Pharmaceutical Benefits Scheme

Post-market Review

The use of biologics in the treatment of severe chronic plaque psoriasis

Report to PBAC

Executive summary

FINAL REPORT

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Abbreviations

Abbreviation	Full Name / Wording
AAD	American Academy of Dermatology
ABS	Australian Bureau of Statistics National Health Survey
ACD	Australasian College of Dermatologists
ACR	American College of Rheumatology
AGREE	Appraisal of Guidelines for Research and Evaluation
BAD	British Association of Dermatology
CPP	chronic plaque psoriasis
DHS	Department of Human Services
DLQI	Dermatology Life Quality Index
EQ-5D	The EuroQOL five dimensions questionnaire
EU	European Union
NICE	National Institute for Health and Care Excellence
PASI	Psoriasis Area and Severity Index
PBAC	Pharmaceutical Benefits Advisory Committee
PBS	Pharmaceutical Benefits Scheme
PsA	Psoriatic arthritis
RG	Reference Group
ToR	term of reference
UK	United Kingdom
US	United States

Executive Summary

Background and context

Psoriasis is a life-long skin condition, commonly characterised by red, scaly areas and patches. The cause is unknown; however, evidence suggests that it is a disorder of the immune system. (1) It is more common in people who have a relative with psoriasis and affects approximately 2% of people worldwide. (1, 2)

Plaque psoriasis occurs in 90% of psoriasis sufferers and has characteristic thick, with a sharp edge (marginated), red scaly lesions, most commonly on the elbows, knees, lower back and scalp. (1) Psoriasis can also affect the nails and joints and can impact on the emotional and social wellbeing of the affected person. (1) Chronic plaque psoriasis (CPP) is persistent psoriasis that can be improved with treatment, but is difficult to clear completely. (2) It is characterised by large plaques that may join together to form large areas, and can be localised (e.g. elbows and knees) or generalised (e.g. scalp, trunk and limbs). (2)

Biologics (biologic therapies, biologic response modifiers) are drugs derived from living material, which interfere with the immune system to treat and prevent immune-mediated inflammatory disorders. (2)

Efalizumab and etanercept were the first biologics listed for CPP in 2006. Infliximab, adalimumab and ustekinumab were listed during the following four years, and there was a four year gap between listings until secukinumab and ixekizumab were listed in 2015 and 2017, respectively (Figure ES.1). The Pharmaceutical Benefits Scheme (PBS) restrictions around use of prior therapies and the Psoriasis Area and Severity Index (PASI) thresholds (PASI >15) are based on those proposed for efalizumab and etanercept. Subsequently listed biologics for CPP were recommended on the basis that the restrictions were consistent with those already listed (dosing and the initiation periods were amended where appropriate).

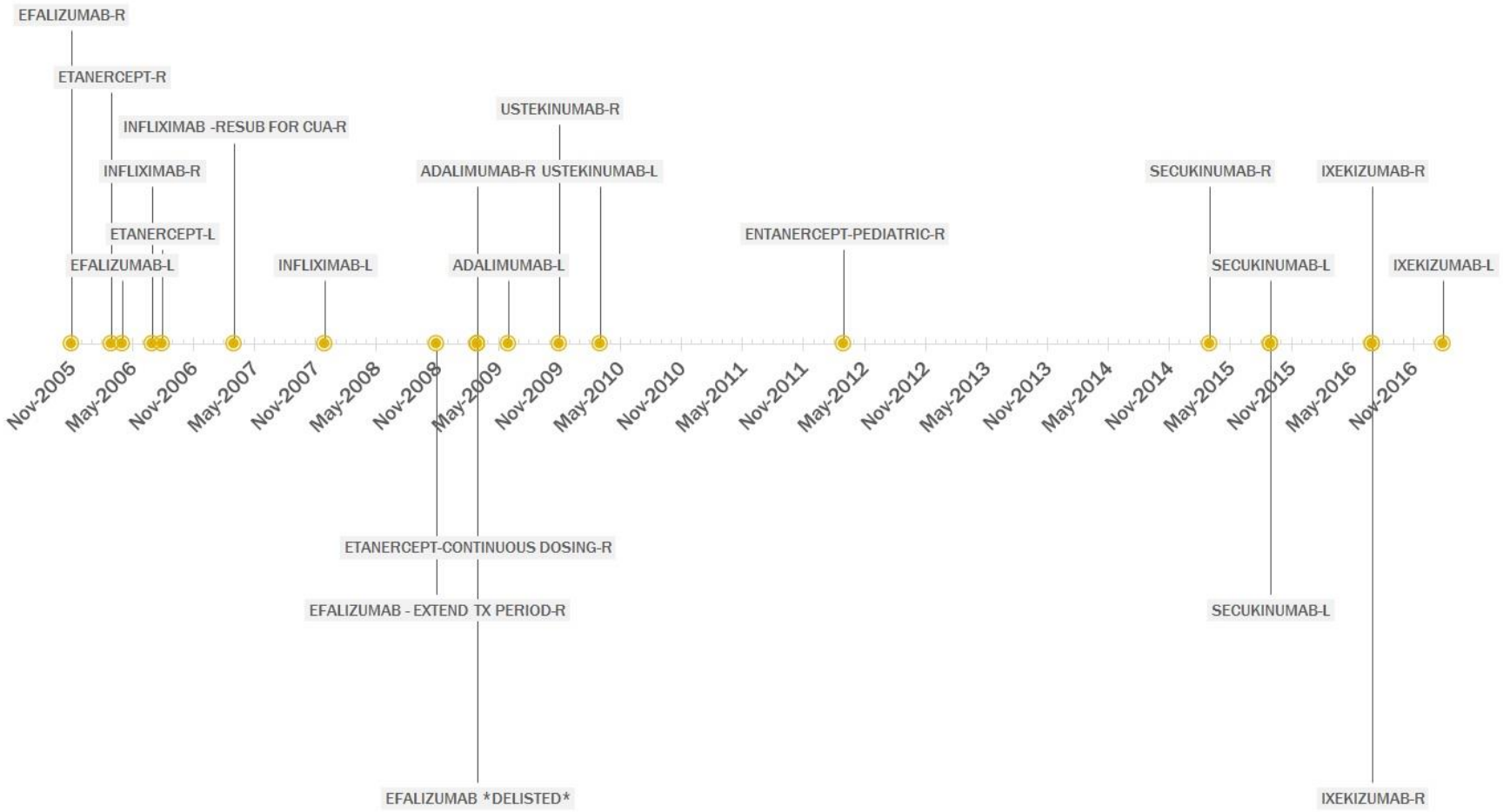

Figure ES.1: Timeline for PBAC recommendations and listings of medicines on the PBS

R = recommended; L = Listed. Those below the date line are changes to existing recommended listings.

In March 2015, the Pharmaceutical Benefits Advisory Committee (PBAC) considered the submission for secukinumab for severe CPP and noted that etanercept was the main comparator for the current PBS-listed biological medicines for this indication. The PBAC noted that there was emerging evidence of variation in response to Tumour Necrosis Factor-alpha (TNF-α) inhibitors in psoriasis, with etanercept appearing to be less effective than other agents. The PBAC recommended to the Minister for Health that a post market review be undertaken on the use of biologics in the treatment of severe chronic plaque psoriasis.

The review has the overall aim of continuing safe and cost-effective access to biologic medicines used in the treatment of severe CPP.

The review's draft Terms of Reference (ToR) were provided for public consultation from 2 May 2016 to 18 May 2016. The PBAC considered the draft ToR and comments from stakeholders at its August 2016 meeting. The Minister for Health approved the final ToR for the review.

Review Terms of Reference

The Post-market Review of the use of biologics in the treatment of severe CPP consists of four ToR. This report addresses the first three in full and introduces ToR 4.

