

**6.05 IXEKIZUMAB,
pre-filled syringe & pen,
80mg, Taltz[®],
Eli Lilly Australia**

1 Purpose of application

- 1.1 The submission requested an Authority Required listing for ixekizumab for treatment of severe active psoriatic arthritis (PsA) in patients meeting certain criteria. This is the first submission of ixekizumab for PsA to be considered by the PBAC. Ixekizumab was listed on the PBS for the treatment of severe chronic plaque psoriasis in February 2017.
- 1.2 The basis for the requested listing was a cost-minimisation analysis to secukinumab, a pharmacological analogue to ixekizumab. The submission also nominated three other biologic disease-modifying anti-rheumatic drugs (bDMARDs) currently listed on the PBS as supplementary comparators but did not include them in the cost-minimisation analysis: adalimumab, certolizumab pegol, and ustekinumab.

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

Component	Description
Population	Adults with severe active psoriatic arthritis
Intervention	IXE: <ul style="list-style-type: none"> - Without coexisting moderate-severe plaque psoriasis: 160mg SC at wk 0, then 80mg Q4W. - With coexisting moderate-severe plaque psoriasis: 160mg SC at wk 0, then 80mg at wk 2, 4, 6, 8, 10, 12, then 80mg Q4W
Comparator	Main comparator SEC: <ul style="list-style-type: none"> - TNFα naïve without coexisting moderate-severe plaque psoriasis: 150mg SC at wk 0, 1, 2, 3, 4, then monthly (~Q4W). - TNFα inadequate responders or with coexisting moderate-severe plaque psoriasis: 300mg SC at wk 0, 1, 2, 3, 4, then monthly (~Q4W). Supplementary comparators ADA: 40mg SC Q2W. CZP: 400mg SC at wk 0, 2, 4, then 400mg Q4W or 200mg Q2W. UST: 45mg SC at wk 0, 4, then Q12W.
Outcomes	Main outcomes ACR50 (Wk12), ACR20 (Wk12). Supplementary outcomes ACR50 (Wk24), ACR20 (Wk24), ACR70 (Wk12, 24), PASI75 (Wk12, 24), PASI90 (Wk12, 24).
Clinical claim	The submission described IXE to be non-inferior in terms of comparative effectiveness and safety versus the main comparator (SEC) and all supplementary comparators (ADA, CZP and UST). Based on the evidence presented in the submission and additional sensitivity analyses conducted during the evaluation, the claim appeared to be supported.

Abbreviations: ACR20/50/70 = $\geq 20\%$ /50%/70% improvement on the American College of Rheumatology Criteria; PASI75/90 = $\geq 75\%$ /90% reduction in the Psoriasis Area and Severity Index; ADA = adalimumab; CZP = certolizumab pegol; UST = ustekinumab; SEC = secukinumab; IXE = ixekizumab; Q2W = every 2 weeks; Q4W = every 4 weeks; Q12W = every 12 weeks

Source: Table 1.1.1, p6 of the submission

2 Requested listing

2.1 PBS listing of ixekizumab was requested for a pre-filled pen and a pre-filled syringe for subcutaneous (SC) injection. The restrictions provide initial and continuing treatment for patients with coexisting psoriasis who meet the clinical criteria for psoriatic arthritis, consistent with the current listing of secukinumab and other bDMARDs. The clinical criteria for Initial 1 (new patient or patient recommencing treatment after a break of 5 years or more) and continuing treatment are summarised in the table below. Listing was also sought for Initial 2 (patients changing or recommencing treatment after a break of less than 5 years), Initial 3 (grandfathering of patients on non-PBS ixekizumab), and 'balance of supply'.

Name, Restriction, Manner of administration and form	Max. Qty	No. of Rpts	Dispensed Price for Max. Qty	Proprietary Name and Manufacturer	
<i>Initial treatment 1 & 2, balance of supply</i>					
<i>IXEKIZUMAB, pre-filled pen, 80mg (1)</i>	2	3	\$3,409.58 [#]		
<i>IXEKIZUMAB, pre-filled syringe, 80mg (1)</i>	2	3	\$3,409.58 [#]		
<i>Initial treatment 3, continuing treatment, balance of supply:</i>					
<i>IXEKIZUMAB, pre-filled pen, 80mg (1)</i>	2	2	\$3,409.58 [#]	Taltz®	Eli Lilly
<i>IXEKIZUMAB, pre-filled syringe, 80mg (1)</i>	2	2	\$3,409.58 [#]		

Category/Program:	General Schedule
PBS indication:	Severe active psoriatic arthritis
Treatment phase:	Initial 1 (new patient or patient recommencing treatment after a break of 5 years or more)
Clinical criteria:	Patient must have severe active psoriatic arthritis, AND Patient must have received no prior PBS-subsidised treatment with a biological agent for this condition; OR Patient must have received no PBS-subsidised treatment with a biological agent for at least 5 years if they have previously received PBS-subsidised treatment with a biological agent 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 16 weeks of treatment under this restriction.
Treatment phase:	Continuing treatment
Clinical criteria:	Patient must have a documented history of severe active psoriatic arthritis AND Patient must have received this drug as their most recent course of PBS-subsidised treatment with a biological agent for this condition in the current Treatment Cycle AND Patient must demonstrate, at the time of application, an adequate response to treatment with this drug AND Patient must not receive more than 24 weeks of treatment per continuing treatment course authorised under this restriction.

[#] requested published price to align with the current published price for plaque psoriasis; the submission calculated an effective price of \$[REDACTED] based on a cost-minimisation analysis to the published price of SEC but noted that the effective price of SEC was unknown; a special pricing arrangement for ixekizumab was requested.

Source: Table 1.4.1, p25 of the submission.

- 2.2 The ESC noted that some PsA patients with coexisting psoriasis could be accessing PBS subsidized ixekizumab therapy via the current plaque psoriasis listing. The ESC considered that a reasonable proportion of PsA patients with psoriasis may already be treated, so the proportion of current patients who would require the initial higher dosing within this listing is unclear.
- 2.3 The PBAC recommended that reference to coexistent psoriasis should be removed from the PBS restriction for ixekizumab in PsA. The PBAC considered that no data was presented in the submission which demonstrated improved PsA or psoriasis outcomes between the two dosing regimens. The PBAC recommended that ixekizumab for PsA should be subsidised at the following dosage regimen; 160mg at week 0, then 80mg every 4 weeks thereafter. The maximum quantities and repeats should be amended to align with the recommended dosage regimen.

- 2.4 A special pricing arrangement was proposed. The Sponsor requested the published DPMQ of ixekizumab for PsA align with the current published DPMQ of ixekizumab for plaque psoriasis (\$3,409.52), and an effective price based on a cost-minimisation analysis to secukinumab. No other details of the special pricing arrangement were provided.

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

3 Background

Registration status

- 3.1 The submission was made under TGA/PBAC Parallel Process. At the time of PBAC consideration, the ACM outcome was available and ixekizumab was registered on the ARTG for following PsA indications;
- the treatment of active psoriatic arthritis in adult patients who have responded inadequately, or who are intolerant, to previous DMARD therapy; and
 - may be used as monotherapy or in combination with a conventional DMARD (e.g. methotrexate)
- 3.2 The TGA delegate considered the efficacy and safety of ixekizumab at the dose requested to be satisfactorily established for the treatment of active psoriatic arthritis (PsA) in adults. Specifically, the delegate requested advice from ACM relating to the appropriateness of the proposed dosing regimens for patients with co-existent psoriatic arthritis and moderate to severe plaque psoriasis. The ACM noted that there were no data in the PsA pivotal phase 3 studies (RHAB, RHBE) in patients with coexistent PsA and moderate-to-severe plaque psoriasis treated with the proposed regimen. However, the committee was of the view that the current dosage regimen for moderate to severe plaque psoriasis is appropriate for patients with co-existing conditions.
- 3.3 Ixekizumab is TGA registered for moderate-severe plaque psoriasis and listed on the PBS for the treatment of severe chronic plaque psoriasis.

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

4 Population and disease

- 4.1 PsA is an inflammatory joint disease associated with psoriasis. It is an irreversible, progressive and heterogeneous disease which can involve the peripheral joints (arthritis), axial skeleton (spondylitis), insertion of tendons and ligaments into bone (enthesitis), inflammation of whole digits (dactylitis), skin and nails. Joint damage can lead to marked disability and reduced quality of life.

- 4.2 Ixekizumab is a humanised immunoglobulin G subclass 4 (IgG4) monoclonal antibody that binds with high affinity to IL-17A, a pro-inflammatory cytokine. Inhibition of the IL-17A receptor prevents the release of pro-inflammatory cytokines, chemokines and mediators of tissue damage, which contribute to the pathogenesis in a number of autoimmune and inflammatory diseases including PsA.
- 4.3 Ixekizumab would become one of eight bDMARDs (and the second IL-17 inhibitor) listed on the PBS for patients with severe active PsA who have failed to achieve an adequate response to non-biologic DMARDs.

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

5 Comparator

- 5.1 Based on a similar mechanism of action, the submission nominated secukinumab as the main comparator. The submission also nominated adalimumab, certolizumab pegol and ustekinumab as supplementary comparators, and acknowledged that ixekizumab would also substitute for etanercept, infliximab and golimumab. The ESC considered that any of the biologic agents on the PBS for PsA may be replaced and hence be a relevant comparator.
- 5.2 The Pre-Sub-Committee Response (PSCR) noted benefits in terms of skin response to justify a cost-minimisation analysis versus secukinumab as opposed to other bDMARDs. However the PBAC previously recommended secukinumab on a cost-minimisation basis to the lowest priced bDMARD at the time irrespective of improved skin response.
- 5.3 The ESC noted that if treatment with ixekizumab were substantially more costly than any of the relevant comparators, the PBAC could only recommend listing of ixekizumab if it was satisfied that ixekizumab provides, for some patients, a significant improvement in efficacy or reduction of toxicity over the alternative therapy or therapies (National Health Act 1953, Section 101(3B)). The PBAC noted that no evidence was presented in the submission to support a claim of superiority of ixekizumab compared to any of the currently listed bDMARDs.

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 (3), health care professionals (1) and organisations (2) via the Consumer Comments facility on the

PBS website. The comments described a range of benefits of treatment with ixekizumab including the importance of choice between biological agents for the treatment of autoimmune conditions.

Clinical trials

- 6.3 The submission was based on nine placebo-controlled trials comparing ixekizumab, secukinumab, adalimumab, certolizumab pegol or ustekinumab to placebo. Details of the trials presented in the submission are provided in the table below.
- 6.4 For comparison with adalimumab, the submission also relied on direct evidence reported in SPIRIT 1. That trial included an active-control arm using adalimumab but was not powered to test equivalence or non-inferiority of ixekizumab and adalimumab.

