

6.06 GUSELKUMAB,

**Injection 100 mg in 1 mL single use pre-filled syringe,
Injection 100 mg in 1 mL single use pre-filled pen,
Tremfya[®],**

Janssen-Cilag Australia Pty Ltd

1 Purpose of submission

- 1.1 The submission requested an Authority Required listing for guselkumab for the treatment of severe psoriatic arthritis (PsA) in patients meeting the specified criteria. This was the first submission for guselkumab for PsA to be considered by the PBAC. Guselkumab is listed on the PBS for treatment of severe chronic plaque psoriasis (CPP).
- 1.2 The listing was requested on the basis of a cost-minimisation analysis (CMA) versus ustekinumab. Table 1 summarises the key components of the clinical issue addressed by the submission.

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

Component	Description
Population	Severe PsA in adult patients who have failed to respond to methotrexate and sulfasalazine or leflunomide.
Intervention	Guselkumab: administered subcutaneously as 100 mg pre-filled syringe or pen ^a at Week 0, Week 4, and every 8 weeks thereafter. Treatment is administered until loss of response or unacceptable toxicity.
Comparator	Primary clinical and pricing comparator: ustekinumab. Secondary clinical comparators: certolizumab pegol, secukinumab, tofacitinib, adalimumab.
Outcomes	ACR20, ACR50 and safety.
Clinical claim versus ustekinumab (primary comparator) - efficacy	In patients with severe PsA, <ul style="list-style-type: none"> The indirect comparisons show that the treatment effect of guselkumab is similar to ustekinumab with respect to ACR20 (RR: 0.97 [95% CI: 0.62, 1.52]; OR: 1.19 [95% CI: 0.71, 2.00]). The lower bound of the 95% CI of the RR is 0.62 which is above 0.46 (the margin of difference previously accepted by the PBAC), and thus guselkumab is non-inferior to ustekinumab in the induction of ACR20. The indirect comparisons show that the treatment effect of guselkumab is similar to ustekinumab with respect to ACR50. When using the RR, the difference in achieving ACR50 is not statistically significant (RR: 0.77 [95% CI: 0.28, 2.11]). Whilst it is noted that the lower bound of the 95% CI is below the margin of difference previously accepted by the PBAC (>0.29), the difference is negligible (0.01). Thus, guselkumab is non-inferior to ustekinumab.
Clinical claim versus certolizumab pegol, secukinumab, tofacitinib, adalimumab (secondary comparators) - efficacy	In patients with severe PsA, <ul style="list-style-type: none"> Guselkumab demonstrates non-inferior comparative effectiveness to the secondary comparators certolizumab pegol, tofacitinib, and secukinumab in induction and maintenance treatment of severe PsA. Consistent with PBAC deliberations for ustekinumab, certolizumab, secukinumab, and tofacitinib; guselkumab did not demonstrate non-inferiority against the secondary comparator adalimumab in induction but demonstrated non-inferiority in maintenance treatment of severe PsA.
Clinical claim - safety	Guselkumab is well tolerated with non-inferior safety compared to ustekinumab and all secondary comparators certolizumab pegol, secukinumab, tofacitinib, adalimumab.

Source: Table 1.1, p14 of the submission.

^a the current guselkumab product information (PI) includes a pre-filled syringe and pen for the psoriasis (PsO) indication. The draft PI for the PsA indication only included the pre-filled syringe, but that is expected to change to include both the pre-filled syringe and pen.

ACR = American College of Rheumatology; ACR20 = ≥20% improvement in tender and swollen joint counts and ≥20% improvement in 3 of 5 remaining ACR core set measures; ACR50 = ≥50% improvement in tender and swollen joint counts and ≥50% improvement in 3 of 5 remaining ACR core set measures; PsA = psoriatic arthritis

2 Background

Registration status

2.1 The submission was made under the Therapeutic Goods Administration (TGA)/PBAC Parallel Process. At the time of PBAC consideration, the Delegate’s Overview was available. The proposed indication, as recommended by the Delegate was “for the treatment of adult patients with active psoriatic arthritis, who have had an inadequate response to, or are intolerant to, prior DMARD therapy”.

2.2 Guselkumab is TGA registered for patients with moderate to severe chronic plaque psoriasis (CPP) and PBS listed for the treatment of patients with severe CPP.

3 Requested listing

Name, Restriction, Manner of administration and form	Max. Qty	No. of Rpts	Dispensed Price for Max. Qty	Proprietary Name and Manufacturer
INITIAL GUSELKUMAB, pre-filled syringe, 100mg	1	2	\$3,811.58 (published) \$ [REDACTED] (effective) ^a	Tremfya®, Janssen-Cilag Pty Ltd
INITIAL GUSELKUMAB, pre-filled pen, 100mg	1	2	\$3,811.58 (published) \$ [REDACTED] (effective) ^a	Tremfya®, Janssen-Cilag Pty Ltd
CONTINUING GUSELKUMAB, pre-filled syringe, 100mg	1	2	\$3,811.58 (published) \$ [REDACTED] (effective) ^a	Tremfya®, Janssen-Cilag Pty Ltd
CONTINUING GUSELKUMAB, pre-filled pen, 100mg	1	2	\$3,811.58 (published) \$ [REDACTED] (effective) ^a	Tremfya®, Janssen-Cilag Pty Ltd

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Category/Program:	General Schedule
PBS indication:	Severe psoriatic arthritis
Restriction:	Authority required
Treatment phase:	Initial treatment – initial 1 (new patient)
Clinical criteria:	<p>Patient must not have received PBS-subsidised treatment with a biological medicine for this condition, AND Patient must have failed to achieve an adequate response to methotrexate at a dose of at least 20 mg weekly for a minimum period of 3 months, AND Patient must have failed to achieve an adequate response to sulfasalazine at a dose of at least 2 g per day for a minimum period of 3 months; OR Patient must have failed to achieve an adequate response to leflunomide at a dose of up to 20 mg daily for a minimum period of 3 months, AND Patient must not receive more than 20 weeks of treatment under this restriction.</p>
Treatment phase:	Initial 2 (change or recommencement of treatment after a break in biological medicine of less than 5 years)
Clinical criteria:	<p>Patient must have received prior PBS-subsidised treatment with a biological medicine for this condition in this treatment cycle, AND Patient must not have already failed, or ceased to respond to, PBS-subsidised treatment with 3 biological medicines for this condition within this treatment cycle, AND Patient must not have already failed, or ceased to respond to, PBS-subsidised treatment with this drug for this condition during the current treatment cycle, AND Patient must not receive more than 20 weeks of treatment under this restriction.</p>
Treatment phase:	Initial 3 (recommencement of treatment after a break in biological medicine of more than 5 years)
Clinical criteria:	<p>Patient must have previously received PBS-subsidised treatment with a biological medicine for this condition, AND Patient must have a break in treatment of 5 years or more from the most recently approved PBS-subsidised biological medicine for this condition, AND The condition must have an elevated erythrocyte sedimentation rate (ESR) greater than 25 mm per hour; OR The condition must have a C-reactive protein (CRP) level greater than 15 mg per L, AND The condition must have either (a) a total active joint count of at least 20 active (swollen and tender) joints; or (b) at least 4 active major joints, AND Patient must not receive more than 20 weeks of treatment under this restriction.</p>
Treatment phase:	Continuing treatment
Clinical criteria:	<p>Patient must have received this drug as their most recent course of PBS-subsidised biological medicine treatment for this condition, AND Patient must have demonstrated an adequate response to treatment with this drug, AND Patient must not receive more than 24 weeks of treatment under this restriction.</p>

^a based on ex-manufacturer price of \$ [REDACTED] (adding \$69.94 wholesale mark-up, \$99.28 AHJ s85 mark-up and \$7.74 dispensing fee)

3.1 The draft PI included two recommended dosing regimens for guselkumab; one with administration of guselkumab 100 mg at Weeks 0, 4 and every 8 weeks thereafter

(q8w) and another with administration of guselkumab 100 mg at Week 0, 4 and every 4 weeks thereafter (q4w). The submission requested the PBS listing of the guselkumab 100 mg q8w dose only. The TGA Delegate stated that “

.” The requested listing for guselkumab would provide a sufficient quantity for initial (20 weeks) and continuing (24 weeks) treatment for patients who meet the specified clinical criteria according to the q8w regimen (which was the basis of the CMA presented). The PBAC considered that a Note specifying “No increase in the maximum quantity or number of units may be authorised” is required to ensure the cost-effective dosing regimen, q8w, is adhered to.

- 3.2 A special pricing arrangement was proposed with a published and effective DPMQ provided in the submission.
- 3.3 The requested price was based on a CMA versus ustekinumab. The submission adopted the pre-anniversary price cut price of ustekinumab of \$ instead of the current effective ex-manufacturer price of \$. The sponsor requested the application of Clause 5.7 of the Strategic Agreement which is determined by the Minister (or Delegate), and is not a matter for the PBAC.
- 3.4 The wording of the restrictions is consistent with the currently PBS-listed biological medicines. No grandfather restriction was requested in the submission and the sponsor confirmed in the pre-sub-committee response (PSCR) that no grandfather restriction was required.

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

4 Population and disease

- 4.1 PsA is a clinically heterogeneous, progressive, and chronic inflammatory condition that causes irreversible joint damage. The Group for Research and Assessment of Psoriasis and Psoriatic Arthritis (GRAPPA), identifies 6 common areas of disease involvement in PsA: peripheral arthritis; axial disease enthesitis; dactylitis; skin and nail psoriasis (PsO).
- 4.2 Guselkumab is a human IgG1 λ monoclonal antibody that selectively binds to the p19 subunit of interleukin (IL)-23 and inhibits its interaction with the IL-23 receptor. Guselkumab may be administered alone or in combination with a conventional synthetic disease-modifying anti-rheumatic drug (csDMARD). By inhibiting IL-23, guselkumab provides a different mechanism of action to the tumour necrosis factor alpha (TNF α) inhibitors and provides an additional treatment option to the range of interleukin inhibitors currently listed on the PBS for severe PsA which target IL-17 or IL12/23, or that inhibit Janus kinase (JAK).
- 4.3 Currently, there are nine biologics listed on the PBS for the treatment of patients with severe PsA who have failed to achieve an adequate response to non-biologic DMARDs.

5 Comparator

- 5.1 The submission nominated ustekinumab as the primary comparator as it has the most similar pharmacological mechanism of action to guselkumab of the current PBS-listed biologics and similar expected patterns of use. In addition, secukinumab, certolizumab pegol, tofacitinib and adalimumab (the most commonly used biologic) were nominated as secondary comparators. Although ustekinumab was considered a reasonable comparator, guselkumab could replace any of the current PBS-listed biological disease modifying anti-rheumatic drugs (bDMARDs). The PSCR disagreed with the evaluation and argued that, in clinical practice, guselkumab would be unlikely to replace IV infliximab as it is generally reserved as a last line therapy.
- 5.2 The PBAC noted ustekinumab, secukinumab, certolizumab pegol and tofacitinib are considered 'lower tier' medicines (i.e., less effective) and etanercept, adalimumab, infliximab, ixekizumab and golimumab are considered 'higher tier' medicines (i.e., more effective) for the treatment of PsA.
- 5.3 In the context of the cost-minimisation approach taken by the submission, a further consideration for PBAC is that, under Section 101(3B) of the National Health Act 1953, when the proposed medicine is substantially more costly than an alternative therapy, the committee cannot make a positive recommendation unless it is satisfied that, for some patients, the proposed medicine provides a significant improvement in efficacy and/or reduction of toxicity over the alternative therapy. The PBAC noted the sponsors claim in the PSCR that guselkumab was unlikely to replace infliximab in clinical practice but considered infliximab was an alternative therapy as it could be replaced by guselkumab.