- 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 PBAC in previous sponsor submissions.
- ToR 3: Review the utilisation of PBS biologics for the treatment of CPP and compare the patient response in practice to those observed in the clinical trial evidence considered by the PBAC.
- ToR 4: Subject to the findings from Terms of Reference 1, 2, 3 and 4, review the cost-effectiveness of biologics for severe CPP (Possible future technical report).

Methodological approach to the technical report

A Review Reference Group (RG) and Griffith University were involved in the preparation of this draft technical report for the review. Research questions relating to the ToR were developed to guide the review. The ToR were addressed through specific reviews of evidence for medicines, guidelines and medicine utilisation (refer to Table ES.1).

Table ES.1: Methodological approach to ToR 1, ToR 2, ToR 3 and ToR 4.

Methodological approach	Criteria and time period
ToR 1: Comparison of prescribing restrictions and clinical guidelines	
A systematic search of the literature and guidelines databases was conducted to identify guidelines for treatment of CPP. Systematic literature searches were also carried out to identify relevant articles about clinical outcomes in psoriasis.	The search was restricted to Australian and international guidelines published from 2007 to June 2017.
ToR 2: Review and evaluate recent clinical evidence on the efficacy and safety of biologics used in the treatment of severe CPP	
A systematic literature review was conducted to evaluate recent clinical evidence of the efficacy and safety of the biologics used in the treatment of severe CPP. Recent evidence was compared to that considered previously by the PBAC.	Publications from 2010 to June 2017.
ToR 3: Estimating the prevalence of chronic plaque psoriasis and the utilisation of PBS listed biologics for this indication	
A systematic literature review was undertaken to identify estimates of the incidence and prevalence of severe CPP (PASI > 15) in the Australian population. An analysis of the utilisation of biologics for severe CPP was undertaken using prescription data from the Department of Human Services Supplied Prescriptions Database.	Publications from 2007 to June 2017. 1 July 2013 to 31 December 2016.
ToR 4: From the findings from ToR 1, 2, 3 consider the impact on the cost-effectiveness of biologics for severe CPP	
A review of previously seen cost effectiveness models from submissions seen by the PBAC for biologics in CPP since 2003.	Pharmaceutical submissions to the PBAC.

CPP = chronic plaque psoriasis; PASI = Psoriasis Area and Severity Index; PBAC = Pharmaceutical Benefits Advisory Committee

Stakeholder consultation

Opportunities for stakeholder consultation throughout the biologics Review, included:

- Public consultation on the draft ToR.
- Public submissions to the Review were open from 4 January 2017 to 15 February 2017. Except where requested otherwise, submissions are published on the Review's website.
- A Stakeholder Forum was held by the Department of Health in Melbourne on 20 October 2017. The discussion from the Stakeholder Forum is summarised in the ToR key findings. A full version of the Stakeholder Forum Summary is available on the Review's website.

Key Review findings

ToR 1: Comparison of prescribing restrictions and clinical guidelines

Q1. Examine whether the PBS restrictions are consistent with the clinical guidelines recommended in Australia for the treatment of severe CPP.

A systematic review was conducted to identify clinical guidelines for the treatment of psoriasis. In the absence of evidence-based Australian guidelines, the search also included international guidance. Guidance documents were assessed for inclusion using the Appraisal of Guidelines for Research and Evaluation (AGREE) II instrument.

Australian clinical guidelines

There are no Australian evidence-based clinical practice guidelines for CPP. However, two Australian consensus statements have been published, noting these were not developed using formal evidence-based guideline processes.

The two Australian consensus statements focus on treatment targets and are:

- Baker 2013, was developed by a consensus panel comprising 12 dermatologists.(3) It was based on a European consensus statement on treatment targets,(4) which the panel adapted to take account of the Australian medical environment and prescribing patterns.
- Australasian College of Dermatologists (ACD) 2017, was based on Baker 2013 and "adapted for use by health professionals" by the ACD.(5)

These two documents are referred to throughout this review as the Australian consensus. The only difference between the two documents is related to terminology about CPP severity, though this did not affect the treatment targets or algorithm. Both statements included two categories of disease severity with the same thresholds and treatment recommendations: Baker 2013 termed the two categories 'mild' and 'moderate-to-severe' CPP; while ACD 2017 termed them 'mild-to-moderate' and 'severe' CPP (refer to Table ES.3).

International clinical guidelines

The literature search conducted for international guidance documents (guidelines and consensus statements) is summarised in Section 1.2 Methodology. The included guidance documents are summarised in the following table.

Table ES.2: Guidance documents included in Term of Reference 1

Guidance	Title
Evidence-based guidelines	
Canada, 2016 update (6, 7)	2016 Addendum to the Canadian Guidelines for the Management of Plaque Psoriasis 2009 Canadian Guidelines for the Management of Plaque Psoriasis, 2009
EU, 2015 (8, 9)	European S3 Guidelines on the systemic treatment of psoriasis vulgaris Update 2015 (6) (European Dermatology Forum (EDF) in cooperation with the European Association for Dermatology and Venereology (EADV) and the International Psoriasis Council (IPC))
UK NICE, 2014 update (10, 11)	Psoriasis: Evidence Update November 2014. A summary of selected new evidence relevant to NICE clinical guideline 153 'The assessment and management of psoriasis' (2012). Evidence Update 68 Psoriasis: assessment and management Clinical guideline 153 (2012). Supplemented with the Technology Appraisal Guidances for: etanercept; infliximab; ustekinumab; secukinumab; ixekizumab; and adalimumab. (12-17)
US AAD, 2011 (18)	Guidelines of care for the management of psoriasis and psoriatic arthritis
UK BAD, 2009(19)	British Association of Dermatologists' guidelines for biologic interventions for psoriasis 2009
Consensus statements	
Australian consensus' (3, 5)	Australasian College of Dermatologists 2017: Treatment goals for psoriasis: The Australian Psoriasis Treatment Goals Project Baker 2013: Treatment goals for moderate to severe psoriasis: An Australian consensus
US NPF, (20) 2017	From the Medical Board of the National Psoriasis Foundation: Treatment targets for plaque psoriasis (20)
EU tx optimisation consensus, 2014 (21)	A consensus report on appropriate treatment optimization and transitioning in the management of moderate-to-severe plaque psoriasis.
EU tx goals consensus, 2011 (4)	European consensus (Mrowietz et al, 2011): Definition of treatment goals for moderate to severe psoriasis: a European consensus

AAD = American Academy of Dermatology; BAD = British Association of Dermatology; CPP = chronic plaque psoriasis; EU = European Union; NICE = National Institute for Health and Care Excellence; NPF = National Psoriasis Foundation; tx = treatment; UK = United Kingdom; US = United States

The only guidance that took cost-effectiveness into account was UK NICE guidance (UK NICE, 2014 update) (10, 11).

PBS restrictions compared with clinical guidelines

a) Do the PBS restrictions reflect the clinical treatment algorithms recommended in Australian clinical Guidelines?

Compared with the Australian consensus and other overseas guidance, the PBS restrictions limit the use of biologics to patients with more severe CPP, who have failed more prior therapies. This is shown in the following table. (Note that only guidance with relevant recommendations is included in tables).

Table ES.3: 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)
Second line treatments				
Phototherapy, methotrexate, cyclosporin, acitretin	To ameliorate CPP: methotrexate cyclosporin, or acitretin; For complete control: biologicals or phototherapy.	Phototherapy methotrexate, cyclosporin (short course), fumaric acid esters. (Not acitretin monotherapy)	PUVA (photochemotherapy), methotrexate, cyclosporin, acitretin	Phototherapy, methotrexate, cyclosporin, acitretin.
Biologics - prior treatments				
≥ 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.[a]	Use if above therapies were inadequate in response or contraindicated or not tolerated. [a] UK BAD included risk of toxicity or unstable life-threatening CPP.	≥ 2 of 4 therapies inadequate in response or contraindicated.
Severity assessment criteria				
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 [b] UK BAD also included BSA ≥10% if PASI not applicable, and allowed exemptions in exceptional circumstances.[c]	PASI >10 and/or DLQI >10 [d] (termed "severe" CPP in ACD 2017, but "moderate-to-severe" in Baker 2013).
CPP of the face, palm of hand or sole of foot				
≥ 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.