Table 2: Trials and associated reports presented in the submission

Trial ID	Protocol title/ Publication title	Publication citation
Ixekizumab versus adalimumab or placebo		
SPIRIT 1	A Multicenter, Randomized, Double-Blind, Active and Placebo-Controlled 24-Week Study Followed by Long-Term Evaluation of Efficacy and Safety of Ixekizumab (LY2439821) in Biologic Disease-Modifying Antirheumatic Drug-Naïve Patients with Active Psoriatic Arthritis. Mease P, van der Heijde D, Ritchlin C, <i>et al.</i> Ixekizumab, an interleukin-17A specific monoclonal antibody, for the treatment of biologic-naïve patients with active psoriatic arthritis: results from the 24-week randomised, double-blind, placebo-controlled and active (adalimumab)-controlled period of the phase III trial SPIRIT-P1.	Clinical Study Report for I1F-MC-RHAP (Amended). August 2016. <i>Annals of the Rheumatic Diseases</i> . 2017. 76:79-87.
SPIRIT 2	A Multicenter, Randomized, Double-Blind, Placebo Controlled 24-Week Study Followed by Long-Term Evaluation of Efficacy and Safety of Ixekizumab (LY2439821) in Biologic Disease-Modifying Antirheumatic Drug-Experienced Patients with Active Psoriatic Arthritis. Nash P, Kirkham B, Okada M, <i>et al.</i> (2017) Ixekizumab for the treatment of patients with active psoriatic arthritis and an inadequate response to tumour necrosis factor inhibitors: results from the 24-week randomised, double-blind, placebo-controlled period of the SPIRIT-P2 phase 3 trial.	Clinical Study Report for I1F-MC-RHAP. December 2016. <i>The Lancet</i> . 2017. 389:2317-27.
Secukinumab versus placebo		
FUTURE 2	McInnes IB, Mease PJ, Kirkham B, <i>et al.</i> 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):1137-46.
Adalimumab versus placebo		
ADEPT	Mease PJ, Gladman DD, Ritchlin C, <i>et al.</i> Adalimumab for the treatment of patients with moderately to severely active psoriatic arthritis: results of a double-blind, randomised, placebo controlled trial.	<i>Arthritis & Rheumatism</i> . 2005. 52(10):3279-89
Genovese 2007	Genovese MC, Mease PJ, Thomson GTD, <i>et al.</i> Safety and efficacy of adalimumab in treatment of patients with psoriatic arthritis who had failed disease modifying antirheumatic drug therapy.	<i>Journal of Rheumatology</i> . 2007. 34(5):1040-50. [Erratum appears in <i>Journal of Rheumatology</i> 2007. 34(6):1439]
OPAL Broaden	Mease P, Hall S, FitzGerald O, <i>et al.</i> Tofacitinib or Adalimumab versus Placebo for Psoriatic Arthritis.	<i>The New England Journal of Medicine</i> . 2017. 377:1537-50.
Certolizumab pegol versus placebo		
RAPID-PsA	Mease PJ, Fleischmann R, Deodhar AA, <i>et al.</i> 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.
Ustekinumab versus placebo		
PSUMMIT 1	McInnes IB, Kavanaugh A, Gottlieb AB, <i>et al.</i> 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>The Lancet</i> . 2013. 382(9894):780-9.
PSUMMIT 2	Ritchlin C, Rahman P, Kavanaugh A, <i>et al.</i> 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 anti-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 the Rheumatic Diseases</i> . 2014. 73(6):990-9.

Note: Table presents the main publication of the identified trials only.

Source: Table 2(a).2.1, pp65-66 of the submission; Table 2(c).2-1, pp36-37 of Attachment 10 of submission; Table 2(d).2-1, pp4-5 of Attachment 11 of submission; Table 2(e).2-1, pp4-5 of Attachment 12 of submission;

- 6.5 A recently published trial (FUTURE 3¹) that compared secukinumab (auto-injector) to placebo in patients with PsA was identified during the evaluation, indicating a difference in American College of Rheumatology 50% improvement criteria (ACR50) between secukinumab 150mg and 300mg dosages. This would contravene data previously seen by the PBAC (FUTURE 2) that indicated no dose response relationship for joint response. Data from the trial was not able to be included in the commentary since exact values of the relevant outcomes (ACR50 and ACR20 at Week 12) were not reported in the publication.
- 6.6 The key features of the direct randomised trials are summarised in the table below. Only data from relevant treatment arms were included; one trial (OPAL Broaden) was designed to demonstrate superiority of an irrelevant comparator (tofacitinib) to placebo and also included a relevant comparator (adalimumab) as an active control, whereas three trials (PSUMMIT 1, PSUMMIT 2, FUTURE 2) randomised patients to active doses not approved in the Australian setting.

¹ Nash P, Mease P, McInnes I, et al. Efficacy and safety of secukinumab administration by autoinjector in patients with psoriatic arthritis: results from a randomised, placebo-controlled trial (FUTURE 3). *Arthritis Research and Therapy*. 2018. (https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5856314/pdf/13075_2018_Article_1551.pdf)

Table 3: Key features of the included evidence

Trial	N	Design / duration	Relevant comparison	Risk of bias	Patient population	Key outcomes
Ixekizumab versus adalimumab or placebo						
SPIRIT 1	417	Phase 3, MC, R, DB, DD for 24wks; ADA and PBO crossover or active dose escalation at wk16 if 'non-responder' ^a ; PBO crossover at wk24 for responders; dose-blind from 24-264wks;	IXE 160mg wk0, 80mg Q4W; IXE 160mg wk0, 80mg Q2W; ADA 40mg Q2W; vs PBO	Low	Active PsA, TNF- α naïve	1°: ACR20 wk24; 2°: ACR50
SPIRIT 2	363	Phase 3, MC, R, DB for 24wks; PBO crossover at wk16 if 'non-responder' ^a ; PBO crossover at wk24 for responders; dose-blind from 24-156wks;	IXE 160mg wk0, 80mg Q4W; IXE 160mg wk0, 80mg Q2W; vs PBO	Low	Active PsA, TNF- α experienced	1°: ACR20 wk24; 2°: ACR50
Secukinumab versus placebo						
FUTURE 2	298 ^b	Phase 3, MC, R, DB for 24wks; PBO crossover at wk16 if 'non-responder' ^c , or wk24 for responders; OL from 24-256wks.	SEC 150mg or 300mg wk0, 1, 2, 3, 4, Q4W; vs PBO	Low	Active PsA	1°: ACR20 wk24; 2°: ACR50
Adalimumab versus placebo						
ADEPT	313	Phase 3, MC, R, DB for 24 wks. OL from 12-120wks. Rescue meds after Wk 12 ^d .	ADA 40 mg Q2W; vs PBO	Low	Active PsA, TNF- α naïve	1°: ACR20 Wk 12 & Δ mTSS Wk 24, 2°: ACR50
Genovese 2007	100	Phase 3, MC, R, DB for 12 wks. OL from 12-24wks.	ADA 40 mg Q2W; vs PBO	Low	Active PsA, TNF- α naïve	1°: ACR20 Wk 12, 2°: ACR 50
OPAL Broaden	211 ^b	Phase 3, MC, R, DB, DD for 52 wks; PBO crossover at Wk12.	ADA 40 mg Q2W; vs PBO	Low	Active PsA, TNF- α naïve	1°: ACR20 Wk12 & Δ HAQ-DI Wk12, 2°: ACR 50
Certolizumab versus placebo						
RAPID-PsA	409	Phase 3, MC, R, DB for 24wks; PBO crossover at wk16 if 'non-responder' ^e , or wk24 for responders; dose-blind from 24-48wks; OL from 48-216wks.	CZP 400mg SC wk0, 2, 4, 200mg Q2W or 400mg Q4W; vs PBO	Low	Active PsA	1°: ACR20 wk12 & Δ mTSS wk24; 2°: ACR50
Ustekinumab versus placebo						
PSUMMIT 1	411 ^b	Phase 3, MC, R, DB for 24wks; PBO crossover or active dose escalation at wk16 if 'non-responder' ^f , or wk24 for PBO responders; OL from 24-108wks.	UST 45mg SC wk0, 4, Q12W; vs PBO	Low	Active PsA, TNF- α naïve	1°: ACR20 wk24; 2°: ACR50
PSUMMIT 2	207 ^b	Phase 3, MC, R, DB for 24wks; PBO crossover or active dose escalation at wk16 if 'non-responder' ^f , or wk24 for PBO responders; OL from 24-60wks.	UST 45mg SC wk0, 4, Q12W; vs PBO	Low	Active PsA	1°: ACR20 wk24; 2°: ACR50

Abbreviations: OL=open label; PBO = placebo; R = randomised; DB = double blind; DD = double dummy; MC = multicentre; mTSS=modified total sharp score; ACR20/50 = \geq 20% /50% improvement on the American College of Rheumatology Criteria; Δ =change; HAQ-DI = health assessment questionnaire disability index; ADA = adalimumab; CZP = certolizumab pegol; UST = ustekinumab; SEC = secukinumab; IXE = ixekizumab; Q2W = every 2 weeks; Q4W = every 4 weeks; Q12W = every 12 weeks; 1°=primary outcome, 2°=secondary outcomes

^a patients on ADA or PBO with <20% improvement in swollen and tender joint count at week 16 from baseline were re-randomised to IXE 80mg q2w or q4w; In SPIRIT 1, non-responders on IXE q4w at Wk16 commenced IXE q2w.

^b excluding patients randomised to arms which were not relevant to the submission.

^c patients on PBO with <20% improvement in swollen and tender joint count at week 16 from baseline were re-randomised to SEC 300mg or 150mg

^d <20% decrease in both swollen and tender joint counts on two consecutive visits – rescued with corticosteroids or DMARDs.

^e patients on PBO with <10% improvement in swollen and tender joint count at week 16 from baseline were re-randomised to CZP 200mg q2w or 400mg q4w after the loading doses; all PBO patients were re-randomised at week 24.

^f patients on PBO or UST 45mg with < 5% improvement in swollen and tender joint count at week 16 from baseline were initiated on UST 45mg and UST 90mg respectively; all PBO patients commenced UST 45mg at week 24.

Source: compiled during the evaluation from the trial publications

- 6.7 There were much higher rates of discontinuation for patients treated with placebo compared with active treatment across the trials. However, the overall risk of bias was considered low as the potential for un-blinding related to discontinuation would likely affect all of the included trials equally.
- 6.8 There were differences in trial design that may bias indirect comparisons after Week 16, particularly due to differences in placebo crossover and active dose escalation for non-responders (<5%, <10% or <20% improvement in swollen joints). However, comparisons at earlier time points should not be affected by these differences.
- 6.9 While all trials enrolled adults with PsA with active disease and either active psoriasis or a history of psoriasis, there were differences in diagnostic criteria (minor) and prior use of NSAIDs, DMARDs or bDMARDs. There were also differences with the eligibility criteria on the PBS, which requires more severe disease with higher joint counts.

