

5.11 TILDRAKIZUMAB, Injection 100 mg in 1 mL single use pre-filled syringe, Ilumya®, Sun Pharma ANZ Pty Ltd

1 Purpose of Application

- 1.1 Authority Required (in writing) listing for tildrakizumab (TIL) for treatment of severe chronic plaque psoriasis (CPP) in patients meeting specified PBS criteria. The PBAC has not previously considered TIL.
- 1.2 The basis for the requested listing was a cost-minimisation analysis versus ustekinumab (UST). Other biologic disease-modifying anti-rheumatic drugs (bDMARDs) currently listed on the PBS for CPP include adalimumab (ADA), etanercept (ETN), infliximab (IFX), secukinumab (SEC) and ixekizumab (IXE). Biosimilars are also available on PBS for IFX and ETN. The submission also presented supportive comparative evidence against ETN (suggesting superiority) and ADA (suggesting non-inferiority).

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

Component	Description
Population	Adult patients with severe CPP who have failed conventional therapy
Intervention	TIL (2 x 100 mg) subcutaneously at Weeks 0, 4 then Q12W thereafter.
Comparator	Primary: UST; Supplementary: ETN; ADA
Outcomes	PASI 75 response at Week 12
Clinical claims	<p>In patients with severe CPP, the submission claimed TIL to be:</p> <ul style="list-style-type: none"> • No worse than UST at improving PASI 75 response at Week12 and no worse than UST in terms of safety. The claim of non-inferior efficacy might not be supported. Results of indirect comparisons using PBO as common reference generally did not favour TIL for attainment of PASI75 response at Week 12, with lower 95%CI exceeding -10% for the RD statistic. The indirect comparison also reached statistical significance for the OR statistic between TIL and UST 90mg (OR (95%CI): 0.45 (0.24, 0.86)), indicating TIL may be inferior to UST 90mg. Inappropriately, a non-inferiority margin was not nominated by the submission. • More effective than ETN at improving PASI 75 response at Week 12 and superior to ETN in terms of safety. The claim of superior safety may not be reasonable based on the trial evidence. TIL patients have significantly less injection site reactions compared to ETN patients, but serious AEs and discontinuations due to AEs were similar between TIL and ETN. • No worse than ADA at improving PASI 75 response Week 12, and no worse than ADA in terms of safety. This claim appeared to be reasonable.

CPP = chronic plaque psoriasis; PASI = Psoriasis Area Severity Index; AE = adverse events; ADA = adalimumab; ETN = etanercept; TIL = tildrakizumab; PASI 75 = achieving at least a 75% improvement on the Psoriasis Area Severity Index; Q12W = every 12 weeks
Source: Table 1-1, p3 of the submission. Appendix 1 Section 2c, p88, and Appendix 1 Section 2b, p.30.

2 Requested listing

- 2.1 An identical listing to that of existing biologic therapies in CPP was requested by the submission. The requested quantities (including repeats) would permit for up to 28

weeks of initial treatment (3 doses) followed by 24 weeks of continuing therapy (2 doses) on each prescription.

Name, Restriction, Manner of administration and form	Max. Qty (units)	No. of Rpts	Dispensed Price for Max. Qty	Proprietary Name and Manufacturer
TILDRAKIZUMAB 100 mg/1 mL solution for injection, pre-filled single use syringe	2	2 ^a 1 ^b	\$ [REDACTED] #	Ilumya® Sun Pharma Ltd
Category/Program:	General Schedule (Code GE)			
PBS indication:	Severe chronic plaque psoriasis			
Treatment phase:	Initial treatment, and continuing treatment			
Restriction:	<input checked="" type="checkbox"/> Authority Required - In Writing			
Treatment criteria:	Must be treated by a dermatologist			
Clinical criteria:	As per current PBS listed ustekinumab.			

^a Initial treatment; ^b Continuing treatment.

Note: Calculated in the submission based on cost-minimisation of ex-manufacturer prices to published price of ustekinumab over 104 weeks of treatment.

Source: Table 1.4-2, p17 of the submission.

2.2 The Sponsor requested a special pricing arrangement, the effective price for TIL to be determined on a cost-minimisation basis using the indication-specific effective price for UST. The proposed price for TIL was derived based on a cost-minimisation analysis versus the published UST price over 104 weeks (2 years) of treatment.

2.3 The maximum quantity and the number of repeats requested would be sufficient to complete a 28-week initial treatment course of TIL (3 doses) and a 24-week continuing treatment course of TIL (2 doses). The requested treatment duration for continuing therapy was consistent with all listed biologics for severe CPP (all provide up to 24 weeks of therapy). The initial treatment period was similar to UST (also 28 weeks) but differed to IFX (22 weeks) and 16 weeks for the others agents.

The submission proposed that a grandfather clause be incorporated in the listing, to allow approximately 250-350 patients in a TIL Patient Familiarisation Program (PFP) to transition to PBS subsidised TIL. Furthermore, the submission stated that 58 patients currently enrolled in clinical trials would need to be grandfathered across to PBS supply. The submission stated that these patients are not likely to meet the clinical criteria specified in the proposed initial treatment restrictions. Given no further details (e.g. baseline PASI score, BSA or prior therapies) were provided on these patients in the submission, it was uncertain why these patients would not fit the PBS eligibility criteria.

2.4 The Pre-Sub-Committee-Response (PSCR) clarified that what was meant by ‘patients not fitting the PBS eligibility criteria’ was ‘patients not fitting the eligibility criteria for initial treatment’. The submission requested that up to approximately 400 patients in a TIL Patient Familiarisation Program (PFP) and currently enrolled in clinical trials, be grandfathered into initiation of PBS-subsidised continuing therapy. The PSCR explained that these patients would have demonstrated response to initial treatment and would not now fit the eligibility criteria for initial treatment.

- 2.5 The requested PBS restriction was narrower than the proposed TGA indication with stricter criteria for prior failed therapies and disease severity. However, the evidence is comparable to that for all other biologics listed on the PBS. Overall, the requested restriction was appropriate.
- 2.6 It was noted that primary endpoints in the included TIL trials (reSURFACE 1-2) were measured at 12 weeks and in the TIL phase IIb trial at 16 weeks, which is significantly shorter than the proposed length of the initial treatment period of 28 weeks.

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

3 Background

Registration status

- 3.1 The submission was made under the TGA/PBAC Parallel Process. The TGA's clinical evaluator's reports, and TGA delegate overview was available at the time of the PBAC meeting. The proposed indication for TIL was: "Tildrakizumab is indicated for the treatment of adults with moderate-to-severe plaque psoriasis who are candidates for systemic therapy".
- 3.2 The approved dosage of TIL in the US differs to those proposed in Australia. The approved US dosage is 100 mg at Weeks 0, 4 and every 12 weeks thereafter (approved by the FDA in March 2018) whereas the draft Australian PI proposed the same dosing frequency regimen but at the higher 200 mg dose.

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

4 Population and disease

- 4.1 Psoriasis manifests as chronic inflammation of the skin, characterised by disfiguring, scaling and erythematous plaques that may be painful and severely pruritic and may cause significant reductions in quality of life (QoL). The target population proposed for TIL is the same as that for other biologics on the PBS for severe CPP. The initial treatment criteria for PBS-subsidised biologic therapy for whole body psoriasis requires patients to have a PASI > 15 and have failed to achieve an adequate response, are intolerant or contraindicated to at least three of the four systemic therapies (methotrexate, cyclosporin and acitretin) and/or phototherapy (either PUVA or UVB).
- 4.2 TIL is proposed as an alternative bDMARD in the treatment of severe chronic plaque psoriasis. TIL will become one of several bDMARDs listed on PBS for patients with severe CPP who have failed to achieve adequate response to non-biologic therapies. The addition of TIL to the clinical management algorithm will not alter current practice, but will allow for an additional option with a different mechanism of action. The submission suggested that TIL would mostly replace therapy with UST followed by ADA (in maintenance). However, given the therapeutic relativities of listed biologics

and that clinicians are free to choose among them, TIL could replace any of the listed bDMARDs.

- 4.3 The ESC noted that currently six bDMARDs are PBS listed for this indication. The ESC acknowledged that the direct comparison demonstrated superior efficacy of TIL versus ETN. However, the ESC was not satisfied that TIL offers any significant clinical benefits over the currently listed bDMARDs for this indication in terms of efficacy and safety profile nor any administration advantages. The ESC considered that there did not appear to be a clinical need for the listing of a seventh biological agent for CPP. The Pre-PBAC response argued that there is a clinical need for TIL, concluding ‘as there is no cure for chronic plaque psoriasis, patients require continuous treatment over their lifetime and many patients will relapse over time despite receiving treatment. Consequently, the availability of several therapies which have different methods of action is critically important to allow physicians to provide patients with a treatment with a different mode of action when relapse occurs.’

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

5 Comparator

- 5.1 The submission nominated UST as the main comparator (and the only comparator considered in the cost-minimisation analysis). This was based on UST being the most commonly used PBS-subsidised biologic for severe CPP and TIL being an exclusive IL-23 inhibitor, having a similar mechanism of action to UST an IL-12/23 inhibitor. The submission also nominated ETN and ADA as supplementary efficacy comparators, based on ETN being the active comparator (up to 28 weeks) in one of the main trials supporting the submission (the reSURFACE 2 trial) and citing ADA as the most commonly used PBS-subsidised biologic for severe CPP in maintenance therapy (although current utilisation illustrate its usage is behind UST).
- 5.2 Given all PBS listed biologics for CPP share a similar listing, other listed biologics will be replaced in practice.
- 5.3 The *National Health Act 1953*, Section 101(3B) stipulates if the requested treatment is substantially more costly than alternative therapies, then the PBAC could only recommend listing at a higher price, if it is satisfied that the treatment provides, for some patients, a significant improvement in efficacy or reduction of toxicity over the existing therapies. Insufficient data was presented in the submission to permit this assessment to be conducted for TIL:
- As acknowledged by the submission, similar to UST, IFX was also listed on a cost effectiveness basis versus ETN, and given recent introduction of biosimilar brands on the PBS, IFX is also now less costly than other listed bDMARDs. To attain a higher price than IFX, TIL must therefore provide evidence that it is better than IFX. Evidence versus IFX was not presented in the submission.

- ETN, ADA, SEC and IXE were cost-minimised against each other or the least expensive biological. Data in the draft report to the PBAC for the Post-market review (PMR) of biologics in the treatment of severe chronic plaque psoriasis suggested IXE may be the most effective of the PBS listed biologics¹. This was echoed in a recent PBAC decision for guselkumab for CPP in March 2018, the PBAC rejected the application stating that evidence versus IFX and IXE would also be required. No comparative evidence versus IXE was presented in this submission.
- 5.4 A drug with similar mechanism of action to TIL, guselkumab (GUS) was rejected at the March 2018 PBAC meeting for CPP. In making its decision, the PBAC considered that UST was an inappropriate choice as a main comparator. The PBAC considered that any of the biologic agents on the PBS for CPP may be replaced by GUS and hence be a relevant comparator. Comparative evidence versus IFX and IXE was also requested by the PBAC. A minor resubmission to request an Authority Required listing of GUS for the treatment of severe chronic plaque psoriasis has been lodged for the July 2018 PBAC meeting.

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 that no consumer comments were received for this item.

Clinical trials

- 6.3 Overall, the submission was based on 16 trials that formed the basis for 3 indirect and 1 direct comparison versus the nominated comparators. The trial evidence included:
- three RCTs comparing TIL to PBO and active comparator ETN: reSURFACE 1 and reSURFACE 2 (results reported at 12 weeks) and Phase IIb trial (results reported at 12 and 16 weeks);
 - eight RCTs comparing UST to either PBO or active comparator ETN: PHOENIX-1, PHOENIX-2, Igarashi 2012, PEARL, LOTUS. AMAGINE-2, AMAGINE-3 and ACCEPT(results reported at 12 weeks);

¹ Figure ES.2 of Pharmaceutical Benefits Scheme. Post-market Review: The use of biologics in the treatment of severe chronic plaque psoriasis, draft Report to PBAC. (Executive Summary available at <http://www.pbs.gov.au/info/reviews/biologics-review-public-consultation>)

- five RCTs comparing ADA to PBO: CHAMPION, REVEAL, Gordon 2006, Asahina 2010 and Cai 2017 (results reported at 12 and 16 weeks).

6.4 The comparisons presented in the submission were:

- an indirect comparison of TIL versus UST based on PBO as the common reference;
- a direct comparison of TIL versus ETN from the reSURFACE 2 trial;
- an indirect comparison of TIL versus UST based on ETN as the common reference; and
- an indirect comparison of TIL versus ADA based on PBO as the common reference.