Number of prior therapies to be eligible for biologics:

To be eligible for biologics to treat CPP, the PBS restrictions require patients to have failed to achieve an adequate response to, be contraindicated to, or intolerant of at least three of

the following four treatments: phototherapy, methotrexate, cyclosporin, and/or acitretin. The Australian consensus statement recommended that fewer prior therapies could be trialled prior to biologics (i.e. at least two of the four). Other guidance documents do not state a specific number of prior therapies (European Union (EU), United Kingdom (UK) National Institute for Health and Care Excellence (NICE), United States (US) American Academy of Dermatology (AAD)).(8, 11, 18)

The Canadian guidelines state that there is no clinical reason to reserve biologics for second-line systemic use (i.e. after methotrexate, cyclosporin, and acitretin), noting their less severe toxicities. They recommend acitretin, cyclosporin, or methotrexate to ameliorate moderate to severe CPP; while biologicals or phototherapy are recommended to achieve complete control.(6)

Regarding drugs used in prior therapy, the EU and Canadian guidelines do not recommend long term use of cyclosporin and also note there is limited evidence for acitretin monotherapy.

CPP severity and patient impacts required to be eligible for biologics:

Under the PBS, biologics are restricted to patients with more severe CPP than in the Australian consensus and other guidance.

The PBS restrictions require patients to have:

- PASI greater than 15. (Note this is termed "severe" CPP in the PBS restriction, though terminology relating to mild, moderate and severe CPP varies between guidelines); or
- CPP of the face, palm of hand or sole of foot, with two or more of the PASI symptom sub-scores (erythema, scale and duration) rated as 'severe' or 'very severe', or 30% or more of the area is affected.

As PASI incorporates body surface area, more than 20% of a patient's body surface area would need to be affected to achieve a PASI greater than 15. Thus, patients with severe disease localised to a small area would only be eligible under the latter criterion (i.e. only if face, palm of hand or sole of foot is involved).

The Australian consensus recommends biologics in patients with PASI greater than ten and/or Dermatology Life Quality Index (DLQI) greater than ten (i.e. large effect on quality of life). The differences between the Australian consensus and the PBS restrictions include: the PASI threshold is lower (>10) in the Australian consensus and includes DLQI criteria >10. The Australian consensus notes that quality of life may be impaired (high DLQI) in less severe disease (low PASI) in patients who have involvement of: visible areas, scalp, genitals, palms/soles, two or more fingernails, or pruritus leading to excoriation.(3) The PBS restrictions do not include patients with PASI ≤15 and involvement of visible areas other than face, palm of hand or sole of foot.

The UK NICE and UK British Association of Dermatology (BAD) guidelines (10, 12-17, 19) use a less severe PASI threshold than the PBS, but also require that patients have impaired quality of life. They generally recommend biologics in patients with PASI of 10 or higher and DLQI higher than 10.(11, 19) The UK NICE guidelines do not have specific exemptions for CPP of the face, hand or foot but these patients may be more likely to be included given the lower PASI threshold.

The Canadian guidelines do not specify numerical cut-offs for initiating biologics, stating these measures do not adequately reflect patients' actual burden of disease.(6)

PBS discontinuation criteria compared with clinical guidelines

b) Are the discontinuation criteria in the PBS restrictions consistent with those recommended in Australian or other relevant international clinical guidelines?

Compared with other guidance documents, the PBS restrictions require patients to have a greater response in order to continue therapy, as shown in following table.

Table ES.4: Continuation and discontinuation criteria for biologics in CPP

PBS restrictions	Evidence-based Guidelines		Consensus	
	Canada (6)	UK NICE (10)	Australian [a] (3, 5)	EU consensus tx goals (4)
To continue with the same biologic regimen unchanged (all indicators are versus baseline)				
ΔPASI ≥ 75% [b]	Pt satisfaction, HRQoL and "traditional objective indicators of response".	ΔPASI ≥ 75%; or ΔPASI 74-50% and DLQI ≤5.	Same as UK NICE (but noted if ΔPASI ≥ 75% but DLQI ≥ 5: use physician assessment whether to continue, modify or change tx[c])	Same as UK NICE
If adequate response not achieved (i.e. responses above are not achieved)				
Discontinue. If inadequate response to 3 biologics, cease all biologics for 5 years.		Discontinue drug if above response not achieved. If inadequate response to a 2nd biological drug, seek supra-specialist advice.	Modify regimen.	Modify regimen. Modification strategies: adjust dose; add another tx (combination tx); switch tx.

CPP = chronic plaque psoriasis; DLQI = Dermatology Life Quality Index; EU = European Union; HRQoL = health related quality of life; NICE = National Institute for Health and Care Excellence; PASI = Psoriasis Area and Severity Index; tx = treatment; UK = United Kingdom

[a] Based on text and the treatment algorithm diagram.

[b] For face, palm of hand and sole of foot: A reduction in all three PASI subscores to 'slight' or 'none' or ≥75% reduction in the area affected. The Australian consensus considered the PBS definitions were appropriate and could be combined with the proposed DLQI assessment.

[c] Noted ΔPASI ≥75 but DLQI ≥ 5 may occur if the psoriasis is on a visible site, genital, palmoplantar, nail involvement or pruritus or response is discordant with patient's expectations.

To continue PBS-subsidised use of a particular biologic agent, patients must experience a reduction in PASI score of 75% or more compared with the baseline level (PASI 75).

- Many guidance documents, including the Australian consensus, also classify patients who experience a reduction in PASI of 74-50% and a DLQI of five or less as having an adequate response. This represents patients with a lesser improvement in disease severity, but whose psoriasis only has a 'small' impact on their quality of life.(3, 4, 11, 19)
- The Australian consensus notes that patients may achieve an adequate response in terms of disease severity (reduction in PASI of 75% or more), but their psoriasis may still have a moderate-or-higher impact on their quality of life (DLQI higher than five). In this

case, the consensus recommends physician judgement whether to continue, modify or change therapy.

Under the PBS, if the continuation criteria are not met (i.e. change in PASI of 75% or more is not achieved), the biologic must be discontinued. Further, patients who fail to respond to three biologics must cease biologic therapy for a minimum of five years.

- On the other hand, the consensus documents outline other options in addition to discontinuation if adequate response is not achieved such as, adjusting the dose, changing the dosing interval, adding another therapy (combination therapy) or switching to another therapy.(3, 4, 20, 21)
- The evidence-based guidelines do not make specific recommendations in this regard, although the Canadian guidelines discuss instances where response may improve by maintaining therapy (etanercept) or increasing the dose (ustekinumab).(6)

No guidance document recommended a maximum number of biologics that should be trialled before discontinuing biologic therapy.

PBS switching criteria compared with clinical guidelines

c) Are the recommendations for switching between biologic agents described in Australian or other relevant clinical guidelines? If so are these recommendations consistent with PBS restrictions?

Under the PBS, patients can switch to a different biologic agent, as long as they have not already failed or ceased to respond to that particular agent, or to three biological agents within the five-year treatment cycle. Switching can be for any reason, and is not limited to a lack of response. However, if a patient is switching despite having achieved an adequate response, then a demonstration of response would need to be submitted within one month (otherwise it would be classed as a treatment failure).

The ability to switch between biologics is consistent with guideline recommendations about individualising therapies, taking risks and benefits into account, and the differing adverse effect profiles of the biologics. For instance, the Australian consensus recognised that a patient with a satisfactory response may have reasons to wish to modify the treatment regimen.(3)

The only guidance document that included information on switching between therapies was the EU consensus on treatment optimisation, but the advice was limited to whether treatment-free intervals are required.(21)

No guidance document provided information as to the number of biologic agents a patient should trial.