Comparative effectiveness

- 6.10 Response to bDMARDs on the PBS is assessed using a combination of the American College of Rheumatology 20% and 50% improvement criteria (ACR20 and ACR50, respectively). The PBAC had previously considered that ACR50 was more relevant than ACR20 because it better reflected the current PBS criteria for response to initial therapy (see Ustekinumab PSD, November 2014).
- 6.11 Assessment of response to initial therapy must be made no later than 4 weeks before the end of the initial course of treatment, which corresponds to about 12 weeks for ixekizumab, adalimumab, secukinumab and certolizumab pegol (~14/16 weeks), and 24 weeks for ustekinumab. The PBAC had considered Week 12 data in past considerations of adalimumab, secukinumab and certolizumab pegol, and Week 24 data for ustekinumab (see Certolizumab PSD, November 2014; Ustekinumab PSD, November 2014; Secukinumab PSD, March 2016).
- 6.12 The submission presented indirect comparisons for ACR50 and ACR20, summarised in Tables 4 and 5 respectively at Week 12, and in Attachment 2.5-2.6 of the commentary at Week 24. Data from two adalimumab trials (ADEPT, Genovese 2007) were excluded due to concern over differences in placebo response rates (see paragraph 6.14 below), and the indirect comparisons were limited to the following doses and populations:
- Ixekizumab Q4W versus secukinumab 150mg/300mg (ITT);
 - Ixekizumab Q2W versus secukinumab 300mg (ITT);
 - Ixekizumab Q4W versus adalimumab (TNF α naïve);

- Ixekizumab Q4W versus certolizumab pegol (TNF α naïve & experienced);
 - Ixekizumab Q4W versus ustekinumab (TNF α naïve & experienced).
- 6.13 The trial results demonstrated that all of the bDMARDs were more effective than placebo at producing a response at Week 12 (and Week 24 where applicable). Although SPIRIT 1 and SPIRIT 2 were not designed/powerd to test equivalence/non-inferiority of the active therapies, the response rates of ixekizumab Q2W and ixekizumab Q4W were similar. In SPIRIT 1, results numerically favoured ixekizumab versus adalimumab.
- 6.14 Non-inferiority margins for ACR50 and ACR20 were not nominated in the submission. While not expressly endorsed, the PBAC has considered non-inferiority margins for ACR50 and ACR20 in previous considerations of bDMARDs for PsA. Based on the secukinumab PSD (March 2016), for non-inferiority to be demonstrated, there must not be a statistically significant difference in the indirect comparisons, and the lower bound of the 95% confidence interval (CI) around the relative risk (RR) must not be less than: 0.29 for ACR50, and 0.46 for ACR20.
- 6.15 The indirect comparisons did not show a significant difference in ACR50 or ACR20 response at Week 12 (or Week 24) between ixekizumab and the nominated comparisons. Based on thresholds of 0.29 for ACR50 and 0.46 for ACR20 (see above), non-inferiority was established between ixekizumab and all of the comparisons presented by the submission with the exception of those in the TNF α experienced population. The relatively small numbers in the TNF α experienced subgroup contributed to wide confidence intervals (that cross the thresholds), making interpretation based on the non-inferiority margins problematic.
- 6.16 Several issues were identified with the submission's methodology used for selecting data, doses and populations in the indirect comparisons; these are pointed out below, but ultimately conclusions from the indirect comparisons were reasonably robust.
- The decision to exclude data from the adalimumab trials may not have been completely reasonable given placebo response rates of ACR50 at Week 12 were comparable, and the PBAC had considered clinical data from ADEPT and Genovese 2007 in previous decisions of other bDMARDs;
 - The partitioning of ixekizumab data (and focus on the Q4W arm) to align with recommended dosing for patients with and without plaque psoriasis was not reasonable and poorly justified. First, the SPIRIT trials did not assign doses based on plaque psoriasis; therefore, both dose regimens in the trials included patients with and without plaque psoriasis. Second, there was no dose response relationship between the two doses of ixekizumab for ACR response. The different doses were recommended based on post-hoc analysis of PASI response. Third, both arms/doses (i.e. Q2W and Q4W) are relevant to the Australian setting. Finally, it is inconsistent with both the submission's approach for pooling

the two doses of secukinumab (150mg and 300mg) based on a similar set of circumstances and was previously considered by the PBAC.

- Comparison of ixekizumab and secukinumab in the ITT population was justified on the basis that it improved the applicability of the results and increased the precision around the point estimates despite increasing heterogeneity across the population. Whereas, comparisons of ixekizumab with adalimumab, certolizumab pegol and ustekinumab by TNF α experience were justified on the basis that it reduced heterogeneity across the populations despite reducing applicability of results and increasing the imprecision around the point estimates. While there were some differences in terms of the proportions of TNF α naïve across the comparisons (ixekizumab ~46%; secukinumab ~65%; adalimumab 100%; certolizumab pegol ~80%; ustekinumab ~80%), the submission did not adequately justify the reliance on subgroups.
- 6.17 Indirect comparisons across other outcomes (including ACR70, PASI75 and PASI90 at Weeks 12 and 24) presented by the submission are summarised in Attachment 2.5-2.6 of the commentary. The results indicated no statistically significant differences across the majority of outcomes. Based on the direct evidence reported in SPIRIT 1, more patients treated with ixekizumab Q2W and ixekizumab Q4W achieved a PASI75 or PASI90 response at Week 12 or 24 compared with adalimumab.
- 6.18 Overall, it was unclear whether the trials enrolled patients who were sufficiently i) representative of patients who would likely access bDMARDs on the PBS, or ii) similar/exchangeable to support the indirect comparison presented by the submission. However, past PBAC recommendations of bDMARDs for PsA were based on the same or a similar set of trials with similar issues.

Table 4: ACR50 response in the trials of ixekizumab, secukinumab, adalimumab, certolizumab pegol and ustekinumab at Week 12, and the indirect comparisons presented by the submissions

Trial	Drug n/N (%)	Control n/N (%)	RR (95%CI)	OR (95%CI)	RD (95%CI)		NNT (95%CI)
IXE vs ADA (12 weeks)							
SPIRIT 1 Q2W	41/103 (40)	30/101 (30)	1.34 (0.91,1.96)	1.57 (0.88,2.80)	0.10 (-0.03,0.23)		NA
SPIRIT 1 Q4W	36/107 (34)		1.13 (0.76,1.69)	1.20 (0.67,2.16)	0.04 (-0.09,0.17)		NA
SPIRIT 1 pooled	77/210 (37)		1.23 (0.87,1.75)	1.37 (0.82,2.28)	0.07 (-0.04,0.18)		NA
IXE vs PBO (12 weeks)							
SPIRIT 1 Q2W	41/103 (40)	5/106 (5)	8.44 (3.47,20.51)	13.36(5.01,35.62)	0.35 (0.25,0.45)		3 (2,4)
SPIRIT 1 Q4W	36/107 (34)		7.13 (2.91,17.47)	10.24(3.83,27.38)	0.29 (0.19,0.39)		3 (3,5)
SPIRIT 1 pooled	77/210 (37)		7.77 (4.66,12.95)	11.70(6.69,20.45)	0.32 (0.27,0.37)		3 (3,4)
SPIRIT 2 Q2W	41/123 (33)	4/118 (3)	9.83 (3.64,26.60)	14.25(4.91,41.34)	0.30 (0.21,0.39)		3 (3,5)
SPIRIT 2 Q4W	38/122 (31)		9.19 (3.38,24.94)	12.89(4.43,37.52)	0.28 (0.19,0.37)		3 (3,5)
SPIRIT 2 pooled	79/245 (32)		9.51 (3.57,25.35)	13.56(4.83,38.08)	0.29 (0.22,0.36)		3 (3,5)
Meta-analysis Q2W	82/226 (36)	9/224 (4)	9.03 (4.66,17.52)	13.76(6.69,28.31)	0.32 (0.25,0.39)		3 (3,4)
Meta-analysis Q4W	74/229 (32)		7.99 (4.10,15.56)	11.38(5.52,23.47)	0.28 (0.22,0.35)		4 (3,5)
Meta-analysis pooled	156/455 (34)		8.50 (4.43,16.32)	12.51(6.24,25.07)	0.30 (0.25,0.35)		3 (3,4)
SEC vs PBO (12 weeks)							
FUTURE 2 150mg	32/100 (32)	5/98 (5)	6.27 (2.55,15.43)	8.75 (3.24,23.63)	0.27 (0.17,0.37)		4 (3,6)
FUTURE 2 300mg	30/100 (30)		5.88 (2.38,14.53)	7.97 (2.94,21.59)	0.25 (0.15,0.35)		4 (3,7)
Pooled	62/200 (31)		6.08 (2.52,14.63)	8.36 (3.24,21.57)	0.26 (0.18,0.34)		4 (3,6)
ADA vs PBO (12 weeks)							
ADEPT	55/151 (36)	7/162 (4)	8.43 (3.96,17.93)	12.69(5.55,29.00)	0.32 (0.24,0.40)		3 (3,4)
Genovese 2007	13/51 (26)	1/49 (2)	12.49(1.70,91.90)	16.42(2.06,131.18)	0.23 (0.11,0.36)		4 (3,9)
OPAL Broaden	35/106 (33)	10/105 (10)	3.47 (1.81,6.63)	4.68 (2.17,10.09)	0.23 (0.13,0.34)		4 (3,8)
Meta-analysis	103/308 (33)	18/316 (6)	5.85 (2.73,12.52)	8.35 (3.75,18.60)	0.28 (0.22,0.34)		4 (3,5)
CZP vs PBO (12 weeks)							
RAPID-PsA 200mg	50/138 (36)	15/136 (11)	3.29 (1.94,5.56)	4.58 (2.42,8.68)	0.25 (0.16,0.35)		4 (3,6)
RAPID-PsA 400mg	44/135 (33)		2.96 (1.73,5.05)	3.90 (2.04,7.44)	0.22 (0.12,0.31)		5 (3,8)
Pooled, ITT	94/273 (34)		3.12 (1.88,5.17)	4.24 (2.34,7.66)	0.23 (0.16,0.31)		4 (3,6)
Pooled, TNFa naïve	74/219 (34)	14/110 (13)	2.65 (1.57,4.48)	3.50 (1.87,6.55)	0.21 (0.12,0.30)		5 (3,8)
Pooled, TNFa exp.	20/54 (37)	1/26 (4)	9.63 (1.31,67.89)	14.71(1.85,116.97)	0.33 (0.18,0.48)		3 (2,6)
UST vs PBO (12 weeks)							
PSUMMIT 1 45mg	38/205 (19)	11/206 (5)	3.47 (1.83,6.60)	4.03 (2.00,8.14)	0.13 (0.07,0.19)		8 (4,14)
Indirect comparisons, ITT (Wk 12)							
IXE Q4W (meta) v SEC (pooled)			1.31 (0.44,3.96)	1.36 (0.41,4.49)	0.02 (-0.08,0.12)		NA
IXE Q2W (meta) v SEC 300mg			1.54 (0.50,4.71)	1.73 (0.50,5.91)	0.07 (-0.05,0.19)		NA
Indirect comparisons, TNFa naïve (Wk 12)							
IXE Q4W (SPIRIT 1) v ADA (OPAL Broaden)			2.06 (0.68, 6.21)	2.19 (0.63,7.62)	0.06 (-0.09,0.21)		NA
IXE Q4W (SPIRIT 1) v CZP (pooled TNFa naïve)			2.69 (0.95,7.60)	2.93 (0.91,9.39)	0.08 (-0.05,0.21)		NA
IXE Q4W (SPIRIT 1) v UST (PSUMMIT 1)			2.06 (0.68,6.19)	2.54 (0.76,8.51)	0.16 (0.04,0.28)		6 (4,25)
Indirect comparisons, TNFa exp. (Wk 12)							
IXE Q4W (SPIRIT 2) v CZP (pooled TNFa exp.)			0.95 (0.10,8.72)	0.88 (0.09,9.03)	-0.05(-0.22,0.12)		NA