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 and welcomed the input from individuals (1), health care professionals (2) and organisations (1) via the Consumer Comments facility on the PBS website. The comments described a range of benefits of treatment with guselkumab including a lower risk of infections or complications compared to currently available treatments and easy self-administration.
- 6.3 The PBAC noted the comments received from Creaky Joints Australia describing the debilitating symptoms of PSA and clarifying the likely use of guselkumab in clinical practice. The PBAC specifically noted the advice that guselkumab would provide an additional treatment option for patients with PsA.

Clinical trials

6.4 The submission was based on eleven placebo-controlled trials comparing guselkumab to ustekinumab, secukinumab, certolizumab pegol, tofacitinib and adalimumab. Details of the trials presented in the submission are provided in Table 2.

Table 2: Trials and key associated reports presented in the submission

Trial	Protocol title/ Publication title	Publication citation
Guselkumab versus placebo		
DISCOVER 1	Janssen. A Phase 3, Multicentre, Randomized, Double-blind, placebo-controlled Study Evaluating the Efficacy and Safety of Guselkumab Administered Subcutaneously in Subjects With Active Psoriatic Arthritis Including Those Previously Treated With Biologic Anti-TNF α Agent(s).	CSR Induction 2019 CSR Maintenance 2020
	Deodhar, Atul, et al. Guselkumab in patients with active psoriatic arthritis who were biologic-naive or had previously received TNF α inhibitor treatment (DISCOVER-1): a double-blind, randomised, placebo-controlled phase 3 trial.	<i>The Lancet</i> 2020; 395(10230); 1115-1125
DISCOVER 2	Janssen. A Phase 3, Multicentre, Randomized, Double-blind, Placebo-controlled Study Evaluating the Efficacy and Safety of Guselkumab Administered Subcutaneously in Subjects with Active Psoriatic Arthritis.	CSR Induction 2019 CSR Maintenance 2020
	Mease, Philip J., et al. Guselkumab in biologic-naive patients with active psoriatic arthritis (DISCOVER-2): a double-blind, randomised, placebo-controlled phase 3 trial.	<i>The Lancet</i> 2020; 395 (10230); 1126-1136
Ustekinumab versus placebo		
PSUMMIT-1	Janssen. A Phase 3 Multicentre, Randomized, Double-blind, Placebo-controlled Trial of Ustekinumab, a Fully Human Anti-IL-12/23p40 Monoclonal Antibody, Administered Subcutaneously, in Subjects with Active Psoriatic Arthritis.	CSR 2013
	McInnes I.B., et al. Efficacy and safety of ustekinumab in patients with active psoriatic arthritis: 1 year results of the phase 3, multicentre, double-blind, placebo-controlled PSUMMIT-1 trial.	<i>Lancet</i> 2013; 382; 780-789
	Kavanaugh, A., Puig, L., Gottlieb, A.B., Ritchlin, C., Li, S., Wang, Y., Mendelsohn, A.M., Song, M., Zhu, Y., Rahman, P. and McInnes, I.B. Maintenance of clinical efficacy and radiographic benefit through two years of ustekinumab therapy in patients with active psoriatic arthritis: results from a randomized, placebo-controlled Phase III trial.	<i>Arthritis Care & Research</i> 2015; 67(12); 1739-1749
PSUMMIT-2	Janssen A Phase 3, Multicentre, Randomized, Double-blind, Placebo-controlled Trial of Ustekinumab, a Fully Human Anti-IL-12/23 p40 Monoclonal Antibody, Administered Subcutaneously, in Subjects With Active Psoriatic Arthritis Including Those Previously Treated With Biologic Anti-TNF α Agent(s).	CSR 2013
	Ritchlin C., et al. Efficacy and safety of the anti-IL-12/23 p40 monoclonal antibody, ustekinumab, in patients with active psoriatic arthritis despite conventional non-biological and biological tumour necrosis factor therapy: 6-month and 1-year results of the phase 3, multicentre, double-blind, placebo-controlled, randomised PSUMMIT-2 trial.	<i>Annals of Rheumatic Disease</i> 2014; 73 (6); 990-999
Adalimumab versus placebo		
Genovese 2007	Genovese M.C., et al. Safety and Efficacy of Adalimumab in Treatment of Patients with Psoriatic Arthritis Who Had Failed Disease Modifying Antirheumatic Drug Therapy.	<i>The Journal of Rheumatology</i> 2007; 34(5); 1040-1050
ADEPT	Mease P.J et al. Adalimumab for the Treatment of Patients With Moderately to Severely Active Psoriatic Arthritis.	<i>Arthritis and Rheumatism</i> 2005; 52(10); 3279-3289
	Mease, Philip J., et al. Adalimumab for long-term treatment of psoriatic arthritis: 2-year data from the Adalimumab Effectiveness in Psoriatic Arthritis Trial (ADEPT).	<i>Annals of the Rheumatic Diseases</i> 2009; 68(5); 702-709

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Trial	Protocol title/ Publication title	Publication citation
OPAL-Broaden	Mease, Philip, et al. Tofacitinib or adalimumab versus placebo for psoriatic arthritis.	<i>New England Journal of Medicine</i> 2017; 377(16); 1537-1550.
Secukinumab versus placebo		
FUTURE 2	McInnes, Iain B., et al. Secukinumab, a human anti-interleukin-17A monoclonal antibody, in patients with psoriatic arthritis (FUTURE 2): a randomised, double-blind, placebo-controlled, phase 3 trial.	<i>The Lancet</i> 2015; 386(9999); 1137-1146
	McInnes, I.B., Mease, P.J., Ritchlin, C.T., Rahman, P., Gottlieb, A.B., Kirkham, B., Kjekkar, R., Delicha, E.M., Pricop, L. and Mpfu, S. Secukinumab sustains improvement in signs and symptoms of psoriatic arthritis: 2 year results from the phase 3 FUTURE 2 study.	<i>Rheumatology</i> 2017; 56(11), 1993-2003
FUTURE 3	Nash, P., Mease, P.J., McInnes, I.B., Rahman, P., Ritchlin, C.T., Blanco, R., Dokoupilova, E., Andersson, M., Kjekkar, R., Mpfu, S. and Pricop, L. Efficacy and safety of secukinumab administration by autoinjector in patients with psoriatic arthritis: results from a randomized, placebo-controlled trial (FUTURE 3).	<i>Arthritis Research & Therapy</i> 2018; 20(1); 47
FUTURE 5	Mease, Philip, et al. Secukinumab improves active psoriatic arthritis symptoms and inhibits radiographic progression: primary results from the randomised, double-blind, phase III FUTURE 5 study.	<i>Annals of the Rheumatic Diseases</i> 2018; 77(6); 890-897
	van der Heijde, D., Mease, P.J., Landewé, R.B., Rahman, P., Tahir, H., Singhal, A., Boettcher, E., Navarra, S., Zhu, X., Ligozio, G. and Readie, A. Secukinumab provides sustained low rates of radiographic progression in psoriatic arthritis: 52-week results from a phase 3 study, FUTURE 5.	<i>Rheumatology</i> 2020; 59(6); 1325-1334
Certolizumab pegol versus placebo		
RAPID-PsA	Mease, P. J., et al. Effect of certolizumab pegol on signs and symptoms in patients with psoriatic arthritis: 24-week results of a Phase 3 double-blind randomised placebo-controlled study (RAPID-PsA).	<i>Annals of the Rheumatic Diseases</i> 2014; 73(1); 48-55
	Van Der Heijde, D., Deodhar, A., FitzGerald, O., Fleischmann, R., Gladman, D., Gottlieb, A.B., Hoepken, B., Bauer, L., Irvin-Sellers, O., Khraishi, M. and Peterson, L. 4-year results from the RAPID-PsA phase 3 randomised placebo-controlled trial of certolizumab pegol in psoriatic arthritis.	<i>RMD Open</i> 2018; 4(1); e000582.
Tofacitinib versus placebo		
OPAL-Broaden	Mease, Philip, et al. Tofacitinib or adalimumab versus placebo for psoriatic arthritis.	<i>New England Journal of Medicine</i> 2017; 377(16); 1537-1550.

Source: Table 2.5, p66 of the submission.

6.5 The key features of the trials included in the indirect comparisons are summarised in Table 3.

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Table 3: Key features of the included trials

Trial (Biologic) N	Design / Duration	Interventions	Population	Main Outcomes
DISCOVER 1 (Guselkumab) N=253 ^a	Phase 3, MC, R, PC, DB study up to 52 weeks. Safety follow-up up to 60 Weeks.	<ul style="list-style-type: none"> • SC guselkumab 100 mg at Week 0, 4, and: <ul style="list-style-type: none"> - every 4 weeks thereafter, or - every 8 weeks thereafter • PBO at Week 0, 4 and every 4 weeks thereafter <p>At Week 24, PBO-treated patients crossed over to receive guselkumab 100 mg q4w.</p>	Adults (≥18 years) with active PsA. Anti-TNFα naïve and experienced patients.	ACR20, ACR50, at Week 24 and 52. Safety
DISCOVER 2 (Guselkumab) N=494 ^a	Phase 3, MC, R, PC, DB study up to 52 weeks. Study has treatment phase to Week 100, but to date, efficacy and safety results are available through Week 52.	<ul style="list-style-type: none"> • SC guselkumab 100 mg at Week 0, 4, and: <ul style="list-style-type: none"> - every 4 weeks thereafter, or - every 8 weeks thereafter • PBO at Week 0, 4 and every 4 weeks thereafter. <p>At Week 24, PBO-treated patients crossed over to receive guselkumab 100 mg q4w.</p>	Adults (≥18 years) with active PsA. Anti-TNFα naïve patients.	ACR20, ACR50, at Week 24 and 52. Safety
PSUMMIT-1 (Ustekinumab) N=411 ^a	Phase 3, MC, R, PC, DB study up to 100 weeks. Safety follow-up up to 108 Weeks.	<ul style="list-style-type: none"> • SC ustekinumab 45 mg, ustekinumab 90 mg • PBO <p>at Week 0, 4 and every 12 weeks thereafter. At Week 24 or 28, PBO-treated patients crossed over to receive ustekinumab 45 mg.</p>	Adults (≥18 years) with active PsA. Anti-TNFα naïve patients only.	ACR20, ACR50, response at Wk 24, 60 and 108. Safety
PSUMMIT-2 (Ustekinumab) N=207 ^a	Phase 3, MC, R, PC, DB study up to 52 weeks. Safety follow-up up to 60 Weeks.	<ul style="list-style-type: none"> • SC ustekinumab 45 mg, ustekinumab 90 mg • PBO <p>at Week 0, 4 and every 12 weeks thereafter. At Week 24 or 28, PBO-treated patients crossed over to receive ustekinumab 45 mg.</p>	Adults (≥18 years) with active PsA. Anti-TNFα naïve and experienced patients.	ACR20, ACR50, response at Week 24 and 52 Safety
ADEPT (Adalimumab) N=313	Phase 3, MC, R, PC, DB study up to 24 weeks. OL extension additional 120 weeks	<ul style="list-style-type: none"> • SC adalimumab 40 mg • PBO <p>every other week.</p>	Adults (≥18 years) with moderate to severe active PsA. Anti-TNFα naïve patients.	ACR20, ACR50, at Week 12 and 24 Safety
Genovese 2007 (Adalimumab) N=100	Phase 3, MC, R, PC, DB study up to 24 weeks. After Week 12, OL provided.	<ul style="list-style-type: none"> • SC adalimumab 40 mg • PBO <p>every other week. At Week 12, all patients (adalimumab or PBO) cross over to receive open-label adalimumab.</p>	Adults (≥18 years) with moderate to severe active PsA. Anti-TNFα naïve patients.	ACR20, ACR50, at Week 12 and 24. Safety
FUTURE 2 (Secukinumab) N=298 ^a	Phase 3, MC, R, PC, DB study up to 52 weeks. OL extension up to 256 weeks.	<ul style="list-style-type: none"> • SC secukinumab 75 mg, 150 mg or 300 mg • PBO <p>at Week 0, 1, 2, 3 and 4 then every 4 weeks thereafter. PBO arm re-randomised to 150 mg or 300 mg secukinumab at Week 16 (non-responders)/24 (responders).</p>	Adults (≥18 years) who had moderately to severely active PsA. Anti-TNFα naïve and experienced patients.	ACR20, ACR50 at Week 24 and 52. Safety