6.5 Details of the trials presented in the submission are provided in Table 2.

Table 2: Trials and associated reports presented in the submission

Trial ID	Protocol title/ Publication title	Publication citation
TIL vs PBO and ETN		
reSURFACE 1 (TIL ₁)	A 64-week, Phase 3, Randomized, Placebo-controlled, Parallel Design Study to Evaluate the Efficacy and Safety/Tolerability of Subcutaneous Tildrakizumab (SCH 900222/MK-3222), Followed by an Optional Long-Term Safety Extension Study, in Subjects With Moderate-to-Severe Chronic Plaque Psoriasis. Reich K, Papp K, Blauvelt A, et al. Tildrakizumab versus placebo or etanercept for chronic plaque psoriasis (reSURFACE 1 and reSURFACE 2): Results from two randomised controlled, phase 3 trials.	February 2017 Lancet 2017; 390: 276-288.
reSURFACE 2 (TIL ₂)	A 52-week, Phase 3, Randomized, Active Comparator and Placebo-controlled, Parallel Design Study to Evaluate the Efficacy and Safety/Tolerability of Subcutaneous Tildrakizumab (SCH 900222/MK-3222), Followed by an Optional Long-Term Safety Extension Study, in Subjects With Moderate-to-Severe Chronic Plaque Psoriasis. Reich K, Papp K, Blauvelt A, et al. Tildrakizumab versus placebo or etanercept for chronic plaque psoriasis (reSURFACE 1 and reSURFACE 2): Results from two randomised controlled, phase 3 trials.	February 2017 Lancet 2017; 390: 276-288.
Phase IIb trial (TIL ₃)	Randomized, double-blinded, placebo-controlled, parallel-design, dose-range finding study of subcutaneous tildrakizumab (SCH 900222/MK-3222) in subjects with moderate-to-severe chronic plaque psoriasis. Papp K, Thaci D, Reich K et al. Tildrakizumab (MK-3222), an anti-interleukin-23p19 monoclonal antibody, improves psoriasis in a phase IIb randomised placebo-controlled trial.	February 2017 British Journal of Dermatology 2015; 173: 930-939
UST vs ETN		
ACCEPT (UST ₁)	Griffiths CE, Strober BE, van de Kerkhof P et al. Comparison of ustekinumab and etanercept for moderate-to-severe psoriasis.	NEJM 2010; 362: 118-128
UST vs PBO		
PHOENIX 1 (UST ₂)	Leonardi C, Kimball A, Papp K et al. Efficacy and safety of ustekinumab, human interleukin-12/23 monoclonal antibody, in patients with psoriasis: 76-week results from a randomised, double blind, placebo-controlled trial (PHOENIX 1)	Lancet 2008; 371: 1665-1674.
PHOENIX 2 (UST ₃)	Papp K, Langley R, Lebwohl G et al. Efficacy and safety of ustekinumab, human interleukin-12/23 monoclonal antibody, in patients with psoriasis: 52-week results from a randomised, double blind, placebo-controlled trial	Lancet 2008; 371: 1675-1684.

Trial ID	Protocol title/ Publication title	Publication citation
	(PHOENIX 2)	
Igarashi 2012 (UST ₄)	Igarashi A, Kato T, Kato M et al. Efficacy and safety of ustekinumab in Japanese patients with moderate-to-severe plaque-type psoriasis: Long-term results from a phase 2/3 clinical trial.	J Dermatol. 2012; 39: 242-252..
PEARL (UST ₅)	Tsai T, Ho, J, Song M et al. Efficacy and safety of ustekinumab for the treatment of moderate-to-severe psoriasis: A phase III, randomized, placebo-controlled trial in Taiwanese and Korean patients (PEARL).	J Dermatol Sci 2011; 63: 154-163.
LOTUS (UST ₆)	Zhu X, Zheng M, Song M et al. Efficacy and safety of ustekinumab in Chinese patients with moderate to severe plaque-type psoriasis: Results from a phase 3 clinical trial (LOTUS).	J Drugs Dermatol. 2013; 12 (2): 166-174.
AMAGINE-2 (UST ₇)	Lebwohl M, Strober B, Menter A et al. Phase 3 studies comparing brodalumab with ustekinumab in psoriasis.	NEJM 2015; 373 (14): 1318-1328
AMAGINE-3 (UST ₈)		
ADA vs PBO		
CHAMPION (ADA ₁)	Saurat JH, et al. Efficacy and safety results from the randomized controlled comparative study of adalimumab vs. methotrexate vs. placebo in patients with psoriasis (CHAMPION).	Br J Dermatol. 2008; 158(3): 558-566.
REVEAL (ADA ₂)	Menter A, et al. Adalimumab therapy for moderate to severe psoriasis: A randomized, controlled phase III trial.	J Am Acad Dermatol. 2008; 58(1): 106-115.
Gordon 2006 (ADA ₃)	Gordon KB, et al. Clinical response to adalimumab treatment in patients with moderate to severe psoriasis: double-blind, randomized controlled trial and open-label extension study.	J Am Acad Dermatol. 2006; 55(4): 598-606.
Asahina 2010 (ADA ₄)	Asahina A, et al. Adalimumab in Japanese patients with moderate to severe chronic plaque psoriasis: efficacy and safety results from a Phase II/III randomized controlled study.	J Dermatol. 2010; 37(4): 299-310.
Cai 2017 (ADA ₅)	Cai L, Gu J, Zheng J et al. Efficacy and safety of adalimumab in Chinese patients with moderate-to-severe plaque psoriasis: results from a phase 3, randomized, placebo-controlled, double-blind study.	J European Acad Dermatol & Venereol 2017; 31(1): 89-95.

ADA = adalimumab; ETN = etanercept; PBO = placebo; TIL = tildrakizumab; UST= ustekinumab
 Source: Table 2(a).2-2, pp36-37 of the submission, Table 2(c).2-1 of Appendix 9 of the submission.

6.6 The key features of the included trials are summarised in Table 3.

Table 3: Key features of evidence included in the submission

Trial	N	Design/ duration of follow-up	Within trial risk of bias	Patient population	Key Outcomes
TIL vs PBO and ETN					
TIL ₁ (reSURFACE 1)	772	R, DB, MC, 64 wks Patients crossed over (PBO to TIL and TIL to PBO) at Week 12.	Low	Moderate to severe CPP; PGA _{≥3} , PASI score _{≥12} , BSA _{≥10%}	PASI 75 & PGA 0/1 & _≥ two-grade improvement in PGA at Wk 12.
TIL ₂ (reSURFACE 2)	1090	R, DB, MC, 52 wks PBO patients crossed over to TIL at Week 12.	Low		
TIL ₃ (phase IIb)	355	R, DB, MC, 52 wks PBO patients crossed over to TIL at Week 16. .	Low		PASI 75 at Wk 16
UST vs ETN					
UST ₁ (ACCEPT)	903	R, DB MC, 64 wks. ETN patients crossed-over to UST at Week 12.	Low ^a	Moderate to severe CPP; PGA _{≥3} ; PASI score _{≥12} , BSA _{≥10%}	PASI 75 at Wk 12

Public Summary Document – July 2018 PBAC Meeting

Trial	N	Design/ duration of follow-up	Within trial risk of bias	Patient population	Key Outcomes
UST vs PBO					
UST ₂ (PHOENIX 1)	766	R, DB MC, 40 wks. PBO patients crossed-over to UST at Week 12. Wk 40 to 72: randomised withdrawal phase ^b	Low	Moderate to severe CPP; PASI score ≥ 12 , BSA $\geq 10\%$	PASI 75 at Wk 12.
UST ₃ (PHOENIX 2)	1230	R, DB, MC, 28 wks, PBO patients crossed-over to UST at Week 12. Wk28 - 52: randomised dose intensification phase.	Low		
UST ₄ (Igarashi 2012)	158	R, DB, MC, 72 wks (efficacy results up to 64 wks), PBO patients crossed-over to UST at Week 12.	Low	Same as UST ₂ and UST ₃ , but in Japanese pts	Maintenance of PASI response thru to trial end.
UST ₅ (PEARL)	121	R, DB, MC, 36 wks (efficacy results up to 28 weeks). PBO patients crossed-over to UST at Week 12.	Low	Same as UST ₂ and UST ₃ , but in Korean or Taiwanese pts	
UST ₆ (LOTUS)	322	R, DB, MC, 36 wks (efficacy results up to 28 weeks). PBO patients crossed-over to UST at Week 12.	Low	Same as UST ₂ and UST ₃ , but in Chinese pts	
UST ₇ (AMAGINE-2)	1831	R, DB, MC, 52 wks. Trial compared brodalumab, UST and PBO. PBO patients crossed-over to brodalumab at Week 12.	Low	Moderate to severe CPP; PASI score ≥ 12 , BSA $\geq 10\%$, sPGA ≥ 3	PASI 75 & sPGA (0,1) at Wk 12. Maintenance of PASI response thru to Wk 52.
UST ₈ (AMAGINE-3)	1881		Low		
ADA vs PBO					
ADA ₁ (CHAMPION)	271	R, DB, MC, 16wks	Low	Moderate to severe; PASI score ≥ 10 AND BSA $\geq 10\%$	PASI 75 at 16 weeks
ADA ₂ (REVEAL)	1,212	R, DB, MC, 52wks. PBO patients crossed over to ADA at Week 16.	Low	Moderate to severe; PASI score ≥ 12 AND PGA ≥ 3 AND BSA $\geq 10\%$	
ADA ₃ (Gordon 2006)	148	R, DB, MC, 60wks. PBO patients crossed over to ADA at Week 12.	Low	Moderate to severe; BSA $\geq 5\%$	PASI 75 at 12 weeks
ADA ₄ (Asahina 2010)	235	R, DB, MC, 24wks	Low	Moderate to severe; PASI score ≥ 12 AND BSA $\geq 10\%$; Japanese pts	PASI 75 at 16 weeks
ADA ₅ (Cai 2017)	425	R, DB, MC, 12wks PBO patients crossed over to ADA at Week 12.	Low	Moderate to severe; PASI score ≥ 10 AND PGA ≥ 3 AND BSA $\geq 10\%$; Chinese pts	PASI 75 at 12 weeks

ADA = adalimumab; BSA = body surface area; CPP = chronic plaque psoriasis; DB = double blind; ETN = etanercept; MC = multicentre; PASI = Psoriasis Area Severity Index; PC = placebo control; pts = patients; R = randomised; PGA = physician global assessment (3 corresponds to moderate CPP; 0-2 correspond to clear to mild); sPGA = static physician global assessment; TIL = tildrakizumab; UST = ustekinumab

^a Patients were aware of treatment assignment but study personnel were unaware of treatment assignment.

Source: compiled during the evaluation from trial publications.

- 6.7 In brief, all trials were multicentre, double blind RCTs, with the exception of the UST ACCEPT trial, which was single-blinded, with patients aware of whether they were assigned UST or ETN. Overall, the risks of bias in the placebo-controlled phase of the trials were considered low. As most of the trials allowed patients to switch from placebo to active treatment beyond the initial placebo-controlled phase (12/16 weeks) outcomes from subsequent periods would be subject to bias. However, appropriately, trial outcomes were assessed at the end of the placebo-controlled periods.
- 6.8 In the TIL reSURFACE 2 trial switching was not permitted at Week 12 for those randomised to the active comparator of ETN until Week 28. As a result, direct comparative efficacy results comparing TIL and ETN were available for up to 28 weeks in this trial. The TIL, UST trials and most of the ADA trials enrolled similar patient populations, consisting of adult patients with moderate to severe plaque psoriasis (PASI score > 12, and body surface area involvement > 10%). The exceptions were: two ADA trials (CHAMPION and Cai 2017) enrolled patients with PASI score > 10; and one ADA trial (Gordon 2006) trial enrolled patients with body surface area involvement > 5% with no inclusion criteria for PASI scores (mean participant PASI score was approximately 16, lower than other trials, range: 18.6-30.3). The TIL trials, three UST trials (ACCEPT, and AMAGINE 2 and AMAGINE 3) and two ADA trials (REVEAL and Cai 2017) in addition, required patients to have a Physician's Global Assessment (PGA) score > 3. A PGA score of 3, 4 and 5 corresponds to moderate, severe and very severe symptoms, respectively, and PGA scores of 0-2 correspond to clear to mild symptoms.
- 6.9 As discussed, the TIL and UST trial populations differed to the requested PBS population (which has stricter requirements for number of prior failed therapies and severity) but overall the trial populations were similar to other trials of biologics previously considered by the PBAC and were generally representative of the likely PBS population.
- 6.10 The dosing regimens of TIL and ETN in the trials were consistent with those recommended in the (draft) PIs. Both TIL 100 mg and TIL 200 mg were used in all of the TIL trials. The submission excluded the TIL 100 mg dose as it is not the proposed dose in the draft PI. The commentary focused on TIL 200 mg as this is the proposed dose in the draft PI, however, PASI outcomes for TIL 100 mg versus TIL 200 mg was also summarised in the evaluation of the submission. For UST, except for the AMAGINE-2 and -3 trials which administered UST based on the recommended weight based dosing (45 mg for patients ≤ 100 kg and 90 mg for patients >100 kg), the doses used in the UST trials generally deviated from its PI, as patients were randomly allocated to either 45 mg or 90 mg UST treatment.

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

Comparative effectiveness

- 6.11 The PBAC had previously based recommendations for listing of biologics for the treatment of CPP on the proportion of patients i) achieving and ii) maintaining a PASI 75 response ($\geq 75\%$ improvement from baseline in the Psoriasis Area and Severity Index score). This is also consistent with the PBS eligibility criteria for continued treatment with biologics. PASI 75 response was the primary outcome in all included trials. In addition, results were reported for PASI 90 and PASI 100 response (90% or 100% improvement from baseline in PASI score respectively), PGA (Physician's Global Assessment) and DLQI (Dermatology Life Quality Index).
- 6.12 Appropriately, the submission's clinical claims were based on the outcome of PASI 75 response.
- 6.13 Table 4 below summarises both direct and indirect comparative results of PASI 75 responses for TIL versus the nominated comparators, based on the results for the ITT population at either 12 or 16 weeks:
- A. direct comparisons of TIL vs ETN from reSURFACE 2;
 - B. indirect comparisons for TIL vs UST via the common reference of ETN;
 - C. indirect comparisons for TIL vs UST via the common reference of placebo; and
 - D. indirect comparisons for TIL vs ADA via the common reference of placebo.