Abbreviations: ACR50 = ≥50% improvement on the American College of Rheumatology Criteria; ADA = adalimumab; CZP = certolizumab pegol; UST = ustekinumab; SEC = secukinumab; IXE = ixekizumab; PBO = placebo Q2W = every 2 weeks; Q4W = every 4 weeks; Source: Table 2(a).6.20, p134 of the submission; Table 2c.6-4, p59 of Attachment 10 of the submission; Table 2(d).6-5, p57 of Attachment 11 of the submission; Table 2(e).6-7, p60 of Attachment 12 of the submission;

Table 5: ACR20 response in the trials of ixekizumab, secukinumab, adalimumab, certolizumab pegol and ustekinumab at Week 12, and the indirect comparisons presented by the submission

Trial	Drug n/N (%)	Control n/N (%)	RR (95%CI)	OR (95%CI)	RD (95%CI)		NNT (95%CI)
IXE vs ADA (12 weeks)							
SPIRIT 1 Q2W	62/103 (60)	52/101 (52)	1.17 (0.91,1.50)	1.42 (0.82,2.48)	0.09(-0.05,0.22)	+	NA
SPIRIT 1 Q4W	61/107 (57)		1.11 (0.86,1.42)	1.25 (0.72,2.16)	0.06(-0.08,0.19)	+	NA
SPIRIT 1 pooled	123/210 (59)		1.14 (0.91,1.42)	1.33 (0.83,2.15)	0.07(-0.05,0.19)	+	NA
IXE vs PBO (12 weeks)							
SPIRIT 1 Q2W	62/103 (60)	33/106 (31)	1.93 (1.40,2.67)	3.35 (1.89,5.91)	0.29 (0.16,0.42)	+	3 (2,6)
SPIRIT 1 Q4W	61/107 (57)		1.83 (1.32,2.54)	2.93 (1.67,5.14)	0.26 (0.13,0.39)	+	4 (3,8)
SPIRIT 1 pooled	123/210 (59)		1.88 (1.39,2.55)	3.13 (1.91,5.13)	0.27 (0.16,0.38)	+	4 (3,6)
SPIRIT 2 Q2W	59/123 (48)	26/118 (22)	2.18 (1.48,3.20)	3.26 (1.86,5.72)	0.26 (0.14,0.38)	+	4 (3,7)
SPIRIT 2 Q4W	61/122 (50)		2.27 (1.55,3.33)	3.54 (2.02,6.20)	0.28 (0.16,0.40)	+	4 (3,6)
SPIRIT 2 pooled	120/245 (49)		2.22 (1.55,3.19)	3.40 (2.06,5.61)	0.27 (0.17,0.37)	+	4 (3,6)
Meta-analysis Q2W	121/226 (54)	59/224 (26)	2.03 (1.58,2.60)	3.30 (2.21,4.93)	0.27 (0.19,0.36)	+	4 (3,5)
Meta-analysis Q4W	122/229 (53)		2.00 (1.56,2.57)	3.22 (2.17,4.79)	0.27 (0.18,0.36)	+	4 (3,6)
Meta-analysis pooled	243/455 (53)		2.02 (1.60,2.55)	3.26 (2.29,4.63)	0.27 (0.20,0.34)	+	4 (3,5)
SEC vs PBO (12 weeks)							
FUTURE 2 150mg	56/100 (56)	25/98 (26)	2.20 (1.50,3.21)	3.72 (2.04,6.78)	0.30 (0.17,0.43)	+	3 (2,6)
FUTURE 2 300mg	57/100 (57)		2.23 (1.53,3.26)	3.87 (2.12,7.07)	0.31 (0.19,0.44)	+	3 (2,5)
Pooled	113/200 (57)		2.21 (1.55,3.17)	3.79 (2.22,6.46)	0.31 (0.20,0.42)	+	3 (2,5)
ADA vs PBO (12 weeks)							
ADEPT	88/151 (58)	23/162(14)	4.10 (2.75,6.14)	8.44(4.88,14.59)	0.44 (0.35,0.54)	+	2 (2,3)
Genovese 2007	20/51 (39)	8/49 (16)	2.40 (1.17,4.94)	3.31 (1.29,8.49)	0.23 (0.06,0.40)	+	4 (3,17)
OPAL Broaden	55/106 (52)	35/105 (33)	1.56 (1.12,2.16)	2.16 (1.24,3.76)	0.19 (0.05,0.32)	+	5 (3,20)
Meta-analysis	163/308 (53)	66/316 (21)	2.47 (1.24,4.95)	3.97(1.57,10.06)	0.29 (0.11,0.47)	+	3 (2,9)
CZP vs PBO (12 weeks)							
RAPID-PsA 200mg	80/138 (58)	33/136 (24)	2.39 (1.72,3.32)	4.31 (2.57,7.22)	0.34 (0.23,0.45)	+	3 (2,4)
RAPID-PsA 400mg	70/135 (52)		2.14 (1.52,3.00)	3.36 (2.00,5.64)	0.28 (0.16,0.39)	+	4 (3,6)
Pooled, ITT	150/273 (55)		2.26 (1.65,3.11)	3.81 (2.41,6.02)	0.31 (0.21,0.40)	+	3 (3,5)
Pooled, TNFa naïve	121/219 (55)	29/110 (26)	2.10 (1.50,2.93)	3.45 (2.09,5.69)	0.29 (0.18,0.39)	+	3 (3,6)
Pooled, TNFa exp.	30/54 (56)	4/26 (15)	3.61 (1.42,9.18)	6.88(2.09,22.67)	0.40 (0.21,0.59)	+	3 (2,5)
UST vs PBO (12 weeks)							
PSUMMIT 1 45mg	85/205 (42)	44/206 (21)	1.94 (1.43,2.64)	2.61 (1.69,4.02)	0.20 (0.11,0.29)	+	5 (3,9)
PSUMMIT 2 45mg	41/103 (40)	18/104 (17)	2.30 (1.42,3.73)	3.16 (1.66,6.01)	0.22 (0.11,0.34)	+	5 (3,9)
TNFa naïve	17/43 (40)	8/42 (19)	2.08 (1.01,4.28)	2.78 (1.04,7.43)	0.20 (0.02,0.39)	+	5 (3,50)
TNFa exp.	24/60 (40)	10/62 (16)	2.48 (1.30,4.73)	3.47 (1.48,8.12)	0.24 (0.08,0.39)	+	4 (3,13)
Meta-analysis, ITT	126/308 (41)	65/310 (21)	2.04 (1.57,2.64)	2.77 (1.93,3.97)	0.21 (0.14,0.28)	+	5 (4,7)
Meta-analysis, TNF naïve	102/248 (41)	52/248 (21)	1.96 (1.48,2.60)	2.64 (1.77,3.92)	0.20 (0.12,0.28)	+	5 (4,8)
Indirect comparisons, ITT (Wk12)							
IXE Q4W (meta) v SEC (pooled)			0.91 (0.59,1.40)	0.85 (0.44,1.65)	-0.04(-0.18,0.10)	+	NA
IXE Q2W (meta) v SEC 300mg			0.91 (0.58,1.43)	0.85 (0.41,1.76)	-0.04(-0.19,0.11)	+	NA
Indirect comparisons, TNFa naïve (Wk12)							
IXE Q4W (SPIRIT 1) v ADA (OPAL Broaden)			1.17 (0.74,1.87)	1.36 (0.62,2.99)	0.07(-0.12,0.26)	+	NA
IXE Q4W (SPIRIT 1) v CZP (pooled TNFa naïve)			0.87 (0.55,1.39)	0.85 (0.40,1.80)	-0.03(-0.20,0.14)	+	NA
IXE Q4W (SPIRIT 1) v UST (meta, TNFa naïve)			0.93 (0.61,1.44)	1.11 (0.56,2.21)	0.06(-0.09,0.21)	+	NA
Indirect comparisons, TNFa exp. (Wk12)							
IXE Q4W (SPIRIT 2) v CZP (pooled TNFa exp.)			0.63 (0.23,1.72)	0.52 (0.14,1.92)	-0.12(-0.34,0.10)	+	NA
IXE Q4W (SPIRIT 2) v UST (PSUMMIT 2, TNFa exp)			0.92 (0.43,1.94)	1.02 (0.37,2.83)	0.04 (-0.16,0.24)	+	NA

Abbreviations: ACR20 = ≥20% improvement on the American College of Rheumatology Criteria; ADA = adalimumab; CZP = certolizumab pegol; UST = ustekinumab; SEC = secukinumab; IXE = ixekizumab; PBO = placebo Q2W = every 2 weeks; Q4W = every 4 weeks; Source: Table2(a).6.18, p132 of the submission; Table 2(c).6-3, p58 of Attachment 10 of the submission; Table 2(d).6-3, p55 of Attachment 11 of the submission; Table 2(e).6-5, p58 of Attachment 12 of the submission;

Comparative harms

- 6.19 More patients reported a treatment emergent adverse event on ixekizumab compared to placebo in SPIRIT 1 ($p < 0.05$) but not in SPIRIT 2 ($p = 0.587$). Most adverse events were mild to moderate in severity. The rate of infections was similar across the arms in SPIRIT 1 but was more common for ixekizumab than placebo in SPIRIT 2; injection site reactions were more common for ixekizumab than adalimumab in SPIRIT 1 and placebo in both trials.
- 6.20 The submission presented indirect comparisons of serious AEs and discontinuation due to AEs for ixekizumab, secukinumab, certolizumab pegol and ustekinumab, and a direct comparison of ixekizumab versus adalimumab (in SPIRIT 1), summarised in Table 6. Ixekizumab was associated with a similar percentage of adverse events compared to secukinumab, adalimumab, certolizumab pegol and ustekinumab.

