Patient must have demonstrated an adequate response to treatment with sarilumab, AND • Patient must have received sarilumab as their most recent course of PBS-subsidised biological disease modifying anti-rheumatic (bDMARD) treatment, AND • Patients must not receive more than 24 weeks of treatment per continuing treatment course under this restriction.
SAR 150mg formulation	
Restriction:	Authority required- Streamlined
Treatment phase:	Continuing treatment
Clinical criteria:	<ul style="list-style-type: none"> • Patient must have a history of severe active rheumatoid arthritis, AND • Patient must have demonstrated an adequate response to treatment with sarilumab, AND • Patient must have received sarilumab as their most recent course of PBS-subsidised biological disease modifying anti-rheumatic (bDMARD) treatment

^a Requested effective price, updated from \$ [REDACTED] in the submission based on most recent pharmacy mark up and dispensing fees; requested published price is \$ [REDACTED].
Source: pp24-30 of the submission

2.2 The submission stated that a STREAMLINED listing of the 150mg formulation is necessary to ensure the availability of continuous treatment for patients without a break while awaiting approval. The Sponsor did not request repeats for the 150mg

strength formulation because the dose is temporary and patients require regular follow-up and monitoring of adverse events. The PBAC considered that a streamlined authority listing was not appropriate and any listing for the 150mg strength should be more closely aligned with the standard criteria for continuation with bDMARDs for RA.

- 2.3 The wording of the restrictions are consistent with other bDMARDs listed on the PBS for RA, although additional wording should be considered to clarify that patients treated with the 150mg formulation must also abide by the same total treatment durations as patients treated with the 200mg formulation.
- 2.4 A special pricing arrangement was requested that included a published price of \$[REDACTED] and an effective price of \$[REDACTED]. The effective price requested in the submission (\$[REDACTED]) was amended during the evaluation to account for updated pharmacy mark up and dispensing fees.
- 2.5 The same price was requested for both the 200mg and 150mg strength formulations on the basis that treatment response is maintained 24 weeks after dose reduction in the long-term extension study (EXTEND). However, the proposed price equivalence between the SAR 150mg and SAR 200mg formulations would result in a significant price advantage (double the cost) for SAR compared to TCZ at the reduced dosages for the management of adverse events.

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

3 Background

Registration status

- 3.1 TGA status at the time of PBAC consideration: The submission was made under the TGA/PBAC Parallel Process and the second round Clinical Evaluation Report was provided with the submission. Sarilumab was TGA registered on 14 September 2018, with the following indication:

“Kevzara in combination with non-biological Disease-Modifying Anti-Rheumatic Drugs (DMARDs) or as monotherapy is indicated for the treatment of moderate to severe active Rheumatoid Arthritis in adult patients who have had an inadequate response or intolerance to one or more DMARDs.”
- 3.2 The TGA previously considered an application to register SAR for the treatment of RA in December 2016, but the Sponsor voluntarily withdrew the application due to disagreement over the recommended starting dose (150mg q2w, with the option to increase to 200mg q2w if clinically appropriate). The most recent TGA application, which included new evidence, was approved with a recommended starting dose of 200mg every two weeks (q2w) with subsequent (temporary) dose reduction to 150mg q2w for the management of adverse events.

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

4 Population and disease

- 4.1 RA is a chronic, progressive, debilitating autoimmune disease that occurs in approximately 1% of the adult population. The disease is characterised by chronic inflammation of the synovium, which over time results in damage to the joints leading to pain and disability, and reduces life expectancy. The onset of RA may occur at any age, but most commonly occurs in people aged 40 to 70 years.
- 4.2 The clinical management algorithm for severe RA is well established. To qualify for initial therapy with a biologic Disease-Modifying Anti-Rheumatoid Drug (bDMARD) or target synthetic DMARD (tsDMARD), patients must first have failed to achieve an adequate response to at least six months of therapy with conventional DMARDs (such as methotrexate). Continued treatment is dependent on demonstrating and maintaining a response to therapy. Over a lifetime, patients are restricted to fail or cease to respond to a maximum of five bDMARDs/tsDMARDs, and patients may only fail or cease to respond to each drug once.
- 4.3 SAR is a humanised immunoglobulin G subclass 1 (IgG1) monoclonal antibody that binds to interleukin 6 (IL-6) receptors. IL-6 is involved in diverse physiological processes such as migration and activation of T-cells, B-cells, monocytes and osteoclasts leading to systemic inflammation, synovial inflammation and bone erosion in patients with RA. The reduction of inflammation that occurs with IL-6 receptor blockade is associated with laboratory changes such as decrease in absolute neutrophil count and elevation in lipids.
- 4.4 SAR would become one of several bDMARDs and the second IL-6 inhibitor listed on the PBS listed for patients with severe active RA. The recommended dose is SAR 200mg SC every two weeks (q2w) with dose modification (interruption and temporary dose reduction to 150mg q2w) recommended for management of neutropenia, thrombocytopenia and elevated liver enzymes.

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

5 Comparator

- 5.1 The submission nominated tocilizumab (TCZ), and specifically the SC formulation, as an appropriate comparator. TCZ is an IL-6 inhibitor (a pharmacological analogue), the only IL-6 inhibitor listed on the PBS for RA, and the SC formulation is the same route of administration as SAR. However, abatacept, adalimumab, certolizumab pegol, etanercept, golimumab, infliximab, rituximab and tofacitinib are also listed on the PBS listed for the treatment of severe RA and may be replaced by TCZ, and are therefore also relevant comparators. The PBAC has previously noted that tocilizumab is non-inferior to other bDMARDs for the treatment of RA (PSD, paragraph 6.5, March 2016).
- 5.2 Under section 101(3B) of the National Health Act (1953) where therapy involving the use of a particular drug or medicinal preparation, or a class of drugs and medicinal

preparations, is substantially more costly than an alternative therapy or alternative therapies, whether or not involving the use of other drugs or preparations, the Committee shall not recommend to the Minister that the drug, preparation or class be made available as pharmaceutical benefits under this Part unless the Committee is satisfied that the first-mentioned therapy, for some patients, provides a significant improvement in efficacy or reduction of toxicity over the alternative therapy or therapies. The PBS therapeutic relativity sheets show that all bDMARDs (and tofacitinib) currently PBS listed for RA are cost-minimised with one or more of the alternative bDMARD therapies.

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

6 Consideration of the evidence

Sponsor hearing

6.1 There was no hearing for this item.

Consumer comments

6.2 The PBAC noted there were no consumer comments received for this item.

Clinical trials

- 6.3 The submission identified but excluded one head-to-head safety trial from the efficacy comparison (ASCERTAIN) comparing SAR+MTX vs TCZ IV+MTX on the basis that the trial dose of TCZ IV (4mg-8mg/kg q4w titration regimen) does not match the approved dose (8mg/kg q4w). This was reasonable. Patients commenced on TCZ 4mg/kg q4w but 60.8% increased to TCZ 8mg/kg q4w during the treatment period, most after Week 4. Results from ASCERTAIN indicated similar efficacy (not powered) and safety for patients treated with SAR 200mg q2w and the TCZ IV titration dose.
- 6.4 The submission was based on three placebo (PBO) or adalimumab (ADA) controlled trials of SAR, seven PBO or ADA controlled trials of TCZ IV, one PBO controlled trial of TCZ SC, and one trial comparing TCZ IV and TCZ SC dosing regimens, summarised in the table below. Long-term safety data was presented from one extension study (EXTEND), which investigated safety and efficacy of SAR for up to five years.

Table 2: Trials and associated reports^A presented in the submission

Trial ID	Protocol title/ Publication title	Publication citation
SAR (+MTX) vs PBO (+MTX)		
MOBILITY-B	A randomized, double-blind, placebo-controlled, multicenter, two-part, dose ranging and confirmatory study with an operationally seamless design, evaluating efficacy and safety of SAR153191 on top of methotrexate (MTX) in patients with active rheumatoid arthritis who are inadequate responders to MTX therapy. Genovese M.C., Fleischmann R., Kivitz A.J., et al, Sarilumab plus methotrexate in patients with active rheumatoid arthritis and inadequate response to methotrexate: results of a phase III study.	Clinical study report – report date: 20/08/2015 Arth Rheumatol 2015: 67:1424–37

