

## Agenda item 7 Post-market review of the use of biologics in the treatment of severe chronic plaque psoriasis (CPP)

### 1 Purpose of Item

Request that PBAC members:

- 1.1 **Consider** the draft report for the Post-market review of the use of biologics in the treatment of severe CPP (the Review) and make recommendations to the Minister for Health regarding the Pharmaceutical Benefits Scheme (PBS) listings of these medicines and the Review Options.

**Table 1: Current PBS listed biologics for the treatment of CPP**

Adalimumab Sponsor: • AbbVie	40 mg/0.8 mL injection, 2 x 0.8 mL syringes; (9425C, 9427E), 40 mg/0.8 mL injection, 2 x 0.8 mL cartridges; (9426D, 9428F)
Etanercept Sponsor: • Pfizer • Merck, Sharpe and Dohme	50 mg in 1 mL single use auto-injector x 4; (11221N, 11222P, 1964J, 9461Y, 9462B), Injections 50 mg in 1 mL single use pre-filled syringes x 4; (11224R, 11225T, 1963H, 9091L, 9431J), 25 mg injection x 4 vials (&) inert substance diluent 4 x 1 mL syringes; (11223Q, 1954W, 9037P, 9429G),
Infliximab: Sponsor: • Pfizer • Merck, Sharpe and Dohme • Janssen- Cilag	100 mg injection, 1 vial; (5758C, 9617E)
Ustekinumab Sponsor: • Janssen-Cilag	45 mg/0.5 mL injection, 0.5 mL vial; (9304Q, 9305R)
Ixekizumab Sponsor: • Eli Lilly	80 mg/mL injection, 2 x 1 mL injection devices; (11032P, 11033Q)
Secukinumab Sponsor: • Novartis	150 mg/mL injection, 2 x 1 mL injection devices; (10425Q, 10494H, 10910F)

## 2 Background

- 2.1 In August 2016, the PBAC endorsed the following terms of reference (ToR) for the Review:
- ToR 1: Review current clinical guidelines for the treatment of severe CPP and compare to the PBS restrictions for use of biologics in this indication.
  - ToR 2: Review and evaluate recent clinical evidence on the efficacy and safety of biologics used in the treatment of severe CPP and compare to the evidence considered by the PBAC in previous sponsor submissions.
  - ToR 3: Review the utilisation of PBS biologics for the treatment of CPP including time on treatment and discontinuation from treatment, and compare this with that observed in the clinical trial evidence considered by the PBAC.
  - ToR 4: Subject to the findings from Terms of Reference 1, 2 and 3, review the cost-effectiveness of biologics for severe CPP.
- 2.2 The department commissioned an independent contractor to undertake research to assist in informing the Review's response to each ToR.
- 2.3 An independent Reference Group was established to guide and provide advice to the Review. The Reference Group provided advice on issues raised by stakeholders, considered the evidence provided in analyses/reports, and informed the development of the draft report and options.
- 2.4 In line with the published Post-market Review Framework, there were a number of opportunities for stakeholder consultation including:
- the opportunity to comment on the draft ToR
  - a public submission process addressing the Review ToR
  - a stakeholder forum held in Melbourne
  - the opportunity to comment on the draft report.

## 3 Key findings of the Review

The PBAC noted the key findings under the following four ToR.

- 3.1 ***ToR 1: Review current clinical guidelines for the treatment of severe CPP and compare to the PBS restrictions for use of biologics in this indication.***
- 3.1.1 A systematic literature review was conducted to identify clinical guidelines for the treatment of psoriasis. In the absence of evidence based Australian Guidelines the search included international guidance. Two Australian consensus statements were identified that focus on treatment targets:
- a. Baker 2013, was developed by a consensus panel comprising 12 dermatologists. It was based on a European consensus statement on treatment targets, which the panel adapted to take account of the Australian medical environment and prescribing patterns.

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- b. Australasian College of Dermatologists (ACD) 2017, was based on Baker 2013 and “adapted for use by health professionals” by the ACD

Table 2 provides a summary of the key difference between international and Australian Guidance Statements and the current PBS restrictions for use of biologics in the treatment of Chronic Plaque Psoriasis. The only guidance that considered cost-effectiveness was the UK NICE guidance (UK NICE, 2014 update).