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Trial (Biologic) N	Design / Duration	Interventions	Population	Main Outcomes
FUTURE 3 (Secukinumab) N=414	Phase 3, MC, R, PC, DB study up to 52 weeks. Study design is up to Week 156, but efficacy and safety results are available through Week 52.	<ul style="list-style-type: none"> • SC 150 mg, SC 300 mg secukinumab • PBO at Week 0, 1, 2, 3 and 4, and every 4 weeks thereafter. PBO arm re-randomised to 150 mg or 300 mg secukinumab at Week 16 (non-responders)/24 (responders).	Adults (≥18 years) who had a diagnosis of PsA. Anti-TNFα naïve and experienced patients.	ACR20, ACR50 at Week 24 and 52. Safety
FUTURE 5 (Secukinumab) N=774 ^a	Phase 3, MC, R, PC, DB study up to 52 weeks. Study design is up to Week 104 but efficacy and safety results are available through Week 52.	<ul style="list-style-type: none"> • SC secukinumab 300 mg (with LD), • SC secukinumab 150 mg (with LD), • SC secukinumab 150 mg (without LD) • PBO at Week 0, 1, 2, 3 and every 4 weeks thereafter. PBO arm re-randomised to 150 mg or 300 mg secukinumab at Week 16 (non-responders)/24 (responders).	Adults (≥18 years) who had moderately to severely active PsA. Anti-TNFα naïve and experienced patients.	ACR20, ACR50 at Week 16, 24 and 52. Safety
RAPID-PsA N=409	Phase 3, MC, R, DB, PC study up to 216 weeks. After Week 48, OL provided.	<ul style="list-style-type: none"> • SC certolizumab pegol 400 mg at Week 0, 2 and 4, followed by: <ul style="list-style-type: none"> - Certolizumab pegol 200 mg every 2 weeks, or - Certolizumab pegol 400 mg every 4 weeks • PBO at Week 0, 2 and 4 and every 2 weeks thereafter. PBO arm re-randomised to 200 mg or 400 mg certolizumab pegol with loading dose at Week 16 (non-responders) /24 (responders).	Adults (≥18 years) who had a diagnosis of active PsA of ≥6 months' duration. Anti-TNFα naïve and experienced patients.	ACR20, ACR50, at Week 12, 24 and 48 through Week 216. Safety
OPAL Broaden N=318	Phase 3, R, DB, PC study up to 52 weeks.	<ul style="list-style-type: none"> • Oral tofacitinib 5 mg or 10 mg twice daily • SC adalimumab 40 mg every 2 weeks, • PBO. At Week 12, PBO-treated patients were re-randomised to receive oral tofacitinib 5 mg or 10 mg.	Adults (≥18 years) who had a diagnosis of PsA of ≥6 months. Anti-TNFα naïve patients.	ACR20, ACR50, at Week 12 and 52. Safety

ACR20/50 = ≥20% /50% improvement on the American College of Rheumatology Criteria DB= double-blind; LD = loading dose; MC = multicentre; OL = open-label; PBO = placebo; PsA = psoriatic arthritis; PC = placebo-controlled; R= randomised, SC = subcutaneous; TNFα = tumour necrosis factor alpha

Source: Table 2.6, p71 of the submission

^a excluding patients randomised to arms which were not relevant to the ITC in the submission.

- 6.6 Discontinuation rates were generally higher in the placebo arms of the trials. However, the overall risk of bias was considered low as the potential for unblinding related to discontinuation would likely affect all of the included trials equally.
- 6.7 The clinical criteria for meeting early escape and dose escalation varied between the trials (ranging from <5% improvement – 20% improvement in both tender and swollen joint counts) and there were differences in the timing of placebo crossover. However, comparisons at earlier time points should not be affected by these differences.
- 6.8 Though eligibility criteria for the included trials were less severe than the requested restriction of severe PsA (for example, at least ≥3 swollen joints and ≥3 tender joints

at screening and baseline, or C-reactive protein (CRP) ≥ 0.3 mg/dL at screening), it was noted that at baseline, the observed mean number of swollen/tender joints and CRP were higher and more comparable to the requested restriction. The guselkumab trials accounted for TNF α inhibitor naïve and TNF α inhibitor experienced participants, which aligns with the proposed PBS listing that does not preclude prior TNF inhibitor therapy.

Comparative effectiveness

- 6.9 The clinically relevant outcomes presented in the submission include the American College of Rheumatology response criteria of an improvement of $\geq 20\%$ (ACR20) as the primary outcome, and ACR50 as the secondary outcome. The PBAC has previously considered that “ACR50 was more relevant than ACR20 because it better reflected the current PBS criteria for response to initial therapy. However, ACR20 has also been used to support non-inferiority” (paragraph 6.8, tofacitinib Public Summary Document (PSD), November 2018).
- 6.10 The non-inferiority margins nominated by the submission for ACR50 and ACR20 are consistent with the PBAC’s previous consideration of biologics in PsA. As outlined in the tofacitinib PSD, “for non-inferiority to be demonstrated, the submission stated that the lower bound of the 95% confidence interval (CI) around the relative risk (RR) must exceed 0.29 for ACR50 and 0.46 for ACR20” (paragraph 6.9, tofacitinib PSD, November 2018).
- 6.11 Indirect comparisons of outcomes were assessed at time points consistent with the timing of assessment for response on the PBS, with the exception of ustekinumab. The submission used an earlier time point claiming results would be confounded due to early escape. However, it is also important to consider which time points are the most informative and align with the review of response to initial treatment on the PBS. Given ustekinumab was previously considered by the PBAC as assessed at the 24 week time point in the same trials (paragraph 6.8, ustekinumab PSD, November 2014), and this is in line with ustekinumab’s initial treatment period, it may be more appropriate to compare guselkumab with ustekinumab assessed at Week 24 (instead of Week 16 as performed in the submission). The evaluation noted the submission’s claim that ustekinumab’s results at Week 24 are confounded by non-responders crossing over. However, the clinical criteria for early escape was relatively low (<5% improvement) in the ustekinumab trials, though it is unknown what proportion of participants who entered early escape may have developed a response by Week 24 or remained as non-responders. In the ustekinumab trials, the “data at or prior to Week 16 were carried forward to Week 20 and Week 24” for participants who qualified for early escape at Week 16 (PSUMMIT-1 CSR p 51; PSUMMIT-2 CSR p49). That is, these participants were in effect treated as non-responders at Week 24 (PSUMMIT-1 table attachment 3.24, p 287; PSUMMIT-2 table attachment 3.24, p299). The evaluation noted the results of ustekinumab assessed at Week 24 should be considered with the potential risk of bias in mind.

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- 6.12 The guselkumab DISCOVER 1 and DISCOVER 2 trials had two active treatment arms – 100 mg at Week 0, Week 4, and every 8 weeks thereafter (q8w), and 100 mg at Week 0 and every 4 weeks thereafter (q4w). Although the submission was requesting the PBS listing of guselkumab q8w dose only, the results for the q4w regimen were provided for completeness.
- 6.13 The results for ACR20 and ACR50 (from the individual trials, meta-analyses and indirect comparisons) are shown in Table 4 and Table 5, respectively.

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Table 4: Results of ACR20 at induction phase (non-inferiority margin of 0.46 for RR)

Trial	bDMARD	Placebo	RD (95% CI)	RR (95%CI)	OR (95%CI)
Guselkumab 100mg q8w vs placebo (Week 16)					
DISCOVER 1	66/127 (52)	32/126 (25)	0.27 (0.15, 0.38)	2.05 (1.45, 2.90)	3.18 (1.87, 5.41)
DISCOVER 2	137/248 (55)	83/246 (34)	0.22 (0.13, 0.30)	1.64 (1.33, 2.02)	2.42 (1.68, 3.49)
Meta-analysis	203/375 (54)	115/372 (31)	0.23 (0.16, 0.30)	1.75 (1.43, 2.15)	2.64 (1.96, 3.57)
Guselkumab 100mg q4w vs placebo (Week 16)					
DISCOVER 1	77/128 (60)	32/126 (25)	0.35 (0.23, 0.46)	2.35 (1.69, 3.27)	4.39 (2.57, 7.49)
DISCOVER 2	137/245 (56)	83/246 (34)	0.22 (0.14, 0.31)	1.66 (1.35, 2.04)	2.49 (1.73, 3.59)
Meta-analysis	214/373 (57)	115/372 (31)	0.28 (0.16, 0.40)	1.93 (1.37, 2.74)	3.21 (1.83, 5.63)
Ustekinumab 45mg vs placebo (Week 16)					
PSUMMIT-1	70/205 (34)	44/206 (21)	0.13 (0.04, 0.21)	1.60 (1.16, 2.21)	1.91 (1.23, 2.97)
PSUMMIT-2	31/103 (30)	13/104 (13)	0.18 (0.07, 0.28)	2.41 (1.34, 4.33)	3.01 (1.47, 6.18)
Meta-analysis	101/308 (33)	57/310 (18)	0.15 (0.08, 0.21)	1.82 (1.25, 2.64)	2.19 (1.45, 3.30)
Indirect analysis (GUS q8w vs UST [16] meta-analyses)*			0.09 (-0.01, 0.18)	0.96 (0.63, 1.47)	1.21 (0.73, 2.01)
Indirect analysis (GUS q4w vs UST [16] meta-analyses)*			0.13 (-0.01, 0.27)	1.06 (0.64, 1.77)	1.47 (0.73, 2.91)
Ustekinumab 45mg vs placebo (Week 24)					
PSUMMIT-1	87/205 (42)	47/206 (23)	0.20 (0.11, 0.28)	1.86 (1.39, 2.51)	2.49 (1.59, 3.92)
PSUMMIT-2	45/103 (44)	21/104 (20)	0.23 (0.11, 0.35)	2.16 (1.41, 3.38)	3.07 (1.59, 6.00)
Meta-analysis	132/308 (43)	68/310 (22)	0.21 (0.14, 0.28)	1.95 (1.52, 2.50)	2.67 (1.88, 3.79)
Indirect analysis (GUS q8w vs UST [24] meta-analyses)*			0.02 (-0.08, 0.12)	0.90 (0.65, 1.24)	0.99 (0.62, 1.57)
Indirect analysis (GUS q4w vs UST [24] meta-analyses)*			0.07 (-0.07, 0.21)	0.99 (0.65, 1.52)	1.20 (0.62, 2.33)
Certolizumab pegol 200/400 mg pooled vs placebo (Week 12)					
RAPID PsA	150/273 (55)	33/136 (24)	0.31 (0.21, 0.40)	2.26 (1.65, 3.11)	3.81 (2.41, 6.02)
Indirect analysis (GUS q8w vs CZP meta-analyses)*			-0.07 (-0.19, 0.04)	0.77 (0.54, 1.11)	0.69 (0.40, 1.20)
Indirect analysis (GUS q4w vs CZP meta-analyses)*			-0.03 (-0.18, 0.12)	0.85 (0.53, 1.37)	0.84 (0.41, 1.74)
Secukinumab 150/300mg pooled versus placebo (Week 12)					
FUTURE-2	113/200 (57)	25/98 (26)	0.31 (0.20, 0.42)	2.21 (1.55, 3.17)	3.79 (2.22, 6.46)
FUTURE-3 ^a	137/277 (50)	27/137 (20)	0.34 (0.26, 0.43)	2.51 (1.78, 3.62)	3.99 (2.41, 6.72)
FUTURE-5	245/442 (55)	90/332 (27)	0.29 (0.22, 0.35)	2.04 (1.69, 2.49)	3.34 (2.44, 4.60)
Meta-analysis	495/919 (54)	142/567 (25)	0.31 (0.26, 0.36)	2.16 (1.85, 2.52)	3.57 (2.83, 4.50)
Indirect analysis (GUS q8w vs SEC meta-analyses)*			-0.06 (-0.15, 0.02)	0.81 (0.63, 1.05)	0.74 (0.51, 1.08)
Indirect analysis (GUS q4w vs SEC meta-analyses)*			-0.03 (-0.16, 0.10)	0.90 (0.61, 1.31)	0.90 (0.49, 1.65)
Tofacitinib 5mg vs placebo (Week 12)					
OPAL-Broaden	54/107 (51)	35/105 (33)	0.17 (0.04, 0.30)	1.51 (1.09, 2.10)	2.04 (1.17, 3.55)
Indirect analysis (GUS q8w vs TOF meta-analyses)*			0.06 (-0.09, 0.21)	1.16 (0.80, 1.68)	1.30 (0.69, 2.44)
Indirect analysis (GUS q4w vs TOF meta-analyses)*			0.11 (-0.07, 0.29)	1.28 (0.79, 2.06)	1.57 (0.71, 3.47)
Adalimumab 40mg vs placebo (Week 12)					
ADEPT	88/151 (58)	23/162 (14)	0.44 (0.35, 0.54)	4.10 (2.75, 6.14)	8.44 (4.88, 14.59)
Genovese 2007	20/51 (39)	8/49 (16)	0.23 (0.06, 0.40)	2.40 (1.17, 4.94)	3.31 (1.29, 8.49)
OPAL Broaden	55/106 (52)	35/105 (33)	0.19 (0.05, 0.32)	1.56 (1.12, 2.16)	2.16 (1.24, 3.76)
Meta-analysis	163/308 (53)	66/316 (21)	0.29 (0.11, 0.47)	2.47 (1.24, 4.95)	3.97 (1.57, 10.06)
Indirect analysis (GUS q8w vs ADA meta-analyses)*			-0.06 (-0.25, 0.13)	0.71 (0.34, 1.46)	0.67 (0.25, 1.77)
Indirect analysis (GUS q4w vs ADA meta-analyses)*			-0.01 (-0.23, 0.21)	0.78 (0.36, 1.69)	0.81 (0.27, 2.39)