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Trial ID	Protocol title/ Publication title	Publication citation
TARGET	A randomized, double-blind, double-dummy study assessing the safety and tolerability of sarilumab and tocilizumab (in combination with conventional DMARD therapy) in patients with rheumatoid arthritis who are inadequate responders to or intolerant of TNF antagonists. Fleischmann, R., van Adelsberg, J., Lin, Y., et al. Sarilumab and Nonbiologic Disease-Modifying Antirheumatic Drugs in Patients With Active Rheumatoid Arthritis and Inadequate Response or Intolerance to Tumor Necrosis Factor Inhibitors.	Clinical study report – report date: 24/07/2014 Arth Rheumatol 2017; 69(2): 277-290
SAR vs ADA		
MONARCH	A randomized, double-blind, parallel-group study assessing the efficacy and safety of sarilumab monotherapy versus adalimumab monotherapy in patients with rheumatoid arthritis. Burmester, G., Yong, L., Patel, R., et al. Efficacy and safety of sarilumab monotherapy versus adalimumab monotherapy for the treatment of patients with active rheumatoid arthritis (MONARCH): a randomised, double-blind, parallel-group phase III trial.	Clinical study report – report date: 17/05/2016 Ann Rheum Dis 2017; 76:840–847
TCZ IV (+MTX) vs PBO (+MTX)		
OPTION	Smolen J.S., Beaulieu A., Rubbert-Roth A., et al, Effect of interleukin-6 receptor inhibition with tocilizumab in patients with RA (OPTION study): a double-blind, placebo-controlled, randomised trial.	Lancet 2008; 371(9617):987- 997
MEASURE	McInnes I.B., Thompson L., Giles J.T., et al, Effect of interleukin-6 receptor blockade on surrogates of vascular risk in rheumatoid arthritis: MEASURE, a randomised, placebo-controlled study.	Ann Rheum Dis 2015; 74: 694–702.
LITHE	Kremer J.M., Blanco R., Brzosko M., et al, Tocilizumab inhibits structural joint damage in rheumatoid arthritis patients with inadequate responses to methotrexate: Results from the double-blind treatment phase of a randomized placebo-controlled trial of tocilizumab safety and prevention of structural joint damage at one year.	Arthritis and Rheumatism 2011; 63(3): 609-621
TOWARD	Genovese J., McKay J.D., Nasonov E.L., et al, Interleukin-6 receptor inhibition with tocilizumab reduces disease activity in rheumatoid arthritis with inadequate response to disease-modifying anti-rheumatic drugs.	Arthritis and Rheumatism 2008, 58(10): 2968-2980
ROSE	Yazici Y., Curtis J.R., Ince A., et al. Efficacy of tocilizumab in patients with moderate to severe active rheumatoid arthritis and a previous inadequate response to disease-modifying antirheumatic drugs: the ROSE study.	Ann Rheum Dis 2012;71:198–205
BREVACTA	Kivitz A., Olech E., Borofsky M., et al, Subcutaneous tocilizumab versus placebo in combination with disease-modifying antirheumatic drugs in patients with rheumatoid arthritis.	Arthritis Care and Research 2014, 66(11): 1653-1661
RADIATE	Emery P., Keystone E., Tony H.P., et al, IL-6 receptor inhibition with tocilizumab improves treatment outcomes in patients with rheumatoid arthritis refractory to anti-tumour necrosis factor biologicals: results from a 24-week multicentre randomised placebo-controlled trial.	Annals of the Rheumatic Diseases 2008; 67: 1516-1523
TCZ IV vs ADA		
ADACTA	Gabay C., Emery P., van Vollenhoven R., et al. Tocilizumab monotherapy versus adalimumab monotherapy for treatment of rheumatoid arthritis (ADACTA): a randomised, double-blind, controlled phase 4 trial.	Lancet 2013; 381: 1541–50
TCZ IV vs TCZ SC		
SUMMACTA	Burmester G., Rubbert-Roth A., Cantagrel A., et al, A randomised, double-blind, parallel-group study of the safety and efficacy of subcutaneous tocilizumab versus intravenous tocilizumab in combination with traditional disease-modifying antirheumatic drugs in patients with moderate to severe rheumatoid arthritis (SUMMACTA study).	Annals of the Rheumatic Diseases 2014, 73: 69-74.
EXTENSION STUDY		
EXTEND	A multi-center, uncontrolled extension study evaluating the efficacy and safety of sarilumab in patients with active Rheumatoid Arthritis (RA) (interim analysis).	Interim clinical study report – report date 23/5/2016.

[^] only main publication presented in table
Source: Table 2.2.1, pp37-44 of the submission.

- 6.5 The submission presented indirect comparisons for all combinations of SAR, TCZ IV and TCZ SC at full and reduced doses reported in the trials. The evaluation considered that comparisons at the recommended doses without dose reduction is most relevant for assessing patient response on the PBS, given all patients will commence treatment at the recommended doses, dose reduction is temporary, and it will likely affect a minority of patients (~15%).
- 6.6 The key features of the direct randomised trials are summarised in the table below. Treatment arms at the reduced dose regimens of SAR and TCZ are not presented. Only five of the TCZ trials (TOWARD, ROSE, SUMMACTA, ADACTA, RADIATE) and none of the SAR trials seemingly permitted patients to undergo the dose interruption / dose reduction recommended in the respective product information. To account for differences across the trial populations and concomitant therapy, the submission appropriately categorised the trials into three populations, based on failed prior treatment (cDMARD or bDMARD) and concomitant therapy (combined use with cDMARDs or monotherapy).
- 6.7 The PBAC previously considered evidence from five of the nine TCZ trials (OPTION, LITHE, TOWARD, RADIATE, SUMMACTA) when it recommended the IV and SC formulations in 2010 and 2016 respectively (see TCZ IV PSD March 2010, TCZ SC PSD March 2016). The other trials included in the submission were published after the Committee considered the TCZ IV formulation (MEASURE, ROSE, ADACTA), or did not investigate the recommended dose of TCZ SC (BREVACTA). Patients in BREVACTA (not presented below) received PBO or TSC SC at the reduced dosing frequency (162mg q2w), which is not the relevant dose of TSC SC for assessing initial response.

Table 3: Key features of the included evidence (excluding BREVACTA#)

Trial	N	Design / duration	Relevant comparison (recommended starting dose)	Bias	Patient population	Key outcomes
POPULATION: cDMARD IR, cDMARD concomitant						
MOBILITY-B	797*	P3,MC,R,DB 52wks; bDMARD rescue wk16 ^a	SAR 200mg SC q2w + MTX; PBO + MTX	Low	Active RA (M-S); MTX IR	ACR response
OPTION	409*	P3,MC,R,DB 24wks; bDMARD rescue wk16 ^b	TCZ 8mg/kg IV q4w + MTX; PBO + MTX	Low	Active RA (M-S); MTX IR	ACR response
MEASURE	132	P3,MC,R,DB 24wks; bDMARD rescue wk16 ^c	TCZ 8mg/kg IV q4w + MTX; PBO + MTX	Low	Active RA (M-S); MTX IR	ACR response
LITHE	791*	P3,MC,R,DB 52wks; bDMARD rescue wk16 ^d	TCZ 8mg/kg IV q4w + MTX; PBO + MTX	Low	Active RA (M-S); MTX IR	ACR response
TOWARD	1220	P3,MC,R,DB 24wks; cDMARD rescue wk16 ^e	TCZ 8mg/kg IV q4w+cDMARD; PBO + cDMARD	Low	Active RA (M-S); cDMARD IR	ACR response
ROSE	619	P3b,MC,R,DB 24wks; bDMARD rescue wk16 ^f	TCZ 8mg/kg IV q4w+cDMARD; PBO + cDMARD	Low	Active RA (M-S); cDMARD IR	ACR response
SUMMACTA	1262	P3,MC,R,DD,DB 24wks; No rescue.	TCZ 8mg/kg IV q4w+cDMARD; TCZ 162mg SC qw+cDMARD	Low	Active RA (M-S); cDMARD IR	ACR response
POPULATION: cDMARD IR, monotherapy						
MONARCH	369	P3,MC,R,DD, DB 24wk; bDMARD rescue wk16 ^g	SAR 200mg SC q2w; ADA 40mg SC q2w	Low	Active RA (M-S); MTX IR/INT	ACR response
ADACTA	326	P4,MC,R,DD,DB 24wks; bDMARD rescue wk16 ^h	TCZ 8mg/kg IV q4w; ADA 40mg SC q2w	Low	Active RA (M-S); MTX IR/INT	ACR response
POPULATION: bDMARD-IR, cDMARD concomitant						
TARGET	365*	P3,MC,R,DB 24wks; bDMARD rescue wk12 ⁱ	SAR 200mg SC q2w+cDMARD; PBO + cDMARD	Low	Active RA (M-S); TNF α IR	ACR response
RADIATE	335*	P3,MC,R,DB 24wks; bDMARD rescue wk16 ^j	TCZ 8mg/kg IV q4w + MTX; PBO + MTX	Low	Active RA (M-S); TNF α IR	ACR response

BREVACTA randomised patients to the reduced dose regimen of TCZ SC 162mg q2w, and was not relevant for the primary comparison

* Number randomised to treatment arms included in the submission.

^a SAR 200mg q2w offered from Week 16 if <20% improvement from baseline in SJC or TJC at two consecutive assessments

^b TCZ 8mg/kg q4w (and steroids) offered from Week 16 if <20% improvement from baseline in both TJC and SJC.

^c TCZ 8mg/kg q4w offered from Week 16 if <20% improvement from baseline in both TJC and SJC after doses at Week 8/12.

^d TCZ 4 and 8mg/kg q4w (and steroids) offered from Week 16 to patients in the control arm and TCZ 8mg/kg arm respectively, if <20% improvement from baseline in both TJC and SJC. If no improvement persisted after three doses, TCZ 8mg/kg offered.

^e DMARD adjustment (and steroids) offered from Week 16 if <20% improvement from baseline in both TJC and SJC.

^f TCZ 8mg/kg q4w offered from Week 16 if <20% improvement from baseline in both TJC and SJC.

^g ADA 40mg qw or matching placebo in SAR arm offered from Week 16 if <20% improvement from baseline in both TJC and SJC.

^h ADA 40mg qw or matching placebo in TCZ arm offered from Week 16 if <20% improvement from baseline in both TJC and SJC.

ⁱ SAR 200mg q2w offered from Week 12 if <20% improvement from baseline in the SJC or TJC for 2 joint assessments \geq 4 weeks apart.

^j TCZ 8mg/kg q4w offered from Week 16 if <20% improvement from baseline in both TJC and SJC.

Abbreviations: P=phase; OL=open label; PBO = placebo; R = randomised; DB = double blind; DD = double dummy; MC = multicentre; SAR=sarilumab; TCZ=tocilizumab; MTX=methotrexate; cDMARD=conventional disease-modifying anti-rheumatic drug; PBO=placebo; TNF α = tumour necrosis factor alpha blocker

Source: Compiled during the evaluation; Table 2.3.1, pp49-59 of the submission; Table 2.3.2, pp62-64 of the submission

6.8 All trials were phase 3 or 4, multicentre, randomised, PBO or active controlled superiority trials (with the exception of SUMMACTA, a non-inferiority trial) with a double-blind period of at least 24 weeks. However, all but one trial permitted patients with <20% improvement in tender joint count (TJC) and/or swollen joint count (SJC) by Week 12 or 16 access to rescue therapy ('early escape'), with many patients in the control arm receiving active bDMARD therapy and patients in the active arms becoming un-blinded to treatment. With the exception of TOWARD (which only offered cDMARD adjustment as a rescue), between 28-43% of patients randomised to

PBO and 9-17% randomised to a SAR or TCZ received rescue therapy. All trials classified patients who received rescue therapy (or withdrew prematurely) as non-responders after Week 12/16 irrespective of response.