**Table 2: Treatment algorithms for use of biologics in CPP: PBS versus other guidance**

PBS restrictions	Evidence-based Guidelines			Consensus
	Canada (6)	EU (8)	UK NICE Technology appraisals and UK BAD (10, 12-17, 19)	Australian (3, 5)
<b>Second line treatments</b>				
Phototherapy, methotrexate, cyclosporin, acitretin	To ameliorate CPP: methotrexate, cyclosporin, or acitretin; For complete control: biologics or phototherapy.	Phototherapy, methotrexate, cyclosporin (short course), fumaric acid esters. (Not acitretin monotherapy)	PUVA (photochemotherapy), methotrexate, cyclosporin, acitretin	Phototherapy, methotrexate, cyclosporin, acitretin.
<b>Biologics - prior treatments</b>				
≥ 3 of the above 4 therapies failed, contraindicated or intolerant	No clinical reason to reserve the biologics for second-line use.	Use if above therapies were inadequate in response or contraindicated or not tolerated. <sup>a</sup>	Use if above therapies were inadequate in response or contraindicated or not tolerated. <sup>a</sup> UK BAD included risk of toxicity or unstable life-threatening CPP.	≥ 2 of 4 therapies inadequate in response or contraindicated.
<b>Severity assessment criteria</b>				
PASI >15 (termed "severe" CPP)	Numerical cut-offs not specified as they don't reflect actual burden of disease. More patient-centred standards needed.	-	PASI ≥10 and DLQI >10 <sup>b</sup> UK BAD also included BSA ≥10% if PASI not applicable, and allowed exemptions in exceptional circumstances. <sup>c</sup>	PASI >10 and/or DLQI >10 <sup>d</sup> (termed "severe" CPP in ACD 2017, but "moderate-to-severe" in Baker 2013).
<b>CPP of the face, palm of hand or sole of foot</b>				
≥ 2 of 3 PASI symptom sub-scores rated as 'severe' or 'very severe' or ≥ 30% of area affected	1st-line: topical 2nd line: acitretin, methotrexate, infliximab, adalimumab, ustekinumab, cyclosporin	-	UK NICE: may be more likely to be included given the lower PASI threshold. UK BAD: covered in exceptional circumstances.	Considered the PBS definition for severity was appropriate and could be combined with the proposed DLQI assessment.

ACD = Australasian College of Dermatologists; BAD = British Association of Dermatologists; BSA = body surface area; CPP = chronic plaque psoriasis; DLQI = Dermatology Life Quality Index; EU = European Union; NICE = National Institute for Health and Care Excellence; PBS = Pharmaceutical Benefits Scheme; PASI = Psoriasis Area and Severity Index; PUVA = psoralen and ultraviolet A; UK = United Kingdom  
a Number of prior therapies that should be trialled was not stated.

b Except infliximab which is PASI ≥20 and DLQI >18.

c UK BAD guidelines also state: In exceptional circumstances patients with severe disease may fall outside this definition but should be considered for treatment, e.g. disease affecting high-impact sites with associated significant functional or psychological morbidity such as acral psoriasis, or psoriasis affecting the genitalia, hands, feet, head and neck.

d Upgrade mild disease to moderate-to-severe if there is: major involvement of visible areas or the scalp, involvement of genitals, onycholysis or onychodystrophy of at least two fingernails, presence of itch leading to excoriation.

- 3.1.2 In addition to the above treatment criteria, PBS restrictions include criteria on the circumstance where treatment can be continued beyond the first 4-6 months. If the continuation criteria are not met (i.e. reduction in Psoriasis Area and Severity Index (PASI) score of 75% or more is not achieved), the biologic must be discontinued and patient switched to a different biologic. Further, patients who fail to respond to three biologics must cease all biologic therapy for a minimum of five years. However, the Australian consensus statements consider an adequate treatment response includes patients who experience a reduction in PASI of 74-50% and a response measured using the Dermatology Life Quality Index (DLQI) of five or less.
- 3.1.3 In the guidance statements, the most commonly recommended clinical assessment measures are PASI, DLQI and an assessment of body surface area. For measuring disease severity, there are no other validated tools that are clearly superior to the PASI. The correlation between absolute PASI and DLQI scores is not strong (studies have found R2 (correlation) values between 0.49 and 0.81). However, there appears to be good correlation between an improvement in PASI and an improvement in the DLQI.
- 3.1.4 Stakeholders stated that CPP significantly impacts quality of life and influences the patient's mental health and wellbeing as well as their ability to work and be productive.
- 3.2 ***ToR 2: Review and evaluate recent clinical evidence on the efficacy and safety of biologics used in the treatment of severe CPP and compare to the evidence considered by the PBAC in previous sponsor submissions.***
- 3.2.1 A systematic literature review was conducted to identify randomised controlled trials that evaluated the efficacy and safety of the PBS listed biologics for the treatment of CPP (including psoriatic arthritis [PsA]). The searches identified 65 trials and four observational studies in total.
- 3.2.2 New evidence for each biologic was compared with that already considered by the PBAC in terms of the proportion of patients achieving a PASI 75 improvement and mean change in DLQI score. In total, 21 trials were not previously seen by the PBAC. Overall, the trials were similar in terms of inclusion criteria, risk of bias and disease severity. Etanercept and ustekinumab were the two biologics with the most unseen trials. When comparing efficacy and safety of these trials and for each PBS-listed biologic, the new evidence was highly consistent with that already considered by the PBAC.
- 3.2.3 As etanercept was one of the earlier biologics PBS listed for treatment of severe psoriasis, it was used in the comparator arm of trials for the newer biologics. Five trials were identified that compared etanercept with other PBS listed medications (PIECE versus infliximab; UNCOVER 2 and 3 versus ixekizumab; FIXTURE versus

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secukinumab; and ACCEPT versus ustekinumab) and one trial, the CLEAR trial, directly compared secukinumab and ustekinumab. In each of the trials that utilised etanercept as a comparator, etanercept was dosed at 50 mg twice weekly for up to 12 weeks, as approved in the Australian Product Information. The results of these trials are presented in Table 3.