Source: Table 2.59 and 2.60, p 167 of the submission.

^a Exact proportions were not reported in the FUTURE-3 trials at Week 12 and were therefore estimated by visual inspection of graphs in the publications.

* Note that the results presented in Table 4 are derived from post-hoc analyses conducted by the applicant specifically for the purposes of informing the PBAC consideration. These analyses were not part of the pre-specified statistical plan for any of the included biologic trials. Interpretation of the results and their application should therefore be limited to seeking to understand the basis for the PBAC outcome and should not be used for any other purpose.

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Table 5: Results of ACR50 at induction phase (non-inferiority margin of 0.29 for RR)

Trial	bDMARD	Placebo	RD (95% CI)	RR (95%CI)	OR (95%CI)
Guselkumab 100mg q8w vs placebo (Week 16)					
DISCOVER 1	29/127 (23)	16/126 (13)	0.10 (0.01, 0.19)	1.80 (1.03, 3.14)	2.03 (1.04, 3.97)
DISCOVER 2	71/248 (29)	23/246 (9)	0.19 (0.12, 0.26)	3.06 (2.00, 4.74)	3.89 (2.29, 6.78)
Meta-analysis	100/375 (27)	39/372 (10)	0.15 (0.07, 0.24)	2.42 (1.44, 4.06)	2.92 (1.55, 5.49)
Guselkumab 100mg q4w vs placebo (Week 16)					
DISCOVER 1	34/128 (27)	16/126 (13)	0.14 (0.04, 0.24)	2.09 (1.23, 3.59)	2.49 (1.24, 5.13)
DISCOVER 2	51/245 (21)	23/246 (9)	0.11 (0.05, 0.18)	2.23 (1.42, 3.52)	2.55 (1.46, 4.53)
Meta-analysis	85/373 (23)	39/372 (10)	0.12 (0.07, 0.17)	2.17 (1.53, 3.08)	2.52 (1.67, 3.81)
Ustekinumab 45mg vs placebo (Week 16)					
PSUMMIT-1	31/205 (15)	14/206 (7)	0.08 (0.02, 0.14)	2.23 (1.22, 4.06)	2.44 (1.26, 4.74)
PSUMMIT-2	17/103 (17)	3/104 (3)	0.14 (0.06, 0.21)	5.72 (1.73, 18.94)	6.66 (1.89, 23.48)
Meta-analysis	48/308 (16)	17/310 (6)	0.10 (0.05, 0.15)	3.09 (1.27, 7.52)	3.48 (1.35, 8.94)
Indirect analysis (GUS q8w vs UST [16] meta-analyses)*			0.05 (-0.05, 0.15)	0.78 (0.28, 2.19)	0.84 (0.27, 2.62)5
Indirect analysis (GUS q4w vs UST [16] meta-analyses)*			0.02 (-0.05, 0.09)	0.72 (0.27, 1.83)	0.72 (0.26, 2.03)
Ustekinumab 45mg vs placebo (Week 24)					
PSUMMIT-1	51/205 (25)	18/206 (9)	0.16 (0.09, 0.23)	2.85 (1.74, 4.70)	3.46 (1.89, 6.55)
PSUMMIT-2	18/103 (18)	7/104 (7)	0.11 (0.02, 0.20)	2.60 (1.17, 5.86)	2.93 (1.10, 8.69)
Meta-analysis	69/308 (22)	25/310 (8)	0.14 (0.09, 0.20)	2.78 (1.81, 4.27)	3.30 (2.02, 5.39)
Indirect analysis (GUS q8w vs UST [24] meta-analyses)*			0.01 (-0.09, 0.11)	0.87 (0.44, 1.71)	0.89 (0.40, 1.97)
Indirect analysis (GUS q4w vs UST [24] meta-analyses)*			-0.02 (-0.09, 0.05)	0.78 (0.45, 1.36)	0.76 (0.40, 1.45)
Certolizumab pegol 200/400 mg pooled vs placebo (Week 12)					
RAPID PsA	94/273 (34)	15/136 (11)	0.23 (0.16, 0.31)	3.12 (1.88, 5.17)	4.24 (2.34, 7.66)
Indirect analysis (GUS q8w vs CZP meta-analyses)*			-0.08 (-0.19, 0.03)	0.78 (0.38, 1.60)	0.69 (0.29, 1.64)
Indirect analysis (GUS q4w vs CZP meta-analyses)*			-0.11 (-0.20, -0.02)	0.70 (0.38, 1.29)	0.59 (0.29, 1.22)
Secukinumab 150/300mg pooled versus placebo (Week 12)					
FUTURE-2	62/200 (31)	5/98 (5)	0.26 (0.18, 0.34)	6.08 (2.52, 14.63)	8.36 (3.24, 21.57)
FUTURE-3 ^a	73/277 (26)	6/137 (4)	0.22 (0.16, 0.28)	6.02 (2.69, 13.48)	7.81 (3.30, 18.48)
FUTURE-5	148/442 (34)	24/332 (7)	0.26 (0.21, 0.31)	4.63 (3.08, 6.96)	6.46 (4.08, 10.23)
Meta-analysis	283/919 (31)	35/567 (6)	0.25 (0.21, 0.28)	5.04 (3.60, 7.06)	6.97 (4.80, 10.12)
Indirect analysis (GUS q8w vs SEC meta-analyses)*			-0.10 (-0.19, -0.01)	0.48 (0.26, 0.89)	0.42 (0.20, 0.87)
Indirect analysis (GUS q4w vs SEC meta-analyses)*			-0.13 (-0.19, -0.07)	0.43 (0.27, 0.70)	0.36 (0.21, 0.63)
Tofacitinib 5mg vs placebo (Week 12)					
OPAL-Broaden	30/107 (28)	10/105 (10)	0.19 (0.08, 0.29)	2.94 (1.52, 5.71)	3.70 (1.70, 8.04)
Indirect analysis (GUS q8w vs TOF meta-analyses)*			-0.04 (-0.18, 0.10)	0.82 (0.36, 1.91)	0.79 (0.29, 2.15)
Indirect analysis (GUS q4w vs TOF meta-analyses)*			-0.07 (-0.33, 0.19)	0.74 (0.35, 1.56)	0.68 (0.28, 1.6)
Adalimumab 40mg vs placebo (Week 12)					
ADEPT	55/151 (36)	7/162 (4)	0.32 (0.24, 0.40)	8.43 (3.96, 17.93)	12.69 (5.55, 29.00)
Genovese 2007	13/51 (26)	1/49 (2)	0.23 (0.11, 0.36)	12.49 (1.70, 91.90)	16.42 (2.06, 131.18)
OPAL Broaden	35/106 (33)	10/105 (10)	0.23 (0.13, 0.34)	3.47 (1.81, 6.63)	4.68 (2.17, 10.09)
Meta-analysis	103/308 (33)	18/316 (6)	0.28 (0.22, 0.34)	5.85 (2.73, 12.52)	8.35 (3.75, 18.60)
Indirect analysis (GUS q8w vs ADA meta-analyses)*			-0.13 (-0.23, -0.03)	0.41 (0.17, 1.04)	0.35 (0.13, 0.97)
Indirect analysis (GUS q4w vs ADA meta-analyses)*			-0.16 (-0.24, -0.08)	0.37 (0.16, 0.86)	0.30 (0.12, 0.74)

Source: Table 2.61 and 2.62, p 169 of the submission.

^a Exact proportions were not reported in the FUTURE-3 trials at Week 12 and were therefore estimated by visual inspection of graphs in the publications.

* Note that the results presented in Table 5 are derived from post-hoc analyses conducted by the applicant specifically for the purposes of informing the PBAC consideration. These analyses were not part of the pre-specified statistical plan for any of the included biologic

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trials. Interpretation of the results and their application should therefore be limited to seeking to understand the basis for the PBAC outcome and should not be used for any other purpose

- 6.14 The results for ACR20 demonstrated that all bDMARDs were more effective than placebo in achieving a response.
- 6.15 The results for ACR50 demonstrated that all bDMARDs were more effective than placebo in achieving a response. However, the DISCOVER 1 q8w dose arm did not demonstrate statistical significance versus placebo for ACR50 at Week 16. In comparing q4w and q8w: it is noted that “ [REDACTED] ” in DISCOVER 1 (TGA CER). However, the TGA concluded “ [REDACTED] ” (TGA CER). The PSCR stated that for the purposes of economic evaluation, the use of the p-value at the 5% significance level was justified (as opposed to the global multiplicity adjusted p-value), and therefore guselkumab was shown to be statistically superior to placebo.
- 6.16 The results from the indirect comparisons indicated no statistically significant differences across the majority of outcomes. However, statistically significantly fewer patients treated with guselkumab 100 mg q8w achieved an ACR50 response compared with secukinumab (for all statistical estimates) and compared with adalimumab (risk difference and odds ratio). The nominated non-inferiority margins of 0.46 for ACR20 and 0.29 for ACR50 were met for some biologics, but not all, as shown in Table 6.

Table 6: Summary of non-inferiority outcomes by bDMARD – guselkumab 100 mg q8w versus*

bDMARD	ACR20 non-inferiority met	ACR50 non-inferiority met
Ustekinumab 45 mg (Week 16)	✓	✗ (lower 95% CI 0.28)
Ustekinumab 45 mg (Week 24)	✓	✓
Certolizumab pegol	✓	✓
Secukinumab	✓	✗ (lower 95% CI 0.26 ¹)
Adalimumab	✗ (lower 95% CI 0.34)	✗ (lower 95% CI 0.17)
Tofacitinib	✓	✓

Source: compiled during the evaluation.