Comparative effectiveness

- 6.9 Under the PBS restrictions for bDMARDs for RA, continued treatment is dependent on demonstrating and maintaining response to therapy, assessed after a minimum of 12 weeks following initiation (and every 24 weeks ongoing thereafter). The response criteria is a composite outcome requiring a 50% improvement from baseline in TJC/SJC and a 20% (or below absolute thresholds) improvement in acute phase reactants erythrocyte sedimentation rate (ESR) or C-reactive protein (CRP). The response criteria on the PBS are most similar to the American College of Rheumatology (ACR) 50% response criteria.
- 6.10 The submission presented indirect comparisons across several outcomes (ACR20, ACR50, ACR70, Δ HAQ-DI, Δ DAS28-ESR), primarily at Week 24. In its consideration of past submissions for RA, the PBAC has accepted that an ACR50 response represented a reasonable treatment target, and assessment of response at Week 12 corresponded with assessment of response to initial treatment on the PBS.
- 6.11 ACR50 at Week 24 is summarised in Table 4 below. Given large variations between PBO response rates (observed across multiple outcomes), the submission concluded that indirect comparison using risk difference (RD) would be less biased than using odds ratio (OR). Due to incomplete reporting in the submission, the RD statistics presented below were calculated during the evaluation. There were slight differences between the RD in the submission and those presented below due largely to rounding error. The results demonstrated:
- in combination with cDMARDs, SAR 200mg q2w and TCZ IV 8mg/kg q4w were more effective than PBO at producing a response at Week 24;
 - in combination with cDMARDs, response at Week 24 was similar for TCZ SC 162mg qw and TCZ IV 8mg/kg q4w;
 - as monotherapy, SAR 200mg q2w and TCZ IV 8mg/kg q4w were more effective than ADA 40mg q2w at producing a response at Week 24; and
 - indirect comparison based on RD did not show any statistically significant differences between SAR 200mg q2w, TCZ IV 8mg/kg q4w or TCZ SC 162mg qw, either as monotherapy or in combination with cDMARDs.
- 6.12 The submission did not nominate or apply a minimum clinically important difference (MCID) for ACR response. The PBAC previously considered an MCID for ACR20 at Week 12 based on the RR statistic of 0.4, but no statistical rationale was provided. No established MCID for ACR was identified in the literature.

Table 4: ACR50 response at Week 24 at the recommended doses of SAR and TCZ without dose reduction (SAR 200mg q2w, TCZ IV 8mg/kg q4w and TCZ SC 162mg qw), and indirect comparisons presented by the submission

Trial	Drug n/N (%)	Control n/N (%)	OR# (95%CI)	RD# (95%CI)	NNT# (95%CI)
cDMARD IR, cDMARD concomitant					
COMPARISON: SAR v PBO					
MOBILITY-B. SAR 200mg	182/399(46)	66/398(17)	4.22 (3.03,5.87)	0.29 (0.23,0.35)	+ 3(3,4)
COMPARISON: TCZ v PBO					
OPTION. TCZ IV 8mg/kg	90/205(44)	22/204(11)	6.47(3.84,10.90)	0.33 (0.25,0.41)	+ 3(2,4)
MEASURE. TCZ IV 8mg/kg	22/69(32) ^a	10/63(15) ^a	2.48 (1.07,5.77)	0.16 (0.02,0.30)	+ 6(3,50)
LITHE. TCZ IV 8mg/kg	131/398(33) ^a	39/393(10) ^a	4.45 (3.01,6.59)	0.23 (0.18,0.28)	+ 4(4,6)
TOWARD. TCZ IV 8mg/kg	302/803(38) ^b	37/413(9) ^b	6.13 (4.25,8.84)	0.29 (0.24,0.33)	+ 3(3,4)
ROSE. TCZ IV 8mg/kg	123/409(30) ^b	23/205(11) ^b	3.40 (2.10,5.51)	0.19 (0.13,0.25)	+ 5(4,8)
Meta-analysis (TCZ IV)	668/1884(35)	131/1278(10)	4.65 (3.47,6.24)	0.25 (0.19,0.30)	+ 4(3,5)
COMPARISON: TCZ SC qw v TCZ IV					
SUMMACTA 162mg v 8mg/kg	262/558(47) ^b	263/537(49) ^b	0.92 (0.73,1.17)	-0.02 (-0.08,0.04)	+ NA
cDMARD IR, monotherapy					
COMPARISON: SAR v ADA 40mg					
MONARCH. SAR 200mg	84/184(46)	55/185(30)	1.99 (1.29,3.05)	0.16 (0.06,0.26)	+ 6(4,17)
COMPARISON: TCZ v ADA 40mg					
ADACTA. TCZ IV 8mg/kg	77/163(47)	45/162(28)	2.33 (1.47,3.69)	0.19 (0.09,0.30)	+ 5(3,11)
bDMARD-IR, cDMARD concomitant					
COMPARISON: SAR v PBO					
TARGET. SAR 200mg	75/184 (41)	33/181 (18)	3.09 (1.91,4.98)	0.23 (0.13,0.32)	+ 4(3,8)
COMPARISON: TCZ v PBO					
RADIATE. TCZ IV 8mg/kg	49/170 (29)	6/158 (4)	10.26(4.25,24.75)	0.25 (0.18,0.32)	+ 4(3,6)
cDMARD/bDMARD-IR, cDMARD concomitant					
Meta-analysis SAR*	257/583(44)	99/579(17)	3.79 (2.84,5.07)	0.27 (0.21,0.33)	+ 4(3,5)
Meta-analysis TCZ IV*	717/2054(35)	137/1436(10)	4.96 (3.65,6.73)	0.25 (0.20,0.29)	+ 4(3,5)
Indirect comparisons					
cDMARD IR, cDMARD concomitant					
SAR (MOBILITY-B) v TCZ IV (Meta IV)			0.91 (0.58,1.41)	0.04(-0.04,0.12)	+ NA
SAR (MOBILITY-B) v TCZ SC qw (SUMMACTA), IV (Meta IV)			0.99 (0.60,1.63)	0.06 (-0.04,0.16)	+ NA
cDMARD IR, monotherapy					
SAR (MONARCH) vs TCZ IV (ADACTA)			0.85 (0.46,1.60)	-0.03 (-0.18,0.12)	+ NA
bDMARD-IR, cDMARD concomitant					
SAR (TARGET) vs TCZ IV (RADIATE)			0.30 (0.11,0.82)	-0.02 (-0.14,0.10)	+ NA
cDMARD/bDMARD-IR, cDMARD concomitant					
SAR (Meta SAR*) v TCZ IV (Meta IV*)			0.76 (0.50,1.17)	0.02 (-0.06,0.10)	+ NA
SAR (Meta SAR*) v TCZ SC qw (SUMMACTA), IV (Meta IV*)			0.83 (0.51,1.35)	0.04 (-0.06,0.14)	+ NA

^a Outcome presented in graph only in main publication or supplementary material; exact values not reported in manuscript

^b Outcome reported as % rather than n/N

Calculated during the evaluation

Abbreviations: OR=odds ratio; RD=risk difference; CI=confidence interval; SAR=sarilumab; TCZ=tocilizumab; ADA=adalimumab

Source: Table 2.5.6, pp118-119 of the submission; Figure 2.4, p218 of the submission

6.13 Other ACR response outcomes presented in the submission are summarised in Table 5. The findings were consistent with the results of ACR50 at Week 24 outlined in Table 4, and did not show any statistically significant differences across the SAR and TCZ treatment arms. Overall, the results support a conclusion of similar efficacy across the full dose regimens of SAR and TCZ.

Table 5: Indirect comparison of other ACR response outcomes at the recommended doses of SAR and TCZ without dose reduction (SAR 200mg q2w, TCZ IV 8mg/kg q4w and TCZ SC 162mg qw) presented by the submission

Outcome	Comparison	Indirect comparison RD (95%CI)
cDMARD IR, cDMARD concomitant		
ACR20(wk24)	SAR 200mg q2w v TCZ IV 8mg/kg q4w	0.037 (-0.056, 0.130)
ACR20(wk24)	SAR 200mg q2w v TCZ SC 162mg qw via TCZ IV 8mg/kg q4w (two step)	0.058 (-0.048, 0.164)
ACR70(wk24)	SAR 200mg q2w v TCZ IV 8mg/kg q4w	0.035 (-0.030, 0.100)
ACR70(wk24)	SAR 200mg q2w v TCZ SC 162mg qw via TCZ IV 8mg/kg q4w (two step)	0.065 (-0.016, 0.146)
cDMARD IR, monotherapy		
ACR20(wk24)	SAR 200mg q2w v TCZ IV 8mg/kg q4w	-0.023 (-0.166, 0.120)
ACR70(wk24)	SAR 200mg q2w v TCZ IV 8mg/kg q4w	-0.031 (-0.151, 0.089)
bDMARD-IR, cDMARD concomitant		
ACR20(wk12)	SAR 200mg q2w v TCZ IV 8mg/kg q4w	-0.033 (-0.170, 0.105)
ACR50(wk12)	SAR 200mg q2w v TCZ IV 8mg/kg q4w	-0.003 (-0.106, 0.112)
ACR70(wk12)	SAR 200mg q2w v TCZ IV 8mg/kg q4w	0.044 (-0.025, 0.113)
ACR20(wk24)	SAR 200mg q2w v TCZ IV 8mg/kg q4w	-0.127 (-0.270, 0.016)
ACR70(wk24)	SAR 200mg q2w v TCZ IV 8mg/kg q4w	-0.020 (-0.104, 0.064)
cDMARD/bDMARD-IR, cDMARD concomitant		
ACR20(wk24)	SAR 200mg q2w v TCZ IV 8mg/kg q4w	0.002 (-0.080, 0.084)
ACR20(wk24)	SAR 200mg q2w v TCZ SC 162mg qw via TCZ IV 8mg/kg q4w (two step)	0.023 (-0.073, 0.119)
ACR70(wk24)	SAR 200mg q2w v TCZ IV 8mg/kg q4w	0.001 (-0.090, 0.092)
ACR70(wk24)	SAR 200mg q2w v TCZ SC 162mg qw via TCZ IV 8mg/kg q4w (two step)	0.031 (-0.072, 0.134)

Source: Figures 2.3, 2.4 and 2.5, pp217-219 of the submission

6.14 Indirect comparisons of ACR response between the reduced dose regimens (SAR 150mg q2w, TCZ IV 4mg/kg, TCZ SC 162mg q2w) did not show a significant difference between the treatment arms based on RD for most of the comparisons. Overall, the results support a conclusion of similar efficacy across the reduced dose regimens of SAR and TCZ.

Comparative harms

6.15 Table 6 summarises safety outcomes for SAR 200mg q2w treatment arms in MOBILITY-B, TARGET, MONARCH and ASCERTAIN. There was a higher incidence of neutropenia / leukopenia and injection site reactions reported for SAR compared with all trial comparators (PBO, ADA, and TCZ 4-8mg/kg titration), and a higher incidence of upper respiratory infections and urinary tract infections compared to PBO. Increased ALT (hepatic disorders) was also more common for SAR compared with PBO and ADA, but numerically less common compared with TCZ IV 4-8mg/kg titration. Overall, the safety profile of SAR is consistent with the anticipated effects of IL-6 inhibition.