Table 6: Indirect comparison of safety outcomes ixekizumab, secukinumab, certolizumab pegol and ustekinumab presented by the submission

	RR (95%CI)	OR (95%CI)	RD (95%CI)
Serious AE			
IXE Q4W (SPIRIT 1), Wk16 vs SEC (150mg), Wk16	4.04 (0.22,74.55)	4.17 (0.21,80.85)	0.03 (-0.03,0.08)
IXE Q4W (SPIRIT 2), Wk16 vs SEC (300mg), Wk16	0.26 (0.02,2.89)	0.25 (0.02,2.95)	-0.04 (-0.10,0.02)
IXE Q4W (SPIRIT 1), Wk16 vs ADA (SPIRIT 1), Wk16	1.26 (0.29,5.49)	1.27 (0.28,5.81)	0.01 (-0.04,0.06)
IXE Q4W (meta-analysis), Wk24 vs CZP (pooled), Wk24	0.82 (0.16,4.23)	0.80 (0.15,4.42)	-0.02 (-0.09,0.04)
IXE Q4W (meta-analysis), Wk16 vs UST (meta-analysis), Wk16	2.80 (0.19,40.41)	2.88 (0.19,43.72)	0.02 (-0.03,0.08)
Discontinuation due to AE			
IXE Q4W (SPIRIT 1), Wk16 vs SEC (150mg), Wk16	3.54 (0.08,157.7)	3.61 (0.08,167.01)	0.02 (-0.03,0.07)
IXE Q4W (SPIRIT 2), Wk16 vs SEC (300mg), Wk16	0.74 (0.06,8.47)	0.74 (0.06,8.91)	-0.01 (-0.07,0.05)
IXE Q4W (SPIRIT 1), Wk16 vs ADA (SPIRIT 1), Wk16	0.94 (0.06,14.89)	0.94 (0.06,15.29)	0 (-0.03, 0.03)
IXE Q4W (meta-analysis), Wk24 vs CZP (pooled), Wk24	0.34 (0.06,2.07)	0.33 (0.05,2.11)	-0.03 (-0.07,0.02)
IXE Q4W (meta-analysis), Wk16 vs UST (meta-analysis), Wk16	1.77 (0.27,11.43)	1.82 (0.27,12.22)	0.02 (-0.05,0.08)

Abbreviations: ADA = adalimumab; CZP = certolizumab pegol; UST = ustekinumab; SEC = secukinumab; IXE = ixekizumab; PBO = placebo; Q4W = every 4 weeks;

Source: Table 2(a).6.31 and Table 2(a).6.32, pp147-148 of the submission; Table 2(b).6-4, p29 of Attachment 10 of the submission; Table 2(d).6-15 and Table 2(d).6-16, pp68-69 of Attachment 11 of the submission; Table 2(e).6-16 and Table 2(e).6-17, pp69-70 of Attachment 12 of the submission

Benefits/harms

- 6.21 On the basis of direct evidence (SPIRIT 1), ixekizumab appeared to have the same effect as adalimumab in term of improving tender and swollen joints (ACR20 and ACR50), which is a main feature of PsA.
- 6.22 Based on an indirect comparison using placebo as the common comparator, ixekizumab also appears to be no worse than secukinumab, adalimumab, certolizumab pegol and ustekinumab in terms of improving tender and swollen joints (ACR20 and ACR50).
- 6.23 The PBAC had previously considered joint response (defined by ACR20 and ACR50) to be the more important criteria in considering comparative efficacy of bDMARDs in PsA rather than skin responses (defined by PASI75).

- 6.24 The PBAC previously considered secukinumab and ustekinumab to be inferior to adalimumab (see Secukinumab PSD, March 2016 and Ustekinumab PSD, November 2015). In this submission, data from OPAL Broaden (2017) showed a reduced treatment effect for adalimumab versus placebo (compared to previously considered ADEPT (2005) and Genovese (2007)).
- 6.25 On the basis of the direct comparisons between ixekizumab and adalimumab (from the SPIRIT 1 trial), the frequency of adverse effects appears to be comparable although there were more injection site reactions with ixekizumab, per 100 patients treated, 12 more patients treated with ixekizumab will have injection site reactions.

Clinical claim

- 6.26 The submission described ixekizumab to be non-inferior in terms of comparative effectiveness and safety versus the main comparator (secukinumab) and all supplementary comparators (adalimumab, certolizumab pegol and ustekinumab). Based on the evidence presented in the submission and additional sensitivity analyses conducted during the evaluation, the claim appeared to be reasonably supported. The ESC considered the claim of non-inferior efficacy and safety versus secukinumab to be reasonable.

Economic analysis

- 6.27 A cost-minimisation analysis was presented between ixekizumab and secukinumab. The equi-effective doses were based on the recommended maintenance doses ('steady state'), weighted by the proportion of the secukinumab 150mg and 300mg dosing regimens on the PBS: ixekizumab 80mg \equiv secukinumab 276mg. The PBAC considered that secukinumab may not be the appropriate cost comparator for ixekizumab (see paragraph 5.3 above).
- 6.28 The PSCR noted benefits in terms of skin response to justify a cost-minimisation analysis versus secukinumab as opposed to other bDMARDs. The ESC noted that although the evidence supported a benefit in terms of skin response (i.e. PASI) over the supplementary comparators, the PBAC had previously dismissed its relevance in this setting given the availability of bDMARDs for plaque psoriasis. Under Section 101(3B) of the *National Health Act 1953*, the PBAC could only recommend listing of ixekizumab at a higher price to alternative therapies (including supplementary comparators) if it was satisfied that ixekizumab provided, for some patients, a significant improvement in efficacy (for relevant outcomes) or reduction of toxicity. The ESC advised that those criteria were not met based on the evidence presented in the submission.
- 6.29 The submission's approach to estimating the equi-effective doses was not consistent with the methodology previously accepted by the PBAC for other bDMARDs in PsA.
- 6.30 The Therapeutic Relativity Sheets list the approved dosing regimens, including for initiation and maintenance therapy, as being equi-effective. The conclusion of non-

inferiority between ixekizumab and secukinumab at the recommended doses supported that the following doses are equi-effective:

- Ixekizumab 160mg (SC) dosed at Week 0, then 80mg at Week 2, 4, 6, 8, 10, 12 and every four weeks thereafter;
- Ixekizumab 160mg (SC) dosed at Week 0, then 80mg every four weeks thereafter;
- Secukinumab 150mg (SC) dosed at Week 0, 1, 2, 3, 4, then every four weeks thereafter;
- Secukinumab 300mg (SC) dosed at Week 0, 1, 2, 3, 4, then every four weeks thereafter.

6.31 The cost-minimisation analysis was based on the following assumptions:

- Total costs were calculated for 48 weeks of maintenance therapy;
- Only drug costs were included;
- Published DPMQs for secukinumab 150mg (\$804.59) and 300mg (1,586.28) were used;
- Cost for secukinumab was weighted by proportional use of 150mg (16%) and 300mg (84%).

6.32 The submission's approach for the cost-minimisation analysis was not consistent with the methodology previously accepted by the PBAC for bDMARDs in PsA. First, costs should be minimised over a two year time horizon including initiation and maintenance doses. Second, ex-man rather than DPMQ prices should be used. Third, secukinumab 150mg and 300mg were recommended at the same price (see Secukinumab PSD, March 2016).

Drug cost/patient/year: \$ [REDACTED]

6.33 \$ [REDACTED] per year for maintenance therapy without accounting for any special pricing arrangement (assuming 13 injections per year and a DPMQ of \$ [REDACTED] per two injections). Treatment in the first year may be slightly higher given additional injections are required (14 for patients without plaque psoriasis and 17 injections for patients with plaque psoriasis). The drug cost per patient-year (including initiation and maintenance) averaged across the first six years in the financial model was \$ [REDACTED].

Estimated PBS usage & financial implications

6.34 This submission was not considered by DUSC. A market share approach was used to estimate the financial implications of the proposed listing, summarised in Table 7. PBS claims data was used to estimate the number of bDMARD initiations, patient-years on initiation therapy and patient-years on maintenance therapy each month over six years. It was assumed that initiation with ixekizumab would substitute for

initiation with all currently listed bDMARDs, but total patient-years on bDMARDs would be unchanged. The ESC considered that this may be inappropriate if patients who have failed TNF alpha inhibitor therapy go onto achieve a maintained response with the IL17 inhibitors.

Table 7: Estimated use and financial implications

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
Estimation of use and financial impact of the proposed medicine (IXE)						
bDMARD patient-years without IXE						
Initiation-patient years						
Maintenance-patient years						
Total						
bDMARD patient-years with IXE						
Initiation-patient years						
Maintenance-patient years						
Total						
Scripts of IXE						
Initiation						
Maintenance						
Total						
IXE net cost to PBS/RPBS	\$	\$	\$	\$	\$	\$
Estimation of changes in use and financial impact of other medicines (bDMARDs)						
Other bDMARD scripts						
Initiation						
Maintenance						
Total						
Net cost to PBS/RPBS						
ADA	-\$	-\$	-\$	-\$	-\$	-\$
SEC	-\$	-\$	-\$	-\$	-\$	-\$
ETN	-\$	-\$	-\$	-\$	-\$	-\$
GOL	-\$	-\$	-\$	-\$	-\$	-\$
UST	-\$	-\$	-\$	-\$	-\$	-\$
CZP	-\$	-\$	-\$	-\$	-\$	-\$
IFX	-\$	-\$	-\$	-\$	-\$	-\$
Total	-\$	-\$	-\$	-\$	-\$	-\$
Estimated financial implications for the PBS/RPBS or the NIP						
Net cost to PBS/RPBS	\$	\$	\$	\$	\$	\$
Estimated financial implications for the health budget						
Infusions (associated with IFX)						
Net cost to MBS (infusions)	-\$	-\$	-\$	-\$	-\$	-\$
Net cost to health budget	\$	\$	\$	\$	\$	\$

Italics reflect updated values assuming 12-month rolling average for initiation periods (stated base case model assumption)
 Abbreviations: ADA = adalimumab; CZP = certolizumab pegol; UST = ustekinumab; SEC = secukinumab; IXE = ixekizumab; ETN = etanercept; IFX = infliximab; GOL = golimumab
 Source: Tables 4.2.1 to 4.5.3, pp181-191 of the submission.

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

6.35 The model predicted fewer total patient-years of initiation therapy with ixekizumab as it has a shorter initiation period compared to some of the other bDMARDs, and hence more patient-years were spent on maintenance therapy (assumption). The model also predicted fewer scripts overall with ixekizumab given the requested

number of scripts for initiation (assumed 2.5 for five injections) was fewer than with other bDMARDs. However, the analysis did not take account of patients with coexisting moderate-severe plaque psoriasis that require eight injections. The overall impact on the financial estimates was unclear as prices should take account of the required number of scripts.

- 6.36 Overall, the financial estimates presented may not be reliable given they were based on the published prices of bDMARDs rather than the effective prices (after accounting for special pricing arrangements). Given the proposed listing of ixekizumab was based on a cost-minimisation analysis to secukinumab, the net cost to the health budget was expected to be zero (or close to zero depending on the relative substitution of cheaper or costlier alternatives).
- 6.37 The PBAC considered that the market share between bDMARDs available for PsA is uncertain and that the addition of another bDMARD may allow some patients to remain on bDMARDs for longer under the current continuing therapy criteria and therefore the number of patients on treatment at any given time will increase.

Quality Use of Medicines

- 6.38 The Sponsor plans to implement a range of activities to support the quality use of medicines in the treatment of PsA and the appropriate use of ixekizumab in accordance with the proposed PBS listing.