¹ Additionally, there was a statistically significant difference in favour of secukinumab for this outcome

*Note that the results presented in Table 6 are derived from post-hoc analyses conducted by the applicant specifically for the purposes of informing the PBAC consideration. These analyses were not part of the pre-specified statistical plan for any of the included biologic trials. Interpretation of the results and their application should therefore be limited to seeking to understand the basis for the PBAC outcome and should not be used for any other purpose

- 6.17 The outcomes of ustekinumab at Week 24 were added during the evaluation to the indirect comparison. As outlined previously, these results may be applicable given that this time point aligns with the review of response to initial treatment for ustekinumab on the PBS. When the Week 24 results were used, the non-inferiority margins were met for ACR20 and ACR50.

- 6.18 The submission highlighted the heterogeneity of placebo rates across the included trials. The submission argued these differences in placebo response rates could indicate that there are underlying differences in patient risk which are not accounted for in Bucher method ITCs, and thus may be biased against guselkumab when comparing to treatments whose trials have lower placebo rates. The ustekinumab, secukinumab and adalimumab trials had lower placebo rates compared to guselkumab. For these bDMARDs, guselkumab was also unable to meet the nominated non-inferiority margins for ACR50. Comparatively, certolizumab pegol and tofacitinib had higher placebo rates and met the specified thresholds for ACR20 and ACR50.
- 6.19 This heterogeneity of placebo rates has been noted by the PBAC in its previous considerations of biologics for PsA. In the PBAC's consideration of ustekinumab, when comparing ustekinumab with certolizumab, "It was noted that the absolute response in the active treatment arm of the CZP [certolizumab pegol] trial was similar to responses observed with the other listed biologics, while response rates due to active treatment in the UST [ustekinumab] trials were substantially lower. The placebo response rate in the CZP trial was higher than the placebo rates in all of the other trials. Without understanding the reason for the higher placebo response rate observed in the CZP trial, the review concluded that it is 'impossible' to determine whether the usual assumption of homogeneous effects in the RR or OR scales is reasonable" (paragraph 5.13, ustekinumab PSD, November 2015). In its consideration of certolizumab pegol, the "PBAC noted there is no obvious explanation for the different placebo response rates in the CZP versus other bDMARD trials." (paragraph 7.4, certolizumab PSD, November 2014).

Comparative harms

- 6.20 Within the guselkumab trials, 41-60% of patients experienced ≥ 1 adverse events during the induction period (up to Week 24). Upper respiratory tract infections, nasopharyngitis and enthesopathy were among the most common AEs reported.
- 6.21 The rates of adverse events were similar across the included trials. There were no statistically significant differences between guselkumab 100 mg q8w versus any of the comparators during the induction period (Table 7).

Table 7: Indirect comparisons of safety outcomes during the induction phase*

Indirect comparisons	RD (95% CI)	RR (95% CI)	OR (95%CI)
Serious AE			
GUS q8w (Week 24) vs UST 45 mg (Week16)	0.01 (-0.05, 0.07)	1.41 (0.11, 17.75)	1.42 (0.11, 18.19)
GUS q8w (Week 24) vs CZP 200/400 mg pooled (Week 24)	-0.04 (-0.09, 0.01)	0.34 (0.09, 1.23)	0.32 (0.08, 1.22)
GUS q8w (Week 24) SEC 150/300mg pooled (Week 16 & 24)	-0.01 (-0.04, 0.03)	0.75 (0.24, 2.31)	0.73 (0.23, 2.35)
GUS q8w (Week 24) TOF 5mg (Week 12)	-0.03 (-0.07, 0.01)	0.20 (0.02, 2.29)	0.19 (0.02, 2.28)
GUS q8w (Week 24) ADA 40mg (Week 12 Genovese & OPAL Broaden, & Week 24 ADEPT) ^a	0.00 (-0.04, 0.04)	0.81 (0.21, 3.08)	0.80 (0.20, 3.15)
Discontinuation due to AE			
GUS q8w (Week 24) vs UST 45 mg (Week16)	0.02 (-0.04, 0.08)	2.57 (0.47, 14.0)	2.73 (0.47, 15.84)
GUS q8w (Week 24) vs CZP 200/400 mg pooled (Week 24)	-0.03 (-0.06, 0.004)	0.29 (0.04, 1.92)	0.28 (0.04, 1.92)
GUS q8w (Week 24) SEC 150/300mg pooled (Week 16 & 24)	0 (-0.02, 0.02)	1.06 (0.28, 4.04)	1.06 (0.27, 4.17)
GUS q8w (Week 24) TOF 5mg (Week 12)	-0.03 (-0.07, 0.01)	0.25 (0.02, 3.06)	0.24 (0.02, 3.06)
GUS q8w (Week 24) ADA 40mg (Week 12 Genovese & OPAL Broaden, & Week 24 ADEPT) ^a	-0.02 (-0.05, 0.01)	0.48 (0.08, 2.83)	0.47 (0.08, 2.87)

Source: Table 2.67 and 2.68, p179 and 181 of the submission.

ADA=adalimumab; CI = confidence interval; CZP=certolizumab pegol; GUS = guselkumab; n = number of participants reporting data; N = total participants in group; OR = odds ratio, PBO=placebo, RD = risk difference; RR = relative risk; SEC=secukinumab; TOF=tofacitinib; UST = ustekinumab;

^a The adverse event values for the ADEPT trial was not reported in the submission. These values were incorporated, and the values for meta-analysis and indirect analysis were updated accordingly. Source: Mease 2005, p 3285.

* Note that the results presented in Table 7 are derived from post-hoc analyses conducted by the applicant specifically for the purposes of informing the PBAC consideration. These analyses were not part of the pre-specified statistical plan for any of the included biologic trials. Interpretation of the results and their application should therefore be limited to seeking to understand the basis for the PBAC outcome and should not be used for any other purpose.

Benefits/harms

6.22 On the basis of the indirect evidence for guselkumab 100 mg q8w, there were no statistically significant differences between guselkumab and its nominated comparators in terms of improving tender and swollen joints (ACR20 and ACR50 response), with the exception of secukinumab (all estimates) and adalimumab (risk difference and odds ratio) for ACR50 response. However, not all comparisons that were non-significant met the nominated non-inferiority criteria.

6.23 On the basis of the indirect evidence, there were no statistically significant differences between guselkumab 100 mg q8w and its nominated comparators in terms of serious adverse events or discontinuation due to adverse events. No non-inferiority criteria were nominated.

Clinical claim

6.24 The submission described guselkumab 100 mg q8w as non-inferior in terms of comparative effectiveness compared to the primary comparator, ustekinumab. The evaluation considered this claim required consideration as the nominated non-inferiority margins were not met for ACR50 (when assessed by the submission using the Week 16 time point for ustekinumab). The evaluation noted heterogeneity of placebo rates and the time point chosen for the assessment of ustekinumab outcomes may have biased the results against guselkumab. All non-inferiority margins were met using the Week 24 time point for ustekinumab. The PBAC has previously considered

ustekinumab response rates at 24 weeks, which is consistent with ustekinumab's initial treatment period on the PBS.

- 6.25 The submission described guselkumab 100 mg q8w as non-inferior in terms of effectiveness compared to secondary comparators certolizumab pegol, secukinumab and tofacitinib. The evaluation considered this claim was adequately supported for certolizumab pegol and tofacitinib (given non-inferiority criteria were met). Indirect comparisons between guselkumab and secukinumab indicated that statistically fewer patients treated with guselkumab would achieve ACR50 compared with those treated with secukinumab. The evaluation noted the PBAC had previously stated that for non-inferiority to be demonstrated, there must not be a statistically significant difference in the indirect comparisons (paragraph 6.9, abatacept PSD, March 2018). The evaluation noted heterogeneity of placebo rates between guselkumab and secukinumab may have biased the results against guselkumab.
- 6.26 Consistent with previous PBAC deliberations for ustekinumab, certolizumab pegol, and secukinumab, the submission stated guselkumab 100 mg q8w did not demonstrate non-inferiority in terms of effectiveness against the secondary comparator adalimumab, which is classed as a 'higher-tier' biologic.
- 6.27 The submission described guselkumab 100 mg q8w as non-inferior in terms of safety compared to ustekinumab, certolizumab pegol, secukinumab, tofacitinib and adalimumab. The evaluation considered this claim was adequately supported.
- 6.28 The PBAC considered that, overall, the claim of non-inferior comparative effectiveness compared to ustekinumab, secukinumab, tofacitinib and certolizumab pegol was reasonably supported by the data.
- 6.29 The PBAC considered that the claim of non-inferior comparative safety ustekinumab, secukinumab, tofacitinib, certolizumab pegol and adalimumab was reasonably supported by the data.

Economic analysis

- 6.30 A cost minimisation analysis was presented for guselkumab versus ustekinumab, based on claimed equi-effective doses of: guselkumab 100 mg subcutaneously at Weeks 0, 4 and then every 8 weeks = ustekinumab 45 mg subcutaneously at Weeks 0, 4 and then every 12 weeks.
- 6.31 The requested effective DPMQ of \$ [REDACTED] was based on the effective AEMP of ustekinumab of \$ [REDACTED] (which was known to the sponsor). The submission cited Clause 5.7 of the Strategic Agreement with Medicines Australia for this approach, such that the statutory price reductions that have been applied to ustekinumab since listing are not taken into consideration in the current cost-minimised requested price. The PBAC have previously considered that the application of Clause 5.7 of the Strategic Agreement is to be determined by the Minister (or Delegate), and is not a matter for PBAC (paragraph 6.41, levonorgestrel PSD, March 2019). Therefore, this remains for consideration by the Minister (or Delegate).

Drug cost/patient/year

- 6.32 Guselkumab 100 mg q8w drug cost per patient per year would be \$ [REDACTED] based on the requested effective DPMQ of \$ [REDACTED] and 7 scripts per year (first script in the initial phase sufficient for 4 weeks, followed by each script sufficient for 8 weeks). A loading dose is required during the initial period. However, both Year 1 and subsequent years require 7 scripts. Comparatively, the drug cost per patient per year for ustekinumab would be \$ [REDACTED] based on the current effective DPMQ of \$ [REDACTED] and 5 scripts per year (first script in the initial phase sufficient for 4 weeks, followed by each script sufficient for 12 weeks). Though an initial loading dose is required in Year 1, both Year 1 and subsequent years require 5 scripts.

Estimated PBS usage & financial implications

- 6.33 This submission was not considered by DUSC.
- 6.34 A market share approach was used to estimate the financial implications for the proposed listing. The biologic market for PsA and the market share of each existing biologic were extrapolated; the rate of substitution by guselkumab was applied, and the number of guselkumab scripts forecasted was estimated.
- 6.35 Table 8 provides a summary of the net financial implications of listing guselkumab for PsA. The estimates in Table 8 were updated during evaluation to correct for an underestimation of guselkumab scripts. However, the DPMQs used in the financial

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estimates provided with the submission (that were not current) have not been updated below.

Table 8: Estimated net financial implications of the proposed guselkumab listing

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
Estimation of use and financial impact of the proposed medicine (GUS)						
Total GUS script numbers ^a	1	2	2	2	3	3
PBS/RPBS cost (effective) ^{b,c}	\$ 6	\$ 7	\$ 8	\$ 8	\$ 9	\$ 12
Estimation of changes in use and financial impact of other medicines (PBS and RPBS)						
Changes in script numbers						
ADA	4	4	1	1	1	1
IFX	11	11	11	11	11	11
ETN	4	4	4	4	4	4
GOL	4	4	4	4	4	4
CZP	4	4	4	4	1	1
UST	4	4	4	4	4	4
SEC	4	4	4	1	1	1
IXE	4	4	4	4	1	4
TOF	4	4	4	4	4	4
Total	1	2	3	3	5	5
PBS/RPBS cost (published) ^b						
ADA	10	10	10	10	10	10
IFX	11	11	11	11	11	11
ETN	10	10	10	10	10	10
GOL	10	10	10	10	10	10
CZP	10	10	10	10	10	10
UST	10	10	10	10	10	10
SEC	10	10	10	10	6	6
IXE	10	10	10	6	6	7
TOF	10	10	10	10	10	10
Total	6	7	8	9	12	13
Estimated financial implications for the PBS/RPBS						
Net cost to PBS/RPBS ^b	10	10	10	10	6	6

Source: Table 4.11 and 4.12, p 216 and 218 of the submission.