- 3.2.4 For the direct comparisons of efficacy, those treated with infliximab, ixekizumab, secukinumab and ustekinumab had a greater PASI 75 response than those treated with etanercept.

**Table 3: Direct comparisons of PBS-listed biologics: efficacy results**

Trial	Time horizon	Arm	N	PASI 75; n (%)	Δ DLQI; mean (SD)
<b>Infliximab versus etanercept</b>					
PIECE	12 weeks	Infliximab <sup>1*</sup>	25	19 (76%)	NR
		Etanercept <sup>2</sup>	23	5 (22%)	NR
	24 weeks	Infliximab <sup>1*</sup>	25	18 (72%)	NR
		Etanercept <sup>2</sup>	23	8 (35%)	NR
<b>Ixekizumab versus etanercept versus placebo</b>					
UNCOVER 2	12 weeks	Ixekizumab <sup>3*</sup>	351	315 (90%)	-10.4 (0.3)
		Etanercept <sup>2</sup>	358	149 (42%)	-7.7 (0.3)
		Placebo	168	4 (2%)	-2.0 (0.4)
UNCOVER 3	12 weeks	Ixekizumab <sup>3*</sup>	385	336 (87%)	-10.2 (0.2)
		Etanercept <sup>2</sup>	382	204 (53%)	-8.0 (0.2)
		Placebo	193	14 (7%)	-1.7 (0.3)
<b>Secukinumab versus etanercept versus placebo</b>					
FIXTURE	12 weeks	Secukinumab <sup>4*</sup>	327	77%	-10.4
		Etanercept <sup>2</sup>	326	44%	-7.9
		Placebo	326	5%	-1.9
<b>Ustekinumab versus etanercept</b>					
ACCEPT	12 weeks	Ustekinumab <sup>5*</sup>	209	141 (68%)	NR
		Ustekinumab <sup>6</sup>	347	256 (74%)	NR
		Etanercept <sup>2</sup>	347	197 (57%)	NR
<b>Secukinumab versus ustekinumab</b>					
CLEAR	16 weeks	Secukinumab <sup>4*</sup>	334	311 (93%)	NR
		Ustekinumab <sup>7*</sup>	335	277 (83%)	NR

DLQI = Dermatology Life Quality Index; IV = intravenous; NR = not reported; PASI 75 = reduction in Psoriasis Area and Severity Index score of 75%; PBS = Pharmaceutical Benefits Scheme; PI = Product Information; SC = subcutaneous; SE = standard error; *Italics = (SE)*; Shaded = previously considered by the PBAC

<sup>1\*</sup> Infliximab 5 mg/kg IV at Weeks 0, 2, 6; then every 8 weeks (PI recommended dose)

<sup>2</sup> Etanercept 50 mg SC twice weekly (PI recommended dose)

<sup>3\*</sup> Ixekizumab 160 mg SC at Week 0; 80 mg at Weeks 2, 4, 6, 8, 10 (PI recommended dose)

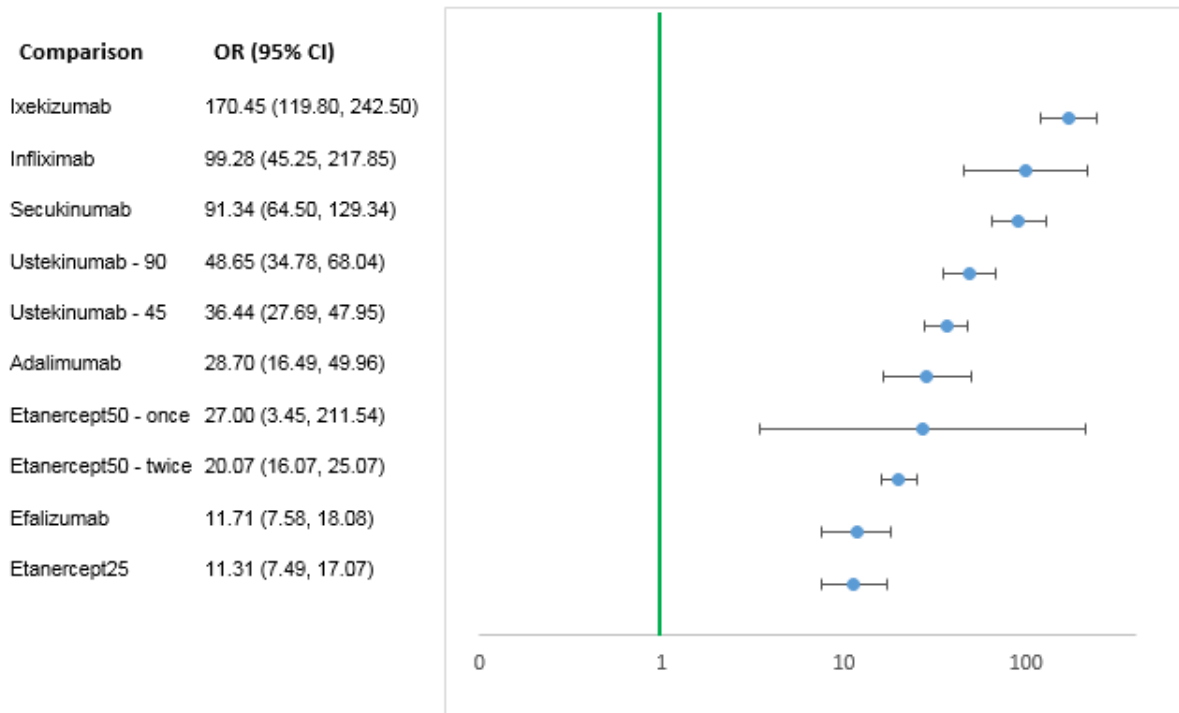
<sup>4\*</sup> Secukinumab 300 mg SC at Weeks 0, 1, 2, 3, 4; then every 4 weeks (PI recommended dose)