Table 4: PASI 75 response at Weeks 16/12 across the trials – ITT populations

Trial	Drug n/N (%)	Control n/N (%)	RR (95% CI) ^A	OR (95% CI) ^A	RD [95% CI] ^A	NNT (95%CI)
A: Direct comparison: TIL vs ETN Wk12						
TIL2	206/314 (65.6)	151/313 (48.2)	1.36 (1.18, 1.56)	2.05 (1.48, 2.82)	– 0.17 (0.10, 0.25)	6 (4, 10)
UST 45 mg vs ETN Wk12						
UST1	141/209 (67.5)	197/347 (56.8)	1.19 (1.04, 1.36)	1.58 (1.10, 2.26)	+ 0.11 (0.02, 0.19)	9 (5, 50)
UST 90 mg vs ETN Wk12						
UST1	256/347 (73.8)	197/347 (56.8)	1.30 (1.16, 1.45)	2.14 (1.56, 2.95)	+ 0.17 (0.10, 0.24)	6 (4, 10)
Pooled UST1	397/556 (71.4)	197/347 (56.8)	1.26 (1.13, 1.40)	1.90 (1.44, 2.52)	+ 0.15 (0.08, 0.21)	7 (5, 13)
TIL vs PBO Wk12						
TIL1	192/308 (62.3)	9/155* (5.8)	<i>10.74 (5.66, 20.36)</i>	<i>26.85 (13.18, 54.70)</i>	+ 0.57 (0.50, 0.63)	2 (2, 2)
TIL2	206/314 (65.6)	9/156 (5.8)	<i>11.37 (6.00, 21.55)</i>	<i>31.15 (15.28, 63.50)</i>	+ 0.60 (0.53, 0.66)	2 (2, 2)
TIL3 ^a	62/86 (72.1)	2/46* (4.3)	<i>16.58 (4.25, 64.72)</i>	<i>56.83 (12.77, 253.0)</i>	+ 0.68 (0.57, 0.79)	1 (1, 2)
Pooled	460/708 (65.0)	20/357 (5.6)	<i>11.50 (7.49, 17.67)</i>	<i>30.98 (19.23, 49.92)</i>	+ 0.60 (0.55, 0.65)	2 (2, 2)
UST 45 mg vs PBO Wk 12						
UST2	171/255 (67.1)	8/255 (3.1)*	21.38 (10.75, 42.50)	62.85 (29.66, 133.2)	+ 0.64 (0.58, 0.70)	2 (1, 2)
UST3	273/409 (66.7)	15/410 (3.7)*	18.24 (11.05, 30.12)	52.86 (30.34, 92.09)	+ 0.63 (0.58, 0.68)	2 (1, 2)
UST4	38/64 (59.4)	2/32 [#] (6.3)	9.50 (2.45, 36.91)	21.92 (4.82, 99.82)	– 0.53 (0.38, 0.68)	2 (1, 2)
UST5	41/61 (67.2)	3/60 (5.0)	13.44 (4.40, 41.07)	38.95 (10.85, 139.8)	+ 0.62 (0.49, 0.75)	2 (1, 2)
UST6	132/160 (82.5)	18/162 (11.1)	7.42 (4.78, 11.54)	37.71 (19.94, 71.34)	+ 0.71 (0.64, 0.79)	1 (1, 2)
Pooled	655/949 (69.0)	46/918 (5.0)	13.17 (7.86, 22.07)	46.50 (33.01, 65.49)	+ 0.64 (0.60, 0.69)	2 (1, 2)
UST 90 mg vs PBO Wk 12						
UST2	170/256 (66.4)	8/255 (3.1)	21.17 (10.64, 42.10)	61.03 (28.82, 129.3)	+ 0.63 (0.57, 0.69)	2 (1, 2)
UST3	311/411 (75.7)	15/410 (3.7)*	20.68 (12.55, 34.09)	81.90 (46.66, 143.8)	– 0.72 (0.67, 0.77)	1 (1, 1)
UST4	42/62 (67.7)	2/32 [#] (6.3)	10.84 (2.80, 41.93)	31.50 (6.84, 145.1)	– 0.61 (0.47, 0.76)	2 (1, 2)
Pooled	523/729 (71.7)	25/696 (3.6)	19.76 (13.41, 29.11)	68.83 (44.70, 106.0)	+ 0.67 (0.60, 0.74)	1 (1, 2)
UST Label vs PBO Wk 12						
UST7	210/300 (70.0)	25/309 (8.1)	8.65 (5.90, 12.69)	26.51 (16.44, 42.74)	+ 0.62 (0.56, 0.68)	2 (1, 2)
UST8	217/313 (69.3)	19/315 (6.0)	11.49 (7.39, 17.88)	35.21 (20.89, 59.37)	+ 0.63 (0.58, 0.69)	2 (1, 2)
Pooled	427/613 (69.7)	44/624 (7.1)	9.77 (7.32, 13.05)	30.17 (21.21, 42.92)	+ 0.63 (0.58, 0.67)	2 (1, 2)
Pooled UST 2-8	1605/2291 (70.1)	90/1542 (5.8)	11.9 (8.4, 16.9)	50.9 (36.4, 71.2)	– 0.65 (0.62, 0.68)	2 (1, 2)
ADA 40 mg eow vs PBO Wk 12/16						
ADA1 ^b	86/108 (79.6)	10/53 (18.9)	<i>4.22 (2.40, 7.44)</i>	<i>16.81 (7.31, 38.64)</i>	+ 0.61 (0.48, 0.74)	2 (1, 2)
ADA2 ^b	578/814 (71.0)	26/398 (6.5)	<i>10.87 (7.48, 15.80)</i>	<i>35.04 (22.90, 53.62)</i>	+ 0.64 (0.61, 0.68)	2 (1, 2)
ADA3	24/46 (52.2)	2/52 (3.9)	<i>13.57 (3.39, 54.29)</i>	<i>27.27 (5.92, 125.6)</i>	+ 0.48 (0.33, 0.64)	2 (2, 3)
ADA4 ^b	27/43 (62.8)	2/46 (4.3)	<i>14.44 (3.65, 57.11)</i>	<i>37.13 (7.91, 174.2)</i>	+ 0.58 (0.43, 0.74)	2 (1, 2)
ADA5	263/338 (77.8)	10/87 (11.5)	<i>6.77 (3.77, 12.16)</i>	<i>27.00 (13.31, 54.76)</i>	+ 0.66 (0.58, 0.74)	2 (1, 2)
Pooled	978/1349 (72.5)	50/636 (7.9)	<i>7.97 (4.96, 12.81)</i>	<i>29.57 (21.49, 40.69)</i>	+ 0.63 (0.58, 0.67)	2 (1, 2)
Indirect comparisons: TIL vs comparators						
B: TIL vs UST45mg (TIL2 v UST1) via ETN			1.14 (0.94, 1.39)	1.30 (0.80, 2.10)	+ 0.06 (-0.05, 0.17)	NA
B: TIL vs UST 90mg (TIL2 v UST1) via ETN			1.05 (0.88, 1.25)	0.96 (0.61, 1.51)	0.00 (-0.10, 0.10)	NA
B: TIL vs UST (45& 90mg) (TIL2 v UST1) via ETN			1.08 (0.91, 1.29)	1.08 (0.70, 1.65)	0.02 (-0.08, 0.12)	NA
C: TIL vs UST45mg (TIL1-3 v UST2-8) via PBO			0.87 (0.45, 1.71)	0.67 (0.37, 1.20)	– 0.04 (-0.11, 0.03)	NA
C: TIL vs UST 90mg (TIL1-3 v UST2-8) via PBO			0.58 (0.33, 1.04)	0.45 (0.24, 0.86)	– 0.07 (-0.16, 0.02)	NA
C: TIL vs UST Label (TIL1-3 v UST2-8) via PBO			1.18 (0.70, 1.98)	1.03 (0.57, 1.89)	– 0.03 (-0.10, 0.04)	NA
C: TIL vs UST (all doses) (TIL1-3 v UST2-8) via PBO			0.96 (0.56, 1.67)	0.77 (0.44, 1.35)	– 0.05 (-0.11, 0.01)	NA
D: TIL versus ADA (TIL1-3 v ADA1-5) via PBO			1.44 (0.76, 2.74)	1.05 (0.59, 1.86)	– 0.03 (-0.1, 0.04)	NA

Grey shading indicate data previously seen by the PBAC. Italics indicate results estimated during the evaluation. Bold typography indicates statistically significant differences. ^A estimated during the evaluation using random effects meta-analysis using RevMan Version 5.3.

TIL₁ = reSURFACE1; TIL₂ = reSURFACE-2; TIL₃ = Phase II trial; UST₁ = ACCEPT; UST₂ = PHOENIX-1; UST₃ = PHOENIX-2; UST₄ = PEARL; UST₅ = LOTUS; UST₆ = Igarashi 2012; UST₇ = AMAGINE-2; UST₈ = AMAGINE-3; UST Label refers to weight-based dosing for UST (UST 45 mg for patients ≤ 100 kg; UST 90 mg for patients > 100 kg); Wk = week; ADA = adalimumab; ETN = etanercept; PBO = placebo; TIL = tildrakizumab; UST = ustekinumab; PASI 75 = ≥ 75% reduction in the Psoriasis Area and Severity Index. *analysis in the ITT population (using NRI) One patient in the PBO arm was randomised but never treated in reSURFACE 1 and the phase IIb trial. #analysis in the ITT population. One patient in the PBO arm was randomised but did not receive active treatment. ^a primary PASI75 outcome was at Wk 16, Week 12 PASI 75 presented here was a secondary outcome ^b Wk 16 PASI75 outcome given primary outcome

was measured at this time. Source: constructed during the evaluation using results reported in Table 2(a).5-2, Table 2(a).5-5, Table 2(a).5-35, Table 2(a).6-40, Tables 2(a).6-57 to Table2(a).6-58; Table 2(b).5-1, p20; Table 2(c).6-13, p72 of Appendix 1, p94,115, 161-162, 175 of the submission.

6.13 Table 5 summarises results of indirect and direct comparisons for other efficacy outcomes at Week 12/16.

Table 5: Summary of direct and indirect comparisons for PASI 90, PASI 100, PGA and DLQI outcomes at 12/16^a weeks – ITT populations

Outcome and comparison	RR [^] (95% CI)	OR [^] (95% CI)	RD [^] (95% CI)
PASI 90			
A: TIL vs ETN (TIL2) direct	1.71 (1.32, 2.21)	2.12 (1.49, 3.02)-	0.15 (0.08, 0.22)
B: TIL vs UST (45&90 mg) (TIL2 v UST1) indirect via ETN	0.95 (0.68, 1.33)	0.90 (0.56, 1.43)-	-0.03 (-0.13, 0.07)
C: TIL vs UST (all doses) (TIL1-3 v UST2-8) indirect via PBO	0.70 (0.29, 1.71)	0.53 (0.21, 1.37)-	-0.11 (-0.21, -0.01)
D: TIL vs ADA (TIL1-3 v ADA1-5) indirect via PBO	1.36 (0.39, 4.76)	1.12 (0.34, 3.75)-	-0.10 (-0.17, -0.03)
PASI 100			
A: TIL vs ETN (TIL2) direct	2.46 (1.38, 4.39)	2.65 (1.42, 4.94)-	0.07 (0.03, 0.11)
C: TIL vs UST (all doses) (TIL1-3 v UST2-8) indirect via PBO	0.33 (0.08, 1.35)	0.30 (0.07, 1.28)	-0.05 (-0.10, 0.00)
D: TIL vs ADA (TIL1-3 v UST2-8) indirect via PBO	0.87 (0.22, 3.48)	0.83 (0.20, 3.39)	-0.03 (-0.08, 0.2)
PGA responder^b			
A: TIL vs ETN (TIL2) direct	1.24 (1.07, 1.44)	1.60 (1.17, 2.19)	0.12 (0.04, 0.19)
B: TIL vs UST (45&90 mg) (TIL2 v UST1) indirect via ETN ^b	0.89 (0.73, 1.07)	0.71 (0.46, 1.07)	-0.08 (-0.18, 0.02)
C: TIL vs UST (all doses) (TIL1-3 v UST2-8) indirect via PBO ^b	0.96 (0.53, 1.74)	0.74 (0.43, 1.27)	-0.04 (-0.10, 0.02)
D: TIL vs ADA (TIL1-3 v ADA1-5) indirect via PBO ^b	1.31 (0.64, 2.65)	0.89 (0.49, 1.60)	-0.04 (-0.10, 0.02)
DLQI 0/1			
A: TIL vs ETN (TIL2) direct	1.34 (1.10, 1.62)	1.63 (1.18, 2.25)	0.12 (0.04, 0.19)
C: TIL vs UST (all doses) (TIL1-3 v UST2-8) indirect via PBO ^a	0.57 (0.29, 1.12)	0.48 (0.22, 1.07)	-0.05 (-0.17, 0.07)
Change DLQI, baseline^c			
	-	-	Mean difference (95%CI)
A: TIL vs ETN (TIL2) direct	--	-	-1.40 (-2.39, -0.41)
B: TIL vs UST (45&90 mg) (TIL2 v UST1) indirect via ETN	-	-	-0.25 (-1.75, 1.25)
C: TIL vs UST (all doses) (TIL1-3 v UST2-8) indirect via PBO	-	-	0.04 (-1.67, 1.75)
D: TIL vs ADA (TIL1-3 v ADA1-5) indirect via PBO	-	-	-2.39 (-5.26, 0.48)

DLQI = Dermatology Life Quality Index; PASI 90 100 = (≥90%, 100%) reduction in the Psoriasis Area and Severity Index; PGA = Physician's Global Assessment

Bolded values reached statistical significance p<0.05; Italics indicates estimates corrected or performed during the evaluation.