Table 6: Summary of adverse events reported in the SAR trials

	MOBILITY-B [^]		TARGET		MONARCH		ASCERTAIN [#]	
	SAR 200mg N=424	PBO N=427	SAR 200mg N=184	PBO N=181	SAR 200mg N=184	ADA 40mg N=184	SAR 200mg N=51	TCZ IV 4/8mg/kg N=102
Summary of treatment emergent adverse events								
Any AE	331(78.1)	263(61.6)	120(65.2)	90 (49.7)	118(64.1)	117(63.6)	36 (70.6)	68 (66.7)
Any serious AE	48 (11.3)	23 (5.4)	10 (5.4)	6 (3.3)	9 (4.9)	12 (6.5)	3 (5.9)	7 (6.9)
AE to discontinuation	59 (13.9)	20 (4.7)	17 (9.2)	8 (4.4)	11 (6.0)	13 (7.1)	8 (15.7)	4 (3.9)
AE to death	1 (0.2)	2 (0.5)	0 (0.0)	1 (0.6)	1 (0.5)	0 (0.0)	0 (0.0)	1 (1.0)
Adverse events of special interest								
Serious Infections	17 (4.0)	10 (2.3)	2 (1.1)	2 (1.1)	2 (1.1)	2 (1.1)	1 (2.0)	2 (2.0)
Neutropenia/Leukopenia	67 (15.8)	2 (0.5)	26 (14.1)	3 (1.7)	26 (14.1)	3 (1.6)	9 (17.6)	7 (6.9)
Thrombocytopenia	6 (1.4)	0 (0.0)	5 (2.7)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Hepatic disorders	50 (11.8)	20 (4.7)	19 (10.3)	4 (2.2)	9 (4.9)	7 (3.8)	3 (5.9)	7 (6.9)
Diverticulitis/GI ulcer/perforation	4 (0.9)	2 (0.5)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.0)
Elevation in lipids	17 (4.0)	8 (1.9)	15 (8.2)	5 (2.8)	3 (1.6)	8 (4.3)	3 (5.9)	13 (12.7)
Anaphylaxis	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Malignancy	3 (0.7)	1 (0.2)	1 (0.5)	1 (0.6)	0 (0.0)	1 (0.5)	0 (0.0)	0 (0.0)
Lupus-like syndrome	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Demyelinating disorders	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	1 (0.5)	1 (0.5)	0 (0.0)	0 (0.0)
Injection site reactions	43 (10.1)	5 (1.2)	15 (8.2)	2 (1.1)	17 (9.2)	8 (4.3)	5 (9.8)	4 ^a (3.9)

[^] Safety outcomes in MOBILITY-B included patients enrolled in MOBILITY-A at the relevant doses

[#] Supplementary trial, excluded by the submission given TCZ arm doesn't use the approved dose

^a For SC placebo

Abbreviations: SAR=sarilumab; TCZ=tocilizumab; PBO=placebo

Source: Tables 2.5.19, 2.5.20, 2.5.24, 2.5.25, 2.5.26, 2.5.30, 2.5.31, 2.5.32, 2.5.36, 2.5.37, 2.5.38, 2.5.42, pp158-183 of the submission

- 6.16 Based on data reported in the extension study EXTEND, there is no evidence to suggest that longer-term cumulative exposure to SAR would lead to adverse events not already identified in clinical trials.
- 6.17 The submission did not undertake an indirect comparison of SAR and TCZ for any safety outcomes. Given the limited comparable safety data available, drawing any conclusions is difficult; however, the safety profiles of SAR and TCZ appeared to be similar. Based on naïve comparison, there may be a slightly higher incidence of neutropenia associated with SAR compared to TCZ 8mg/kg.
- 6.18 The ESC considered the overall safety profiles of SAR and TCZ were comparable and consistent with the established profile for IL-6 inhibitors.

Clinical claim

- 6.19 The submission described SAR as non-inferior in terms of effectiveness and safety compared with TCZ. The ESC considered that the evidence presented in the submission reasonably supported the clinical claim. While the majority of the evidence presented in the submission compared ACR response between SAR 200mg q2w and TCZ IV 8mg/kg q4w, the PBAC has previously accepted that TCZ SC 162mg qw is equivalent to TCZ IV 8mg/kg q4w. The ESC considered that the evidence also supported non-inferiority between SAR and TCZ over 24 weeks when given at the reduced dosages (SAR 150mg q2w, TCZ IV 4mg/kg q4w, and TCZ SC 162mg q2w).

Although formal comparisons of safety outcomes were not presented, overall the rates of adverse events appeared to be generally similar for SAR and TCZ. The ESC also considered that SAR was likely to be non-inferior to the other bDMARDs PBS listed for the treatment of RA.

- 6.20 The submission did not present any data that indicated SAR could be considered superior in terms of efficacy or safety to any of the other bDMARDs available for the treatment of severe RA.
- 6.21 The PBAC considered that the claim of non-inferior comparative effectiveness with tocilizumab (and the other bDMARDs listed for RA) was reasonable.
- 6.22 The PBAC considered that the claim of non-inferior comparative safety with tocilizumab was reasonable.

Economic analysis

- 6.23 The submission presented a cost-minimisation analysis between SAR 200mg and TCZ SC 162mg, based on the published ex-manufacturer price over 52 weeks. The equi-effective doses were based on the recommended doses (without dose reduction for adverse events): SAR 200mg q2w = TCZ SC 162mg qw.
- 6.24 The cost-minimisation analysis to TCZ did not take into account the differential dosing regimens recommended in the PI for management of adverse events for TCZ or SAR. At the reduced doses for management of adverse events the strength of TCZ SC remains the same but the frequency is reduced, whereas the strength of SAR is reduced but the frequency remains the same. As a result, the proposed price equivalence between the SAR 150mg and SAR 200mg formulations would result in a significant price advantage (double the cost) for SAR compared to TCZ at the reduced dosages for the management of adverse events.
- 6.25 The PSCR argued the 150 mg strength of SAR should not be listed at a lower price than the standard 200 mg SAR injection for the following reasons:
 - evidence from the EXTEND study demonstrated that for patients receiving treatment with and responding to the 200mgQ2W and who require a reduction in dose to 150mg Q2W, clinical efficacy in terms of ACR response and improvements in quality of life are maintained for up to 1.5 years of follow up after dose reduction; and
 - the likelihood of relatively short time to resolution of adverse events (and therefore a limited time on the 150 mg dose).
- 6.26 The PSCR also stated that the cost per dose for a patient receiving a reduced dose of tocilizumab is related to pack size and that based on the information available in the Public Summary Documents for tocilizumab “the Sponsor has never specifically requested reimbursement of the reduced dose of tocilizumab in response to AEs, and

therefore the appropriate cost-minimised price of this reduced dose has never been determined.”

- 6.27 The ESC considered that the proposed price equivalence between the SAR 150mg and SAR 200mg formulations may not be appropriate.
- 6.28 The pre-PBAC response reiterated the price of the 150mg and 200mg presentations should be equivalent because they provide the same clinical outcome.
- 6.29 On the basis that non-inferiority to TCZ is accepted, a cost-minimisation approach is appropriate. However, as the submission did not present any data that indicated SAR could be considered superior in terms of efficacy or safety to TCZ or any of the other bDMARDs available for the treatment of severe RA, the cost-minimisation should be to the lowest cost bDMARD for the treatment of severe RA currently listed on the PBS.

Drug cost/patient/course/year

- 6.30 \$ [REDACTED] per year, with or without dose reduction (assuming DPMQ of \$ [REDACTED] and 13.05 scripts per year).

Estimated PBS usage & financial implications

- 6.31 The submission was not considered by DUSC. A market share approach was used to estimate the financial implications of the proposed listing, summarised in Table 7. PBS claims data and the 10% sample was used to estimate script numbers for initial treatment of TCZ SC (without SAR). The submission assumed SAR would only substitute for patients otherwise treated with TCZ SC. This assumption is not reasonable given substitution of other bDMARDs (including from the TCZ IV formulation) is possible; the eligible population and assumed uptake were therefore likely to have been underestimated.

Table 7: Estimated net cost of SAR to the PBS/RPBS (effective prices)

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
Estimation of use and financial impact of the proposed medicine						
TCZ SC init. scripts without SAR	6,817	7,445	8,073	8,701	9,328	9,956
SAR init. market share	%	%	%	%	%	%
SAR (200mg) init. scripts						
SAR grandfathered scripts	0	0	0	0	0	0
SAR cont. scripts (init. Yr_n-1 + Yr_n)						
SAR cont. scripts (cont. Yr_n-1)						
SAR annual discontinuation rate	%	%	%	%	%	%
SAR cont. scripts total						
SAR 200mg scripts						
SAR 150mg scripts						
TCZ SC cont. scripts without SAR#						
SAR cont. market share#	%	%	%	%	%	%
SAR total scripts						
SAR PBS/RPBS cost [^]	\$	\$	\$	\$	\$	\$
SAR patient co-payment	\$	\$	\$	\$	\$	\$
SAR net PBS/RPBS cost[^]	\$	\$	\$	\$	\$	\$
Estimation of changes in use and financial impact of other medicines						
TCZ SC init. scripts						
TCZ SC cont. scripts						
TCZ 162mg qw						
TCZ 162mg q2w						
TCZ SC PBS/RPBS cost [^]	\$	\$	\$	\$	\$	\$
TCZ SC patient co-payment	\$	\$	\$	\$	\$	\$
TCZ SC net PBS/RPBS cost[^]	\$	\$	\$	\$	\$	\$
Estimated financial implications						
Net cost to PBS/RPBS [^]	\$	\$	\$	\$	\$	\$
Net cost to health budget[^]	\$	\$	\$	\$	\$	\$

Not used in the calculations

[^] Based on updated DPMQ, \$

Source: Tables 4.2.2, 4.2.3, 4.2.4, 4.2.5, 4.2.6, 4.2.7, 4.2.8, 4.2.9, 4.2.10, 4.2.11, 4.3.1, 4.3.2, 4.4.1, 4.4.2, pp249-260 of the submission.