<sup>5\*</sup> Ustekinumab 45 mg SC at Weeks 0, 4; then every 12 weeks (PI recommended dose)

<sup>6</sup> Ustekinumab 90 mg SC at Weeks 0, 4; then every 12 weeks (PI recommended dose)

<sup>7\*</sup> Ustekinumab 45 mg SC for patients ≤ 100 kg and 90 mg for patients > 100 kg at Weeks 0, 4; then every 12 weeks (PI recommended dose)

3.2.5 A network meta-analysis was conducted to analyse the comparative effectiveness of the PBS-listed biologics in the treatment of CPP. Efficacy was assessed by comparing the proportion of patients achieving a PASI 75 improvement at 12 weeks. Of the 65 trials identified, 36 randomised control trials were identified for inclusion in this analysis (N = 22,253). The majority (32 of the 36) of trials were placebo controlled trials with only 13 trials including comparison treatment arms other than placebo. Figure 1 demonstrates the results of the network meta-analysis of each biologic compared to placebo.

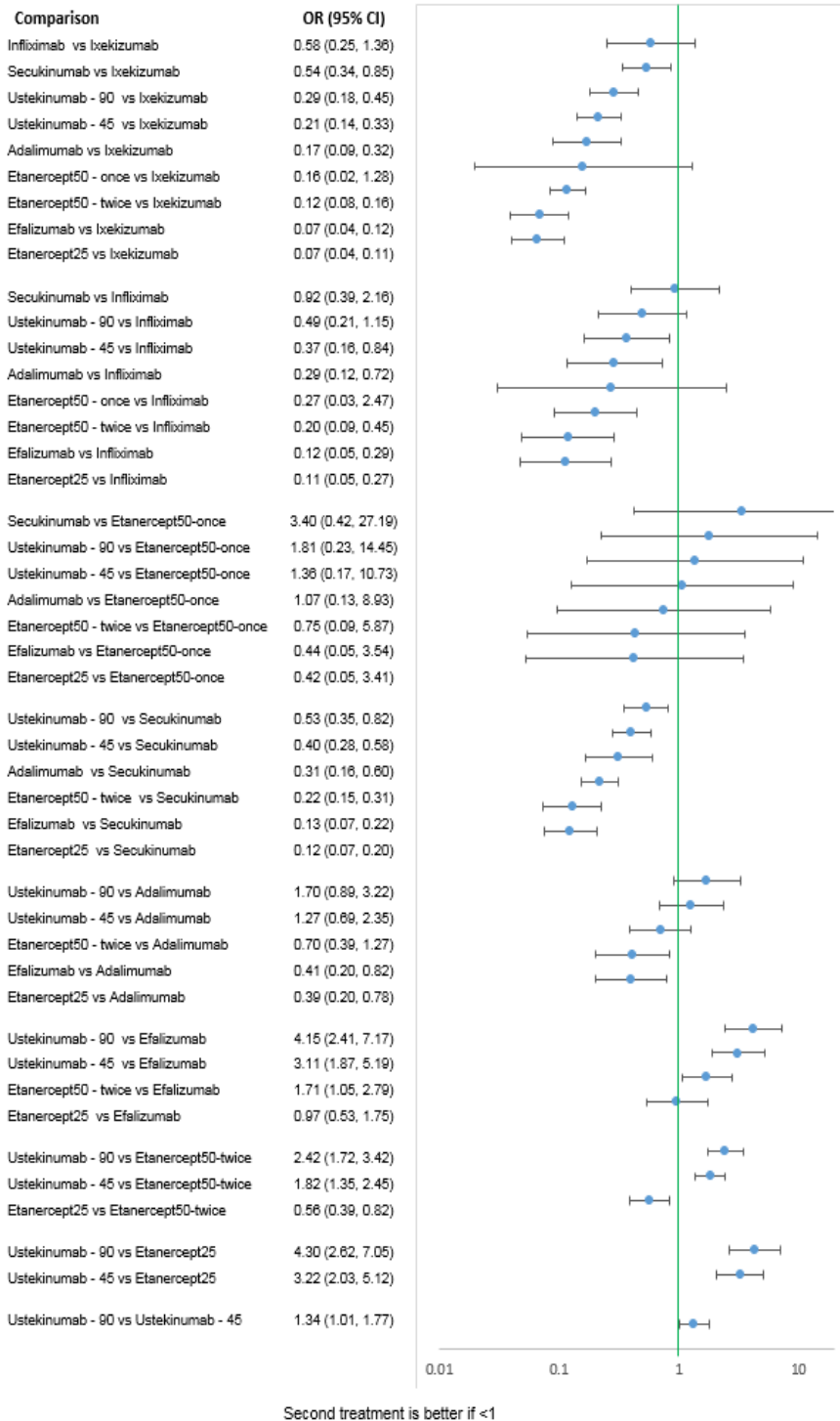


**Figure 1: Forest plot of the OR (95% CI) for the proportion of patients achieving a PASI 75 response at 12 weeks – PBS-listed biologic versus placebo.**

3.2.6 Overall, the efficacy of biological compared to placebo demonstrated that all PBS listed biologics provide patients with clinically meaningful improvements in their psoriasis severity. There was some variation in the efficacy and safety results between different biologics.