GUS=guselkumab; ADA=adalimumab; INF=infliximab; ETN=etanercept; GOL=golimumab; CZP=certolizumab pegol; UST=ustekinumab; SEC=secukinumab; IXE=ixekizumab; TOF=tofacitinib

^a Corrected for an underestimate of the number of guselkumab scripts.

^b less co-payment

^c effective price for guselkumab

The redacted values correspond to the following ranges:

¹15,000 to <10,000

²10,000 to <20,000

³20,000 to <30,000

⁴500 to <5,000

⁵30,000 to <40,000

⁶\$10 million to <\$20 million

⁷\$20 million to <\$30 million

⁸\$30 million to <\$40 million

⁹\$40 million to <\$50 million

¹⁰\$0 to <\$10 million

¹¹<500

¹²\$50 to <\$60 million

¹³\$60 million to <\$70million

- 6.36 The total net cost saving to the PBS/RPBS of listing guselkumab was estimated to be \$10 to <\$20 million in Year 6, and a total of \$30 to <\$40 million in the first 6 years of listing.
- 6.37 The PBAC noted the financial estimates were based on published prices for the substituted therapies.

7 PBAC Outcome

- 7.1 The PBAC recommended the Authority Required listing for guselkumab on a cost minimisation basis with the least costly biological disease modifying anti-rheumatic drug (bDMARD) for severe psoriatic arthritis (PsA). In making this recommendation, the PBAC accepted that any of the currently PBS listed bDMARDs for severe PsA could be an alternative therapy to guselkumab. The PBAC considered that guselkumab must be less expensive than the 'higher tier' bDMARDs to account for the lack of evidence to support non-inferiority to the higher tier medicines, and could not be any more costly than any of the 'lower tier' bDMARDs currently listed on the PBS for this condition.
- 7.2 The PBAC noted that nine alternative bDMARDs were listed on the PBS for the treatment of PsA at the time of consideration. The PBAC considered that while the clinical need for an additional treatment is low, the addition of another option may be useful for some patients.
- 7.3 The PBAC considered the equi-effective doses of guselkumab (100 mg at week 0 and 4 then every 8 weeks) and alternative bDMARDs could be derived from the product information and with reference to previously recommended equi-effective doses collated in the PBS Therapeutic Relativity Sheets. The cost minimisation analysis should be conducted over two years using approved ex-manufacturer prices consistent with methodology previously accepted by the PBAC for bDMARDs.
- 7.4 The PBAC considered the nominated comparators of ustekinumab (primary comparator), certolizumab pegol, secukinumab, tofacitinib and adalimumab were reasonable; however, noted any of the bDMARDs currently listed on the PBS for PsA were relevant alternative therapies. The PBAC noted no evidence demonstrating superiority against any of the other alternative therapies was provided.
- 7.5 The PBAC noted non-inferiority margins were not met for the indirect comparison of guselkumab to ustekinumab (lower tier medicine) for the ACR50 outcome at 16 weeks. However, the PBAC noted the lower 95% CI (0.28) was reasonably similar to the non-inferiority margin (0.29), non-inferiority was met for ACR50 at 24 weeks and there was some heterogeneity in placebo response across the studies that may bias against guselkumab. The PBAC considered that, overall, the claim of non-inferior comparative effectiveness compared to ustekinumab was reasonably supported by the data.

- 7.6 The PBAC considered that the claim of non-inferior comparative effectiveness compared to certolizumab pegol and tofacitinib (lower tier medicines) was reasonably supported by the data. The PBAC noted there was a statistically significant difference in favour of secukinumab (lower tier medicine) for the ACR50 outcome. The PBAC noted there was no statistically significant difference for the ACR20 outcome (and the non-inferiority margin was met) and differences in placebo response rates across the studies may bias against guselkumab. The PBAC considered that, overall, the claim of non-inferior comparative effectiveness compared to secukinumab was reasonable.
- 7.7 The PBAC agreed with the submission that the evidence presented for the ACR20 and ACR50 outcomes did not support non-inferiority of guselkumab to adalimumab (higher tier medicine) for comparative effectiveness (paragraph 6.26).
- 7.8 The PBAC considered that the claim of non-inferior comparative safety of guselkumab compared to ustekinumab, secukinumab, tofacitinib certolizumab pegol and adalimumab was reasonably supported by the data.
- 7.9 The PBAC considered that guselkumab would be classed as a ‘lower tier’ bDMARD for the treatment of PsA given its non-inferiority to other ‘lower tier’ bDMARDs. The PBAC considered that when listing a new ‘lower tier’ bDMARD it should not be priced the same or higher than a ‘higher tier’ bDMARD. The PBAC considered that guselkumab, should be cost-minimised to the lowest cost alternative bDMARD for PsA, and must be less expensive than the ‘higher tier’ bDMARDs.
- 7.10 The PBAC considered it would be appropriate to align the listing of guselkumab with the other written authority bDMARD listings for PsA, and that flow-on changes to notes in the other listings to include guselkumab in the list of therapies would be required to facilitate the listing. The PBAC noted that the sponsor had not requested a grandfather listing.
- 7.11 The PBAC considered the restriction should include a note specifying “No increase in the maximum quantity or number of units may be authorised” to ensure the cost-effective 100 mg q8w dosing regimen is adhered to.
- 7.12 The PBAC considered that the listing of guselkumab for PsA based on a cost minimisation basis with the least costly bDMARD (as recommended in paragraph 7.9) using effective prices should result in no increase in net cost to the PBS.
- 7.13 The PBAC noted that its recommendation was on a cost-minimisation basis and advised that, because guselkumab is not expected to provide a substantial and clinically relevant improvement in efficacy, or reduction of toxicity, over alternative therapies, or not expected to address a high and urgent unmet clinical need given the presence of an alternative therapy, the criteria prescribed by the National Health (Pharmaceuticals and Vaccines – Cost Recovery) Regulations 2009 for Pricing Pathway A were not met.
- 7.14 The PBAC noted that this submission is not eligible for an Independent Review as it received a positive recommendation.

Outcome:

Recommended

8 Recommended listing

8.1 Add indication (severe psoriatic arthritis) to guselkumab as follows:

MEDICINAL PRODUCT medicinal product pack	PBS item code	Max. qty packs	Max. qty units	№.of Rpts	Available brands
GUSELKUMAB					
guselkumab 100 mg/mL injection, 1 x 1 mL syringe	11614G	1	1	2	Tremfya
guselkumab 100 mg/mL injection, 1 x 1 mL pen device	NEW	1	1	2	Tremfya
Restriction Summary 9192 / Treatment of Concept: 9184 (as per ixekizumab; current as at 1 November 2020)					
Category / Program: GENERAL – General Schedule (Code GE)					
Prescriber type: <input checked="" type="checkbox"/> Medical Practitioners					
Restriction Type: <input checked="" type="checkbox"/> Authority Required – non-immediate/delayed assessment by Services Australia (in-writing only via mail/postal service or electronic upload to Hobart)					
Administrative Advice: (-----see end of document for updated concept-----)					
Administrative Advice: No increase in the maximum quantity or number of units may be authorised.					
Administrative Advice: No increase in the maximum number of repeats may be authorised.					
Administrative Advice: Special Pricing Arrangements apply					
Indication: Severe psoriatic arthritis					
Treatment Phase: Initial treatment – Initial 1 (new patient)					
Treatment criteria:					
Must be treated by a rheumatologist; or					
Must be treated by a clinical immunologist with expertise in the management of psoriatic arthritis					
AND					
Clinical criteria:					
Patient must not have received PBS-subsidised treatment with a biological medicine for this condition					
AND					
Clinical criteria:					
Patient must have failed to achieve an adequate response to methotrexate at a dose of at least 20 mg weekly for a minimum period of 3 months					
AND					
Clinical criteria:					
Patient must have failed to achieve an adequate response to sulfasalazine at a dose of at least 2 g per day for a minimum period of 3 months; or					
Patient must have failed to achieve an adequate response to leflunomide at a dose of up to 20 mg daily for a minimum period of 3 months					
AND					
Clinical criteria:					
Patient must not receive more than 20 weeks of treatment under this restriction					
AND					
Population criteria:					
Patient must be aged 18 years or older					

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	<p>Prescribing instructions: Where treatment with methotrexate, sulfasalazine or leflunomide is contraindicated according to the relevant TGA-approved Product Information, details must be provided at the time of application.</p>
	<p>Prescribing instructions: Where intolerance to treatment with methotrexate, sulfasalazine or leflunomide developed during the relevant period of use, which was of a severity to necessitate permanent treatment withdrawal, details of the degree of this toxicity must be provided at the time of application.</p>
	<p>Prescribing Instructions: The following initiation criteria indicate failure to achieve an adequate response and must be demonstrated in all patients at the time of the initial application: 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 (a) an active joint count of at least 20 active (swollen and tender) joints; or (b) at least 4 active joints from the following list of major joints: (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). 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>Prescribing Instructions: The authority application must be made in writing and must include: (1) a completed authority prescription form(s); and (2) a completed Severe Psoriatic Arthritis PBS Authority Application - Supporting Information Form.</p>
	<p>Prescribing Instructions: An assessment of a patient's response to an initial course of treatment must be conducted following a minimum of 12 weeks of therapy. An application for the continuing treatment must be accompanied with the assessment of response and submitted to the Department of Human Services no later than 4 weeks from the date of completion of the most recent course of treatment. This will enable ongoing treatment for those who meet the continuing restriction for PBS-subsidised treatment.</p>
	<p>Prescribing Instructions: Where the response assessment is not submitted within this timeframe, the patient will be deemed to have failed to respond to treatment with this drug.</p>
	<p>Prescribing Instructions: If a patient fails to demonstrate a response to treatment with this drug they will not be eligible to receive further PBS-subsidised treatment with this drug for this condition. Serious adverse reaction of a severity resulting in the necessity for permanent withdrawal of treatment is not considered as a treatment failure.</p>
	<p>Administrative Advice: Details of the toxicities, including severity, which will be accepted as a reason for exempting a patient from the requirement for 3 months treatment with methotrexate and 3 months treatment with sulfasalazine or leflunomide can be found on the Services Australia website (www.servicesaustralia.gov.au)</p>
	<p>Administrative Advice: Any queries concerning the arrangements to prescribe may be directed to Services Australia on 1800 700 270 (hours of operation 8 a.m. to 5 p.m. EST Monday to Friday). Prescribing information (including Authority Application forms and other relevant documentation as applicable) is available on the Services Australia website at www.servicesaustralia.gov.au Applications for authority to prescribe should be submitted online using the form upload facility in Health Professional Online Services (HPOS) at www.servicesaustralia.gov.au/hpos Or mailed to: Services Australia Complex Drugs Reply Paid 9826 HOBART TAS 7001</p>
Restriction Summary 9076 / Treatment of Concept: 9194 (as per ixekizumab; current as at 1 November 2020)	
	<p>Administrative Advice: (-----see end of document for updated concept-----)</p>
	<p>Administrative Advice: No increase in the maximum quantity or number of units may be authorised.</p>