The redacted table shows that at Year 6 the estimated number of scripts was less than 10,000 per year, and the net cost to the PBS would be substantially less than \$10 million per year.

6.32 The model predicted a net cost to the government of less than \$10 million over the first six years of listing. As noted above, at the reduced doses for management of adverse events the strength of TCZ SC remains the same but the frequency is reduced, whereas the strength of SAR is reduced but the frequency remains the same. Therefore, patients who require the reduced dosing regimen will require twice as many scripts of SAR compared to TCZ SC. Given the submission requested the same price for SAR 200mg and SAR 150mg formulations, the 150mg formulation is associated with a net cost to the PBS.

6.33 The submission did not present sensitivity analyses given the expectation of minimal impact on the health budget. As the listing should be on a cost-minimisation basis to the lowest cost bDMARD for RA, and only current market growth was assumed, the listing would be expected to have nil or negligible financial impact.

Quality Use of Medicines

- 6.34 The Sponsor plans to conduct prescriber education including management of adverse events, and implement a patient training program for safe administration of SC injections and reporting of adverse events.

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

7 PBAC Outcome

- 7.1 The PBAC recommended the authority required listing of sarilumab on a cost minimisation basis with the least costly biological disease modifying anti-rheumatic drug (bDMARD) for severe active rheumatoid arthritis (RA). In making this recommendation, the PBAC accepted any of the current PBS listed bDMARDs that include conditions for severe RA could be an alternative therapy to sarilumab.
- 7.2 The PBAC considered the equi-effective doses of the 200mg strength of sarilumab (at the recommended dose of 200mg every two weeks) and alternative bDMARDs could be derived from the product information and with reference to the previously recommended equi-effective doses collated in the PBS Therapeutic Relativity Sheets.
- 7.3 The PBAC noted that ten alternative bDMARDs were listed on the PBS for the treatment of RA at the time of consideration. The PBAC considered that the clinical need for an additional bDMARD was modest, however also acknowledged the addition of another option may be useful to some patients.
- 7.4 The PBAC considered that the nominated comparator of tocilizumab was appropriate, however also considered any of the bDMARDs (and tsDMARDs) listed for severe active RA were relevant alternative therapies.
- 7.5 The submission described sarilumab as non-inferior in terms of comparative effectiveness and safety in RA versus tocilizumab, a pharmacological analogue of sarilumab (IL-6 inhibitor). Based on the evidence presented in the submission, the PBAC considered the claim of non-inferiority to be adequately supported for the 200mg formulation of sarilumab once every two weeks and tocilizumab 162mg given subcutaneously every week. The PBAC noted it had previously considered tocilizumab to be of non-inferior comparative safety and efficacy to other alternative bDMARDs PBS listed for RA and therefore considered sarilumab was also likely to be non-inferior to these alternatives. The PBAC noted no data was presented to demonstrate that sarilumab could be considered superior in terms of efficacy or safety to any of the other bDMARDs available for the treatment of severe RA.
- 7.6 The PBAC noted the 150mg strength of sarilumab was intended for patients who experience adverse events including neutropenia, thrombocytopenia and elevated liver enzymes, similar to the indication for the reduced frequency regimen of tocilizumab. The PBAC agreed with the ESC and considered that sarilumab 150mg once every two weeks was of non-inferior efficacy and safety to a reduced dose regimen of

tocilizumab 162mg subcutaneously given once every two weeks to patients who experienced adverse events necessitating a reduction in dose.

- 7.7 The PBAC considered it was appropriate to align the listings of the 200mg strength of sarilumab with the other bDMARDs currently listed for use in severe RA including tocilizumab, and noted the flow-on changes to the administrative notes in the other bDMARDs (abatacept, adalimumab, baricitinib, certolizumab pegol, etanercept, golimumab, infliximab, rituximab, tocilizumab and tofacitinib) to include sarilumab as one of the bDMARDs for this indication.
- 7.8 The PBAC considered it was appropriate for the 150mg strength of sarilumab to be available for patients who experience adverse events necessitating a reduction in dosage. The PBAC noted the evidence indicated a durability of response at 24 weeks following dose reduction, and considered it appropriate that if a patient maintains a response as defined by the same continuation criteria for the 200mg strength, continuation on the 150mg strength was a matter of clinical judgment. The PBAC considered it appropriate for the 150mg strength to have the same restrictions as the 200mg strength and that a note in the prescriber instructions indicating that the purpose of the 150mg strength is for dose reduction purposes.
- 7.9 The PBAC noted the submission requested a grandfather restriction for patients currently enrolled in a product familiarisation program and considered this was reasonable. The PBAC advised that grandfathered patients will be required to meet the PBS eligibility criteria and noted the grandfather restriction will be removed from the listing after 12 months, in line with standard procedure.
- 7.10 The PBAC considered that listing of the 200mg strength of sarilumab on a cost minimisation basis with the lowest cost alternative bDMARD was appropriate. For the 150mg strength, the PBAC considered pricing consistent with the cost of a reduced-frequency dose regimen of subcutaneous tocilizumab 162mg once every two weeks, was appropriate given the purpose of use and likely non-inferiority of these regimens.
- 7.11 The PBAC considered the market share approach taken by the submission was reasonable and agreed sarilumab was most likely to substitute for subcutaneous tocilizumab, and to a lesser extent, intravenous tocilizumab and other bDMARDs currently listed for RA. The PBAC considered that listing on a cost minimisation basis with the least costly bDMARD for the 200mg strength, and at the same price as a reduced frequency regimen of tocilizumab for the 150mg strength would most likely result in a cost-neutral listing to the PBS.
- 7.12 Under section 101(3BA) of the *National Health Act 1953*, the PBAC advised that sarilumab may be treated as interchangeable on an individual patient basis with the other therapies listed for severe active RA including abatacept, adalimumab, baricitinib, certolizumab pegol, etanercept, golimumab, infliximab, rituximab, tocilizumab and tofacitinib.

- 7.13 The PBAC advised that sarilumab is not suitable for prescribing by nurse practitioners, similar to the other bDMARDs for RA.
- 7.14 The PBAC recommended that the Early Supply Rule should apply.
- 7.15 The PBAC noted the sponsor's intention to request a Special Pricing Arrangement (SPA), and advised that under the SPA criteria it considered sarilumab does not have unique characteristics compared to any available alternative therapies for severe active RA.
- 7.16 The PBAC noted that this submission is not eligible for an Independent Review as it received a positive recommendation.

Outcome:

Recommended

8 Recommended listing

Note regarding restriction flow-ons:

The administrative notes and prescribing instructions for all restrictions should be updated to include sarilumab in the list of permissible drugs in the following sections:

- 1) The following information applies to the prescribing under the Pharmaceutical Benefits Scheme (PBS) of the biological disease modifying antirheumatic drugs (bDMARDs) for adults with severe active rheumatoid arthritis. Where the term bDMARD appears in the following notes and restrictions it refers to the tumour necrosis factor (TNF) alfa antagonists (adalimumab, certolizumab pegol, etanercept, golimumab, and infliximab), the chimeric anti-CD20 monoclonal antibody (rituximab), the interleukin-6 inhibitors (**sarilumab**, tocilizumab), the T-cell co-stimulation modulator (abatacept) and the Janus-associated kinase (JAK) inhibitor (tofacitinib).
- 2) Initial treatment authorisations will be limited to provide a maximum of 16 weeks of therapy for abatacept, adalimumab, etanercept, golimumab, **sarilumab**, tocilizumab and tofacitinib, 18 to 20 weeks of therapy with certolizumab pegol (depending upon the dosing regimen), 22 weeks of therapy for infliximab and 2 infusions of rituximab.
- 3) For the purposes of this restriction bDMARD means abatacept, adalimumab, certolizumab pegol, etanercept, golimumab, infliximab, rituximab, **sarilumab**, tocilizumab or tofacitinib.

Suggestions and additions are in italics and ~~striketrough~~ is used for deletions.

Administrative advice common to all bDMARD restrictions:

Administrative Advice	<p>TREATMENT OF ADULT PATIENTS WITH SEVERE ACTIVE RHEUMATOID ARTHRITIS</p> <p>The following information applies to the prescribing under the Pharmaceutical Benefits Scheme (PBS) of the biological disease modifying antirheumatic drugs (bDMARDs) for adults with severe active rheumatoid arthritis. Where the term bDMARD appears in the following notes and restrictions it refers to the tumour necrosis factor (TNF) alfa antagonists (adalimumab, certolizumab pegol, etanercept, golimumab, infliximab), the chimeric anti-CD20 monoclonal antibody (rituximab), the interleukin-6 inhibitor (sarilumab, tocilizumab), the T-cell co-stimulation modulator (abatacept) and the Janus-associated kinase (JAK) inhibitor (tofacitinib).</p> <p>Patients are eligible for PBS-subsidised treatment with only 1 of the above biological disease modifying anti-rheumatic drugs at any 1 time.</p> <p>In order to be eligible to receive PBS-subsidised treatment with rituximab, a patient must have already failed to demonstrate a response to at least 1 course of treatment with a PBS-subsidised TNF-alfa antagonist.</p> <p>A patient receiving PBS-subsidised bDMARD therapy may swap to an alternate bDMARD without having to experience a disease flare. Under these interchangeability arrangements:</p> <ul style="list-style-type: none">- a patient may continue to receive long-term treatment with a PBS-subsidised bDMARD while they continue to show a response to therapy,- a patient cannot trial and fail, or cease to respond to, the same PBS-subsidised bDMARD more than once, and- once a patient has either failed or ceased to respond to treatment 5 times, they will not be eligible to receive further PBS-subsidised bDMARDs for the treatment of rheumatoid arthritis. <p>For patients who have failed PBS-subsidised treatment with 2 or 3 TNF-alfa antagonists prior to 1 August 2010 please contact the Department of Human Services on 1800 700 270. A patient whose most recent course of PBS-subsidised therapy was with rituximab and whose response to this treatment is sustained for more than 12 months, may apply for a further course of rituximab under the Continuing treatment restriction. A patient who has failed fewer than 5 bDMARDs and who has a break in therapy of less than 24 months may commence a further course of treatment with a bDMARD without having to requalify under the Initial 1 treatment restriction. A patient who has failed fewer than 5 bDMARDs and who has had a break in therapy of longer than 24 months must requalify for treatment under the Initial 1 treatment restriction. The length of a treatment break is measured from the date the most recent treatment with PBS-subsidised bDMARD treatment is stopped to the date of the new application for treatment with a bDMARD.</p> <p>(1) How to prescribe PBS-subsidised bDMARD therapy after 1 August 2010.</p> <p>(a) Initial treatment. Applications for initial treatment should be made where:</p> <ul style="list-style-type: none">(i) a patient has received no prior PBS-subsidised bDMARD treatment and wishes to commence such therapy, excluding rituximab (Initial 1); or(ii) a patient wishes to re-commence treatment with a bDMARD following a break in PBS-subsidised therapy of more than 24 months (Initial 1); or(iii) a patient has received prior PBS-subsidised (initial or continuing) bDMARD therapy and wishes to trial an alternate agent (Initial 2) [further details are under 'Swapping therapy' below]; or(iv) a patient wishes to re-commence treatment with a specific bDMARD following a break of less than 24 months in PBS-subsidised therapy with that agent (Initial 2).
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**Administrative
Advice
(continued)**

Initial applications for new or re-commencing patients (Initial 1) must include a joint count and ESR and/or CRP measured at the completion of the 6-month intensive DMARD trial, but prior to ceasing DMARD therapy.