[^] estimated using random effects meta-analysis using RevMan Version 5.3 following Bucher 1997 methods.

^a Week 16 PASI75 outcome used in some ADA trials (ADA1, ADA2, and ADA4) given primary outcome was measured at this time

^b defined as (s)PGA 0/1, in the TIL1 and TIL2 trials patients also need to attain a > two-grade improvement, however should not impact comparability of the outcomes since TIL1 and TIL2 only enrolled patients with baseline PGA≥3.

^c Least Squares means from TIL1 and TIL2 trials.

Source: Table 2(a).5-3-4, Table 2(a).5-13-14, Table 2(a).5-36, Table 2(a).6-37-39, Table 2(a).6-48-49, Table 2(a).6-50-51, Table 2(a).6-59-60, p93-94, 98, 116, 159-161, 167-170, 176 of the submission; Table 2(b).5-4 Table 2(b).5-9-10, p22, 25 of Appendix 1 of the submission

Summary of efficacy results

TIL versus UST

- 6.14 Both TIL and UST were significantly more effective than placebo in terms of proportions of patients attaining PASI 75 response at 12 weeks. This was also affirmed by Physician Global Assessment responses (PGA) and Dermatology Life Quality Index (DLQI) outcome measures (see pp.95-99, 102-111 of the submission).
- 6.15 Results of indirect comparisons using PBO as common reference generally did not favour TIL for attainment of PASI 75 response at Week 12, with lower 95%CI exceeding -10% for the RD statistic. The indirect comparison also reached statistical significance for the OR statistic between TIL and UST 90 mg (OR (95%CI): 0.45 (0.24, 0.86)), indicating TIL may be inferior to UST 90 mg. Using results of UST1 (ACCEPT trial) and TIL2 (reSURFACE 2) the submission also conducted indirect comparisons between TIL and UST using ETN as common comparator, these comparisons by contrast did not find any significant differences between TIL and UST. However, given only two trials were included in these indirect comparisons, the relevance of these results to decision making may be limited.
- 6.16 Results of indirect comparisons for PASI 90, PASI 100, PGA and DLQI outcomes also generally indicated that fewer patients treated with TIL attained these outcomes compared to UST treated patients. The result also reached statistical significance for PASI 90 in the indirect comparison of TIL vs UST (all doses) when placebo was used as common reference (comparison C) in the RD statistic: RD (95%CI): -0.11 (-0.21, -0.01).

TIL versus ETN

- 6.17 Based on direct trial evidence from the reSURFACE 2 trial, TIL was significantly more effective than ETN in terms of proportions of patients attaining PASI 75 response at Week 12. This was also consistent with directly comparative results for PASI 90, PASI 100, PGA and DLQI outcome at Week 12 and results for PASI90, PASI 100 and PGA at Week 28.

TIL versus ADA

- 6.18 Both TIL and ADA were significantly more effective than placebo in terms of proportions of patients attaining PASI 75 response at Week 12. Based on indirect comparisons using PBO as common reference, no significant differences were detected between TIL and ADA with respect to PASI 75 response, suggesting that a conclusion of non-inferiority of TIL versus ADA would be reasonable. Results of indirect comparisons for PASI 100, and PGA outcomes also appeared to support this conclusion.

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

Comparative harms

- 6.19 The results of the indirect comparison of safety outcomes at the end of the placebo-controlled periods Weeks 12/16 and up to Week 28 in the reSURFACE 2 trial (providing direct comparative data for TIL versus ETN) are presented in Table 6. Adverse events (AEs) were generally similar between TIL and comparators, except for fewer injection site reactions versus ETN (but overall numbers of AEs did not differ significantly) and fewer AEs overall versus UST (but only in indirect comparison using PBO as common comparator). During Weeks 0-28 of the reSURFACE 2 trial, TIL patients had also reported significantly less AEs compared to ETN patients, most likely due to fewer injection site events. However despite this, the proportion of patients with serious AEs and discontinuations due to AEs were similar between TIL and ETN. Like UST, the most frequently reported AEs for TIL was nasopharyngitis and headaches. The results would appear to support a conclusion of non-inferior safety for TIL versus UST, ETN and ADA. This was consistent with the submission's safety claims versus UST and ADA but not ETN (refer Clinical Claims).

Table 6: Summary of safety direct and indirect comparisons: TIL vs comparators

	RR [^] (95% CI)	OR [^] (95% CI)	RD [^] (95% CI)
Weeks 0-12/16 (placebo-controlled period)			
A: TIL vs ETN (direct)			
Any AE	<i>0.91 (0.79, 1.06)</i>	<i>0.83 (0.61, 1.14)</i>	<i>-0.05 (-0.12, 0.03)</i>
Serious AE	<i>0.85 (0.29, 2.51)</i>	<i>0.85 (0.28, 2.56)</i>	<i>-0.00 (-0.03, 0.02)</i>
Discontinuation due to AE	<i>0.50 (0.13, 1.98)</i>	<i>0.49 (0.12, 1.99)</i>	<i>-0.01 (-0.03, 0.01)</i>
Injection site reactions	0.14 (0.03, 0.62)	0.14 (0.03, 0.61)	-0.04 (-0.06, -0.01)
Infections	<i>0.92 (0.69, 1.22)</i>	<i>0.89 (0.61, 1.30)</i>	<i>-0.02 (-0.09, 0.05)</i>
B: TIL vs UST all doses (indirect via ETN)			
Any AE	<i>0.94 (0.79, 1.11)</i>	<i>0.91 (0.60, 1.40)</i>	<i>-0.03 (-0.13, 0.07)</i>
Serious AE	<i>0.68 (0.14, 3.39)</i>	<i>0.68 (0.13, 3.51)</i>	<i>0 (-0.03, 0.03)</i>
Discontinuation due to AE	<i>0.81 (0.15, 4.28)</i>	<i>0.79 (0.14, 4.40)</i>	<i>0 (-0.03, 0.03)</i>
Injection site reactions	<i>0.88 (0.18, 4.26)</i>	<i>1.08 (0.22, 5.20)</i>	0.17 (0.11, 0.23)
Infections	<i>0.89 (0.63, 1.27)</i>	<i>0.85 (0.53, 1.37)</i>	<i>-0.03 (-0.12, 0.06)</i>
C: TIL vs UST all doses (indirect via PBO)			
Any AE	0.85 (0.74, 0.97)	0.70 (0.52, 0.93)	-0.09 (-0.16, -0.02)
Serious AE	<i>1.99 (0.57, 6.86)</i>	<i>2.00 (0.57, 7.06)</i>	<i>0.01 (-0.01, 0.03)</i>
Discontinuation due to AE	<i>1.76 (0.46, 6.77)</i>	<i>1.79 (0.45, 7.09)</i>	<i>0.01 (-0.02, 0.02)</i>
Injection site reactions	<i>0.49 (0.06, 3.94)</i>	<i>0.48 (0.06, 3.93)</i>	<i>0 (-0.01, 0.01)</i>
Infections	<i>0.86 (0.65, 1.14)</i>	<i>0.82 (0.57, 1.18)</i>	<i>-0.03 (-0.09, 0.03)</i>
D: TIL vs ADA (indirect via PBO)			
Any AE	<i>0.87 (0.74, 1.01)</i>	0.64 (0.46, 0.89)	-0.10 (-0.18, -0.02)
Serious AE	<i>1.46 (0.40, 5.29)</i>	<i>1.48 (0.40, 5.51)</i>	<i>0.01 (-0.01, 0.03)</i>
Discontinuation due to AE	<i>1.07 (0.27, 4.22)</i>	<i>1.07 (0.26, 4.38)</i>	<i>0 (-0.02, 0.02)</i>
Injection site reactions	<i>0.36 (0.05, 2.54)</i>	<i>0.33 (0.05, 2.41)</i>	<i>-0.04 (-0.09, 0.01)</i>
Infections	<i>0.85 (0.63, 1.13)</i>	<i>0.76 (0.52, 1.12)</i>	<i>-0.05 (-0.12, 0.02)</i>
Weeks 0-28			
A: TIL vs ETN (direct)			
Any AE	0.85 (0.76, 0.95)	0.60 (0.43, 0.84)	-0.11 (-0.18, -0.04)
Serious AE	<i>0.55 (0.27, 1.13)</i>	<i>0.53 (0.25, 1.13)</i>	<i>-0.03 (-0.06, 0.01)</i>
Discontinuation due to AE	<i>0.44 (0.14, 1.42)</i>	<i>0.44 (0.13, 1.43)</i>	<i>-0.02 (-0.04, 0.01)</i>
Injection site reactions	0.23 (0.08, 0.69)	0.22 (0.07, 0.68)	-0.04 (-0.07, -0.01)
Infections	<i>0.93 (0.77, 1.12)</i>	<i>0.88 (0.64, 1.21)</i>	<i>-0.03 (-0.11, 0.05)</i>

Italics indicate results estimated during the evaluation, bold typography indicates statistically significant results.

ADA = adalimumab; ETN = etanercept; TIL = tildrakizumab; UST = ustekinumab; AE = adverse event; CI = confidence interval; OR =

Odds Ratio; RD = Risk Difference; RR = Relative Risk

[^] estimated during the evaluation in RevMan Version 5.3 following the Bucher 1997 method.

Source: Estimated during the evaluation using results reported in Table 2(a).6-52 to 56, pp.170-174 of the submission; Table 2(b).5-11, p26-27; Table 2(c).6-23 to 27, pp.80-84 of Appendix 1 of the submission; Table 12-4, Table12-8; Table 14.3-27; p241, 249, 1105-6 of CSR for re SURFACE 2.

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

Clinical claim

6.20 The submission described TIL as:

- non-inferior in terms of effectiveness and safety compared to UST
- superior in terms of effectiveness and safety compared to ETN; and
- non-inferior in terms of effectiveness and safety compared to ADA.

6.21 Based on the evidence presented in the submission, the claims appeared reasonable except for:

- The claim of non-inferior efficacy against UST. Results of indirect comparisons using PBO as common reference generally did not favour TIL for attainment of PASI75 response at Week 12. The ESC considered that the PASI 75 outcome at Week 12 (including odds ratio (OR), 95% CI: 0.77: 0.44-1.35) indicated possible inferiority based on the lower 95% CI exceeding -10% for the RD statistic (-0.05: -0.11-0.01). The ESC noted that the PSCR questioned the introduction of -10% as a criteria for non-inferiority in the indirect comparison of TIL versus UST. The indirect comparison also reached statistical significance for the OR statistic between TIL and UST 90 mg (OR (95%CI): 0.45 (0.24, 0.86)), indicating TIL may be inferior to UST 90 mg. Using results of UST1 (ACCEPT trial) and TIL2 (reSURFACE 2) the submission also conducted indirect comparisons between TIL and UST using ETN as common comparator. Although these comparisons did not find any significant differences between TIL and UST at any dose, given only two trials were included in the comparisons, the relevance of these results to decision making may be limited. The ESC considered that the nominated main comparator of ustekinumab (UST) is reasonable on the basis of use and mechanism but cannot be used for cost minimisation since the indirect comparison does not show unequivocal non-inferiority. It is noted that other evidence in the submission indicate that tildrakizumab (TIL) is probably superior to etanercept (ETN) on direct comparison and non-inferior to adalimumab (ADA) on indirect comparison.
- The claim of superior safety of TIL vs ETN. Although TIL reduced injection site reactions compared to ETN, the proportion of patients with serious AEs and discontinuations due to AEs were similar between TIL and ETN. Although TIL significantly reduced overall AEs up to 28 weeks (Part 1 and 2 of re SURFACE 2 trial) compared to ETN, it did not significantly reduce overall AEs in the first 12 weeks of treatment. The PSCR acknowledged the assessment in the

commentary that a conclusion of non-inferior safety of TIL vs ETN may be more reasonable.

- 6.22 The ESC noted that no comparative evidence of TIL vs either IFX or IXE was presented in the submission. In addition, the ESC noted that a submission for guselkumab (GUS), a drug with a similar mechanism of action to TIL, will be considered at the July PBAC meeting. The PSCR reiterated that the choice of UST as main comparator and ETN and ADA as supplementary comparators is appropriate, but acknowledged that IFX is less costly than UST due to the availability of biosimilars.
- 6.23 In the PSCR, the sponsor:
- expressed that the submission did not nominate a non-inferiority margin because ‘there is not published evidence that support the use of this statistic for PASI 75’, and argued that previously the PBAC has recommended listing of other bDMARDs without applying non-inferiority margin.
 - argued that the dosing regimen used in the UST clinical trial may have biased the results of the indirect comparison against tildrakizumab
 - argued that the indirect comparison via ETN as common reference supports the claims of non-inferiority of TIL to UST.