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	Administrative Advice: No increase in the maximum number of repeats may be authorised.
	Administrative Advice: Special Pricing Arrangements apply
	Indication: Severe psoriatic arthritis
	Treatment Phase: Initial treatment – Initial 2 (change or recommencement of treatment after a break in biological medicine of less than 5 years)
	Treatment criteria:
	Must be treated by a rheumatologist; or
	Must be treated by a clinical immunologist with expertise in the management of psoriatic arthritis
	AND
	Clinical criteria:
	Patient must have received prior PBS-subsidised treatment with a biological medicine for this condition in this treatment cycle
	AND
	Clinical criteria:
	Patient must not have already failed, or ceased to respond to, PBS-subsidised treatment with 3 biological medicines for this condition within this treatment cycle
	AND
	Clinical criteria:
	Patient must not have already failed, or ceased to respond to, PBS-subsidised treatment with this drug for this condition during the current treatment cycle
	AND
	Clinical criteria:
	Patient must not receive more than 20 weeks of treatment under this restriction
	AND
	Population criteria:
	Patient must be aged 18 years or older
	Prescribing instructions:
	The authority application must be made in writing and must include: (1) a completed authority prescription form(s); and (2) a completed Severe Psoriatic Arthritis PBS Authority Application - Supporting Information Form
	Prescribing Instructions:
	An application for a patient who has received PBS-subsidised biological medicine treatment for this condition who wishes to change or recommence therapy with this drug, must be accompanied by evidence of a response to the patient's most recent course of PBS-subsidised biological medicine treatment, within the timeframes specified below.
	Prescribing Instructions:
	Where the most recent course of PBS-subsidised biological medicine treatment was approved under either Initial 1, Initial 2, Initial 3 or continuing treatment restrictions, an assessment of a patient's response must have been conducted following a minimum of 12 weeks of therapy and submitted to the Department of Human Services no later than 4 weeks from the date of completion of treatment.
	Prescribing Instructions:
	An application for the continuing treatment must be accompanied with the assessment of response following a minimum of 12 weeks of therapy with this drug and submitted to the Department of Human Services no later than 4 weeks from the date of completion of treatment. This will enable ongoing treatment for those who meet the continuing restriction for PBS-subsidised treatment.
	Prescribing Instructions:
	Where the response assessment is not submitted within this timeframe, the patient will be deemed to have failed to respond to treatment with this drug.
	Prescribing Instructions:
	If a patient fails to demonstrate a response to treatment with this drug they will not be eligible to receive further PBS-subsidised treatment with this drug for this condition. Serious adverse reaction of a severity resulting in the necessity for permanent withdrawal of treatment is not considered as a treatment failure.

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	<p>Prescribing Instructions: A patient may re-trial this drug after a minimum of 5 years have elapsed between the date the last prescription for a PBS-subsidised biological medicine was approved in this cycle and the date of the first application under a new cycle under the Initial 3 treatment restriction.</p>
	<p>Administrative Advice: Any queries concerning the arrangements to prescribe may be directed to Services Australia 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 Services Australia website at www.servicesaustralia.gov.au</p> <p>Applications for authority to prescribe should be submitted online using the form upload facility in Health Professional Online Services (HPOS) at www.servicesaustralia.gov.au/hpos</p> <p>Or mailed to: Services Australia Complex Drugs Reply Paid 9826 HOBART TAS 7001</p>
Restriction Summary 9193 / Treatment of Concept: 9118 (as per ixekizumab; current as at 1 November 2020)	
	Administrative Advice: (-----see end of document for updated concept-----)
	Administrative Advice: No increase in the maximum quantity or number of units may be authorised.
	Administrative Advice: No increase in the maximum number of repeats may be authorised.
	Administrative Advice: Special Pricing Arrangements apply
	Indication: Severe psoriatic arthritis
	Treatment Phase: Initial treatment – Initial 3 (recommencement of treatment after a break in biological medicine of more than 5 years)
	Treatment criteria:
	Must be treated by a rheumatologist; or
	Must be treated by a clinical immunologist with expertise in the management of psoriatic arthritis
	AND
	Clinical criteria:
	Patient must have previously received PBS-subsidised treatment with a biological medicine for this condition
	AND
	Clinical criteria:
	Patient must have a break in treatment of 5 years or more from the most recently approved PBS-subsidised biological medicine for this condition
	AND
	Clinical criteria:
	The condition must have an elevated erythrocyte sedimentation rate (ESR) greater than 25 mm per hour; or
	The condition must have a C-reactive protein (CRP) level greater than 15 mg per L
	AND
	Clinical criteria:
	The condition must have either (a) a total active joint count of at least 20 active (swollen and tender) joints; or (b) at least 4 active major joints
	AND
	Clinical criteria:
	Patient must not receive more than 20 weeks of treatment under this restriction
	AND
	Population criteria:
	Patient must be aged 18 years or older

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	<p>Prescribing instructions: Major joints are defined as (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>
	<p>Prescribing instructions: All measures of joint count and ESR and/or CRP must be no more than one month old at the time of initial application.</p>
	<p>Prescribing instructions: 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>Prescribing Instructions: 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>Prescribing Instructions: The authority application must be made in writing and must include: (1) a completed authority prescription form(s); and (2) a completed Severe Psoriatic Arthritis PBS Authority Application - Supporting Information Form.</p>
	<p>Prescribing Instructions: An application for a patient who has received PBS-subsidised biological medicine treatment for this condition who wishes to recommence therapy with this drug, must be accompanied by evidence of a response to the patient's most recent course of PBS-subsidised biological medicine treatment, within the timeframes specified below.</p>
	<p>Prescribing Instructions: Where the most recent course of PBS-subsidised biological medicine treatment was approved under either Initial 1, Initial 2, Initial 3 or continuing treatment restrictions, an assessment of a patient's response must have been conducted following a minimum of 12 weeks of therapy and submitted to the Department of Human Services no later than 4 weeks from the date of completion of treatment.</p>
	<p>Prescribing Instructions: An application for the continuing treatment must be accompanied with the assessment of response following a minimum of 12 weeks of therapy with this drug and submitted to the Department of Human Services no later than 4 weeks from the date of completion of treatment. This will enable ongoing treatment for those who meet the continuing restriction for PBS-subsidised treatment.</p>
	<p>Prescribing Instructions: Where the response assessment is not submitted within this timeframe, the patient will be deemed to have failed to respond to treatment with this drug.</p>
	<p>Prescribing Instructions: If a patient fails to demonstrate a response to treatment with this drug they will not be eligible to receive further PBS-subsidised treatment with this drug for this condition. Serious adverse reaction of a severity resulting in the necessity for permanent withdrawal of treatment is not considered as a treatment failure.</p>
	<p>Administrative Advice: Any queries concerning the arrangements to prescribe may be directed to Services Australia 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 Services Australia website at www.servicesaustralia.gov.au</p> <p>Applications for authority to prescribe should be submitted online using the form upload facility in Health Professional Online Services (HPOS) at www.servicesaustralia.gov.au/hpos</p> <p>Or mailed to: Services Australia Complex Drugs Reply Paid 9826 HOBART TAS 7001</p>
Restriction Summary 9158 / Treatment of Concept: 9172 (as per ixekizumab; current as at 1 November 2020)	
	Administrative Advice: (-----see end of document for updated concept-----)
	Administrative Advice: No increase in the maximum quantity or number of units may be authorised.
	Administrative Advice: No increase in the maximum number of repeats may be authorised.

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Administrative Advice: Special Pricing Arrangements apply
Indication: Severe psoriatic arthritis
Treatment Phase: Initial 1 (new patient) or Initial 2 (change or recommencement of treatment after a break in biological medicine of less than 5 years) or Initial 3 (recommencement of treatment after a break in biological medicine of more than 5 years) - balance of supply
Treatment criteria:
Must be treated by a rheumatologist; or
Must be treated by a clinical immunologist with expertise in the management of psoriatic arthritis
AND
Clinical criteria:
Patient must have received insufficient therapy with this drug under the Initial 1 (new patient) restriction to complete 20 weeks treatment; or
Patient must have received insufficient therapy with this drug under the Initial 2 (change or recommencement of treatment after a break in biological medicine of less than 5 years) restriction to complete 20 weeks treatment; or
Patient must have received insufficient therapy with this drug for this condition under the Initial 3 (recommencement of treatment after a break in biological medicine of more than 5 years) restriction to complete 20 weeks treatment
AND
Clinical criteria:
The treatment must provide no more than the balance of up to 20 weeks treatment available under the above restrictions
Administrative Advice: Authority approval for sufficient therapy to complete the balance of supply 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).
Restriction Summary 9117 / Treatment of Concept: 9116 (as per ixekizumab; current as at 1 November 2020)
Administrative Advice: (-----see end of document for updated concept-----)
Administrative Advice: No increase in the maximum quantity or number of units may be authorised.
Administrative Advice: No increase in the maximum number of repeats may be authorised.
Administrative Advice: Special Pricing Arrangements apply
Indication: Severe psoriatic arthritis
Treatment Phase: Continuing treatment
Treatment criteria:
Must be treated by a rheumatologist; or
Must be treated by a clinical immunologist with expertise in the management of psoriatic arthritis
AND
Clinical criteria:
Patient must have received this drug as their most recent course of PBS-subsidised biological medicine treatment for this condition
AND
Clinical criteria:
Patient must have demonstrated an adequate response to treatment with this drug
AND
Clinical criteria:
Patient must not receive more than 24 weeks of treatment under this restriction
Population criteria:
Patient must be aged 18 years or older

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	<p>Prescribing instructions: An adequate response to treatment is defined as: an erythrocyte sedimentation rate (ESR) no greater than 25 mm per hour or a C-reactive protein (CRP) level no greater than 15 mg 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 major active joints, from at least 4, by at least 50%: (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>
	<p>Prescribing instructions: The same indices of disease severity used to establish baseline at the commencement of treatment with each initial treatment application must be used to determine response for all subsequent continuing treatments.</p>
	<p>Prescribing Instructions: The authority application must be made in writing and must include: (1) a completed authority prescription form(s); and (2) a completed Severe Psoriatic Arthritis PBS Authority Application - Supporting Information Form.</p>
	<p>Prescribing Instructions: Where the most recent course of PBS-subsidised treatment with this drug was approved under either Initial 1, Initial 2, or Initial 3 treatment restrictions, an assessment of a patient's response must have been conducted following a minimum of 12 weeks of therapy and submitted to the Department of Human Services no later than 4 weeks from the date of completion of treatment.</p>
	<p>Prescribing Instructions: An application for the continuing treatment must be accompanied with the assessment of response following a minimum of 12 weeks of therapy with this drug and submitted to the Department of Human Services no later than 4 weeks from the date of completion of treatment. This will enable ongoing treatment for those who meet the continuing restriction for PBS-subsidised treatment.</p>
	<p>Prescribing Instructions: Where the response assessment is not submitted within this timeframe, the patient will be deemed to have failed to respond to treatment with this drug.</p>
	<p>Prescribing Instructions: If a patient fails to demonstrate a response to treatment with this drug they will not be eligible to receive further PBS-subsidised treatment with this drug for this condition. Serious adverse reaction of a severity resulting in the necessity for permanent withdrawal of treatment is not considered as a treatment failure.</p>
	<p>Administrative Advice: A patient may re-trial this drug after a minimum of 5 years have elapsed between the date the last prescription for a PBS-subsidised biological medicine was approved in this cycle and the date of the first application under a new cycle under the Initial 3 treatment restriction.</p>
	<p>Administrative Advice: Any queries concerning the arrangements to prescribe may be directed to Services Australia on 1800 700 270 (hours of operation 8 a.m. to 5 p.m. EST Monday to Friday). Prescribing information (including Authority Application forms and other relevant documentation as applicable) is available on the Services Australia website at www.servicesaustralia.gov.au Applications for authority to prescribe should be submitted online using the form upload facility in Health Professional Online Services (HPOS) at www.servicesaustralia.gov.au/hpos Or mailed to: Services Australia Complex Drugs Reply Paid 9826 HOBART TAS 7001</p>
<p>Restriction Summary 9121 / Treatment of Concept 9063 (as per adalimumab, certolizumab, golimumab, secukinumab and ustekinumab; current as of 1 November 2020)</p>	
	<p>Administrative Advice: (-----see end of document for updated concept-----)</p>
	<p>Administrative Advice: No increase in the maximum quantity or number of units may be authorised.</p>

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	Administrative Advice: No increase in the maximum number of repeats may be authorised.
	Administrative Advice: Special Pricing Arrangements apply
	Indication: Severe psoriatic arthritis
	Treatment Phase: Continuing treatment – balance of supply
	Clinical criteria:
	Patient must have received insufficient therapy with this drug for this condition under the continuing treatment restriction to complete 24 weeks treatment
	AND
	Clinical criteria:
	The treatment must provide no more than the balance of up to 24 weeks treatment available under the above restriction
	AND
	Treatment criteria:
	Must be treated by a rheumatologist; or
	Must be treated by a clinical immunologist with expertise in the management of psoriatic arthritis
	Administrative Advice: Authority approval for sufficient therapy to complete the balance of supply 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).