PBS restrictions for patients in specific sub-populations

d) Examine the criteria in PBS restrictions for treating patients with biologics who have: pre-existing disease (e.g. viral infection); recent vaccination; or who are pregnant. Are these criteria consistent with Australian and other relevant international treatment guidelines?

Patients under the age of 18 years

Etanercept is the only biologic that is PBS-listed for the treatment of CPP in patients aged under 18 years. This aligns with the guidelines that make recommendations in this regard (Canadian, US AAD and UK British Association of Dermatology (BAD) guidelines), which all state that etanercept is the best-studied biologic for paediatric psoriasis.(19, 22) However, there is some clinical evidence for the use of adalimumab in children (four to 18 years old) and ustekinumab in adolescents (12 to 17 year olds).

Pregnancy

The PBS restrictions do not include specific criteria for the use of biologics in pregnancy.

However, the restrictions enable pregnant women to forgo the requirement to have failed methotrexate and acitretin, which aligns with clinical guidelines.

The PBS restrictions do not specifically restrict (nor enable) use of biologics in pregnancy. This aligns with the Canadian and US AAD guidelines, which recommend that prescribers assess the risks and benefits and, if required, use biologics with caution.

Under the PBS restrictions, patients who are pregnant could temporarily cease biologic therapy, but would need to submit a demonstration of response to current treatment within one month of stopping treatment to facilitate re-initiation.

Use of biologics to treat CPP in other special populations and circumstances

The PBS restrictions for the use of biologics in CPP do not contain specific criteria around pre-existing disease (e.g. viral infection) or recent vaccination.

A key point in the Canadian guidelines is that "large, controlled clinical studies are almost unknown in special populations with psoriasis, so physicians must rely largely on the case literature and clinical judgment when treating these patients."(22)

Clinical assessment measures used to evaluate the severity of CPP

Q2. Review the most commonly recommended clinical assessment measures used to evaluate the severity of CPP or stages for disease progression

A systematic literature search was performed to identify relevant articles about clinical outcomes in psoriasis. This section summarises the outcomes that are commonly recommended in guidance documents and the findings of the literature review on outcome measures. A number of these are commonly used in clinical trials and include:

<u>Proportion of body surface area (BSA) affected</u>

- determination of the area affected by psoriasis in relation to the whole BSA.(4)

Psoriasis Area and Severity Index (PASI) score

- evaluates lesions by their characteristics of erythema, induration and scaling, as well as by the surface area affected (4, 23);
- score ranges from 0 to 72, with higher scores indicating more severe disease;
- in the majority of the identified trials a PASI of < 10 represents mild disease and a PASI of ≥ 10 represents moderate-to-severe psoriasis.

Dermatology Life Quality Index (DLQI) score

- assesses the impact of psoriasis on the quality of life of the patient (4, 23);
- score ranges from 0 to 30, with higher scores indicating a worse quality of life;
- a DLQI score of > 10 indicates a significant impact on quality of life. (4, 23).

Most commonly recommended clinical assessment measures in the guidance

In the guidance statements, the most commonly recommended clinical assessment measures are PASI, DLQI and BSA, as shown in the table below. A tick indicates that the outcome was recommended or provided as an example of an outcome that could be used. A cross indicates an outcome that was specifically not recommended. Note that PASI includes an assessment of BSA.

Table ES.5: Outcome measures recommended or noted in guidelines

		Evidence-based guidelines					Consensus statements		
	PBS	**Canada (6)**	**EU [a] (8)**	**UK NICE [b] (10)**	**US AAD (24)**	**UK BAD (19)**	**US NPF (20)**	**Australian (3, 5)**	**EU tx goals (4)**
PASI	✓		✓	✓	x	✓	x	✓	✓
DLQI	x	✓	✓	✓		✓	x	✓	✓
BSA	x		✓	✓	✓		✓	x	✓
PGA	x		✓	✓	✓		x	x	x
Other	Face, hands, feet (specific tool)	PDI, DQOLS, SF-36, or PSA (HRQoL should be central).	Skindex	Patient's Global Assessment					
Children	PASI			PASI & BSA are not validated in children				CDLQI	

AAD = American Academy of Dermatology; BAD = British Association of Dermatology; BSA = body surface area; CDLQI = Children's Dermatology Life Quality Index; DLQI = Dermatology Life Quality Index; DQOLS = Dermatology Quality-of-Life Scales; EU = European Union; HRQoL = Health-Related Quality of Life; NICE = National Institute for Health and Care Excellence; NPF = National Psoriasis Foundation; PASI = Psoriasis Area and Severity Index; PBS = Pharmaceutical Benefits Scheme; PDI = Psoriasis Disability Index; PGA = Physician's Global Assessment; PSA Scale = Psoriatic Arthritis Scale; SF-36 = Short Form Health Survey; tx = treatment; UK = United Kingdom; US = United States

[a] The EU guidelines recommend objective assessment of the disease (using instruments such as PASI, BSA or PGA) and assessment of HRQoL (e.g. using DLQI or Skindex) before and during treatment.

[b] The UK NICE guidelines state that in specialist settings, a validated tool should be used to assess severity and the impact on physical, psychological and social wellbeing, e.g. DLQI (or CDLQI for younger people). In any healthcare setting, record: PGA; the patient's assessment of current disease severity, for example, using the static Patient's Global Assessment; the BSA; any involvement of nails, high-impact and difficult-to-treat sites.

The PBS restrictions use only PASI (a disease severity measure) to determine eligibility and treatment success. However, many guidelines also recommend assessing quality of life. For example, the Australian consensus recommends use of both PASI and DLQI with DLQI having been selected to assess health related quality of life. (3)

Of all the guidelines, UK NICE had the most comprehensive literature review and assessment of the validity and reliability of tools for measuring psoriasis. The UK NICE guideline committee:

- Chose PASI for assessing disease severity in specialist settings because: it performed at least at an adequate level for outcomes such as validity, sensitivity, interpretation, and reliability.
- Chose DLQI for assessing quality of life because it is a simple, practical tool that performs at least adequately for outcomes such as validity, sensitivity, and reliability. Further, there was an absence of high quality evidence to indicate other tools were better.

Correlation between PASI and DLQI

The correlation between absolute PASI and DLQI scores is not strong (studies have found R^2 (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.(8, 31-34)

Overall

Overall, there is limited reliable clinical evidence comparing the various measures. None of the measures are perfect. Each has strengths and limitations, with the appropriateness of particular measures being dependent on the specific circumstances.

For measuring disease severity, there are no other validated tools that are clearly superior to the PASI. Further, many of the limitations of the PASI may not be relevant to assessing PBS eligibility for biologics, for example:

- While the PASI is complex, with its reliability dependent on physician experience, PBS eligibility requires that the patient be treated by a dermatologist;
- While it does not incorporate the patient perspective, it could be used in conjunction with DLQI; and
- While it lacks sensitivity at the lower end of its range, biologics would not be used on the PBS for mild disease.

Similarly, for measuring health related quality of life, the DLQI has limitations notably that it is self-reported, and is open to interpretation which may be problematic if relied on for PBS eligibility.

Stakeholder views (Public consultation and stakeholder forum)

Stakeholders generally supported the Australasian College of Dermatologist's (ACD) treatment goals for psoriasis, particularly the following:

- Patients with a PASI score greater than 10 require systemic treatment for CPP;
- Inclusion of quality of life assessment measures (such as DLQI) in the assessment of disease severity. This would capture the presence of CPP in more difficult or problematic areas including the scalp, genitals and fingernails or patients with a significant itch from their CPP; and
- Require patients to have failed two (rather than three) out of the four prior therapies. This acknowledges the fact that there may be clinical reasons outside of the PBS toxicity criteria, why doctors choose not to prescribe acitretin, methotrexate or cyclosporin.

Stakeholders stated that CPP impacts quality of life, and influences the patient's mental health and wellbeing, as well as their ability to work and be productive.