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

Economic analysis

- 6.24 The submission presented a cost-minimisation analysis of TIL versus UST. The ESC considered the cost-minimisation analysis against UST was not supported by the results of indirect comparisons that indicate that TIL may be inferior to UST in terms of efficacy. The Pre-PBAC Response maintained that the cost-minimisation analysis versus UST was supported on the basis of that the totality of the evidence which demonstrated that TIL is non-inferior to UST via indirect comparison and to etanercept via direct comparison.
- 6.25 In addition, given all PBS listed biologics for CPP share a similar listing, other listed biologics will also be replaced in practice. No evidence was presented in the submission against potentially more effective but less costly comparators (IXE and IFX). The analyses compared total drug costs over a 2-year treatment period (without discounting), which was consistent with approach previously accepted by the PBAC in CPP.
- 6.26 The submission estimated equi-effective doses for TIL and UST based on the recommended maintenance doses (‘steady state’), weighted by the estimated proportional use of the UST 45 mg (65%) and 90 mg (35%) dosing regimens in Australia. It was noted that the UST dose according to its PI is 45 mg (for patients weighing ≤ 100 kg) or UST 90 mg (for patients weighing > 100 kg) at Weeks 0, 4 and then every 12 weeks thereafter. Based on DHS data, the submission estimated that TIL 200 mg Q12W was equi-effective to UST 60.57mg Q12W for maintenance therapy.

- 6.27 UST is currently listed on the PBS under a Special Pricing Arrangement (SPA). As the Sponsor for TIL did not have access to SPA details for UST in CPP, the cost-minimisation analysis was based on the published price of UST.
- 6.28 The Approved Ex-Manufacturer Price (AEMP) of TIL cost-minimised to UST over a 104-week period was estimated to be \$██████████, based on published prices.
- 6.29 The submission reasonably assumed that there would be no additional administration costs for TIL compared to UST.
- 6.30 Despite claiming non-inferiority versus ADA, the submission did not present a cost minimisation analysis against this comparator. Based on trial doses and established therapeutic relativities between listed bDMARDs, the equi-effective dose versus ADA would be: TIL 200 mg at Weeks 0, 4 and every 12 weeks thereafter ≡ ADA initial dose 80 mg, then 40 mg fortnightly, starting one week after the initial dose.
- 6.31 In the PSCR and Pre-PBAC Response, the sponsor stated it would consider accepting a listing for tildrakizumab on a cost-minimisation basis to the least costly bDMARD over a 2-year treatment period based on the effective ex-manufacturer indication-specific prices using equi-effective doses that are derived directly from the relevant clinical trial.

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

Drug cost/patient/year: \$██████████ (based on published price of TIL).

- 6.32 Using the requested DPMQ of \$5,846.15 per pack of two 100 mg injections, and assuming 4.33 TIL injections per patient per year will be used in the maintenance treatment phase, the drug cost of TIL was estimated to be \$██████████ per patient per year. PBS treatment is only permitted to continue if the patients achieve and maintain a PASI 75 response. Using the DPMQ for UST of \$4,346.86 and assuming 4.33 UST injections per patient per year dispensed in the maintenance treatment phase, the drug cost of UST was estimated to be \$██████████ for maintenance for an UST patient weighing < 100 kg (hence requiring a dose of UST 45 mg).

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

Estimated PBS usage & financial implications

- 6.33 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 were 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 TIL would substitute for initiation with all currently listed bDMARDs, but total patient-years on bDMARDs would be unchanged.

Table 7: Estimated net financial implications of the proposed TIL listing

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

^a Initiation periods are converted to initiation patient-years by multiplying by (length of initiation period in weeks / 52 weeks in a year)
 Source: Tables 4.2-2 to 4.5-3 pp203-213 of the submission; '4D.Treatment-Years' worksheet of Tildrakizumab Section 3 – 4 FINALEXCEL file.

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

- 6.34 The model predicted more patient-years of initiation therapy with TIL due to a longer initiation period of 28 weeks compared to some of the other alternative bDMARDs such as SEC, IXE and ADA with an initiation period of 16 weeks, and hence shorter duration on maintenance therapy.
- 6.35 The submission requested a listing for grandfathered patients (less than 10,000 patients); it was unclear from the submission whether the assumed uptake rates had incorporated this population.

- 6.36 Overall, the financial estimates presented (totalling \$10 - \$20 million over the first 6 years) may not be accurate given they were based on published prices of bDMARDs rather than effective prices (after accounting for special pricing arrangements). While the proposed listing of TIL was based on a cost-minimisation analysis to UST, the net cost to the health budget will depend on the relative substitution of differently priced alternatives. The evaluation noted that listing of TIL based on a cost-minimisation analysis with the least costly bDMARD and based on the methodology in the submission, the net cost to the health budget might be negative as more costly alternatives may be substituted. The PSCR acknowledged that the effective indication-specific prices of bDMARDs are confidential and therefore the estimation of cost to the Health Budget presented in the submission is not accurate.

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

7 PBAC outcome

- 7.1 The PBAC recommended an Authority Required listing of tildrakizumab on a cost-minimisation basis against the lowest cost biological agent for the treatment of adult patients with severe chronic plaque psoriasis (CPP). In making this recommendation, the PBAC accepted any of the current PBS listed bDMARDs for severe CPP could be an alternative therapy to tildrakizumab.
- 7.2 The PBAC noted that six alternative bDMARDs were listed on the PBS for the treatment of severe CPP at the time of the July 2018 meeting; specifically: adalimumab, etanercept, infliximab, ixekizumab, secukinumab and ustekinumab. The PBAC noted that guselkumab for the same indication was also considered at the same meeting. 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 PBAC recommended that the restrictions for tildrakizumab should be consistent with those for the bDMARDs that are currently listed on the PBS for the treatment of CPP and that flow-on changes for all PBS listings to the note 'Treatment of adult patients with Severe Chronic Plaque Psoriasis' would be required to include tildrakizumab as one of the bDMARDs for this indication. However, the PBAC noted that the registration of tildrakizumab (TIL) had not been finalised at the time of the Committee's consideration of the submission. The final product information on the dosage of treatment would inform the maximum quantities for the initial and continuing treatments (currently proposed to be 2 x 100 mg pre-filled single use syringes for a dose of 200 mg). In light of the FDA decision recommending only the 100 mg dosage, the PBAC noted that the evaluation of the submission presented the trial data of patients using TIL 200 mg and TIL 100 mg. There were no significant differences between TIL 200 mg and TIL 100 mg with respect to PASI responses at Week 12/16 in the TIL trials (the time point at which comparative efficacy was assessed).

- 7.4 The submission requested grandfather restrictions for patients currently enrolled in clinical trials and those in the tildrakizumab Patient Familiarisation Program (PFP). The PBAC advised that it would be appropriate to provide grandfathered PBS supply to those patients, receiving tildrakizumab, who had met initial treatment criteria at the time of entering the clinical trials or the tildrakizumab PFP. The grandfather provision should be removed from the listing after 12 months.
- 7.5 The PBAC noted that the direct comparison with etanercept supported a conclusion of superior efficacy of tildrakizumab, while the indirect comparisons supported non-inferiority efficacy to adalimumab and likely non-inferiority efficacy to ustekinumab. The PBAC considered that the evidence supported a claim of non-inferior safety to etanercept, adalimumab and ustekinumab. The PBAC noted that comparisons to ixekizumab and infliximab were not presented in the submission. In the absence of these comparisons, and noting that etanercept, adalimumab, secukinumab and ixekizumab were cost-minimised against each other or the least expensive biological, the PBAC considered overall it would be appropriate for tildrakizumab to also be cost-minimised to the least expensive biological agent for this condition.
- 7.6 In the Pre-Subcommittee Response and Pre-PBAC Response, the sponsor expressed willingness to consider listing of tildrakizumab on a cost-minimisation basis versus the least costly bDMARD over a 2-year treatment period based on the effective ex-manufacturer indication-specific prices using equi-effective doses that are derived directly from the relevant clinical trials. The PBAC considered the equi-effective doses between tildrakizumab 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.
- 7.7 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 tildrakizumab. The PBAC considered that listing of tildrakizumab would have minimal financial impact on the PBS. However, the PBAC noted that the responses from the sponsor had not clarified the evaluations concern that it was unclear from the submission whether the assumed uptake rates had incorporated the requested grandfathered patients.
- 7.8 Under section 101(3BA) of the *National Health Act 1953*, the PBAC advised that tildrakizumab may be treated as interchangeable on an individual patient basis with adalimumab, etanercept, infliximab, ixekizumab, secukinumab, guselkumab and ustekinumab on the PBS for the treatment of severe CPP.
- 7.9 The PBAC advised that tildrakizumab is not suitable for prescribing by nurse practitioners.
- 7.10 The PBAC recommended that the Early Supply rule should apply for continuing therapy only.
- 7.11 The PBAC noted that this submission is not eligible for an Independent Review, as the

PBAC has made a positive recommendation.

Outcome:

Recommended

8 Recommended listing

8.1 Add new item [note: Maximum Quantity is based on proposed dose of 200 mg].

Summary of listings presented below

TILDRAKIZUMAB 100mg in 1 mL single use pre-filled syringes, 2 pack				
Restriction	Treatment Phase	Max Qty (units)	Max Qty (packs)	Repeats
1	Initial 1, Whole body (new patient (no prior biological agent) or patient recommencing treatment after a break of 5 years or more)	2	1	2
2	Initial 2, Whole body (change or recommencement of treatment after a break of less than 5 years)	2	1	2
3	Initial 1, Face, hand, foot (new patient (no prior biological agent) or patient recommencing treatment after a break of 5 years or more)	2	1	2
4	Initial 2, Face, hand, foot (change or recommencement of treatment after a break of less than 5 years)	2	1	2
5	Initial 1, Whole body or Face, hand, foot (new patient or patient recommencing treatment after a break of 5 years or more) or Initial 2, Whole body or Face, hand, foot (change or recommencement of treatment after a break of less than 5 years) - balance of supply	2	1	2
6	Grandfather treatment, Whole body (initial PBS-subsidised supply for continuing treatment in a patient commenced on non-PBS-subsidised therapy)	2	1	1
7	Grandfather treatment, Face, hand, foot (initial PBS-subsidised supply for continuing treatment in a patient commenced on non-PBS-subsidised therapy)	2	1	1
8	Continuing treatment, Whole body	2	1	1
9	Continuing treatment, Face, hand, foot	2	1	1
10	Continuing treatment, Whole body or Continuing treatment, Face, hand, foot - balance of supply	2	1	1

General Administrative Advice for all chronic plaque psoriasis listings

TREATMENT OF ADULT PATIENTS WITH SEVERE CHRONIC PLAQUE PSORIASIS

The following information applies to the prescribing under the Pharmaceutical Benefits Scheme (PBS) of the biological agents adalimumab, etanercept, infliximab, ixekizumab, secukinumab, ustekinumab and tildrakizumab for adult patients with severe chronic plaque psoriasis. Therefore, where the term 'biological agents' appears in notes and restrictions, it refers to adalimumab, etanercept, infliximab, ixekizumab, secukinumab, ustekinumab and tildrakizumab only.

Patients receiving PBS-subsidised treatment for chronic plaque psoriasis are deemed to have commenced a 'Biological Treatment Cycle' (Cycle), where they may trial biological agents without having to meet the initial treatment criteria, that is they will not need to experience a disease flare, when swapping to an 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.

Patients are eligible for PBS-subsidised treatment with only 1 biological agent at any 1 time.

Within the same Treatment Cycle, a patient cannot trial and 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 a PBS-subsidised biological agent, they must change to an alternate agent if they wish to continue PBS-subsidised biological treatment.

Patients must be assessed for response to each course of treatment according to the criteria included in the relevant continuing treatment restriction.

Once a patient has either failed or ceased to respond to treatment 3 times, they are deemed to have completed a Treatment Cycle and they must have, at a minimum, a 5-year break in PBS-subsidised biological agent therapy before they are eligible to commence the next Cycle. The duration of the break in therapy is measured from the date of the last approval for PBS-subsidised biological agent treatment in the most recent Cycle to the date of the first application for initial treatment with a biological agent under the new Treatment Cycle.

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

Patients for whom a break in PBS-subsidised therapy of 5 years or more has occurred, and, who have failed therapy fewer than 3 times within a particular Cycle, as defined in the relevant restriction, are eligible to commence a new Cycle.

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 chronic plaque psoriasis.

There are separate restrictions for both the initial and continuing treatment for psoriasis affecting the whole body, versus psoriasis affecting the face, hands and feet.

(1) Application for approval for initial treatment.

Applications for a course of initial treatment should be made in the following situations:

(i) patients who have received no prior PBS-subsidised biological treatment and wish to commence such therapy (Initial 1); or

(ii) patients who wish to recommence treatment following a break of 5 years or more and commence a new treatment cycle (Initial 1); or

(iii) patients who have received prior PBS-subsidised biological therapy and wish to trial an alternate agent (Initial 2) [further details are under '(4) Swapping therapy' below]; or

(iv) patients who wish to recommence treatment following a break of less than 5 years in PBS-subsidised therapy with that agent (Initial 2).

All applications for initial treatment for non-grandfather patients will be limited to provide for a maximum of 16 weeks of treatment of adalimumab, etanercept, ixekizumab and secukinumab, 22 weeks of treatment of infliximab and 28 weeks of treatment of ustekinumab.

Grandfather patients (ixekizumab only).

Applications for patients who commenced treatment with ixekizumab for chronic plaque psoriasis prior to 1 February 2017 may be made for initial PBS-subsidised treatment as continuing therapy under the relevant initial treatment restriction (Initial 3). These patients access the PBS interchangeability arrangements in the same way as new patients who have not been treated with a biological agent prior to PBS listing of that agent.

Applications for initial PBS-subsidised treatment for grandfather patients will provide for a maximum of 24 weeks of treatment. Approval will be based on the criteria included in the relevant restriction

Grandfather patients (tildrakizumab only).