3.2.7 Ixekizumab appears to have superior efficacy over adalimumab, etanercept, secukinumab and ustekinumab (Figure 2) Infliximab also appears to demonstrate superior efficacy over adalimumab, etanercept and ustekinumab (45mg).

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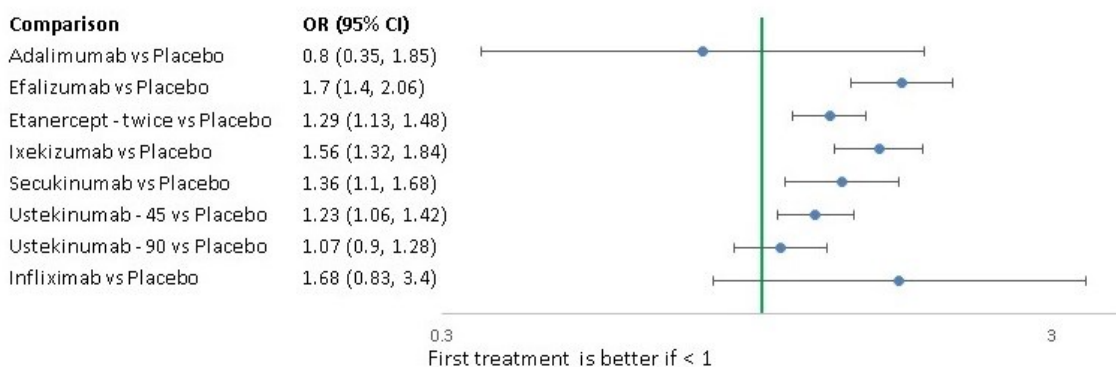


**Figure 2: Forest plot of the OR (95% CI) for the proportion of patients achieving a PASI 75 response at 12 weeks – PBS-listed biologic versus PBS-listed biologic.**

OR values less than one suggest that the first biologic in the comparison is less likely to result in a PASI 75 response compared to the second

CI = confidence interval; Etanercept50 – once = etanercept 50 mg once weekly; Etanercept50 – twice = etanercept 50 mg twice weekly; Etanercept25 = etanercept 25 mg twice weekly; OR = odds ratio; PASI = Psoriasis Area and Severity Index; PBS = Pharmaceutical Benefits Scheme; vs = versus

3.2.8 Efalizumab (de-registered) was most likely, compared to placebo, to result in an adverse event at 12 weeks (OR= 1.70; 95% CI: 1.40, 2.06), Of the current PBS listed biologics, ixekizumab was the most likely treatment to cause an adverse event (OR = 1.56; 95% CI: 1.32, 1.84), while adalimumab and ustekinumab had the lowest point estimates for the likelihood of an adverse event (Figure 3).



**Figure 3: Forest plot of the OR (95% CI) for the proportion of patients experiencing an adverse event at 12 weeks – PBS-listed biologic versus placebo.**

OR values less than one suggest that the first biologic in the comparison is less likely to result in an adverse event compared to the second

CI = confidence interval; Etanercept – once = etanercept 50 mg once weekly; Etanercept – twice = etanercept 25 mg twice weekly; OR = odds ratio; PBS = Pharmaceutical Benefits Scheme; vs = versus

3.2.9 There is very little data available for biologics in the PASI 10 - 15 category, even though the consensus from international and Australian guidelines was that biologics can and should be used in patients with this level of disease severity. The evidence that was identified tended to suggest that in the milder disease categories, efficacy in terms of PASI response would be lower than in those with more severe disease.

3.2.10 There was limited data for severe CPP with concomitant PsA. The trials that addressed concomitant PsA and CPP tended to include patients with a lower baseline PASI score. Therefore, to enable an analysis in the review, a lower cut off PASI score (PASI > 10) was used, as studies were limited. Overall, the efficacy of biological compared to placebo demonstrated that biologics provided patients with clinically meaningful improvements in their PsA severity. It also appeared that the biologics were marginally less effective in terms of the proportion of patients achieving a PASI 75 response in patients with concomitant PsA than in patients without (but this could have been due to the lower baseline PASI criteria).

3.2.11 Trials that examined the efficacy of biologics on specific body areas were limited. Five small trials (including two subgroup analyses) were identified and the results

suggested that the biologics have some effect in treating CPP of the hands and/or feet.

**3.3 ToR 3: Review the utilisation of PBS biologics for the treatment of CPP including time on treatment and discontinuation from treatment, and compare this with that observed in the clinical trial evidence considered by the PBAC.**

3.3.1 There is considerable uncertainty around the prevalence of severe CPP in Australia, with a paucity of data and no Australia wide evidence to guide estimates. A number of Australian and international sources were used to provide an estimate of the prevalence of severe CPP (PASI >15) in Australia of 19,000 people (range 7,000 to 360,000).