Conclusion

While there is some inconsistencies between the PBS restrictions and the Australian consensus concerning the clinical measures e.g. DLQI used for indicating the need for biologics in CPP, the PASI offers the most rigorous clinical measure for PBS restriction. There is also some misalignment concerning the PASI threshold between the Australian consensus and the PBS restrictions. It may be appropriate to investigate the evidence around reducing the PASI threshold for PBS restrictions to >10 and including DLQI, taking into consideration

the evidence and cost effectiveness of biologics in this less severe group. The PBS restrictions do not include certain body sites that are considered appropriate for biologicals in the guidelines (genitals, scalp, fingernails, or visible areas other than face). It may also be appropriate to investigate the evidence for use of biologics in these sub groups for inclusion in the PBS restrictions.

ToR 2: Review of the efficacy and safety of biologics used in the treatment of severe CPP

Q1. Undertake a systematic literature review to identify any new randomised trials or large observational studies (cross-section, cohort, case-control or longitudinal) that compare the efficacy and safety of the PBS listed biologics for severe CPP.

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)).

Efficacy of PBS listed biologics for CPP

a) Comparing efficacy and safety of all PBS listed biologics for CPP and meta- analysis of results where appropriate.

The searches identified 67 trials and four observational studies in total. Table ES.6 presents the number of trials and the condition they investigated.

Table ES.6: Trials (and large observational studies) investigating the use of PBS-listed biologics for the treatment of CPP: overall summary

Biologic	Publication date		CPP	CPP in children	Mild-to-moderate CPP	CPP + PsA	CPP + hands, face and/or feet	Total*
	Earliest	Latest						
Adalimumab	2005	2017	8	1	0	0	1	10
Efalizumab	2003	2008	6	0	0	0	0	6
Etanercept	2003	2017	18 [e] (4)	1	1	2[b]	0	21 (4)
Infliximab	2001[a]	2017	8[f]	0	0	1	1	10
Ixekizumab	2012	2016	4[g]	0	0	0	0	4
Secukinumab	2013	2016	9[h]	0	0	1	3[c]	11
Ustekinumab	2007	2015	10[d]	1	0	0	0	11
TOTAL*	-	-	57 (4)	3	1	4	5	67 (4)

CPP = chronic plaque psoriasis; PBAC = Pharmaceutical Benefits Advisory Committee; PBS = Pharmaceutical Benefits Scheme; PsA = psoriatic arthritis

* The total is a sum of all the trials and is different to the sum of the rows and columns as a number of trials are counted twice:

[a] One trial published prior to 2003 was included as it was used in a PBAC application

[b] Included 1 trial which was in common with etanercept

[c] Included 2 trials which was in common with secukinumab

[d] Included 1 trial which was in common with secukinumab and 1 trial which was in common with etanercept

[e] Included 5 trials which were in common with other biologics

[f] Included 1 trial which was in common with etanercept

[g] Included 2 trials which were in common with etanercept

[h] Included 1 trial which was in common with etanercept and 1 trial which was in common with ustekinumab

Adalimumab

Seven adalimumab trials, with 12 related publications, which assessed the efficacy, safety and/or quality of life of adalimumab in the treatment of moderate-to-severe CPP were identified in the systematic literature review.

Table ES.7 presents a summary of the trials included in the review of adalimumab versus placebo. This includes those previously considered by the PBAC and those that were newly identified in the systematic literature review.

Table ES.7: Adalimumab trials: comparison of trial characteristics and PASI 75 response

Trial	Seen by PBAC?	N	Design	Trial duration (total study)	Risk of bias	Patient population	PASI 75; n/N (%) Adalimumab[1]	PASI 75; n/N (%) Placebo
Adalimumab versus placebo								
REVEAL	Yes: Jul 2008	1,212	R, DB, PC, MC	16 weeks (52 weeks)	Unclear (High[a])	≥ 10% BSA ≥ 12 PASI	NR/814 (71%)	NR/398 (7%)
Gordon (2006)	Yes: Jul 2008, QoL data	147	R, DB, PC, MC	12 weeks (60 weeks)	Unclear (High[a])	≥ 5% BSA	NR/45 (53%)	NR/52 (4%)
Asahina (2010)	Yes: Mar 2013	169	R, DB, PC, MC	16 weeks (24 weeks)	Unclear (High[a])	≥ 10% BSA ≥ 12 PASI	27/43 (63%)	2/46 (4%)
CHAMPION	Yes: Mar 2013	271	R, DB, PC, MC	16 weeks	Low (High[a])	≥ 10% BSA ≥ 10 PASI	NR/108 (80%)	NR/53 (19%)
Cai (2017)	No	425	R, DB, PC, MC	12 weeks (24 weeks)	Unclear (High[a])	Moderate to severe CPP	NR/338 (78%)	NR/87 (12%)
Gordon (2015)	No	293	R, PC, MC	16 weeks (40 weeks)	High (High[a])	≥ 10% BSA ≥ 12 PASI ≥ 3 PGA	30/48 (70%)	2/42 (5%)

BSA = body surface area; CPP = chronic plaque psoriasis; DB = double blind; MC = multi-centre; PASI = Psoriasis Area and Severity Index; PASI 75 = reduction in PASI score of 75%; PBAC = Pharmaceutical Benefits Advisory Committee; PC = placebo-controlled; PGA = Physicians Global Assessment; QoL = quality of life; R = randomised; Shaded = previously considered by the PBAC

[a] Trial was funded by a pharmaceutical company, therefore risk of bias could be considered high

[1] Adalimumab 80 mg SC Week 0; 40 mg every other week from Week 1 or 2 (PI recommended dose)

Etanercept

For the treatment of CPP, 11 etanercept trials and 19 related publications for etanercept were identified. A brief description of the placebo-controlled trial publications, the outcomes, and whether the trial has been previously considered by the PBAC are presented in Table ES.8.

Table ES.8: Etanercept trials: comparison of trial characteristics and PASI75 response of the placebo-controlled trials.

Trial	Seen by PBAC?	N	Design	Trial duration (total study)	Risk of bias	Patient population	PASI 75; n/N (%) Etan	PASI 75; n/N (%) Pbo
Leonardi (2003) [1]	Yes: Mar 2006	652	R, DB, PC, MC	12 weeks (24 weeks)	Unclear (High[a])	≥ 10% BSA ≥ 10 PASI	55/162 (34%)	6/166 (4%)
Gottlieb (2003) [1]	Yes: Mar 2006	122	R, DB, PC, MC	24 weeks	Low (High[a])	≥ 10% BSA	17/57 (30%)	1/55 (2%)
Papp (2005) [1]	Yes: Mar 2006	611	R, DB, PC, MC	12 weeks (24 weeks)	Unclear (High[a])	≥ 10% BSA ≥ 10 PASI	67/196 (34%)	6/193 (3%)
van de Kerkhof (2008) [2]	No	142	R, DB, PC, MC	12 weeks (24 weeks)	Low (High[a])	≥ 10% BSA ≥ 10 PASI	36/96 (38%)	1/46 (2%)
Tyring (2006) [3]	No	618	R, DB, PC, MC	12 weeks (96 weeks)	Unclear (High[a])	≥ 10% BSA ≥ 10 PASI	147/311 (47%)	15/307 (5%)
OPT COMPARE[3]	No	1,106	R, DB, PC, MC	12 weeks	Low (High[a])	≥ 10% BSA ≥ 12 PASI ≥ 3 PGA	197/335 (59%)	6/107 (6%)
M10-114[3]	No	347	R, DB, PC, MC	12 weeks	Unclear (High[a])	≥ 10% BSA ≥ 12 PASI ≥ 3 PGA	NR/141 (56%)	NR/68 (7%)
M10-315[3]	No	139	R, DB, PC, MC	12 weeks	Unclear (High[a])	≥ 10% BSA ≥ 12 PASI ≥ 3 PGA	NR/139 (40%)	NR/72 (7%)

BSA = body surface area; DB = double blind; Etan = etanercept; MC = multi-centre; NR = not reported; PASI = Psoriasis Area and Severity Index; PASI 75 = reduction in PASI score of 75%; PBAC = Pharmaceutical Benefits Advisory Committee; Pbo = placebo; PC = placebo-controlled; PGA = Physicians Global Assessment; QoL = quality of life; R = randomised; Shaded = previously considered by the PBAC

[a] Trial was funded by a pharmaceutical company

[1] Etanercept 25 mg SC twice weekly (PI recommended dose)

[2] Etanercept 50 mg SC once weekly (PI recommended dose)

[3] Etanercept 50 mg SC twice weekly

Infliximab

Eight infliximab trials, with 11 related publications were identified. The citation details, a brief description of the placebo-controlled trial publication, the outcomes, and whether the trial has been previously considered by the PBAC are presented in Table ES.9.