Applications for patients who commenced treatment with tildrakizumab for chronic plaque psoriasis prior to [listing date] may be made for initial PBS-subsidised treatment as continuing therapy under the relevant initial treatment restriction (grandfather treatment). These patients access the PBS interchangeability arrangements in the same way as new patients who have not been treated with a biological agent prior to PBS listing of that agent.

Applications for initial PBS-subsidised treatment for grandfather patients will provide for a maximum of 28 weeks of treatment. Approval will be based on the criteria included in the relevant restriction.

(2) Assessment of response to initial treatment.

When prescribing initial treatment with a biological agent, a PASI assessment must be conducted after at least 12 weeks of treatment. This assessment must be submitted to the Department of Human Services within 1 month of the completion of this initial treatment course. Where a response assessment is not undertaken and submitted to the Department of Human Services within these timeframes, the patient will be deemed to have failed to respond to treatment with that biological agent. In circumstances where it is not possible to submit a response assessment within these timeframes, please call the Department of Human Services on 1800 700 270 to discuss.

The PASI assessment for continuing treatment must be performed on the same affected area as assessed at baseline.

(3) Application for continuing treatment.

Following the completion of an initial treatment course with a biological agent to which an adequate response has been demonstrated, patients may qualify to receive up to 24 weeks of continuing treatment with that biological agent. Patients are eligible to continue to receive continuous treatment with 24 week courses providing they continue to sustain a response.

For second and subsequent courses of PBS-subsidised treatment with a specific biological agent it is recommended that a patient is reviewed in the month prior to completing their current course of treatment and that where applicable an application is submitted to the Department of Human Services.

Where a response assessment is not submitted to the Department of Human Services where required, patients will be deemed to have failed to sustain a response to treatment with that biological agent.

(4) Swapping therapy.

Once an authority for initial treatment with the first PBS-subsidised biological agent is approved, patients may swap to an alternate agent within the same Treatment Cycle without having to requalify with respect to disease severity (i.e. a PASI score of greater than 15), or prior treatment requirements.

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

Patients may trial an alternate biological agent at any time, regardless of whether they are receiving therapy with a biological agent at the time of the application or not. However, they cannot swap to a particular agent if they have failed to respond to treatment with that particular agent within the same 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.

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

(5) Baseline measurements to determine response.

Response to treatment will be determined based on the baseline PASI assessment submitted with the first authority application for a biological agent. However, prescribers may provide new baseline measurements any time that an initial treatment authority is submitted within a Treatment Cycle and subsequent response will be assessed according to this revised PASI score.

To ensure consistency in determining response, the same body area assessed at the baseline PASI assessment must be assessed for demonstration of response to treatment for the purposes of all continuing treatments.

(6) Recommencement of treatment after a 5-year break in PBS-subsidised therapy.

Patients who wish to trial a second or subsequent Biological Treatment Cycle, following a break in PBS-subsidised biological therapy of at least 5 years, must requalify for initial treatment according to the criteria of the relevant restriction and index of disease severity. Patients must have had at least 1 prior treatment, as listed in the criteria, for a minimum of 6 weeks, and must have a PASI

Restriction 1

Name, Restriction,	Max. Qty (pack)	No. of Rpts	Proprietary Manufacturer	Name and
TILDRAKIZUMAB 100mg in 1 mL single use pre-filled syringes, 2 pack	1	2	Ilumya	Sun Pharma ANZ Pty Ltd

Episodicity:	N/A
Severity:	Severe chronic
Condition:	Plaque Psoriasis
PBS Indication:	Severe chronic plaque psoriasis
Treatment phase:	Initial 1, Whole body (new patient (no prior biological agent) or patient recommencing treatment after a break of 5 years or more)

Public Summary Document – July 2018 PBAC Meeting

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 dermatologist.

Clinical criteria:	<p>Patient must have severe chronic plaque psoriasis where the plaque or plaques have been present for at least 6 months from the time of initial diagnosis,</p> <p>AND</p> <p>Patient must not have received any prior PBS-subsidised treatment with a biological agent for this condition; OR</p> <p>Patient must not have received 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 wish to commence a new Treatment Cycle,</p> <p>AND</p> <p>Patient must have failed to achieve an adequate response, as demonstrated by a Psoriasis Area and Severity Index (PASI) assessment, to at least 3 of the following 4 treatments: (i) phototherapy (UVB or PUVA) for 3 treatments per week for at least 6 weeks; and/or (ii) methotrexate at a dose of at least 10 mg weekly for at least 6 weeks; and/or (iii) cyclosporin at a dose of at least 2 mg per kg per day for at least 6 weeks; and/or (iv) acitretin at a dose of at least 0.4 mg per kg per day for at least 6 weeks,</p> <p>AND</p> <p>Patient must have signed a patient and prescriber acknowledgement indicating they understand and acknowledge that PBS-subsidised treatment will cease if they do not meet the predetermined response criterion for ongoing PBS-subsidised treatment, as outlined in the restriction for continuing treatment (whole body),</p> <p>AND</p> <p>The treatment must be as systemic monotherapy (other than methotrexate),</p> <p>AND</p> <p>Patient must not receive more than 28 weeks of treatment under this restriction.</p>
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Population criteria:	Patient must be aged 18 years or older.
Prescriber Instructions	<p>For the purposes of this restriction 'biological agent' means adalimumab, etanercept, infliximab, ixekizumab, secukinumab, tildrakizumab or ustekinumab.</p> <p>Where treatment with methotrexate, cyclosporin or acitretin is contraindicated according to the relevant TGA-approved Product Information, or where phototherapy is contraindicated, details must be provided at the time of application.</p> <p>Where intolerance to treatment with phototherapy, methotrexate, cyclosporin or acitretin 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 criterion indicates failure to achieve an adequate response to prior treatment and must be demonstrated in the patient at the time of the application:</p> <p>(a) A current Psoriasis Area and Severity Index (PASI) score of greater than 15, as assessed, preferably whilst still on treatment, but no longer than 1 month following cessation of the most recent prior treatment.</p> <p>(b) A PASI assessment must be completed for each prior treatment course, preferably whilst still on treatment, but no longer than 1 month following cessation of each course of treatment.</p> <p>(c) The most recent PASI assessment must be no more than 1 month old at the time of application.</p> <p>The authority application must be made in writing and must include:</p> <p>(a) a completed authority prescription form; and</p> <p>(b) a completed Severe Chronic Plaque Psoriasis PBS Authority Application - Supporting Information Form which</p>

	<p>includes the following:</p> <p>(i) the completed current and previous Psoriasis Area and Severity Index (PASI) calculation sheets including the dates of assessment of the patient's condition; and</p> <p>(ii) details of previous phototherapy and systemic drug therapy [dosage (where applicable), date of commencement and duration of therapy]; and</p> <p>(iii) the signed patient and prescriber acknowledgements.</p>
<p>Administrative Advice</p>	<p>No increase in the maximum number of repeats may be authorised</p> <p>Details of the toxicities, including severity, which will be accepted as a reason for exempting a patient from the requirement for 6 weeks treatment with phototherapy, methotrexate, cyclosporin or acitretin can be found on the Department of Human Services website (www.humanservices.gov.au)</p> <p>A PASI assessment of the patient's response to this initial course of treatment must be made after at least 12 weeks of treatment so that there is adequate time for a response to be demonstrated. This assessment, which will be used to determine eligibility for continuing treatment, must be submitted to the Department of Human Services no later than 1 month from the date of completion of this initial course of treatment. Where a response assessment is not undertaken and submitted to the Department of Human Services within these timeframes, the patient will be deemed to have failed to respond to treatment with this drug.</p> <p>In circumstances where it is not possible to submit a response assessment within these timeframes, please call the Department of Human Services on 1800 700 270 to discuss</p> <p>It is recommended that an application is posted to the Department of Human Services no later than 2 weeks prior to the patient completing their current treatment course to</p>

	<p>ensure continuity of treatment for those patients who meet the continuation criterion for PBS-subsidised treatment with this drug.</p> <p>Any queries concerning the arrangements to prescribe may be directed to the Department of Human Services on 1800 700 270 (hours of operation 8 a.m. to 5 p.m. EST Monday to Friday).</p> <p>Prescribing information (including Authority Application forms and other relevant documentation as applicable) is available on the Department of Human Services website at www.humanservices.gov.au</p> <p>Applications for authority to prescribe should be forwarded to:</p> <p>Department of Human Services</p> <p>Complex Drugs</p> <p>Reply Paid 9826</p> <p>HOBART TAS 7001</p>
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Restriction 2

Episodicity:	N/A
Severity:	Severe chronic
Condition:	Plaque Psoriasis
PBS Indication:	Severe chronic plaque psoriasis
Treatment phase:	Initial 2, Whole body (change or recommencement of treatment after a break of less than 5 years)
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

<p>Treatment criteria:</p>	<p>Must be treated by a dermatologist.</p>
<p>Clinical criteria:</p>	<p>Patient must have a documented history of severe chronic plaque psoriasis,</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 for this condition within this Treatment Cycle,</p> <p>AND</p> <p>Patient must not have failed, or ceased to respond to, PBS-subsidised therapy with this drug for the treatment of this condition in the current Treatment Cycle,</p> <p>AND</p> <p>The treatment must be as systemic monotherapy (other than methotrexate),</p> <p>AND</p> <p>Patient must not receive more than 28 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, etanercept, infliximab, ixekizumab, secukinumab, tildrakizumab or ustekinumab.</p> <p>The authority application must be made in writing and must include:</p> <p>(a) a completed authority prescription form; and</p> <p>(b) a completed Severe Chronic Plaque Psoriasis PBS Authority Application - Supporting Information Form which includes the following:</p> <p>(i) the completed current Psoriasis Area and Severity Index (PASI) calculation sheets including the dates of assessment</p>

	<p>of the patient's condition; and</p> <p>(ii) details of prior biological treatment, including dosage, date and duration of treatment.</p> <p>At the time of the authority application, medical practitioners should request the appropriate number of vials, based on the weight of the patient, to provide sufficient for a single injection. Up to a maximum of 2 repeats will be authorised.</p> <p>Applications for patients who have demonstrated a response to PBS-subsidised treatment with this drug within this Treatment Cycle and who wish to recommence treatment with this drug within the same Cycle following a break in therapy, will only be approved where evidence of the patient's response to their most recent course of PBS-subsidised treatment with this drug has been submitted within 1 month of cessation of treatment.</p> <p>An adequate response to treatment is defined as:</p> <p>A Psoriasis Area and Severity Index (PASI) score which is reduced by 75% or more, or is sustained at this level, when compared with the prebiological treatment baseline value for this Treatment Cycle.</p>
<p>Administrative Advice</p>	<p>No increase in the maximum number of repeats may be authorised.</p> <p>A PASI assessment of the patient's response to this initial course of treatment must be made after at least 12 weeks of treatment so that there is adequate time for a response to be demonstrated. This assessment, which will be used to determine eligibility for continuing treatment, must be submitted to the Department of Human Services no later than 1 month from the date of completion of this initial course of treatment. Where a response assessment is not undertaken and submitted to the Department of Human Services within these timeframes, the patient will be deemed to have failed to respond to treatment with this drug.</p> <p>In circumstances where it is not possible to submit a response assessment within these timeframes, please call the Department of Human Services on 1800 700 270 to</p>

	<p>discuss.</p> <p>Patients who fail to demonstrate a response to treatment with 3 biological agents are deemed to have completed this Treatment Cycle and must cease PBS-subsidised therapy. These patients may recommence a new Biological Treatment Cycle after a minimum of 5 years has 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>It is recommended that an application is posted to the Department of Human Services no later than 2 weeks prior to the patient completing their current treatment course to ensure continuity of treatment for those patients who meet the continuation criterion for PBS-subsidised treatment with this drug.</p> <p>Any queries concerning the arrangements to prescribe may be directed to the Department of Human Services on 1800 700 270 (hours of operation 8 a.m. to 5 p.m. EST Monday to Friday).</p> <p>Prescribing information (including Authority Application forms and other relevant documentation as applicable) is available on the Department of Human Services website at www.humanservices.gov.au</p> <p>Applications for authority to prescribe should be forwarded to:</p> <p>Department of Human Services</p> <p>Complex Drugs</p> <p>Reply Paid 9826</p> <p>HOBART TAS 7001</p>
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Restriction 3

Episodicity:	N/A
Severity:	Severe chronic
Condition:	Plaque Psoriasis
PBS Indication:	Severe chronic plaque psoriasis

Treatment phase:	Initial 1, Face, hand, foot (new patient (no prior biological agent) or patient recommencing treatment after a break of 5 years or more)
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 dermatologist.