3.3.2 The number of prevalent patients being treated with biologics has increased by over 60% in recent years, from 3,185 patients in the first quarter of 2014 to 5,144 patients in the last quarter of 2016. Ustekinumab was the most commonly used biologic, with 46% of patients having had at least one prescription for this biologic in 2016.

3.3.3 The Commonwealth expenditure on biologics for CPP has increased from approximately \$79 million in 2014 to approximately \$121 million in 2016. Table 4 presents the total benefits paid (published prices) for biologics used for CPP per calendar year between 2013 and 2016. Special pricing arrangements apply for some PBS-listed biologics for psoriasis, hence the figures in the table are only indicative of trends.

**Table 4: Biologic expenditure for severe CPP**

Listing years	2013 <sup>a</sup>	2014	2015	2016
Adalimumab	\$11,724,985 <sup>b</sup>	\$21,961,118 <sup>b</sup>	\$24,103,684 <sup>b</sup>	\$24,530,716 <sup>b</sup>
Etanercept	\$3,408,964 <sup>b</sup>	\$4,667,700 <sup>b</sup>	\$5,909,870 <sup>b</sup>	\$6,532,959 <sup>b</sup>
Infliximab	\$3,698,230	\$5,307,585	\$7,231,884	\$7,357,199
Secukinumab	-	-	\$3,205,624 <sup>b</sup>	\$20,144,662 <sup>b</sup>
Ustekinumab	\$19,358,908 <sup>b</sup>	\$47,269,588 <sup>b</sup>	\$57,396,604 <sup>b</sup>	\$62,457,372 <sup>b</sup>
<b>Total</b>	<b>\$38,191,087</b>	<b>\$79,205,991</b>	<b>\$97,847,666</b>	<b>\$121,022,908</b>

Source: DHS Supplied prescriptions database (date of supply), extracted May 2017

<sup>a</sup> These figures are for the months July to December only

<sup>b</sup> Special pricing arrangements

3.3.4 There were some differences between the proportion of patients persisting on their first biologic in the PBS data (which assumes a PASI 75 response) and the proportion of people achieving a PASI 75 response in trials (Table 5). In all but etanercept users, a higher proportion of patients were continuing with their initial

biologic therapy than the proportion reported to have achieved a PASI 75 response in the clinical trials. Stakeholders considered the reason for higher responses in community use may be due to the concomitant use of topical treatments or methotrexate that was not permitted in the trials. There is also the potential for some inaccuracy in the assessment of duration of therapy based on PBS dispensing data for biologics that are dosed less frequently such as ustekinumab.

**Table 5: Continuation of first biologics compared with trial PASI 75 outcomes**

Biologic	PBS continuation (6 months ≈ 24 weeks)	PASI 75 response (time)	PBS continuation (12 months ≈52 weeks)	PASI 75 response (time)
Adalimumab	77%	67% <sup>a</sup> -70% <sup>b</sup> (24 weeks)	62%	67% <sup>a</sup> (48 weeks)
Etanercept (adults only)	19%	44% - 62% (24 weeks) <sup>c</sup>	13%	-
Infliximab	100%	77%- 82% (24 weeks) <sup>d</sup>	93%	55% (50 weeks) <sup>e</sup>
Ustekinumab	97%	≈80% <sup>f</sup> (24 weeks)	88%	≈70% <sup>f</sup> (40 weeks)

Source: DHS Supplied prescriptions database (date of supply), extracted May 2017; effectiveness data from Term of Reference 2

Note: Secukinumab was listed on the PBS schedule on 1 September 2015, which was after the 30 June 2015 cut-off for treatment initiation in this study.

PASI 75 = 75% reduction in the Psoriasis Area and Severity Index score

<sup>a</sup> Gordon (2012) Cohort D

<sup>b</sup> Ashina (2010)

<sup>c</sup> Leonardi (2003) and PRESTA trial

<sup>d</sup> EXPRESS and RESTORE trials

<sup>e</sup> Menter (2007) (5mg/kg every 8 weeks dosing)

<sup>f</sup> Kimball (2012)

3.3.5 Stakeholders generally felt that biologics are not being over-utilised. Instead, there is likely to be a pool of people who have disease severe enough to treat, but who have not accessed biologics yet for a variety of reasons including awareness, access to dermatologists and issues with prior therapies. There were conflicting views from stakeholders as to whether the continuation rate of biologics was higher on the PBS than reported in the corresponding trials.

**3.4 ToR 4: Subject to the findings from Terms of Reference 1, 2 and 3, review the cost-effectiveness of biologics for severe CPP.**

3.4.1 According to the review findings for TOR 1-3, there are a number of possible modifications to the PBS restrictions for biologics that would align PBS restrictions more closely to guidelines. These include:

- reducing the number of prior treatments, from three to two, that are to be trialled before allowing treatment to progress to a biologic
- increasing the population with severe CPP (PASI >15) to include:
  - patients with a PASI >12 and a DLQI >10
  - patients with CPP that have ano-genital involvement.