Table ES.9: Infliximab trials: comparison of trial characteristics and PASI 75 response of the placebo-controlled trials

Trial	Seen by PBAC?	N	Design	Trial duration (total study)	Risk of bias	Patient population	PASI 75; n/N (%)Infliximab[1]	PASI 75; n/N (%)Placebo
Chaudhari (2001)	Yes: Jul 2006	33	R, DB, PC	10 weeks	Unclear (High[a])	≥ 5% BSA	9/11 (82%)	2/11 (18%)
EXPRESS	Yes: Jul 2006	378	R, DB, PC, MC	24 weeks (46 weeks)	Unclear (High[a])	≥ 10% BSA ≥ 12 PASI	242/301 (80%)	2/77 (3%)
Gottlieb (2004)	Yes: Jul 2006, QoL data	249	R, DB, PC, MC	10 weeks (30 weeks)	Unclear (High[a])	≥ 10% BSA ≥ 12 PASI	87/99 (88%)	3/51 (6%)
Menter (2007)	No	835	R, DB, PC, MC	10 weeks (50 weeks)	Unclear (High[a])	≥ 10% BSA ≥ 12 PASI	NR/314 (76%)	NR/208 (2%)
Torii (2010)	No	54	R, DB, PC, MC	14 weeks (78 weeks)	Unclear (High[a])	≥ 10% BSA ≥ 12 PASI	NR/35 (69%)	0/19
Yang (2012)	No	129	R, DB, PC, MC	10 weeks (26 weeks)	Unclear (High[a])	≥ 10% BSA ≥ 12 PASI	68/84 (81%)	1/45 (2%)

BSA = body surface area; DB = double blind; MC = multi-centre; OL = open label; PASI = Psoriasis Area and Severity Index; PASI 75 = reduction in PASI score of 75%; PBAC = Pharmaceutical Benefits Advisory Committee; PC = placebo-controlled; QoL = quality of life; R = randomised; SB = single blind; Shaded = previously considered by the PBAC

[a] Trial was funded by a pharmaceutical company

[1] Infliximab 5 mg/kg IV at Weeks 0, 2, 6; and then every 8 weeks (PI recommended dose)

Ixekizumab

Three ixekizumab RCTs, with two related publications, were identified. The trial details, a brief description of the placebo-controlled trial publication, the outcomes, and whether the trial has been previously considered by the PBAC are presented below in Table ES.10.

Table ES.10: Ixekizumab trials: comparison of trial characteristics and PASI 75 response of the placebo-controlled trials

Trial	Seen by PBAC?	N	Design	Trial duration	Risk of bias	Patient population	PASI 75; n/N (%)Ixekizumab[1]	PASI 75; n/N (%)Placebo
UNCOVER 1	Yes: Jul 2006	864	R, DB, PC	12 weeks	Unclear (High[a])	≥ 10% BSA ≥ 12 PASI	NR/433 (89%)	NR/431 (4%)
UNCOVER 2[b]	Yes: Jul 2006	519	R, DB, PC, MC	12 weeks	Unclear (High[a])	≥ 10% BSA ≥ 12 PASI	315/351 (90%)	4/168 (2%)
UNCOVER 3[b]	Yes: Jul 2006, QoL data	578	R, DB, PC, MC	12 weeks	Unclear (High[a])	≥ 10% BSA ≥ 12 PASI	336/385 (87%)	14/193 (7%)

BSA = body surface area; DB = double blind; MC = multi-centre; NR = not reported; OL = open label; PASI = Psoriasis Area and Severity Index; PASI 75 = reduction in PASI score of 75%; PBAC = Pharmaceutical Benefits Advisory Committee; PC = placebo-controlled; QoL = quality of life; R = randomised; SB = single blind; Shaded = previously considered by the PBAC

[a] Trial was funded by a pharmaceutical company

[b] Trial included an etanercept arm not included in the numbers presented

[1] Ixekizumab 160 mg SC at Week 0; 80 mg at Weeks 2, 4, 6, 8, 10 (PI recommended dose)

Secukinumab

Six secukinumab trials, with five related publications, were identified. The citation details, a brief description of the placebo-controlled trial publication, the outcomes, and whether the trial has been previously considered by the PBAC are presented below in Table ES.11.

Table ES.11: Secukinumab trials: comparison of trial characteristics and PASI 75 response of the placebo-controlled trials

Trial	Seen by PBAC?	N	Design	Trial duration (total study)	Risk of bias	Patient population	PASI 75; n/N (%)secukinumab[1]	PASI 75; n/N (%)Placebo
ERASURE	Yes: Mar 2015	738	R, DB, PC, MC	12 weeks (52 weeks)	Low (High[a])	≥ 10% BSA ≥ 12 PASI ≥ 3 PGA	NR/245 (82%)	NR/248 (5%)
FEATURE	Yes: Mar 2015	177	R, DB, PC, MC	12 weeks (208 weeks)	Low (High[a])	≥ 10% BSA ≥ 12 PASI ≥ 3 PGA	NR/59 (76%)	NR/59 (0%)
JUNCTURE	Yes: Mar 2015	182	R, DB, PC, MC	12 weeks (52 weeks)	Low (High[a])	≥ 10% BSA ≥ 12 PASI ≥ 3 PGA	NR/60 (87%)	NR/61 (3%)
FIXTURE[b]	Yes: Mar 2015	737	R, DB, PC, MC	12 weeks (52 weeks)	Low (High[a])	≥ 10% BSA ≥ 12 PASI ≥ 3 PGA	NR/327 (77%)	

BSA = body surface area; DB = double blind; MC = multi-centre; OL = open label; PASI = Psoriasis Area and Severity Index; PASI 75 = reduction in PASI score of 75%; PBAC = Pharmaceutical Benefits Advisory Committee; PC = placebo-controlled; QoL = quality of life; R = randomised; SB = single blind; Shaded = previously considered by the PBAC

[a] Trial was funded by a pharmaceutical company

[b] Trial included an etanercept arm not included in the numbers presented

[1] Secukinumab 300 mg SC at Weeks 0, 1, 2, 3, 4; then every 4 weeks (PI recommended dose)

Ustekinumab

For the treatment of CPP, ten ustekinumab trials (including the CLEAR trial which was also identified for secukinumab), with 11 related publications, were identified. The citation details, a brief description of the placebo-controlled trial publications, the outcomes, and whether the trial has been previously considered by the PBAC are presented below in Table ES.12.