8.2 The edited explanatory NOTE (24357) to add guselkumab to the list of biological medicines is shown below for reference:

	Administrative Advice:
	TREATMENT OF ADULT PATIENTS WITH SEVERE ACTIVE PSORIATIC ARTHRITIS
	The following information applies to the prescribing under the Pharmaceutical Benefits Scheme (PBS) of the biological medicines adalimumab, certolizumab pegol, etanercept, golimumab, <i>guselkumab</i> , infliximab, ixekizumab, secukinumab, tofacitinib and ustekinumab for adult patients with severe active psoriatic arthritis. Therefore, where the term 'biological medicine' appears in notes and restrictions, it refers to adalimumab, certolizumab pegol, etanercept, golimumab, <i>guselkumab</i> , infliximab, ixekizumab, secukinumab, tofacitinib and ustekinumab only.
	A patient is eligible for PBS-subsidised treatment with only 1 of the above biological medicines at any 1 time.
	A patient receiving PBS-subsidised treatment for psoriatic arthritis is able to commence a treatment cycle where they may trial biological medicines without having to experience a disease flare when swapping to the alternate biological medicine. Under these arrangements, within a single cycle, a patient may receive long-term treatment with a biological medicine as long as they sustain a response to therapy.
	A patient who received PBS-subsidised adalimumab, certolizumab pegol, etanercept, golimumab, <i>guselkumab</i> , infliximab, ixekizumab, secukinumab or ustekinumab treatment prior to 1 May 2019 is considered to start their first cycle as of 1 May 2019.
	Within the same treatment cycle, a patient cannot trial and fail, or cease to respond to, the same PBS-subsidised biological medicine more than once. Therefore, once a patient fails to meet the response criteria for a PBS-subsidised biological medicine, they must change to an alternate biological medicine if they wish to continue PBS-subsidised biological treatment.
	Serious adverse reaction of a severity resulting in the necessity for permanent withdrawal of treatment, including serious infusion or injection related reactions, Steven's Johnson Syndrome, development of a demyelinating lesion, progressive multifocal leukoencephalopathy and malignancy related to treatment with the biological medicine, is not considered as a treatment failure.
	Once a patient has either failed or ceased to sustain a response to treatment 3 times, they are deemed to have completed a single cycle and they must have, at a minimum, a 5-year break in PBS-subsidised biological medicine therapy before they are eligible to commence another cycle [further details are under '(5) Recommencement of treatment after a 5-year break in PBS-subsidised therapy' below].

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<p>The duration of the break in therapy will be measured from the date the last prescription for PBS-subsidised treatment was approved in the most recent cycle to the date of the first application for initial treatment with a biological medicine under the new cycle.</p> <p>A patient who has failed fewer than 3 biological medicines in a treatment cycle and who has a break in therapy of more than 5 years may commence a new treatment cycle under Initial 3 treatment restriction.</p> <p>A patient who has failed fewer than 3 biological medicines in a treatment cycle and who has a break in therapy of less than 5 years may commence a further course of treatment within the same treatment cycle under Initial 2 treatment restriction.</p> <p>There is no limit to the number of treatment cycles a patient may undertake in their lifetime.</p> <p>How to prescribe PBS-subsidised biological medicine treatment for severe active psoriatic arthritis.</p> <p>(1) Initial treatment.</p> <p>Applications for initial treatment should be made where:</p> <p>(i) a patient has not received prior PBS-subsidised biological medicine treatment and wishes to commence such therapy (Initial 1 - New patient); or</p> <p>(ii) a patient has received prior PBS-subsidised biological medicine therapy (initial or continuing) and wishes to trial an alternate medicine (Initial 2 - Change or Recommencement of treatment after a break in therapy of less than 5 years) [further details are under 'Swapping therapy' below]; or</p> <p>(iii) a patient wishes to recommence treatment with a specific biological medicine following a break in PBS-subsidised therapy of less than 5 years with the same medicine (Initial 2 - Change or Recommencement of treatment after a break in biological medicine of less than 5 years).</p> <p>(iv) a patient wishes to recommence treatment with a biological medicine following a break in PBS-subsidised therapy of more than 5 years (Initial 3 - Recommencement of treatment after a break in biological medicine of more than 5 years) or</p> <p>An application for initial treatment will be limited to provide for a maximum of 16 weeks of therapy for adalimumab, etanercept, golimumab secukinumab and tofacitinib, 18 to 20 weeks of therapy for certolizumab pegol (depending upon the dosing regimen), 20 weeks of therapy for ixekizumab, 22 weeks of therapy for infliximab, and 28 weeks of therapy for ustekinumab. It is recommended that a patient be reviewed in the month prior to completing their course of initial treatment to ensure uninterrupted biological medicine supply.</p> <p>A patient must be assessed for response to a course of PBS-subsidised initial treatment following a minimum of 12 weeks of therapy and conducted no later than 4 weeks from the cessation of the treatment course. If the response assessment is not submitted within these timeframes, the patient will be deemed to have failed this course of treatment.</p> <p>Grandfather patients (ixekizumab only).</p> <p>A patient who commenced treatment with ixekizumab for severe psoriatic arthritis prior to 1 March 2019 and who continues to receive treatment at the time of application, may qualify for treatment under the 'Grandfather' treatment restriction.</p> <p>A patient may only qualify for PBS-subsidised treatment under this restriction once. A maximum of 24 weeks of treatment will be authorised under this criterion. Following completion of the initial PBS-subsidised course, further subsidised treatment must be prescribed under the continuing treatment restriction of the relevant drug. 'Grandfather' arrangements will only apply for the first treatment cycle.</p> <p>For the second and subsequent cycles, a 'grandfather' patient must qualify for continuing treatment under the criteria that apply to a continuing patient.</p> <p>Grandfather patients (tofacitinib only).</p> <p>A patient who commenced treatment with Tofacitinib for severe psoriatic arthritis prior to 1 May 2019 and who continues to receive treatment at the time of application, may qualify for treatment under the 'Grandfather' treatment restriction.</p> <p>A patient may only qualify for PBS-subsidised treatment under this restriction once. A maximum of 24 weeks of treatment will be authorised under this criterion. Following completion of the initial PBS-subsidised course, further subsidised treatment</p>
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<p>must be prescribed under the continuing treatment restriction of the relevant drug. 'Grandfather' arrangements will only apply for the first treatment cycle.</p> <p>For the second and subsequent cycles, a 'grandfather' patient must qualify for continuing treatment under the criteria that apply to a continuing patient.</p> <p>(2) Continuing treatment.</p> <p>Following the completion of an initial treatment course with a specific biological medicine, 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 biological medicine 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 biological medicine supply.</p> <p>A patient must be assessed for response to a course of continuing therapy, and the assessment must be submitted to Services Australia where applicable. Where a response assessment is not submitted where applicable, the patient will be deemed to have failed to respond to treatment with that biological medicine, unless the patient has experienced a serious adverse reaction of a severity resulting in the necessity for permanent withdrawal of treatment.</p> <p>Infliximab and etanercept only:</p> <p>For the first continuing treatment course of PBS-subsidised biological medicine treatment, it is recommended that a patient is reviewed for response following a minimum of 12 weeks of therapy and no later than 4 weeks from the completion of the most recent course of treatment under the Initial 1 or Initial 2 treatment restrictions.</p> <p>For the second and subsequent continuing courses of PBS-subsidised biological medicine treatment, it is recommended that an assessment of a patient's response is conducted following a minimum of 12 weeks of therapy and no later than 4 weeks from the completion of the most recent course of treatment.</p> <p>(3) Swapping therapy.</p> <p>Once initial treatment with the first PBS-subsidised biological medicine is approved, a patient may swap to an alternate biological medicine without having to re-qualify with respect to either the indices of disease severity (i.e. erythrocyte sedimentation rate (ESR) or C-reactive protein (CRP) level, and active joint count) or the prior non-biological therapy requirements, except if the patient has had a break in therapy of more than 5 years who would need to requalify under the Initial 3 treatment restriction with respect to the indices of disease severity.</p> <p>A patient who is not able to complete a minimum of 12 weeks of an initial treatment course will be deemed to have failed treatment with that biological medicine unless the patient has experienced a serious adverse reaction of a severity resulting in the necessity for permanent withdrawal of treatment.</p> <p>A patient may trial an alternate biological medicine at any time, regardless of whether they are receiving therapy (initial or continuing) with a biological medicine at the time of the application.</p> <p>However, they cannot swap to a particular biological medicine if they have failed to respond to prior treatment with that drug within the same treatment cycle.</p> <p>Within a treatment cycle a patient may alternate between therapy with any biological medicine of their choice (1 at a time) providing:</p> <ul style="list-style-type: none">(i) they have not received PBS-subsidised treatment with that particular biological medicine previously; or(ii) they have demonstrated an adequate response to that particular biological medicine if they have previously trialled it on the PBS; and(iii) they have not previously failed to respond to treatment 3 times in this treatment cycle with that biological medicine. <p>To ensure a patient receives the maximum treatment opportunities allowed under these arrangements, it is important that they are assessed for response to every course of treatment.</p> <p>(4) Baseline measurements to determine response.</p>

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<p>Services Australia will determine whether a response to treatment has been demonstrated based on the baseline measurements of the indices of disease severity submitted with the first authority application for a biological medicine. However, prescribers may provide new baseline measurements any time that an initial or change or recommencement treatment application is submitted within a treatment cycle and these revised baseline measurements will be used to assess response to the PBS-subsidised treatment.</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 to determine response for all subsequent continuing treatments. 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. 20 or more active joints), response will be determined according to a reduction in the total number of active joints.</p> <p>(5) Re-commencement of treatment after a 5-year break in PBS-subsidised therapy.</p> <p>A patient who wishes to trial a second or subsequent course of treatment following a break in PBS-subsidised biological therapy of at least 5 years, must qualify under Initial 3 treatment restriction according to the criteria of the relevant restriction and index of disease severity. The application must include a joint count and ESR and/or CRP measurement that is no more than one month old at the time of application.</p>

This restriction may be subject to further review. Should there be any changes made to the restriction the Sponsor will be informed.

9 Context for Decision

The PBAC helps decide whether and, if so, how medicines should be subsidised through the Pharmaceutical Benefits Scheme (PBS) in Australia. It considers applications regarding the listing of medicines on the PBS and provides advice about other matters relating to the operation of the PBS in this context. A PBAC decision in relation to PBS listings does not necessarily represent a final PBAC view about the merits of the medicine or the circumstances in which it should be made available through the PBS. The PBAC welcomes applications containing new information at any time.

10 Sponsor's Comment

The sponsor had no comment.