3.4.2 The cost-effectiveness of any additional PBS population as a result of aligning restrictions with guidelines is unknown.

3.4.3 The evidence provided in this report under TOR 2 may have implications for the comparative cost-effectiveness of biologics listed for severe CPP. Currently not all PBS biologics are considered therapeutically equivalent. Infliximab was listed on a cost-effective basis to etanercept/efalizumab, and ustekinumab was listed as cost-effective to etanercept. All other biologics have been cost-minimised to etanercept either directly or indirectly.

3.4.4 The review identified eleven prior sponsor submissions/resubmissions to PBAC that included cost-effectiveness analyses for biologics in treatment of severe CPP. These submissions included the following biologics: efalizumab, etanercept, infliximab, ustekinumab, and adalimumab.

3.4.5 Only one submission (adalimumab 2013) has been considered by PBAC that presented a cost-effectiveness analysis for patients with moderate CPP (PASI 10-15). All other submissions have been for patients with severe CPP (PASI >15). Only one submission was for children (etanercept 2012) and this submission was based on a cost per responder analysis, not a cost utility analysis.

#### **4 PBAC outcome**

4.1.1 The PBAC considered the stakeholder submissions to the Review, sponsors' PSCR, pre-PBAC responses, ESC and DUSC advice in addition to the draft Report.

4.1.2 Overall, the PBAC accepted the key findings presented in the Review Report of PBS listed biologics for the treatment of CPP.

- 4.1.3 The PBAC considered the four options presented in the Review Report and made the following comments and recommendations.
- 4.2 ***Option 1 - Alter the PBS restrictions so that patients only need to have failed two of the four prior treatments: phototherapy; methotrexate; cyclosporin; acitretin.***
- 4.2.1 The PBAC noted that the requirement to fail three prior therapies was not an entry criterion for most of pivotal trials presented in past submission to PBAC.
- 4.2.2 The PBS requirement to fail three prior therapies is challenging for patients and clinicians, with many patients exposed to significant side-effects from cyclosporin and acitretin.
- 4.2.3 The option to fail two prior therapies is in alignment with the Australasian College of Dermatologists (ACD) Consensus Statement for the treatment of CPP.
- 4.2.4 The PBAC noted that this option was supported by the Reference Group and stakeholders. This option alone was also considered to have little impact on the size of the population accessing PBS subsidised biologics.
- 4.2.5 PBAC Advice: The PBAC recommended altering the current PBS restriction so that patients are only required to have failed two of the four prior treatments.**
- 4.3 ***Option 2 - Alter the PBS restrictions to enable patients with a baseline PASI score of between 12–15, AND a DLQI > 10, to access PBS-listed biologics for CPP. This population would be in addition to the current PBS eligible population with a baseline PASI >15.***
- 4.3.1 The PBAC noted that this option was supported by stakeholders.
- 4.3.2 The PBAC noted that the current PBS restrictions do not consider quality of life impacts associated with CPP and accepted stakeholder comments that CPP had a significant impact on quality of life, including patients' mental health and wellbeing, social interactions, work opportunities, productivity and self-confidence.
- 4.3.3 The PBAC agreed that the minimum entry criteria for biologic therapies should be a baseline PASI > 12 (not 10). There is insufficient evidence on the effectiveness of biologics in patients with a PASI 10-11 as most of the evidence identified in TOR 2 is from trials with a minimum entry criteria of PASI > 12.

- 4.3.4 The PBAC noted the Reference Group's advice that the requirement of PASI >12 AND DLQI > 10 would potentially result in some patients with a PASI >15 being unable to access biologics if their DLQI was < 10. Consequently, the Reference Group advised PBAC to leave the current restriction for Severe CPP with PASI > 15 and add a new indication for Moderate CPP (PASI 12-15 AND DLQI > 10). PBAC was uncertain that there was sufficient evidence to support the inclusion of DLQI in the restriction criteria.
- 4.3.5 The PBAC considered that the inclusion of DLQI in a restriction for moderate-severe CPP be considered in a separate cost-effectiveness analysis, subject to the available evidence.
- 4.3.6 The PBAC noted that the broader restriction criteria presented in Option 2 could significantly increase the number of people eligible for PBS-listed biologics for CPP. In addition, the cost-effectiveness of biologics in the population with a baseline PASI between 12 and 15 remains unknown, and that the clinical evidence identified in the Review for this population was limited. The PBAC recalled having considered only one prior submission from the sponsor of adalimumab for this population and this submission was rejected on the basis of a high and uncertain ICER.
- 4.3.7 PBAC also noted that both DUSC and ESC considered that the cost-effectiveness of biologics would need to be determined in the moderate-severe CPP population with baseline PASI > 12 and/or DLQI >10 ahead of any recommendation for subsidy.
- 4.3.8 PBAC Advice: The PBAC advised that a cost-effectiveness analysis of biologics in the population proposed under Option 2 would need to be considered prior to making a recommendation for subsidy via the PBS.**

4.4 ***Option 3 - Alter the PBS restrictions to enable patients with ano-genital involvement to access PBS-listed biologics for CPP.***