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

7 PBAC Outcome

- 7.1 The PBAC recommended an Authority Required (in writing) listing of ixekizumab on a cost-minimisation basis against the least costly biological disease modifying anti-rheumatic drug (bDMARD) for psoriatic arthritis. In making this recommendation, the PBAC accepted any of the current PBS listed bDMARDs for severe PsA could be an alternative therapy to ixekizumab.
- 7.2 The PBAC noted that seven alternative bDMARDs were listed on the PBS for the treatment of PsA at the time of the July 2018 meeting; specifically: adalimumab, certolizumab pegol, etanercept, golimumab, infliximab, secukinumab and ustekinumab. The PBAC considered that the clinical need for an additional bDMARD was low however the PBAC acknowledged the addition of another drug may be useful to some patients.
- 7.3 The submission described ixekizumab to be non-inferior in terms of comparative effectiveness and safety in severe PsA versus the main comparator (secukinumab) and all supplementary comparators (adalimumab, certolizumab pegol and ustekinumab). Based on the evidence presented in the submission and additional sensitivity analyses conducted during the evaluation, the PBAC considered that the claim appeared to be reasonably supported. No evidence was presented in the

submission to support a claim of superiority of ixekizumab compared to any of the currently listed bDMARDs.

- 7.4 The Pre-PBAC response claimed benefits in terms of skin response to justify a cost-minimisation analysis versus secukinumab as opposed to other bDMARDs. The ESC noted that although the evidence supported a benefit in terms of skin response (i.e. PASI) over the supplementary comparators, the PBAC had previously dismissed its relevance in this setting given the availability of bDMARDs for plaque psoriasis. Under Section 101(3B) of the *National Health Act 1953*, the PBAC could only recommend listing of ixekizumab at a higher price to alternative therapies if it was satisfied that ixekizumab provided, for some patients, a significant improvement in efficacy or reduction of toxicity. The PBAC considered that, the submission did not demonstrate that ixekizumab provided a significant improvement in efficacy for outcomes of relevance for patients compared with alternative bDMARDs for PsA.
- 7.5 The PBAC did not accept the submissions proposal to include coexistent psoriasis within the PBS restriction for severe PsA. The PBAC considered that no evidence was presented in the submission which demonstrated improved PsA outcomes with the increased dosage regimen.
- 7.6 The PBAC noted that under current PBS criteria, patients are able to swap disease categories. Therefore, patients with more severe psoriasis and PsA can be prescribed under the psoriasis restriction and therefore access the psoriasis dosing regimen (160mg at Week 0, then 80mg at Week 2, 4, 6, 8, 10, 12 and every four weeks thereafter).
- 7.7 The PBAC considered the equi-effective doses between ixekizumab (at the recommended dose of 160mg by SC injection at week 0, followed by 80mg every 4 weeks thereafter) and the 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.
- 7.8 The PBAC advised that it would be appropriate to provide grandfathered PBS supply to those patients receiving non-PBS subsidised ixekizumab including those from the existing product familiarisation program (approximately 100 to 150 patients) and approximately 30 patients accessing ixekizumab from ongoing clinical trials. All grandfathered patients will be required to meet the PBS eligibility criteria and noted that the grandfather provision will be removed from the listing after 12 months in line with standard procedure.
- 7.9 The PBAC recommended that the restrictions for ixekizumab should be consistent with those for the bDMARDs that are currently listed on the PBS for the treatment of severe PsA and that flow-on changes for all PBS listings to the note 'Treatment of adult patients with Psoriatic Arthritis' would be required to include ixekizumab as one of the bDMARDs for this indication.
- 7.10 The PBAC recommended that the maximum quantity in the continuing phase should

be reduced to one unit (pre-filled pen or syringe). This change should also be flowed on to the continuing phase for the currently listed psoriasis indication. The PBAC recalled that at the July 2017 meeting a recommendation was made to amend the maximum quantity of the PBS listing for ixekizumab from two to one injection, to align the ixekizumab listing for severe chronic plaque psoriasis with the PBS listings of other bDMARDs. This will result in a consistent supply of one month per prescription dispensed.

- 7.11 The PBAC noted, based on the utilisation assumptions in the submission, that the net cost to the health budget would depend on the alternative bDMARDs that would be substituted by ixekizumab. The PBAC considered that the addition of a new subsidised treatment for PsA is likely to result in some patients remaining on bDMARDs for longer (due to the current continuing criteria), which may lead to an increase in the number of patients on treatment.
- 7.12 Under section 101(3BA) of the *National Health Act 1953*, the PBAC advised that ixekizumab may be treated as interchangeable on an individual patient basis with adalimumab, certolizumab pegol, etanercept, golimumab, infliximab, secukinumab and ustekinumab for severe PsA.
- 7.13 The PBAC advised that ixekizumab is not suitable for prescribing by nurse practitioners.
- 7.14 The PBAC recommended that the Early Supply Rule should apply for the continuing treatment phase only.
- 7.15 The PBAC advised that the restriction is complex and will include an update to the administrative note which will flow on to the other biologic agents used for PsA adalimumab, certolizumab pegol, etanercept, golimumab, infliximab, secukinumab and ustekinumab.
- 7.16 The PBAC noted that this submission not eligible for an Independent Review as the PBAC has made a positive recommendation.

Outcome:

Recommended

8 Recommended listing

- 8.1 Extend the current listing for ixekizumab to include severe active psoriatic arthritis as follows:

Refer to the end of this document for the following restrictions.

- Initial 1 (new patient or patient recommencing treatment after a break of 5 years or more)

- Initial 2 (change or recommencement of treatment)
- Balance of supply (initial 1 and 2)
- Initial 3 (grandfather)
- Continuing treatment
- Continuing treatment- balance of supply

8.2 Amend NOTE for all the biological medicines listed for the treatment of severe active psoriatic arthritis in adults as follows:

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 agents adalimumab, certolizumab pegol, etanercept, golimumab, infliximab, *ixekizumab*, secukinumab and ustekinumab for adult patients with severe active psoriatic arthritis.

Patients are eligible for PBS-subsidised treatment with only 1 of the above biological agents at any 1 time.

Where the term 'biological agents' appears in notes and restrictions, it refers to adalimumab, certolizumab pegol, etanercept, golimumab, infliximab, *ixekizumab*, secukinumab and ustekinumab only.

Patients receiving PBS-subsidised treatment for psoriatic arthritis are able to commence a 'Biological Treatment Cycle' (Cycle), where they may trial biological agents without having to experience a disease flare when swapping to the alternate agent. Under these interchangeability arrangements, within a single Cycle, patients may receive long-term treatment with a biological agent as long as they sustain a response to therapy.

A patient who received PBS-subsidised adalimumab, certolizumab pegol, etanercept, golimumab, infliximab, secukinumab or ustekinumab treatment prior to [listing date] is considered to start their first cycle as of [listing date].

Following demonstration of response to initial treatment, these biological agents are available under the PBS for continuing treatment as set out in the continuing treatment restrictions for each agent.

Once patients have 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 therapy before they are eligible to commence another Cycle [further details are under '(5) Re-commencement of treatment after a 5-year break in PBS-subsidised therapy' below].

The duration of the break in therapy will be measured from the date the last prescription for PBS-subsidised treatment was issued in the most recent Cycle to the date of the first application for initial treatment with a biological agent under the new Cycle.

Within the same Cycle, patients are not allowed to fail, or cease to respond to, the same PBS-subsidised biological agent more than once. Therefore once a patient fails to meet the response criteria for any biological agent, they must change to an alternate agent which they have not previously failed, if they wish to continue PBS-subsidised biological treatment.

Patients for whom a break in PBS-subsidised therapy of less than 5 years has occurred, and, who have failed therapy fewer than 3 times within a particular treatment Cycle, as defined in the relevant restriction, may commence a further course of treatment within that Cycle (Initial 2).

Patients for whom a break in PBS-subsidised therapy of 5 years or more has occurred are eligible to commence a new Cycle (Initial 1).

There is no limit to the number of Biological Treatment Cycles a patient may undertake in their lifetime.

How to prescribe biological agents for the treatment of severe active psoriatic arthritis.

(1) Initial treatment.

Applications for initial treatment should be made where:

- (i) patients have received no prior PBS-subsidised biological treatment and wish to commence such therapy (Initial 1); and
- (ii) patients have received prior PBS-subsidised biological therapy and wish to trial an alternate agent (Initial 2) [further details are under 'Swapping therapy' below]; and
- (iii) patients wish to re-commence treatment with a specific biological agent following a break in PBS-subsidised therapy with that specific agent (Initial 1 or Initial 2).

All applications for initial treatment will be limited to provide for a maximum of 16 weeks of therapy for adalimumab, etanercept, golimumab and secukinumab, 18 to 20 weeks of therapy for certolizumab pegol (depending upon the dosing regimen), 22 weeks of therapy for infliximab, and 28 weeks of therapy for ustekinumab. It is recommended that patients be reviewed in the month prior to completing their course of initial treatment to ensure uninterrupted biological agent supply.

Patients must be assessed for response to any course of PBS-subsidised initial treatment following a minimum of 12 weeks of therapy and this assessment must be submitted to the Department of Human Services no later than 4 weeks from the date that course was ceased. Where a response assessment is not submitted within these timeframes, patients will be deemed to have failed to respond to treatment with that biological agent.

(2) Continuing treatment.

Following the completion of an initial treatment course with a specific biological agent, patients may qualify to receive up to 24 weeks of continuing treatment with that drug providing they have demonstrated an adequate response to treatment.

Patients are eligible to receive continuing biological treatment with the same drug in courses of up to 24 weeks providing they continue to sustain the response.

Patients must be assessed for response to a course of continuing therapy, and the assessment must be submitted to the Department of Human Services where applicable. Where a response assessment is not submitted where applicable, patients will be deemed to have failed to respond to treatment with that biological agent.

(3) Swapping therapy.

Once an authority for initial treatment with the first PBS-subsidised biological agent is approved, patients may swap to an alternate biological agent 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.

Patients may swap to an alternate biological agent at any time, regardless of whether they are receiving therapy (initial or continuing) with a biological agent at the time of the application or not.

Within a Treatment Cycle patients may alternate between therapy with any biological agent of their choice (1 at a time) providing:

- (i) they have not received PBS-subsidised treatment with that particular biological agent previously; or
- (ii) they have demonstrated an adequate response to that particular biological agent 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.

To ensure patients receive the maximum treatment opportunities allowed under the interchangeability arrangements, it is important that they are assessed for response to every course of treatment within the timeframes specified in the relevant restriction.

To avoid confusion, applications for patients who wish to swap to an alternate biological agent should be accompanied by the authority prescription or remaining repeats for the biological agent the patient is ceasing.

(4) Baseline measurements to determine response.

Determination of whether a response to treatment has been demonstrated will be based on the baseline measurements of the indices of disease severity submitted with the first authority application for a biological agent. However, prescribers may provide new baseline measurements any time that an initial treatment application is submitted within a treatment Cycle and these revised baseline measurements will be used to assess response.

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.