Initial treatment authorisations will be limited to provide a maximum of 16 weeks of therapy for abatacept, adalimumab, etanercept, golimumab, sarilumab, tocilizumab and tofacitinib, 18 to 20 weeks of therapy with certolizumab pegol (depending upon the dosing regimen), 22 weeks of therapy for infliximab and 2 infusions of rituximab.

Abatacept patients:

Patients are eligible to receive one I.V. loading dose when commencing treatment with the subcutaneous formulation. For these patients two prescriptions are required, the first prescription for the I.V. loading dose for sufficient vials for one dose based on the patient's weight with no repeats. The second prescription for the subcutaneous formulation, with a maximum quantity of 4 and up to 3 repeats, must be submitted with the initial application.

Rituximab patients:

A further application may be submitted to the Department of Human Services 24 weeks after the first infusion. New baselines may be submitted with this application if appropriate.

(b) Continuing treatment.

Following the completion of an initial treatment course with a specific bDMARD (excluding rituximab), a patient may qualify to receive up to 24 weeks of continuing treatment with that drug providing they have demonstrated an adequate response to treatment. The patient remains eligible to receive continuing bDMARD treatment with the same drug in courses of up to 24 weeks providing they continue to sustain the response. It is recommended that a patient be reviewed the month prior to completing their current course of treatment to ensure uninterrupted bDMARD supply.

Rituximab patients:

A patient may qualify to receive a further course of treatment (every 24 weeks) with this agent providing they have demonstrated an adequate response to treatment following a minimum of 12 weeks after the first infusion of their most recent treatment with rituximab. The patient remains eligible to receive a course of rituximab every 24 weeks providing they continue to demonstrate a response as specified in the restriction. Where a response assessment is not submitted to the Department of Human Services within these timeframes, the patient will be deemed to have failed to respond to treatment with that bDMARD.

(2) Swapping therapy

Once initial treatment with the first PBS-subsidised bDMARD is approved, a patient may swap to an alternate bDMARD without having to requalify with respect to the indices of disease severity (i.e. the erythrocyte sedimentation rate (ESR), the C-reactive protein (CRP) levels and the joint count) or the prior non- bDMARD therapy requirements, except if the patient has had a break in therapy of more than 24 months. However the requirement for concomitant treatment with methotrexate, where it applies, must be met for each bDMARD trialled.

Patients who are not able to complete a minimum of 12 weeks of an initial treatment course will be deemed to have failed treatment with that agent.

Administrative Advice (continued)	<p>A patient may trial an alternate bDMARD at any time, regardless of whether they are receiving therapy (initial or continuing) with a bDMARD at the time of the application. However, they cannot swap to a particular bDMARD if they have failed to respond to prior treatment with that drug.</p> <p>Abatacept: Patients swapping from I.V. abatacept to subcutaneous abatacept will not be eligible for an I.V. loading dose when commencing treatment with the subcutaneous formulation.</p> <p>Rituximab: In order to trial rituximab, a patient must have trialled and failed to demonstrate a response to at least 1 PBS-subsidised TNF-alfa antagonist treatment.</p> <p>To ensure a patient receives the maximum treatment opportunities allowed under the interchangeability arrangements, it is important that they are assessed for response to every course of treatment, within the timeframes specified in the relevant restriction.</p> <p>PBS subsidy does not allow for patients to receive treatment with another PBS-subsidised bDMARD during the required treatment-free period applying to patients who have demonstrated a response to their most recent course of rituximab. This means that patients who have demonstrated a response to a course of rituximab must have a PBS-subsidised bDMARD therapy treatment-free period of at least 22 weeks, immediately following the second infusion, before swapping to an alternate bDMARD. Patients who fail to respond to rituximab and who qualify and wish to trial a course of an alternate bDMARD may do so without having to have any treatment-free period.</p> <p>To avoid confusion, an application for a patient who wishes to swap to an alternate bDMARD should be accompanied by the prescription or remaining repeats for the bDMARD the patient is ceasing.</p> <p>(3) Baseline measurements to determine response.</p> <p>The Department of Human Services will determine whether a response to treatment has been demonstrated based on the baseline measurements of the joint count, ESR and/or CRP submitted with the first authority application for a bDMARD. However, prescribers may provide new baseline measurements any time that an initial treatment authority application is submitted and the Department of Human Services will assess response according to these revised baseline measurements.</p> <p>To ensure consistency in determining response, the same indices of disease severity used to establish baseline at the commencement of treatment with each initial treatment application must be used for all subsequent continuing treatment applications. Therefore, where only an ESR or CRP level is provided at baseline, an ESR or CRP level respectively must be used to determine response. Similarly, where the baseline active joint count is based on total active joints (i.e. more than 20 active joints), response will be determined according to the reduction in the total number of active joints. Where the baseline is determined on total number of major joints, the response must be demonstrated on the total number of major joints.</p> <p>Except as specified under the Initial 1 treatment restriction, a baseline joint count and ESR and/or CRP should be performed whilst the patient is still on treatment or within 1 month of ceasing prior treatment. Applications under the Initial 1 treatment restriction for new or re-commencing patients must include a joint count and ESR and/or CRP measured at the completion of the 6 month intensive DMARD trial, but prior to ceasing DMARD therapy.</p>
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Name, Restriction, Manner of administration and form	Max. Qty	№.of Rpts	Proprietary Name and Manufacturer	
SARILUMAB injection 200 mg in 1.14 mL pre-filled syringe, 2	1	3	Kevzara®	Sanofi-Aventis Australia Pty Ltd
injection 150 mg in 1.14 mL pre-filled syringe, 2	1	3		

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
Condition:	Severe active rheumatoid arthritis
PBS Indication:	Severe active rheumatoid arthritis
Treatment phase:	Initial treatment – Initial 1 (new patient or patient recommencing treatment after break of more than 24 months)
Restriction Level / Method:	<input type="checkbox"/> Restricted benefit <input checked="" type="checkbox"/> Authority Required - In Writing <input type="checkbox"/> Authority Required - Telephone <input type="checkbox"/> Authority Required - Emergency <input type="checkbox"/> Authority Required - Electronic <input type="checkbox"/> Streamlined
Treatment criteria:	Must be treated by a rheumatologist; OR Must be treated by a clinical immunologist with expertise in the management of rheumatoid arthritis.
Clinical criteria:	Patient must have severe active rheumatoid arthritis, AND Patient must have received no PBS-subsidised treatment with a biological disease modifying anti-rheumatic drug (bDMARD) for this condition in the previous 24 months AND Patient must not have failed previous PBS-subsidised treatment with sarilumab for this condition, and have not already failed, or ceased to respond to, PBS-subsidised bDMARD treatment for this condition 5 times, AND Patient must have failed, in the 24 months immediately prior to the date of the application, to achieve an adequate response to a trial of at least 6 months of intensive treatment with disease modifying anti-rheumatic drugs (DMARDs) which must include at least 3 months continuous treatment with each of at least 2 DMARDs, one of which must be methotrexate at a dose of at least 20 mg weekly and one of which must be: (i) hydroxychloroquine at a dose of at least 200 mg daily; or (ii) leflunomide at a dose of at least 10 mg daily; or (iii) sulfasalazine at a dose of at least 2 g daily, OR Patient must have failed, in the 24 months immediately prior to the date of the application, to achieve an adequate response to a trial of at least 6 months of intensive treatment with DMARDs which, if methotrexate is contraindicated according to the Therapeutic Goods Administration (TGA)-approved Product Information or cannot be tolerated at a 20 mg weekly dose, must include at least 3 months continuous treatment with each of at least 2 of the following DMARDs: (i) hydroxychloroquine at a dose of at least 200 mg daily; and/or (ii) leflunomide at a dose of at least 10 mg daily; and/or (iii) sulfasalazine at a dose of at least 2 g daily, OR (continued over page)

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Clinical criteria (cont'd) :	<p>Patient must have failed, in the 24 months immediately prior to the date of the application, to achieve an adequate response to a trial of at least 6 months of intensive treatment with DMARDs which, if 3 or more of methotrexate, hydroxychloroquine, leflunomide and sulfasalazine are contraindicated according to the relevant TGA-approved Product Information or cannot be tolerated at the doses specified above, must include at least 3 months continuous treatment with each of at least 2 DMARDs, with one or more of the following DMARDs being used in place of the DMARDs which are contraindicated or not tolerated: (i) azathioprine at a dose of at least 1 mg/kg per day; and/or (ii) cyclosporin at a dose of at least 2 mg/kg/day; and/or (iii) sodium aurothiomalate at a dose of 50 mg weekly, AND</p> <p>Patient must not receive more than 16 weeks of treatment per continuing treatment course authorised under this restriction.</p>
Population criteria:	<p>Patient must be aged 18 years or older</p>
Prescriber Instructions:	<p><i>The 150mg strength is for dose reduction purposes.</i></p> <p>For the purposes of this restriction bDMARD means abatacept, adalimumab, baricitinib, certolizumab pegol, etanercept, golimumab, infliximab, rituximab, sarilumab, tocilizumab or tofacitinib.</p> <p>If methotrexate is contraindicated according to the TGA-approved product information or cannot be tolerated at a 20 mg weekly dose, the application must include details of the contraindication or intolerance including severity to methotrexate. The maximum tolerated dose of methotrexate must be documented in the application, if applicable.</p> <p>The application must include details of the DMARDs trialled, their doses and duration of treatment, and all relevant contraindications and/or intolerances including severity.</p> <p>The requirement to trial at least 2 DMARDs for periods of at least 3 months each can be met using single agents sequentially or by using one or more combinations of DMARDs.</p> <p>If the requirement to trial 6 months of intensive DMARD therapy with at least 2 DMARDs cannot be met because of contraindications and/or intolerances of a severity necessitating permanent treatment withdrawal to all of the DMARDs specified above, details of the contraindication or intolerance including severity and dose for each DMARD must be provided in the authority application.</p> <p>The authority application must be made in writing and must include:</p> <ol style="list-style-type: none"> (1) completed authority prescription form(s); and (2) a completed Rheumatoid Arthritis initial PBS Authority Application - Supporting Information Form; and (3) a signed patient acknowledgement. <p><i>(continued over page)</i></p>