Table ES.12: Ustekinumab trials: comparison of trial characteristics and PASI 75 response of the placebo-controlled trials

Trial	Seen by PBAC?	N	Design	Trial duration (total study)	Risk of bias	Patient population	PASI 75; n/N (%)Ustekinumab[1]	PASI 75; n/N (%)Placebo
PHOENIX 1	Yes: Nov 09, Efficacy and safety	766	R, DB, PC, MC	12 weeks (76 weeks)	Low (High[a])	≥ 10% BSA ≥ 12 PASI	171/255 (67%)	8/255 (3%)
PHOENIX 2	Yes: Nov 09, Efficacy and safety	1,230	R, DB, PC, MC	12 weeks (52 weeks)	Low (High[a])	≥ 10% BSA ≥ 12 PASI	273/409 (67%)	15/410 (4%)
PEARL	No	121	R, DB, PC, MC	12 weeks (36 weeks)	Unclear (High[a])	≥ 10% BSA ≥ 12 PASI	41/61 (67%)	3/60 (5%)
LOTUS	No	322	R, DB, PC, MC	12 weeks (36 weeks)	Unclear (High[a])	≥ 10% BSA ≥ 12 PASI	132/160 (83%)	18/162 (11%)
AMAGINE 2	No	1,831	R, DB, PC, MC	12 weeks (52 weeks)	Low (High[a])	≥ 10% BSA ≥ 12 PASI ≥ 3 PGA	210/300 (70%)	25/309 (8%)
AMAGINE 3	No	1,881	R, DB, PC, MC	12 weeks (52 weeks)	Low (High[a])	≥ 10% BSA ≥ 12 PASI ≥ 3 PGA	217/313 (69%)	19/315 (6%)

BSA = body surface area; DB = double blind; MC = multi-centre; OL = open label; PASI = Psoriasis Area and Severity Index; PASI 75 = reduction in PASI score of 75%; PBAC = Pharmaceutical Benefits Advisory Committee; PC = placebo-controlled; QoL = quality of life; R = randomised; SB = single blind; Shaded = previously considered by the PBAC

[1] Ustekinumab 45 mg SC at Weeks 0, 4; then every 12 weeks (PI recommended dose)

Comparison with evidence previously seen by the PBAC

b) Comparing new evidence with that already considered by PBAC for each class of medicines.

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. Tabulated comparisons of those that were previously seen with those that were not are presented above (Table ES.7 to Table ES.13). Results were primarily compared for the PI recommended dose.

In total, 21 trials had not previously been 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. However, the unseen trials for etanercept tended to have doses that were not in line with the currently recommended PI.

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.

Direct comparisons

As etanercept was one of the earlier biologics in the treatment of severe psoriasis, it was used in the comparator arm of the newer biologics. Five trials and five related publications were identified that compared etanercept with other PBS listed medications (PIECE versus infliximab; UNCOVER 2 and 3 versus ixekizumab; FIXTURE versus secukinumab; and ACCEPT versus ustekinumab) and one trial, the CLEAR trial, directly compared secukinumab and ustekinumab. In each of the trials, which utilised etanercept as a comparator, etanercept was dosed at 50 mg twice weekly. This regimen differed from the dosage in the approved Australian Product Information (25 mg twice weekly or 50 mg once weekly). Approved Australian dosage regimens were utilised for infliximab, ixekizumab, secukinumab and ustekinumab. The CLEAR trial, which compared secukinumab and ustekinumab, utilised the recommended dosing regimens for both biologics. The results of these trials are presented in Table ES.13.

Table ES.13: Direct comparisons of PBS-listed biologics: efficacy results

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

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

[2] Etanercept 50 mg SC twice weekly

[3*] Ixekizumab 160 mg SC at Week 0; 80 mg at Weeks 2, 4, 6, 8, 10 (PI recommended dose)

[4*] Secukinumab 300 mg SC at Weeks 0, 1 2, 3, 4; then every 4 weeks (PI recommended dose)

[5*] Ustekinumab 45 mg SC at Weeks 0, 4; then every 12 weeks (PI recommended dose)

[6] Ustekinumab 90 mg SC at Weeks 0, 4; then every 12 weeks

[7*] 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)

Indirect Comparison

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 66 trials above, 35 randomised controlled trials were identified for inclusion in the analysis of PASI 75 improvement at 12 weeks (N = 22,422). The majority (31 of the 35) of trials were placebo-

controlled trials, with only seven trials including comparison treatment arms other than placebo. Figure ES.2 demonstrates the results of the network meta-analysis of each biologic compared to placebo.

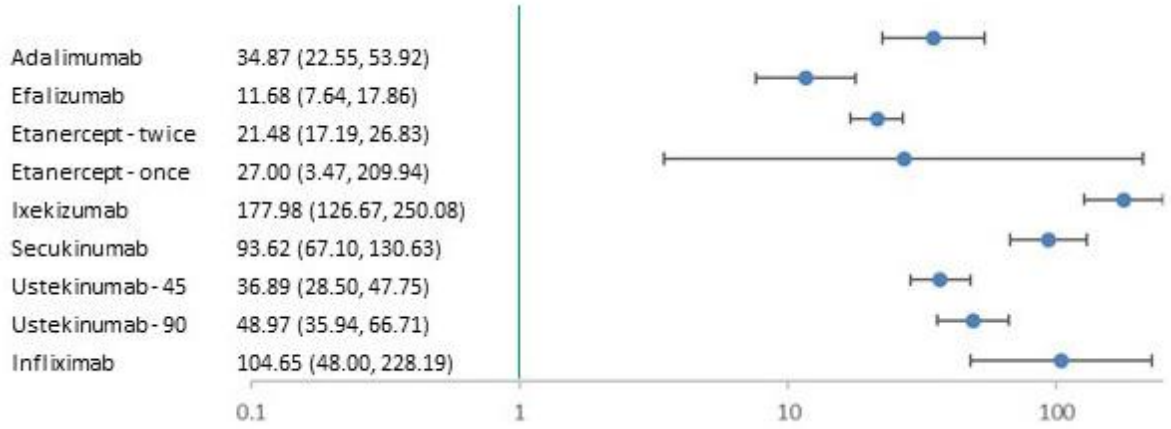

Figure ES.2: Forest plot of the OR (95% CI) for the proportion of patients achieving a PASI 75 response at 12 weeks – PBS-listed biologic versus placebo.

Ixekizumab appears to show some efficacy benefit over adalimumab (OR = 5.11; 95% CI: 2.94, 8.87), etanercept 25 mg twice weekly (OR = 8.29; 95% CI: 6.05, 11.36), secukinumab (OR = 1.90; 95% CI: 1.22, 2.96) and ustekinumab (OR = 4.82; 95% CI: 3.24, 7.18 (45 mg)) (Figure ES.3). Also, infliximab appears to show some efficacy benefit over adalimumab (OR = 5.11; 95% CI: 2.94, 8.87), etanercept 25 mg twice weekly (OR = 8.29; 95% CI: 6.05, 11.36), secukinumab (OR = 1.90; 95% CI: 1.22, 2.96) and ustekinumab (OR = 4.82; 95% CI: 3.24, 7.18 (45 mg)) (Figure ES.3).