(5) Re-commencement of treatment after a 5-year break in PBS-subsidised therapy.

Patients who wish to trial a second or subsequent treatment Cycle following a break in PBS-subsidised biological therapy of at least 5 years must requalify for initial treatment with respect to both the indices of disease severity. Patients must have re-trialled treatment with methotrexate and sulfasalazine or leflunomide, at an adequate dose, for a minimum of 3 months at the time the ESR or CRP levels and the active joint counts are measured.

(6) Patients 'grandfathered' onto PBS-subsidised treatment with ixekizumab.

A patient who commenced treatment with ixekizumab for severe active psoriatic arthritis prior to 1 [listing date] and who continues to receive treatment at the time of application may qualify for treatment under the initial 'grandfather' treatment restriction.

A patient may only qualify for PBS-subsidised treatment under this criterion once. A maximum of 24 weeks of treatment will be authorised under this criterion.

Following completion of the initial PBS-subsidised course, further applications for treatment will be assessed under the continuing treatment restriction of the relevant drug.

Note

No increase in the maximum quantity or number of units may be authorised.

Note

No increase in the maximum number of repeats may be authorised.

Initial 1 (new patient or patient recommencing treatment after a break of 5 years or more)

Name, Restriction, Manner of administration and form	Max. Qty	No. of Rpts	Proprietary Name and Manufacturer	
IXEKIZUMAB				
Injections 80mg in 1mL single use prefilled syringe, 2	1	1	TALTZ®	Eli Lilly Australia Pty Ltd
Injections 80mg in 1mL single use prefilled pens, 2	1	1	TALTZ®	Eli Lilly Australia Pty Ltd

Prescriber Type	Medical Practitioner
Episodicity:	N/A
Severity:	Severe
Condition:	Psoriatic arthritis
PBS Indication:	Severe psoriatic arthritis
Treatment phase:	Initial treatment – Initial 1 (new patient or patient recommencing treatment after a break of 5 years or more)
Restriction Level:	<input type="checkbox"/> Restricted benefit <input checked="" type="checkbox"/> Authority Required - In Writing <input type="checkbox"/> Authority Required - Telephone <input type="checkbox"/> Authority Required – Emergency <input type="checkbox"/> Authority Required - Electronic <input type="checkbox"/> Streamlined
Treatment criteria:	Must be treated by a rheumatologist; OR Must be treated by a clinical immunologist with expertise in the management of psoriatic arthritis.

Clinical criteria:	<p>Patient must have severe active psoriatic arthritis,</p> <p>AND</p> <p>Patient must have received no prior PBS-subsidised treatment with a biological agent for this condition; OR</p> <p>Patient must have received no PBS-subsidised treatment with a biological agent for at least 5 years if they have previously received PBS-subsidised treatment with a biological agent for this condition,</p> <p>AND</p> <p>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,</p> <p>AND</p> <p>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</p> <p>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,</p> <p>AND</p> <p>Patient must not receive more than 16 weeks of treatment under this restriction.</p>
Population criteria:	Patient must be aged 18 years or older.
Foreword	N/A
Definitions	N/A
Prescriber Instructions	<p>For the purposes of this restriction 'biological agent' means adalimumab, certolizumab pegol, etanercept, golimumab, infliximab, ixekizumab, secukinumab or ustekinumab.</p> <p>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>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>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:</p> <p>an elevated erythrocyte sedimentation rate (ESR) greater than 25 mm per hour or a C-reactive protein (CRP) level greater than 15 mg per L; and</p> <p>either</p> <p>(a) an active joint count of at least 20 active (swollen and tender) joints; or</p> <p>(b) at least 4 active joints from the following list of major joints:</p>

	<p>(i) elbow, wrist, knee and/or ankle (assessed as swollen and tender); and/or</p> <p>(ii) shoulder and/or hip (assessed as pain in passive movement and restriction of passive movement, where pain and limitation of movement are due to active disease and not irreversible damage such as joint destruction or bony overgrowth).</p> <p>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>The authority application must be made in writing and must include:</p> <p>(1) a completed authority prescription form; and</p> <p>(2) a completed Psoriatic Arthritis PBS Authority Application - Supporting Information Form;</p>
<p>Administrative Advice</p>	<p>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 Department of Human Services website (www.humanservices.gov.au)</p> <p>The assessment of the patient's response to this initial course of treatment must be made following a minimum of 12 weeks of treatment and submitted to the Department of Human Services 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>Patients who fail to demonstrate a response to treatment with this drug under this restriction will not be eligible to receive further PBS-subsidised treatment with this drug in this Treatment Cycle. Patients may re-trial this drug after a minimum of 5 years have elapsed between the date the last prescription for a PBS-subsidised biological agent was approved in this Cycle and the date of the first application under the new Cycle.</p> <p>Any queries concerning the arrangements to prescribe may be directed to the Department of Human Services on 1800 700 270 (hours of operation 8 a.m. to 5 p.m. EST Monday to Friday).</p> <p>Prescribing information (including Authority Application forms and other relevant documentation as applicable) is available on the Department of Human Services website at www.humanservices.gov.au</p> <p>Applications for authority to prescribe should be forwarded to: Department of Human Services Complex Drugs Reply Paid 9826 HOBART TAS 7001</p> <p>Patients who fail to demonstrate a response to treatment with this drug under this restriction will not be eligible to receive further PBS-subsidised treatment with this drug in this Treatment Cycle. Patients may re-trial this drug after a minimum of 5 years have elapsed between the</p>

	date the last prescription for a PBS-subsidised biological agent was approved in this Cycle and the date of the first application under the new Cycle.
Cautions	N/A

Initial 2 (change or recommencement of treatment)

Name, Restriction, Manner of administration and form	Max. Qty	No. of Rpts	Proprietary Name and Manufacturer	
IXEKIZUMAB				
Injections 80mg in 1mL single use prefilled syringe, 2	1	1	TALTZ®	Eli Lilly Australia Pty Ltd
Injections 80mg in 1mL single use prefilled pens, 2	1	1	TALTZ®	Eli Lilly Australia Pty Ltd

Episodicity:	N/A
Severity:	Severe
Condition:	Psoriatic arthritis
PBS Indication:	Severe psoriatic arthritis
Treatment phase:	Initial treatment – Initial 2 (change or recommencement of treatment)
Restriction:	<input type="checkbox"/> Restricted benefit <input checked="" type="checkbox"/> Authority Required - In Writing <input type="checkbox"/> Authority Required - Telephone <input type="checkbox"/> Authority Required – Emergency <input type="checkbox"/> Authority Required - Electronic <input type="checkbox"/> Streamlined
Treatment criteria:	Must be treated by a rheumatologist; OR Must be treated by a clinical immunologist with expertise in the management of psoriatic arthritis.

<p>Clinical criteria:</p>	<p>Patient must have a documented history of severe active psoriatic arthritis,</p> <p>AND</p> <p>Patient must have received prior PBS-subsidised treatment with a biological agent for this condition in this Treatment Cycle,</p> <p>AND</p> <p>Patient must not have already failed, or ceased to respond to, PBS-subsidised treatment with 3 biological agents within this Treatment Cycle,</p> <p>AND</p> <p>Patient must not have failed, or ceased to respond to, PBS-subsidised treatment with this drug during the current Treatment Cycle,</p> <p>AND</p> <p>Patient must not receive more than 16 weeks of treatment under this restriction.</p>
<p>Population criteria:</p>	<p>Patient must be aged 18 years or older.</p>
<p>Prescriber Instructions</p>	<p>For the purposes of this restriction 'biological agent' means adalimumab, certolizumab pegol, etanercept, golimumab, infliximab, ixekizumab, secukinumab or ustekinumab.</p> <p>Applications for a patient who has previously received PBS-subsidised treatment with this drug within this Treatment Cycle and who wishes to recommence therapy with this drug within this same Cycle, must be accompanied by evidence of a response to the patient's most recent course of PBS-subsidised treatment with this drug.</p> <p>Where the most recent course of PBS-subsidised treatment was approved under either of the initial treatment restrictions (i.e. for patients with no prior PBS-subsidised biological therapy or, under this restriction, for patients who have received previous PBS-subsidised biological therapy), the patient must have been assessed for response following a minimum of 12 weeks of therapy. This assessment must have been submitted no later than 4 weeks from the date that course was ceased.</p> <p>Where the most recent course of PBS-subsidised treatment with this drug was approved under the continuing treatment criteria, the patient must have been assessed for response, and the assessment submitted no later than 4 weeks from the date that course was ceased.</p> <p>Where a response assessment was not submitted within these timeframes, the patient will be deemed to have failed to respond to treatment.</p> <p>An adequate response to treatment is defined as:</p> <p>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</p> <p>either of the following:</p> <p>(a) a reduction in the total active (swollen and tender) joint count by at least 50% from baseline, where baseline is at least 20 active joints; or</p> <p>(b) a reduction in the number of the following major active joints, from at least 4, by at least</p>

	<p>50%:</p> <p>(i) elbow, wrist, knee and/or ankle (assessed as swollen and tender); and/or</p> <p>(ii) shoulder and/or hip (assessed as pain in passive movement and restriction of passive movement, where pain and limitation of movement are due to active disease and not irreversible damage such as joint destruction or bony overgrowth).</p> <p>The authority application must be made in writing and must include:</p> <p>(1) a completed authority prescription form; and</p> <p>(2) a completed Psoriatic Arthritis PBS Authority Application - Supporting Information Form.</p>
<p>Administrative Advice</p>	<p>The assessment of the patient's response to this initial course of treatment must be made following a minimum of 12 weeks of treatment and submitted to the Department of Human Services 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>Patients who fail to demonstrate a response to treatment with this drug under this restriction will not be eligible to receive further PBS-subsidised treatment with this drug in this Treatment Cycle. Patients may re-trial this drug after a minimum of 5 years have elapsed between the date the last prescription for a PBS-subsidised biological agent was approved in this Cycle and the date of the first application under the new Cycle.</p> <p>Any queries concerning the arrangements to prescribe may be directed to the Department of Human Services on 1800 700 270 (hours of operation 8 a.m. to 5 p.m. EST Monday to Friday).</p> <p>Applications for authority to prescribe should be forwarded to:</p> <p>Department of Human Services Complex Drugs Reply Paid 9826 HOBART TAS 7001</p> <p>Prescribing information (including Authority Application forms and other relevant documentation as applicable) is available on the Department of Human Services website at www.humanservices.gov.au</p>
<p>Cautions</p>	<p>N/A</p>

Balance of supply (initial 1 and 2)

Name, Restriction, Manner of administration and form	Max. Qty	No. of Rpts	Proprietary Name and Manufacturer	
IXEKIZUMAB Injections 80mg in 1mL single use prefilled syringe, 2	1	1	TALTZ®	Eli Lilly Australia Pty Ltd
Injections 80mg in 1mL single use prefilled pens, 2	1	1	TALTZ®	Eli Lilly Australia Pty Ltd