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<p>Prescriber Instructions (continued):</p>	<p>If a patient fails to demonstrate a response to treatment with sarilumab under this restriction they will not be eligible to receive further PBS-subsidised treatment with this drug for this condition.</p> <p>The following criteria indicate failure to achieve an adequate response and must be demonstrated in all patients at the time of the initial application:</p> <p>an elevated erythrocyte sedimentation rate (ESR) greater than 25 mm per hour or a C-reactive protein (CRP) level greater than 15 mg per L; AND either</p> <p>(a) a total active joint count of at least 20 active (swollen and tender) joints; or</p> <p>(b) at least 4 active joints from the following list of major joints:</p> <p>(i) elbow, wrist, knee and/or ankle (assessed as swollen and tender); and/or</p> <p>(ii) shoulder and/or hip (assessed as pain in passive movement and restriction of passive movement, where pain and limitation of movement are due to active disease and not irreversible damage such as joint destruction or bony overgrowth).</p> <p>The joint count and ESR and/or CRP must be determined at the completion of the 6 month intensive DMARD trial, but prior to ceasing DMARD therapy. All measures must be no more than one month old at the time of initial application.</p> <p>If the above requirement to demonstrate an elevated ESR or CRP cannot be met, the application must state the reasons why this criterion cannot be satisfied.</p> <p>Where the baseline joint count is based on total active joints (i.e. more than 20 active joints), response will be determined according to the reduction in the total number of active joints. Where the baseline is determined on total number of major joints, the response must be demonstrated on the total number of major joints. If only an ESR or CRP is provided with the initial application, the same marker will be used to determine response.</p>
<p>Administrative advice:</p>	<p>The authority application must be made in writing and must include:</p> <ol style="list-style-type: none"> (1) Completed authority prescription form(s); and (2) A completed Rheumatoid Arthritis PBS Authority Application – Supporting Information Form. <p>All applications for continuing treatment with sarilumab must include a measurement of response to the prior course of therapy. This assessment must be submitted no later than 4 weeks from cessation of that treatment course. If the application is the first application for continuing treatment with sarilumab, it must be accompanied by an assessment of response to a minimum of 12 weeks of treatment with an initial course.</p> <p>Where a response assessment is not undertaken and submitted within these timeframes, the patient will be deemed to have failed to respond to treatment with sarilumab.</p> <p>If a patient fails to demonstrate a response to treatment with sarilumab under this restriction they will not be eligible to receive further PBS-subsidised treatment with this drug for this condition.</p>

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Notes:	<p>NOTE</p> <p>The Department of Human Services website (www.humanservices.gov.au) has details of the toxicities, including severity, which will be accepted for the following purposes:</p> <p>(a) exempting a patient from the requirement to undertake a minimum 3 month trial of methotrexate at a 20 mg weekly dose;</p> <p>(b) substituting azathioprine, cyclosporin or sodium aurothiomalate for another DMARD as part of the 6 month intensive DMARD trial;</p> <p>(c) exempting a patient from the requirement for a 6 month trial of intensive DMARD therapy.</p> <p>NOTE</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 Department of Human Services Complex Drugs Reply Pain 9826 HOBART TAS 7001</p> <p>NOTE</p> <p>No increase in the maximum number of repeats may be authorised.</p> <p>NOTE</p> <p>No increase in the maximum quantity or number of units will be authorised.</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
Condition:	Severe active rheumatoid arthritis
PBS Indication:	Severe active rheumatoid arthritis
Treatment phase:	Initial treatment – Initial 2 (new patient or patient recommencing treatment after break of more than 24 months)
Restriction Level / Method:	<input type="checkbox"/> Restricted benefit <input checked="" type="checkbox"/> Authority Required - In Writing <input type="checkbox"/> Authority Required - Telephone <input type="checkbox"/> Authority Required - Emergency <input type="checkbox"/> Authority Required - Electronic <input type="checkbox"/> Streamlined
Treatment criteria:	Must be treated by a rheumatologist; OR Must be treated by a clinical immunologist with expertise in the management of rheumatoid arthritis.
Clinical criteria:	Patient must have a documented history of severe active rheumatoid arthritis, AND Patient must have received prior PBS-subsidised biological disease modifying anti-rheumatic drug (bDMARD) treatment for this condition and are eligible to receive further bDMARD therapy, AND Patient must not receive more than 16 weeks of treatment under this restriction.
Population criteria:	Patient must be aged 18 years or older
Prescriber Instructions:	<p><i>The 150mg strength is for dose reduction purposes.</i></p> <p>For the purposes of this restriction bDMARD means abatacept, adalimumab, baricitinib, certolizumab pegol, etanercept, golimumab, infliximab, rituximab, sarilumab, tocilizumab or tofacitinib.</p> <p>The authority application must be made in writing and must include:</p> <ol style="list-style-type: none"> (1) Completed authority prescription form(s); and (2) A completed Rheumatoid Arthritis PBS Authority Application – Supporting Information Form. <p>Applications for a patient who has received PBS-subsidised treatment with sarilumab and who wishes to re-commence therapy with this drug, must be accompanied by evidence of a response to the patient's most recent course of PBS-subsidised sarilumab treatment, within the timeframes specified below.</p> <p>Where the most recent course of PBS-subsidised sarilumab treatment was approved under either of the initial 1 or 2 treatment restrictions, the patient must have been assessed for response following a minimum of 12 weeks of therapy. This assessment must be submitted no later than 4 weeks from the date that course was ceased.</p> <p><i>(continued over page)</i></p>

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<p>Prescriber (continued):</p>	<p>Instructions</p> <p>Where the most recent course of PBS-subsidised sarilumab treatment was approved under the continuing treatment criteria, the patient must have been assessed for response, and the assessment must be submitted no later than 4 weeks from the date that course was ceased.</p> <p>Where a response assessment is not undertaken and submitted within these timeframes, the patient will be deemed to have failed to respond to treatment with sarilumab. If a patient fails to demonstrate a response to a treatment with sarilumab under this restriction they will not be eligible to receive further PBS-subsidised treatment with this drug for this condition.</p> <p>If a patient who has demonstrated a response to a course of rituximab must have a PBS-subsidised biological therapy treatment-free period of at least 22 weeks, immediately following the second infusion, before swapping to an alternate bDMARD.</p>
<p>Administrative advice:</p>	<p>An adequate response to treatment is defined as: An ESR no greater than 25mm per hour or a CRP level no greater than 15mg per L or either marker reduced by at least 20% from baseline; AND either of the following: (a) A reduction in the total active (swollen and tender) joint count by at least 50% from baseline, where baseline is at least 20 active joints; or (b) A reduction in the number of the following active joints, from at least 4, by at least 50%: (i) Elbow, wrist, knee and/or ankle (assessed as swollen and tender); and/or Shoulder and/or hip (assessed as pain in passive movement and restriction of passive movement, where pain and limitation of movement are due to active disease and not irreversible damage such as joint destruction or bony overgrowth).</p>
<p>Notes:</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>NOTE 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 Department of Human Services Complex Drugs Reply Pain 9826 HOBART TAS 7001</p> <p>NOTE No increase in the maximum number of repeats may be authorised.</p> <p>NOTE No increase in the maximum quantity or number of units will be authorised.</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
Condition:	Severe active rheumatoid arthritis
PBS Indication:	Severe active rheumatoid arthritis
Treatment phase:	Initial treatment - Initial 1 (new patient or patient recommencing treatment after a break of more than 24 months) or Initial 2 (change or recommencement of treatment after break of less than 24 months) – balance of supply
Restriction Level / Method:	<input type="checkbox"/> Restricted benefit <input type="checkbox"/> Authority Required - In Writing <input checked="" type="checkbox"/> Authority Required - Telephone <input type="checkbox"/> Authority Required - Emergency <input type="checkbox"/> Authority Required - Electronic <input type="checkbox"/> Streamlined
Treatment criteria:	Must be treated by a rheumatologist; OR; Must be treated by a clinical immunologist with expertise in the management of rheumatoid arthritis.
Clinical criteria:	Patient must have received insufficient sarilumab therapy under the Initial 1 (new patient or patient recommencing treatment after break of more than 24 months) restriction to complete 16 weeks treatment OR Patient must have received insufficient sarilumab therapy under the Initial 2 (change or recommencement of treatment after break of less than 24 months) restriction to complete 16 weeks treatment, AND The treatment must provide no more than the balance of up to 16 weeks treatment available under the above restrictions.
Prescriber Instructions:	<i>The 150mg strength is for dose reduction purposes.</i>
Administrative advice:	Authority approval for sufficient therapy to complete a maximum of 24 weeks of treatment may be requested by telephone by contacting the Department of Human Services on 1800 700 270 (hours of operation 8 a.m. to 5 p.m. EST Monday to Friday).