<p>Clinical criteria:</p>	<p>Patient must have severe chronic plaque psoriasis of the face, or palm of a hand or sole of a foot where the plaque or plaques have been present for at least 6 months from the time of initial diagnosis,</p> <p>AND</p> <p>Patient must not have received any prior PBS-subsidised treatment with a biological agent for this condition; OR</p> <p>Patient must not have received 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 wish to commence a new Treatment Cycle,</p> <p>AND</p> <p>Patient must have failed to achieve an adequate response, as demonstrated by a Psoriasis Area and Severity Index (PASI) assessment, to at least 3 of the following 4 treatments: (i) phototherapy (UVB or PUVA) for 3 treatments per week for at least 6 weeks; and/or (ii) methotrexate at a dose of at least 10 mg weekly for at least 6 weeks; and/or (iii) cyclosporin at a dose of at least 2 mg per kg per day for at least 6 weeks; and/or (iv) acitretin at a dose of at least 0.4 mg per kg per day for at least 6 weeks,</p> <p>AND</p> <p>Patient must have signed a patient and prescriber acknowledgement indicating they understand and acknowledge that PBS-subsidised treatment will cease if they do not meet the predetermined response criterion for ongoing PBS-subsidised treatment, as outlined in the restriction for continuing treatment (face, hand, foot),</p> <p>AND</p> <p>The treatment must be as systemic monotherapy (other than methotrexate),</p> <p>AND</p> <p>Patient must not receive more than 28 weeks of treatment under this restriction.</p>
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<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, etanercept, infliximab, ixekizumab, secukinumab, tildrakizumab or ustekinumab.</p> <p>Where treatment with methotrexate, cyclosporin or acitretin is contraindicated according to the relevant TGA-approved Product Information, or where phototherapy is contraindicated, details must be provided at the time of application.</p> <p>Where intolerance to treatment with phototherapy, methotrexate, cyclosporin or acitretin 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 criterion indicates failure to achieve an adequate response to prior treatment and must be demonstrated in the patient at the time of the application:</p> <p>(a) Chronic plaque psoriasis classified as severe due to a plaque or plaques on the face, palm of a hand or sole of a foot where:</p> <p>(i) at least 2 of the 3 Psoriasis Area and Severity Index (PASI) symptom subscores for erythema, thickness and scaling are rated as severe or very severe, as assessed, preferably whilst still on treatment, but no longer than 1 month following cessation of the most recent prior treatment; or</p> <p>(ii) the skin area affected is 30% or more of the face, palm of a hand or sole of a foot, as assessed, preferably whilst still on treatment, but no longer than 1 month following cessation of the most recent prior treatment;</p> <p>(b) A PASI assessment must be completed for each prior treatment course, preferably whilst still on treatment, but no longer than 1 month following cessation of each course of treatment.</p>

	<p>(c) The most recent PASI assessment must be no more than 1 month old at the time of application.</p> <p>The authority application must be made in writing and must include:</p> <p>(a) a completed authority prescription form; and</p> <p>(b) a completed Severe Chronic Plaque Psoriasis PBS Authority Application - Supporting Information Form which includes the following:</p> <p>(i) the completed current and previous Psoriasis Area and Severity Index (PASI) calculation sheets and face, hand, foot area diagrams including the dates of assessment of the patient's condition; and</p> <p>(ii) details of previous phototherapy and systemic drug therapy [dosage (where applicable), date of commencement and duration of therapy]; and</p> <p>(iii) the signed patient and prescriber acknowledgements.</p>
<p>Administrative Advice</p>	<p>No increase in the maximum number of repeats may be authorised</p> <p>Details of the toxicities, including severity, which will be accepted as a reason for exempting a patient from the requirement for 6 weeks treatment with phototherapy, methotrexate, cyclosporin or acitretin can be found on the Department of Human Services website (www.humanservices.gov.au)</p> <p>A PASI assessment of the patient's response to this initial course of treatment must be made after at least 12 weeks of treatment so that there is adequate time for a response to be demonstrated. This assessment, which will be used to determine eligibility for continuing treatment, must be submitted to the Department of Human Services no later than 1 month from the date of completion of this initial course of treatment. The PASI assessment for continuing treatment must be performed on the same affected area as assessed at baseline. Where a response assessment is not</p>

	<p>undertaken and submitted to the Department of Human Services within these timeframes, the patient will be deemed to have failed to respond to treatment with this drug.</p> <p>In circumstances where it is not possible to submit a response assessment within these timeframes, please call the Department of Human Services on 1800 700 270 to discuss</p> <p>It is recommended that an application is posted to the Department of Human Services no later than 2 weeks prior to the patient completing their current treatment course to ensure continuity of treatment for those patients who meet the continuation criterion for PBS-subsidised treatment with this drug.</p> <p>Any queries concerning the arrangements to prescribe may be directed to the Department of Human Services on 1800 700 270 (hours of operation 8 a.m. to 5 p.m. EST Monday to Friday).</p> <p>Prescribing information (including Authority Application forms and other relevant documentation as applicable) is available on the Department of Human Services website at www.humanservices.gov.au</p> <p>Applications for authority to prescribe should be forwarded to:</p> <p>Department of Human Services</p> <p>Complex Drugs</p> <p>Reply Paid 9826</p> <p>HOBART TAS 7001</p>
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Restriction 4

Episodicity:	N/A
Severity:	Severe chronic
Condition:	Plaque Psoriasis

PBS Indication:	Severe chronic plaque psoriasis
Treatment phase:	Initial 2, Face, hand, foot (change or recommencement of treatment after a break of less than 5 years)
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 dermatologist.
Clinical criteria:	<p>Patient must have a documented history of severe chronic plaque psoriasis of the face, or palm of a hand or sole of a foot,</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 for this condition within this Treatment Cycle,</p> <p>AND</p> <p>Patient must not have failed, or ceased to respond to, PBS-subsidised therapy with this drug for the treatment of this condition in the current Treatment Cycle,</p> <p>AND</p> <p>The treatment must be as systemic monotherapy (other than methotrexate),</p> <p>AND</p> <p>Patient must not receive more than 28 weeks of treatment under this restriction</p>

Population criteria:	Patient must be aged 18 years or older.
Prescriber Instructions	<p>For the purposes of this restriction 'biological agent' means adalimumab, etanercept, infliximab, ixekizumab, secukinumab, tildrakizumab or ustekinumab.</p> <p>The authority application must be made in writing and must include:</p> <p>(a) a completed authority prescription form; and</p> <p>(b) a completed Severe Chronic Plaque Psoriasis PBS Authority Application - Supporting Information Form which includes the following:</p> <p>(i) the completed current Psoriasis Area and Severity Index (PASI) calculation sheets and face, hand, foot area diagrams including the dates of assessment of the patient's condition; and</p> <p>(ii) details of prior biological treatment, including dosage, date and duration of treatment.</p> <p>Applications for patients who have demonstrated a response to PBS-subsidised treatment with this drug within this Treatment Cycle and who wish to recommence treatment with this drug within the same Cycle following a break in therapy, will only be approved where evidence of the patient's response to their most recent course of PBS-subsidised treatment with this drug has been submitted within 1 month of cessation of treatment.</p> <p>An adequate response to treatment is defined as the plaque or plaques assessed prior to biological treatment showing:</p> <p>(i) a reduction in the Psoriasis Area and Severity Index (PASI) symptom subscores for all 3 of erythema, thickness and scaling, to slight or better, or sustained at this level, as compared to the pre-biological treatment baseline values; or</p> <p>(ii) a reduction by 75% or more in the skin area affected, or sustained at this level, as compared to the pre-biological treatment baseline value.</p>
Administrative Advice	No increase in the maximum number of repeats may be authorised

	<p>Details of the toxicities, including severity, which will be accepted as a reason for exempting a patient from the requirement for 6 weeks treatment with phototherapy, methotrexate, cyclosporin or acitretin can be found on the Department of Human Services website (www.humanservices.gov.au)</p> <p>A PASI assessment of the patient's response to this initial course of treatment must be made after at least 12 weeks of treatment so that there is adequate time for a response to be demonstrated. This assessment, which will be used to determine eligibility for continuing treatment, must be submitted to the Department of Human Services no later than 1 month from the date of completion of this initial course of treatment. The PASI assessment for continuing treatment must be performed on the same affected area as assessed at baseline. Where a response assessment is not undertaken and submitted to the Department of Human Services within these timeframes, the patient will be deemed to have failed to respond to treatment with this drug.</p> <p>In circumstances where it is not possible to submit a response assessment within these timeframes, please call the Department of Human Services on 1800 700 270 to discuss.</p> <p>Patients who fail to demonstrate a response to treatment with 3 biological agents are deemed to have completed this Treatment Cycle and must cease PBS-subsidised therapy. These patients may recommence a new Biological Treatment Cycle after a minimum of 5 years has 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>It is recommended that an application is posted to the Department of Human Services no later than 2 weeks prior to the patient completing their current treatment course to ensure continuity of treatment for those patients who meet the continuation criterion for PBS-subsidised treatment</p>
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	<p>with this drug.</p> <p>Any queries concerning the arrangements to prescribe may be directed to the Department of Human Services on 1800 700 270 (hours of operation 8 a.m. to 5 p.m. EST Monday to Friday).</p> <p>Prescribing information (including Authority Application forms and other relevant documentation as applicable) is available on the Department of Human Services website at www.humanservices.gov.au</p> <p>Applications for authority to prescribe should be forwarded to:</p> <p>Department of Human Services</p> <p>Complex Drugs</p> <p>Reply Paid 9826</p> <p>HOBART TAS 7001</p>
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Restriction 5

Episodicity:	N/A
Severity:	Severe chronic
Condition:	Plaque Psoriasis
PBS Indication:	Severe chronic plaque psoriasis
Treatment phase:	Initial 1, Whole body or Face, hand, foot (new patient or patient recommencing treatment after a break of 5 years or more) or Initial 2, Whole body or Face, hand, foot (change or recommencement of treatment after a break of less than 5 years) - 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:	

	<p>Must be treated by a dermatologist.</p>
<p>Clinical criteria:</p>	<p>Patient must have received insufficient therapy with this drug under the Initial 1, Whole body (new patient or patient recommencing treatment after a break of 5 years or more) restriction to complete 28 weeks treatment; OR</p> <p>Patient must have received insufficient therapy with this drug under the Initial 2, Whole body (change or recommencement of treatment after a break of less than 5 years) restriction to complete 28 weeks treatment; OR</p> <p>Patient must have received insufficient therapy with this drug under the Initial 1, Face, hand, foot (new patient or patient recommencing treatment after a break of 5 years or more) restriction to complete 28 weeks treatment; OR</p> <p>Patient must have received insufficient therapy with this drug under the Initial 2, Face, hand, foot (change or recommencement of treatment after a break of less than 5 years) restriction to complete 28 weeks treatment,</p> <p>AND</p> <p>The treatment must be as systemic monotherapy (other than methotrexate),</p> <p>AND</p> <p>The treatment must provide no more than the balance of up to 28 weeks treatment available under the above restrictions.</p>
<p>Administrative Advice</p>	<p>No increase in the maximum number of repeats may be authorised</p> <p>Details of the toxicities, including severity, which will be accepted as a reason for exempting a patient from the requirement for 6 weeks treatment with phototherapy, methotrexate, cyclosporin or acitretin can be found on the Department of Human Services website (www.humanservices.gov.au)</p> <p>Authority approval for sufficient therapy to complete a maximum of 28 weeks of treatment may be requested by telephone by contacting the Department of Human Services</p>

	on 1800 700 270 (hours of operation 8 a.m. to 5 p.m. EST Monday to Friday).
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Restriction 6

Name, Restriction,	Max. Qty (pack)	No. of Rpts	Proprietary Manufacturer	Name and
TILDRAKIZUMAB 100mg in 1 mL single use pre-filled syringes, 2 pack	1	1	Ilumya	Sun Pharma ANZ Pty Ltd

Episodicity:	N/A
Severity:	Severe chronic
Condition:	Plaque Psoriasis
PBS Indication:	Severe chronic plaque psoriasis
Treatment phase:	Grandfather treatment, Whole body (initial PBS-subsidised supply for continuing treatment in a patient commenced on non-PBS-subsidised therapy)
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 dermatologist.

<p>Clinical criteria:</p>	<p>Patient must have a documented history of severe chronic plaque psoriasis,</p> <p>AND</p> <p>Patient must have previously received non-PBS-subsidised treatment with this drug for this condition prior to [1 month year],</p> <p>AND</p> <p>Patient must have had a documented history of a Psoriasis Area and Severity Index (PASI) score of greater than 15 prior to commencing non-PBS- subsidised treatment with this drug,</p> <p>AND</p> <p>Patient must have demonstrated an adequate response to their most recent course of non-PBS-subsidised treatment with this drug as specified in the continuing treatment restriction (whole body),</p> <p>AND</p> <p>Patient must have signed a patient and prescriber acknowledgement indicating they understand and acknowledge that PBS-subsidised treatment will cease if they do not meet the predetermined response criterion for ongoing PBS-subsidised treatment, as outlined in the restriction for continuing treatment,</p> <p>AND</p> <p>The treatment must be as systemic monotherapy (other than methotrexate),</p> <p>AND</p> <p>Patient must not receive more than 24 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>The authority application must be made in writing and must include:</p> <p>(a) a completed authority prescription form; and</p> <p>(b) a completed Severe Chronic Plaque Psoriasis PBS Authority Application - Supporting Information Form which includes the following:</p> <p>(i) the completed Psoriasis Area and Severity Index (PASI) calculation sheets including the date of assessment of the patient's condition at baseline (prior to initiation of non-PBS-subsidised therapy with this drug) and the most recent PASI assessment; and</p> <p>(ii) details of previous phototherapy and systemic drug therapy [dosage (where applicable), date of commencement and duration of therapy]; and</p> <p>(iii) the signed patient and prescriber acknowledgements.</p> <p>The most recent PASI assessment must be no more than 1 month old at the time of the application.</p> <p>A patient may qualify for PBS-subsidised treatment under this restriction once only.</p>
<p>Administrative Advice</p>	<p>No increase in the maximum number of repeats may be authorised</p> <p>A PASI assessment of the patient's response to this initial course of therapy must be conducted within 4 weeks prior to completion of this course of treatment. This assessment, which will be used to determine eligibility for continuing treatment, must be submitted to the Department of Human Services no later than 1 month from the date of completion of this initial course of treatment. Where a response assessment is not undertaken and submitted to the Department of Human Services within these timeframes, the patient will be deemed to have failed to respond to treatment with this drug.</p> <p>In circumstances where it is not possible to submit a response</p>

	<p>assessment within these timeframes, please call the Department of Human Services on 1800 700 270 to discuss.</p> <p>It is recommended that an application is posted to the Department of Human Services no later than 2 weeks prior to the patient completing their current treatment course to ensure continuity of treatment for those patients who meet the continuation criterion for PBS-subsidised treatment with this drug.</p> <p>Any queries concerning the arrangements to prescribe may be directed to the Department of Human Services on 1800 700 270 (hours of operation 8 a.m. to 5 p.m. EST Monday to Friday).</p> <p>Prescribing information (including Authority Application forms and other relevant documentation as applicable) is available on the Department of Human Services website at www.humanservices.gov.au</p> <p>Applications for authority to prescribe should be forwarded to:</p> <p>Department of Human Services</p> <p>Complex Drugs</p> <p>Reply Paid 9826</p> <p>HOBART TAS 7001</p>
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Restriction 7

Episodicity:	N/A
Severity:	Severe chronic
Condition:	Plaque Psoriasis
PBS Indication:	Severe chronic plaque psoriasis
Treatment phase:	Grandfather treatment- Face, hand and foot (initial PBS-subsidised supply for continuing treatment in a patient commenced on non-PBS-subsidised therapy)
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 dermatologist.