- 4.4.1 The PBAC noted DUSC's advice that psoriasis affecting the genitals was just one of many specific body areas that may be affected and were therefore not supportive including ano-genital separately in the PBS restriction. The DUSC were more supportive of the inclusion of DLQI in the restriction as a means of capturing people with high clinical need who would otherwise not meet the baseline PASI criteria. PBAC also noted the DUSC advice that this option would increase the number of people eligible to access PBS-listed biologics for psoriasis, thereby impacting the cost-effectiveness that was originally accepted by PBAC.
- 4.4.2 The available trials presented in the Review Report only included patients with genital psoriasis who also had psoriasis in other areas. Therefore it was difficult for PBAC to assess the prevalence of this condition in isolation.
- 4.4.3 The PBAC noted that the Australasian College of Dermatologists Consensus Statement for the treatment of CPP includes genitals as one of the features that may significantly impair quality of life and alter the classification of mild/moderate disease to severe disease.
- 4.4.4 The PBAC accepted the reference groups advice that patients with ano-genital involvement would be unlikely to have a PASI greater than 12, unless their psoriasis extended to other body areas. This means they would not be captured by the broader criteria proposed in Option 2 unless it included patients with a PASI > 12 OR DLQI > 10.
- 4.4.5 The PBAC considered that the cost-effectiveness in patients presenting with ano-genital psoriasis alone would need to be considered before extending the PBS restriction to include this population. PBAC also considered that if cost-effectiveness could be established in the population presenting with a DLQI > 10, that this would be the more appropriate criteria under which to allow treatment for patients with specific psoriasis conditions that significantly impact quality of life.
- 4.4.6 **PBAC Advice: The PBAC did not recommend altering the current PBS restrictions to include the specific population with psoriasis involving the ano-genital area.**

4.5 ***Option 4 - Based on the findings from TOR 1-3, and proposed changes to the eligibility criteria for biologics to treat CPP, review the cost-effectiveness of biologics in the treatment of CPP.***

4.5.1 *Option 4a) review the cost-effectiveness in all PBS listed biologics under the current PBS restriction according to actual PBS utilisation and recent clinical evidence.*

4.5.2 The PBAC noted the ESC advice on the current therapeutic relativities where ustekinumab and infliximab were listed as cost-effective over etanercept and where secukinumab, ixekizumab and adalimumab were cost-minimised to etanercept. These relativities are inconsistent with the clinical evidence and network meta-analysis presented in the PMR report.

4.5.3 The PBAC noted one sponsor's concerns about the use of a network meta-analysis in the PMR. However, the PBAC noted that the report had also included a transparent analysis of available direct trial comparisons between biologics (Table 3) and that the overall conclusions were acceptable. [REDACTED]

4.5.4 PBAC noted that they have not previously considered a cost-effective comparison across all biologics for CPP. The summary in the report of the previous economic models considered by PBAC indicates there were important differences between these models in terms of the time horizon, utilities and costs included.

4.5.5 The PBAC agreed with the ESC advice that the cost-effectiveness should be re-established using current utilisation and effectiveness data and a single model applied consistently across all biologics for the current restriction.

**4.5.6 PBAC Advice – The PBAC advised that in reviewing the cost-effectiveness of the additional population described in Option 4b below, that the cost-effectiveness of biologics under the current PBS restriction would also require re-analysis.**

4.5.7 *Option 4b) review the cost-effectiveness of expanding the restriction to include: reducing the number of prior treatments (from three to two); increasing the population to include patients with a PASI between 12-15 and a DLQI>10; and increasing the population to include patients with CPP that have ano-genital involvement or other specific circumstances as recommended by PBAC.*

- 4.5.8 The PBAC noted that the Reference Group members advocated for the cost-effectiveness review to be conducted in a timely manner, so that implementation of supported options are not overly delayed.
- 4.5.9 The PBAC also noted that stakeholders have not opposed a cost-effectiveness review and the following sponsors had agreed to provide additional data to inform a cost-effectiveness review: Pfizer; Novartis; Eli Lilly; Abbvie and Janssen.
- 4.5.10 The PBAC discussed the need for a cost-effectiveness review in the following three expanded populations:
- *Reducing the number of prior treatments (from three to two):* The PBAC agreed to Option 1 without needing to undertake cost-effectiveness modelling.
  - *Increasing the population to include patients with a PASI between 12-15 AND DLQI >10:* The PBAC considered that there is a clinical need for expanding the current PBS population to include patients under Option 2 and therefore cost-effectiveness modelling is required. The PBAC also requested an additional analysis where possible, to consider the population that includes both patients with PASI >12 or a DLQI > 10.
  - *Increasing the population to include patients with CPP that have ano-genital involvement:* The PBAC did not request cost-effectiveness modelling for patients specifically with ano-genital CPP. The additional cost-effectiveness analyses conducted for Option 2 would determine if there is sufficient evidence to expand the restriction to include patients with a DLQI >10, and in doing so, capture patients with ano-genital CPP that significantly impacts their quality of life.
- 4.5.11 PBAC Advice: The PBAC requested a cost-effectiveness review to consider the additional PBS population's treated with biologics that meet the eligibility criteria of a baseline PASI between 12-15 and DLQI >10. Where possible this analysis should also consider the inclusion of the 'OR DLQI > 10' population in addition to those who meet the combined eligibility requirement of a baseline PASI 12-15 and DLQI >10.**