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Name, Restriction, Manner of administration and form	Max. Qty	№.of Rpts	Proprietary Name and Manufacturer	
SARILUMAB injection 200 mg in 1.14 mL pre-filled syringe, 2	1	3	Kevzara®	Sanofi-Aventis Australia Pty Ltd
injection 150 mg in 1.14 mL pre-filled syringe, 2	1	3		

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
Condition:	Severe active rheumatoid arthritis
PBS Indication:	Severe active rheumatoid arthritis
Treatment phase:	Continuing treatment – Grandfather patients
Restriction Level / Method:	<input type="checkbox"/> Restricted benefit <input checked="" type="checkbox"/> Authority Required - In Writing <input type="checkbox"/> Authority Required - Telephone <input type="checkbox"/> Authority Required - Emergency <input type="checkbox"/> Authority Required - Electronic <input type="checkbox"/> Streamlined
Treatment criteria:	Patient must be aged 18 years or older
Clinical criteria:	Patient must have documented history of severe active rheumatoid arthritis, AND Patient must have been receiving treatment with this drug for this condition prior to <PBS listing date> AND Patient must have demonstrated an adequate response to treatment with sarilumab, AND Patient must have received sarilumab as their most recent course of PBS-subsidised biological disease modifying anti-rheumatic drug (bDMARD) treatment, AND Patient must not receive more than 24 weeks of treatment per continuing treatment course authorised under this restriction.
Population criteria:	Must be treated by a rheumatologist; OR Must be treated by a clinical immunologist with expertise in the management of rheumatoid arthritis.
Prescriber Instructions:	<i>The 150mg strength is for dose reduction purposes.</i> For the purposes of this restriction bDMARD means abatacept, adalimumab, baricitinib, certolizumab pegol, etanercept, golimumab, infliximab, rituximab, sarilumab, tocilizumab or tofacitinib.

Administrative Advice:	<p>An adequate response to treatment is defined as: An ESR no greater than 25mm per hour or a CRP level no greater than 15mg per L or either marker reduced by at least 20% from baseline; AND either of the following:</p> <ul style="list-style-type: none">(a) A reduction in the total active (swollen and tender) joint count by at least 50% from baseline, where baseline is at least 20 active joints; or(b) A reduction in the number of the following active joints, from at least 4, by at least 50%:<ul style="list-style-type: none">(i) Elbow, wrist, knee and/or ankle (assessed as swollen and tender); and/or(ii) Shoulder and/or hip (assessed as pain in passive movement and restriction of passive movement, where pain and limitation of movement are due to active disease and not irreversible damage such as joint destruction or bony overgrowth). <p>An adequate response to treatment is defined as: An ESR no greater than 25mm per hour or a CRP level no greater than 15mg per L or either marker reduced by at least 20% from baseline; AND either of the following:</p> <ul style="list-style-type: none">(c) A reduction in the total active (swollen and tender) joint count by at least 50% from baseline, where baseline is at least 20 active joints; or(d) A reduction in the number of the following active joints, from at least 4, by at least 50%:<ul style="list-style-type: none">(iii) Elbow, wrist, knee and/or ankle (assessed as swollen and tender); and/or(iv) Shoulder and/or hip (assessed as pain in passive movement and restriction of passive movement, where pain and limitation of movement are due to active disease and not irreversible damage such as joint destruction or bony overgrowth). <p>Where the baseline active joint count is based on total active joints (i.e. more than 20 active joints), response will be determined according to the reduction in the total number of active joints. Where baseline is determined on total number of active joints, the response must be demonstrated on the total number of major joints. If only an ESR or CRP level is provided with the initial application, the same marker will be used to determine response.</p> <p>The authority application must be made in writing and must include:</p> <ul style="list-style-type: none">(3) Completed authority prescription form(s); and(4) A completed Rheumatoid Arthritis PBS Authority Application – Supporting Information Form. <p>All applications for continuing treatment with sarilumab must include a measurement of response to the prior course of therapy. This assessment must be submitted no later than 4 weeks from cessation of that treatment course. If the application is the first application for continuing treatment with sarilumab, it must be accompanied by an assessment of response to a minimum of 12 weeks of treatment with an initial course.</p> <p>Where a response assessment is not undertaken and submitted within these timeframes, the patient will be deemed to have failed to respond to treatment with sarilumab.</p> <p>If a patient fails to demonstrate a response to treatment with sarilumab under this restriction they will not be eligible to receive further PBS-subsidised treatment with this drug for this condition.</p>
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Notes:	<p>NOTE</p> <p>The Department of Human Services website (www.humanservices.gov.au) has details of the toxicities, including severity, which will be accepted for the following purposes:</p> <ul style="list-style-type: none">(a) Exempting a patient from the requirement to undertake a minimum 3 month trial of methotrexate at a 20mg weekly dose;(b) Substituting azathioprine, cyclosporine or sodium aurothiomalate for another DMARD as part of the 6 month intensive DMARD trial;(c) Exempting a patient from the requirement for a 6 month trial of intensive DMARD therapy. <p>NOTE</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 Department of Human Services Complex Drugs Reply Pain 9826 HOBART TAS 7001</p> <p>NOTE</p> <p>No increase in the maximum number of repeats may be authorised.</p> <p>NOTE</p> <p>No increase in the maximum quantity or number of units will be authorised.</p>
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Name, Restriction, Manner of administration and form	Max. Qty	№.of Rpts	Proprietary Name and Manufacturer	
SARILUMAB injection 200 mg in 1.14 mL pre-filled syringe, 2	1	3	Kevzara®	Sanofi-Aventis Australia Pty Ltd
injection 150 mg in 1.14 mL pre-filled syringe, 2	1	3		

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
Condition:	Severe active rheumatoid arthritis
PBS Indication:	Severe active rheumatoid arthritis
Treatment phase:	Continuing treatment
Restriction Level / Method:	<input type="checkbox"/> Restricted benefit <input checked="" type="checkbox"/> Authority Required - In Writing <input type="checkbox"/> Authority Required - Telephone <input type="checkbox"/> Authority Required - Emergency <input type="checkbox"/> Authority Required - Electronic <input type="checkbox"/> Streamlined
Treatment criteria:	Must be treated by a rheumatologist; OR Must be treated by a clinical immunologist with expertise in the management of rheumatoid arthritis.
Clinical criteria:	Patient must have a documented history of severe active rheumatoid arthritis, AND Patient must have demonstrated an adequate response to treatment with sarilumab, AND Patient must have received sarilumab as their most recent course of PBS-subsidised biological disease modifying anti-rheumatic drug (bDMARD) treatment, AND Patient must not receive more than 24 weeks of treatment per continuing treatment course authorised under this restriction.
Population criteria:	Patient must be aged 18 years or older.
Prescriber Instructions:	<i>The 150mg strength is for dose reduction purposes.</i> The authority application must be made in writing and must include: (a) a completed authority prescription form; and (b) a completed Rheumatoid Arthritis PBS Authority Application - Supporting Information Form; and (c) a signed patient acknowledgement. All applications for treatment with this drug for this condition under this restriction must include baseline joint count and ESR and/or CRP as determined at the completion of a 6 month intensive DMARD trial but prior to ceasing DMARD therapy. <i>(continued over page)</i>

<p>Prescriber (continued):</p> <p>instructions</p>	<p>If the requirement to demonstrate an elevated ESR or CRP cannot be met, the application must state the reasons why this criterion cannot be satisfied.</p> <p>A patient may qualify for PBS-subsidised treatment under this restriction once only.</p> <p>For the purposes of this restriction bDMARD means abatacept, adalimumab, baricitinib, certolizumab pegol, etanercept, golimumab, infliximab, rituximab, sarilumab, tocilizumab or tofacitinib.</p> <p>An adequate response to treatment is defined as:</p> <p>an ESR no greater than 25 mm per hour or a CRP level no greater than 15 mg per L or either marker reduced by at least 20% from baseline;</p> <p>AND either of the following:</p> <p>(a) a reduction in the total active (swollen and tender) joint count by at least 50% from baseline, where baseline is at least 20 active joints; or</p> <p>(b) a reduction in the number of the following active joints, from at least 4, by at least 50%:</p> <ul style="list-style-type: none"> (i) elbow, wrist, knee and/or ankle (assessed as swollen and tender); and/or (ii) shoulder and/or hip (assessed as pain in passive movement and restriction of passive movement, where pain and limitation of movement are due to active disease and not irreversible damage such as joint destruction or bony overgrowth). <p>Where the baseline active joint count is based on total active joints (i.e. more than 20 active joints), response will be determined according to the reduction in the total number of active joints. Where the baseline is determined on total number of major joints, the response must be demonstrated on the total number of major joints. If only an ESR or CRP level is provided with the initial application, the same marker will be used to determine response.</p> <p>The authority application must be made in writing and must include:</p> <p>(1) completed authority prescription form(s); and</p> <p>(2) a completed Rheumatoid Arthritis PBS Authority Application - Supporting Information Form.</p> <p>All applications for continuing treatment with sarilumab must include a measurement of response to the prior course of therapy. This assessment must be submitted no later than 4 weeks from the cessation of that treatment course. If the application is the first application for continuing treatment with sarilumab, it must be accompanied by an assessment of response to a minimum of 12 weeks of treatment with an initial treatment course.</p> <p>Where a response assessment is not undertaken and submitted within these timeframes, the patient will be deemed to have failed to respond to treatment with sarilumab.</p> <p>If a patient fails to demonstrate a response to treatment with sarilumab under this restriction they will not be eligible to receive further PBS-subsidised treatment with this drug for this condition.</p>
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Administrative advice:	<p>If a patient fails to demonstrate a response to treatment with sarilumab under this restriction they will not be eligible to receive further PBS-subsidised treatment with this drug for this condition.</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> <p>No increase in the maximum number of repeats may be authorised.</p> <p>No increase in the maximum quantity or number of units may be authorised.</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
Condition:	Severe active rheumatoid arthritis
PBS Indication:	Severe active rheumatoid arthritis
Treatment phase:	Continuing treatment – balance of supply
Restriction Level / Method:	<input type="checkbox"/> Restricted benefit <input type="checkbox"/> Authority Required - In Writing <input checked="" type="checkbox"/> Authority Required - Telephone <input type="checkbox"/> Authority Required - Emergency <input type="checkbox"/> Authority Required - Electronic <input type="checkbox"/> Streamlined
Clinical criteria:	Patient must have received insufficient sarilumab therapy under the Continuing Treatment restriction to complete 24 weeks treatment, AND The treatment must provide no more than the balance of up to 24 weeks treatment available under the above restriction.
Treatment criteria:	Must be treated by a rheumatologist; OR; Must be treated by a clinical immunologist with expertise in the management of rheumatoid arthritis.
Prescriber Instructions:	<i>The 150mg strength is for dose reduction purposes.</i>
Administrative advice:	Authority approval for sufficient therapy to complete a maximum of 24 weeks of treatment may be requested by telephone by contacting the Department of Human Services on 1800 700 270 (hours of operation 8 a.m. to 5 p.m. EST Monday to Friday).

9 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.

10 Sponsor's Comment

The sponsor had no comment.