Clinical criteria:	<p>Patient must have a documented history of severe chronic plaque psoriasis of the face or palm of a hand or sole of a foot,</p> <p>AND</p> <p>Patient must have previously received non-PBS-subsidised treatment with this drug for this condition prior to [1 month year],</p> <p>AND</p> <p>Patient must have had a documented history of disease, prior to commencing non-PBS- subsidised treatment with this drug, classified as severe due to a plaque or plaques on the face, palm of a hand or sole of a foot where: (i) at least 2 of the 3 Psoriasis Area and Severity Index (PASI) symptom subscores for erythema, thickness and scaling were rated as severe or very severe; or (ii) the skin area affected was 30% or more of the face, palm of a hand or sole of a foot,</p> <p>AND</p> <p>Patient must have demonstrated an adequate response to their most recent course of non-PBS-subsidised treatment with this drug as specified in the continuing treatment restriction (face, hand and foot),</p> <p>AND</p> <p>Patient must have signed a patient and prescriber acknowledgement indicating they understand and acknowledge that PBS-subsidised treatment will cease if they do not meet the predetermined response criterion for ongoing PBS-subsidised treatment, as outlined in the restriction for continuing treatment (face, hand, foot)</p> <p>AND</p> <p>The treatment must be as systemic monotherapy (other than methotrexate),</p> <p>AND</p> <p>Patient must not receive more than 24 weeks of treatment under this restriction.</p>
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Population criteria:	Patient must be aged 18 years or older.
Prescriber Instructions	<p>The authority application must be made in writing and must include:</p> <p>(a) a completed authority prescription form; and</p> <p>(b) a completed Severe Chronic Plaque Psoriasis PBS Authority Application - Supporting Information Form which includes the following:</p> <p>(i) the completed Psoriasis Area and Severity Index (PASI) calculation sheet and face, hand, foot area diagrams including the date of the assessment of the patient's condition at baseline (prior to initiation of therapy with this drug) and the most recent PASI assessment; and</p> <p>(ii) details of previous phototherapy and systemic drug therapy [dosage (where applicable), date of commencement and duration of therapy]; and</p> <p>(iii) the signed patient and prescriber acknowledgements.</p> <p>The most recent PASI assessment must be no more than 1 month old at the time of the application.</p> <p>The PASI assessment must be performed on the same affected area as assessed at baseline or prior to initiation of treatment with this drug</p> <p>A patient may qualify for PBS-subsidised treatment under this restriction once only.</p>
Administrative Advice	<p>No increase in the maximum number of repeats may be authorised</p> <p>A PASI assessment of the patient's response to this initial PBS-subsidised course of therapy must be conducted within 4 weeks prior to completion of this course of treatment. This assessment, which will be used to determine eligibility for continuing treatment, must be submitted to the Department of Human Services no later than 1 month from the date of completion of this initial course of treatment.</p>

	<p>Where a response assessment is not undertaken and submitted to the Department of Human Services within these timeframes, the patient will be deemed to have failed to respond to treatment with this drug.</p> <p>In circumstances where it is not possible to submit a response assessment within these timeframes, please call the Department of Human Services on 1800 700 270 to discuss.</p> <p>It is recommended that an application is posted to the Department of Human Services no later than 2 weeks prior to the patient completing their current treatment course to ensure continuity of treatment for those patients who meet the continuation criterion for PBS-subsidised treatment with this drug.</p> <p>Any queries concerning the arrangements to prescribe may be directed to the Department of Human Services on 1800 700 270 (hours of operation 8 a.m. to 5 p.m. EST Monday to Friday).</p> <p>Prescribing information (including Authority Application forms and other relevant documentation as applicable) is available on the Department of Human Services website at www.humanservices.gov.au</p> <p>Applications for authority to prescribe should be forwarded to:</p> <p>Department of Human Services Complex Drugs Reply Paid 9826 HOBART TAS 7001</p>
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Restriction 8

Severity:	Severe chronic
Condition:	Plaque Psoriasis
PBS Indication:	Severe chronic plaque psoriasis
Treatment phase:	Continuing treatment, Whole body

<p>Restriction:</p>	<p><input type="checkbox"/> Restricted benefit</p> <p><input checked="" type="checkbox"/> Authority Required - In Writing</p> <p><input type="checkbox"/> Authority Required - Telephone</p> <p><input type="checkbox"/> Authority Required – Emergency</p> <p><input type="checkbox"/> Authority Required - Electronic</p> <p><input type="checkbox"/> Streamlined</p>
<p>Treatment criteria:</p>	<p>Must be treated by a dermatologist.</p>
<p>Clinical criteria:</p>	<p>Patient must have a documented history of severe chronic plaque psoriasis,</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 have demonstrated an adequate response to their most recent course of treatment with this drug,</p> <p>AND</p> <p>The treatment must be as systemic monotherapy (other than methotrexate),</p> <p>AND</p> <p>Patient must not receive more than 24 weeks of treatment per continuing treatment course authorised 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, etanercept, infliximab, ixekizumab, secukinumab, tildrakizumab or ustekinumab.</p> <p>An adequate response to treatment is defined as:</p> <p>A Psoriasis Area and Severity Index (PASI) score which is reduced by 75% or more, or is sustained at this level, when compared with the prebiological treatment baseline value</p>

	<p>for this Treatment Cycle.</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 with this drug.</p> <p>The authority application must be made in writing and must include:</p> <ul style="list-style-type: none"> (a) a completed authority prescription form; and (b) a completed Severe Chronic Plaque Psoriasis PBS Authority Application - Supporting Information Form which includes the following: <ul style="list-style-type: none"> (i) the completed Psoriasis Area and Severity Index (PASI) calculation sheet including the date of the assessment of the patient's condition. <p>The most recent PASI assessment must be no more than 1 month old at the time of application.</p> <p>Approval will be based on the PASI assessment of response to the most recent course of treatment with this drug.</p>
<p>Administrative Advice</p>	<p>No increase in the maximum number of repeats may be authorised</p> <p>A PASI assessment of the patient's response must be conducted within 4 weeks prior to completion of this course of treatment. This assessment, which will be used to determine eligibility for further continuing treatment, must be submitted to the Department of Human Services no later than 1 month from the date of completion of this course of treatment. Where a response assessment is not undertaken and submitted to the Department of Human Services within these timeframes, the patient will be deemed to have failed to respond to treatment with this drug.</p>

	<p>In circumstances where it is not possible to submit a response assessment within these timeframes, please call the Department of Human Services on 1800 700 270 to discuss.</p> <p>Patients who fail to demonstrate a response to treatment with 3 biological agents are deemed to have completed this Treatment Cycle and must cease PBS-subsidised therapy. These patients may recommence a new Biological Treatment Cycle after a minimum of 5 years has 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>It is recommended that an application is posted to the Department of Human Services no later than 2 weeks prior to the patient completing their current treatment course to ensure continuity of treatment for those patients who meet the continuation criterion for PBS-subsidised treatment with this drug.</p> <p>Any queries concerning the arrangements to prescribe may be directed to the Department of Human Services on 1800 700 270 (hours of operation 8 a.m. to 5 p.m. EST Monday to Friday).</p> <p>Prescribing information (including Authority Application forms and other relevant documentation as applicable) is available on the Department of Human Services website at www.humanservices.gov.au</p> <p>Applications for authority to prescribe should be forwarded to:</p> <p>Department of Human Services</p> <p>Complex Drugs</p> <p>Reply Paid 9826</p> <p>HOBART TAS 7001</p>
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Restriction 9

Episodicity:	N/A
Severity:	Severe chronic
Condition:	Plaque Psoriasis
PBS Indication:	Severe chronic plaque psoriasis
Treatment phase:	Continuing treatment, Face, hand, foot
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 dermatologist.
Clinical criteria:	<p>Patient must have a documented history of severe chronic plaque psoriasis of the face, or palm of a hand or sole of a foot,</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 have demonstrated an adequate response to their most recent course of treatment with this drug,</p> <p>AND</p> <p>The treatment must be as systemic monotherapy (other than methotrexate),</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 aged 18 years or older.

Prescriber Instructions	<p>For the purposes of this restriction 'biological agent' means adalimumab, etanercept, infliximab, ixekizumab, secukinumab, tildrakizumab or ustekinumab.</p> <p>An adequate response to treatment is defined as the plaque or plaques assessed prior to biological treatment showing:</p> <p>(i) a reduction in the Psoriasis Area and Severity Index (PASI) symptom subscores for all 3 of erythema, thickness and scaling, to slight or better, or sustained at this level, as compared to the pre-biological treatment baseline values; or</p> <p>(ii) a reduction by 75% or more in the skin area affected, or sustained at this level, as compared to the pre-biological treatment baseline value.</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 with this drug.</p> <p>The authority application must be made in writing and must include:</p> <p>(a) a completed authority prescription form; and</p> <p>(b) a completed Severe Chronic Plaque Psoriasis PBS Authority Application - Supporting Information Form which includes the following:</p> <p>(i) the completed Psoriasis Area and Severity Index (PASI) calculation sheet and face, hand, foot area diagrams including the date of the assessment of the patient's condition.</p> <p>The most recent PASI assessment must be no more than 1 month old at the time of application.</p> <p>Approval will be based on the PASI assessment of response</p>
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	<p>to the most recent course of treatment with this drug.</p> <p>The PASI assessment for continuing treatment must be performed on the same affected area assessed at baseline.</p>
<p>Administrative Advice</p>	<p>No increase in the maximum number of repeats may be authorised</p> <p>A PASI assessment of the patient's response must be conducted within 4 weeks prior to completion of this course of treatment. This assessment, which will be used to determine eligibility for further continuing treatment, must be submitted to the Department of Human Services no later than 1 month from the date of completion of this course of treatment. Where a response assessment is not undertaken and submitted to the Department of Human Services within these timeframes, the patient will be deemed to have failed to respond to treatment with this drug.</p> <p>In circumstances where it is not possible to submit a response assessment within these timeframes, please call the Department of Human Services on 1800 700 270 to discuss.</p> <p>Patients who fail to demonstrate a response to treatment with 3 biological agents are deemed to have completed this Treatment Cycle and must cease PBS-subsidised therapy. These patients may recommence a new Biological Treatment Cycle after a minimum of 5 years has 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>It is recommended that an application is posted to the Department of Human Services no later than 2 weeks prior to the patient completing their current treatment course to ensure continuity of treatment for those patients who meet the continuation criterion for PBS-subsidised treatment with this drug.</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</p>

	<p>Friday).</p> <p>Prescribing information (including Authority Application forms and other relevant documentation as applicable) is available on the Department of Human Services website at www.humanservices.gov.au</p> <p>Applications for authority to prescribe should be forwarded to:</p> <p>Department of Human Services</p> <p>Complex Drugs</p> <p>Reply Paid 9826</p> <p>HOBART TAS 7001</p>
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Restriction 10

Episodicity:	N/A
Severity:	Severe chronic
Condition:	Plaque Psoriasis
PBS Indication:	Severe chronic plaque psoriasis
Treatment phase:	Continuing treatment, Whole body or Continuing treatment, Face, hand, foot - 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 dermatologist.
Clinical criteria:	<p>Patient must have received insufficient therapy with this drug under the Continuing treatment, Whole body restriction to complete 24 weeks treatment; OR</p> <p>Patient must have received insufficient therapy with this</p>

	<p>drug under the Continuing treatment, Face, hand, foot restriction to complete 24 weeks treatment,</p> <p>AND</p> <p>The treatment must provide no more than the balance of up to 24 weeks treatment available under the above restrictions,</p> <p>AND</p> <p>The treatment must be as systemic monotherapy (other than methotrexate).</p>
<p>Administrative Advice</p>	<p>No increase in the maximum number of repeats may be authorised.</p> <p>Authority approval for sufficient therapy to complete a maximum of 28 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).</p>

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

Sun Pharma welcomes the PBACs decision to recommend tildrakizumab for listing on the PBS for the treatment of severe chronic plaque psoriasis.