Episodicity:	N/A
Severity:	Severe
Condition:	Psoriatic arthritis
PBS Indication:	Severe psoriatic arthritis
Treatment phase:	Initial treatment - Initial 1 (new patient or patient recommencing treatment after a break of 5 years or more) or Initial 2 (change or recommencement of treatment) - balance of supply
Restriction:	<input type="checkbox"/> Restricted benefit <input type="checkbox"/> Authority Required - In Writing <input checked="" type="checkbox"/> Authority Required - Telephone <input type="checkbox"/> Authority Required – Emergency <input type="checkbox"/> Authority Required - Electronic <input type="checkbox"/> Streamlined
Treatment criteria:	Must be treated by a rheumatologist; OR Must be treated by a clinical immunologist with expertise in the management of psoriatic arthritis.
Clinical criteria:	Patient must have received insufficient therapy with this drug under the Initial 1 (new patient or patient recommencing treatment after a break of 5 years or more) restriction to complete 16 weeks treatment; OR Patient must have received insufficient therapy with this drug under the Initial 2 (change or recommencement of treatment) restriction to complete 16 weeks treatment, AND The treatment must provide no more than the balance of up to 16 weeks treatment available under the above restrictions.
Population criteria:	Patient must be an adult.
Prescriber Instructions	
Administrative Advice	Authority approval for sufficient therapy to complete a maximum of 16 weeks of treatment may be requested by telephone by contacting the Department of Human Services on 1800 700 270 (hours of operation 8 a.m. to 5 p.m. EST Monday to Friday).
Cautions	N/A

Initial 3 (grandfather)

Name, Restriction, Manner of administration and form	Max. Qty	No. of Rpts	Proprietary Name and Manufacturer	
IXEKIZUMAB				
Injections 80mg in 1mL single use prefilled syringe, 1	1	2	TALTZ®	Eli Lilly Australia Pty Ltd
Injections 80mg in 1mL single use prefilled pens, 1	1	2	TALTZ®	Eli Lilly Australia Pty Ltd

Severity:	Severe active
Condition:	Psoriatic Arthritis
PBS Indication:	Severe active psoriatic arthritis
Treatment phase:	Initial treatment - Initial 3 (grandfather)
Restriction:	<input type="checkbox"/> Restricted benefit <input checked="" type="checkbox"/> Authority Required - In Writing <input type="checkbox"/> Authority Required - Telephone <input type="checkbox"/> Authority Required – Emergency <input type="checkbox"/> Authority Required - Electronic <input type="checkbox"/> Streamlined
Treatment criteria:	Must be treated by a rheumatologist; OR Must be treated by a clinical immunologist with expertise in the management of psoriatic arthritis.
Clinical criteria:	Patient must have a documented history of severe active psoriatic arthritis, AND Patient must have received non-PBS treatment with this drug for this condition prior to (PBS listing date), AND Patient must be receiving treatment with this drug for this condition at the time of application, 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 prior to initiating non PBS-subsidised treatment with this drug for this condition, 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 prior to initiating non PBS-subsidised treatment with this drug for this condition; 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 prior to initiating non PBS-subsidised treatment with this drug 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.
Population criteria:	Patient must be aged 18 years or older.
Prescriber 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

<p>(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).</p> <p>If the above requirement to demonstrate an elevated ESR or CRP cannot be met, the application must state the reasons why this criterion cannot be satisfied.</p> <p>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>The same indices of disease severity used to establish baseline at the commencement of treatment with each initial treatment application must be provided for all subsequent continuing treatment applications.</p> <p>The assessment of the patient's response to this PBS-subsidised course of therapy must be made within the 4 weeks prior to completion of the course of treatment. It is recommended that an application is submitted to the Department of Human Services no less than 2 weeks prior to the date the next dose is due in order to ensure continuity of treatment for those patients who meet the continuation criteria. Where an assessment is not submitted to the Department of Human Services within these timeframes, patients will be deemed to have failed to respond, or to have failed to sustain a response to treatment with this drug.</p> <p>Patients may qualify for PBS-subsidised treatment under this restriction once only. Further applications for treatment with this drug will be assessed under the continuing treatment restriction.</p> <p>The authority application must be made in writing and must include: (1) a completed authority prescription form; and (2) a completed Psoriatic Arthritis PBS Authority Application - Supporting Information Form; and (3) a signed patient acknowledgement; and (4) the date of commencement of this drug; and (5) results of the baseline patient assessment prior to commencing treatment with this drug.</p> <p>Note Any queries concerning the arrangements to prescribe may be directed to the Department of Human Services on 1800 700 270 (hours of operation 8 a.m. to 5 p.m. EST Monday to Friday). Prescribing information (including Authority Application forms and other relevant documentation as applicable) is available on the Department of Human Services website at www.humanservices.gov.au</p> <p>Applications for authority to prescribe should be forwarded to: Department of Human Services Complex Drugs Reply Paid 9826</p>
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	HOBART TAS 7001
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Continuing treatment

Name, Restriction, Manner of administration and form	Max. Qty	№.of Rpts	Proprietary Name and Manufacturer	
IXEKIZUMAB				
Injections 80mg in 1mL single use prefilled syringe, 1	1	2	TALTZ®	Eli Lilly Australia Pty Ltd
Injections 80mg in 1mL single use prefilled pens, 1	1	2	TALTZ®	Eli Lilly Australia Pty Ltd

Episodicity:	N/A
Severity:	Severe
Condition:	Psoriatic arthritis
PBS Indication:	Severe psoriatic arthritis
Treatment phase:	Continuing treatment
Restriction:	<input type="checkbox"/> Restricted benefit <input checked="" type="checkbox"/> Authority Required - In Writing <input type="checkbox"/> Authority Required - Telephone <input type="checkbox"/> Authority Required – Emergency <input type="checkbox"/> Authority Required - Electronic <input type="checkbox"/> Streamlined
Treatment criteria:	<p>Must be treated by a rheumatologist; OR</p> <p>Must be treated by a clinical immunologist with expertise in the management of psoriatic arthritis.</p>
Clinical criteria:	<p>Patient must have a documented history of severe active psoriatic arthritis,</p> <p>AND</p> <p>Patient must have received this drug as their most recent course of PBS-subsidised treatment with a biological agent for this condition in the current Treatment Cycle,</p> <p>AND</p> <p>Patient must demonstrate, at the time of application, an adequate response to treatment with this drug,</p> <p>AND</p> <p>Patient must not receive more than 24 weeks of treatment per continuing treatment course authorised under this restriction.</p>
Population criteria:	Patient must be an adult.
Foreword	N/A

Definitions	N/A
Prescriber Instructions	<p>For the purposes of this restriction 'biological agent' means adalimumab, certolizumab pegol, etanercept, golimumab, infliximab, ixekizumab, secukinumab or ustekinumab.</p> <p>An adequate response to treatment is defined as:</p> <p>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</p> <p>either of the following:</p> <p>(a) a reduction in the total active (swollen and tender) joint count by at least 50% from baseline, where baseline is at least 20 active joints; or</p> <p>(b) a reduction in the number of the following major active joints, from at least 4, by at least 50%:</p> <p>(i) elbow, wrist, knee and/or ankle (assessed as swollen and tender); and/or</p> <p>(ii) shoulder and/or hip (assessed as pain in passive movement and restriction of passive movement, where pain and limitation of movement are due to active disease and not irreversible damage such as joint destruction or bony overgrowth).</p> <p>The same indices of disease severity used to establish baseline at the commencement of treatment with each initial treatment application must be provided for all subsequent continuing treatment applications.</p> <p>All applications for continuing treatment with this drug must include a measurement of response to the most recent course of PBS-subsidised therapy. This assessment must be submitted no later than 4 weeks from the cessation of that treatment course. If the application is the first application for continuing treatment with this drug, it must be accompanied by an assessment of response to a minimum of 12 weeks of treatment with the initial treatment course.</p> <p>Where a response assessment is not submitted within these timeframes, the patient will be deemed to have failed to respond to treatment</p> <p>The authority application must be made in writing and must include:</p> <p>(1) a completed authority prescription form; and</p> <p>(2) a completed Psoriatic Arthritis PBS Authority Application - Supporting Information Form.</p>
Administrative Advice	<p>Patients who fail to demonstrate a response to treatment with this drug under this restriction will not be eligible to receive further PBS-subsidised treatment with this drug in this Treatment Cycle. Patients may re-trial this drug after a minimum of 5 years have elapsed between the date the last prescription for a PBS-subsidised biological agent was approved in this Cycle and the date of the first application under the new Cycle.</p> <p>Any queries concerning the arrangements to prescribe may be directed to the Department of</p>

	<p>Human Services on 1800 700 270 (hours of operation 8 a.m. to 5 p.m. EST Monday to Friday).</p> <p>Applications for authority to prescribe should be forwarded to: Department of Human Services Complex Drugs Reply Paid 9826 HOBART TAS 7001</p> <p>Prescribing information (including Authority Application forms and other relevant documentation as applicable) is available on the Department of Human Services website at www.humanservices.gov.au</p> <p>Patients who fail to demonstrate a response to treatment with this drug under this restriction will not be eligible to receive further PBS-subsidised treatment with this drug in this Treatment Cycle. Patients may re-trial this drug after a minimum of 5 years have elapsed between the date the last prescription for a PBS-subsidised biological agent was approved in this Cycle and the date of the first application under the new Cycle.</p>
Cautions	N/A

Continuing treatment - balance of supply

Name, Restriction, Manner of administration and form	Max. Qty	№.of Rpts	Proprietary Name and Manufacturer	
IXEKIZUMAB				
Injections 80mg in 1mL single use prefilled syringe, 1	1	2	TALTZ®	Eli Lilly Australia Pty Ltd
Injections 80mg in 1mL single use prefilled pens, 1	1	2	TALTZ®	Eli Lilly Australia Pty Ltd

Episodicity:	N/A
Severity:	Severe
Condition:	Psoriatic arthritis
PBS Indication:	Severe psoriatic arthritis
Treatment phase:	Continuing treatment – balance of supply
Restriction:	<input type="checkbox"/> Restricted benefit <input type="checkbox"/> Authority Required - In Writing <input checked="" type="checkbox"/> Authority Required - Telephone <input type="checkbox"/> Authority Required – Emergency <input type="checkbox"/> Authority Required - Electronic <input type="checkbox"/> Streamlined

Treatment criteria:	Must be treated by a rheumatologist; OR Must be treated by a clinical immunologist with expertise in the management of psoriatic arthritis.
Clinical criteria:	Patient must have received insufficient therapy with this drug under the Continuing treatment restriction to complete 24 weeks treatment, AND The treatment must provide no more than the balance of up to 24 weeks treatment available under the above restriction.
Population criteria:	Patient must be aged 18 years or older.
Prescriber Instructions	
Administrative Advice	Authority approval for sufficient therapy to complete a maximum of 24 weeks of treatment may be requested by telephone by contacting the Department of Human Services on 1800 700 270 (hours of operation 8 a.m. to 5 p.m. EST Monday to Friday).
Cautions	N/A

9 Context for Decision

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

10 Sponsor's Comment

The sponsor had no comment.