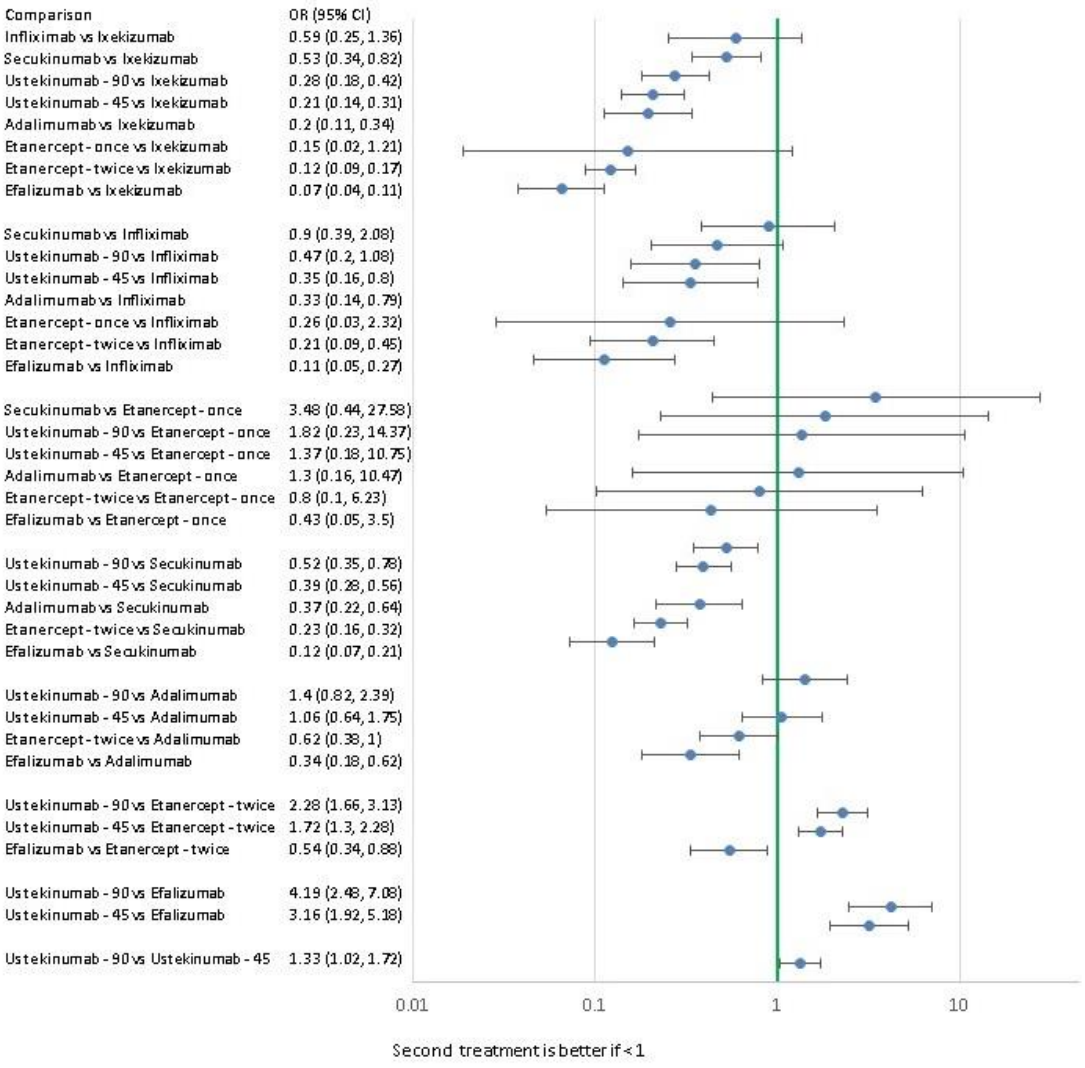

Figure ES.3: Forest plot of the OR (95% CI) for the proportion of patients achieving a PASI 75 response at 12 weeks – PBS-listed biologic versus PBS-listed biologic.

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

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), followed by ixekizumab (OR = 1.56; 95% CI: 1.32, 1.84).

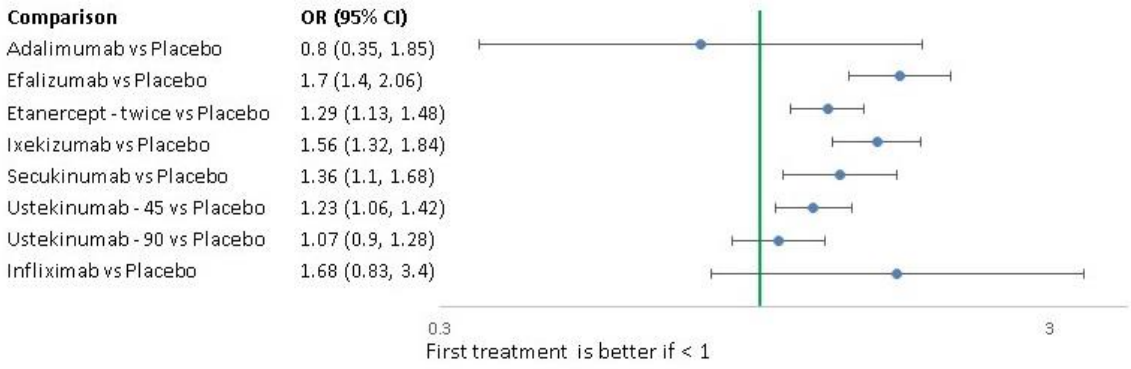

Figure ES.4: Forest plot of the OR (95% CI) for the proportion of patients experiencing an adverse event at 12 weeks – PBS-listed biologic versus placebo.

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

Efficacy and safety of biologics in mild-moderate disease CPP

c) Comparing evidence on the efficacy and safety of biologics for CPP in mild-moderate disease versus severe disease.

The systematic literature review did not identify any trials or studies comparing the use of biologics in mild-moderate CPP versus severe disease. However, one trial was identified that compared etanercept to acitretin in patients with a PASI <15 (there was no lower cut off). As there was no common comparison arm, a naïve indirect comparison seemed to demonstrate that etanercept would be marginally more effective in patients with a baseline PASI greater than 15 than in those with less severe disease (Table ES.14).

Table ES.14: Mild-to-moderate CPP efficacy results, plus a comparison with severe CPP results

Trial	Time horizon	Arm	Baseline PASI	N	PASI 50, n (%)	PASI 75, n (%)
Gisondi (2008)	24 weeks	Etanercept 25 mg SC twice weekly	11.1	22	15 (68%)	10 (45%)
Gottlieb (2003)	24 weeks	Etanercept 25 mg SC twice weekly	17.8	57	NR (77%)	32 (56%)

CPP = chronic plaque psoriasis; NR = not reported; PASI 50, 75 = reduction in Psoriasis Area and Severity Index score of 50% or 75%; PI = Product Information; SC = subcutaneous

Also of note, the majority of trials identified in the systematic review had inclusion criteria of a PASI ≥ 12 with only two biologics (adalimumab and etanercept) having trials that included patients with a PASI ≥ 10. The adalimumab submission of March 2013 presented a comparison of the 'moderate' patient subgroup versus the full ITT (moderate-severe) trial populations. The submission demonstrated that the moderate subgroup had a statistically significantly greater proportion of patients achieve a PASI 75 response when treated with adalimumab compared with placebo. The PBAC rejected the submission based on highly uncertain cost-effectiveness.

The trials in patients with CPP plus PsA (see below) also corroborated this result as these patients had lower PASI at baseline and the response rates were lower than seen in the trials with higher PASI baseline in CPP patients.

Efficacy of biologicals in patients in specific sub populations

d) Consider any evidence on the effectiveness of biologics for CPP on other comorbidities such as psoriatic arthritis.

Psoriatic arthritis

Evidence was found for the use of adalimumab, etanercept, infliximab and ustekinumab in the treatment of PsA in patients with severe CPP; however, these trials did not limit patients to severe CPP and patients had milder psoriasis (lower mean baseline PASI) than the severe CPP trials above. All biologics appeared to have a positive effect on PsA with over half of all treated patients meeting the American College of Rheumatology 20% (ACR 20) improvement criteria for joint response.

Table ES.15: Severe CPP and PsA trials: efficacy results

Trial	Time horizon	Arm	N	ACR 20, %	PsARC, %	PASI 75, %	Δ HAQ DI, mean (SD)	Δ DLQI, mean (SD)
Etanercept								
Mease (2000)	12 weeks	Etan[1*]	30	73%	87%	26%	-1.2	NR
		Pbo	30	13%	23%	0	-0.1	NR
Infliximab								
IMPACT 2	16 weeks	Inf[4*]	100	58%	77%	64%	NR	NR
		Pbo	100	11%	27%	2%	NR	NR
	24 weeks	Inf[4*]	100	54%	70%	60%	NR	NR
		Pbo	100	16%	32%	1%	NR	NR
Secukinumab								
FUTURE 2	16 weeks	Sec[5]	99	29%	NR	28%	-0.3 (0.1)	NR
		Sec[6*]	100	51%	NR	48%	-0.5 (0.1)	NR
		Sec[7*]	100	54%	NR	63%	-0.6 (0.1)	NR
		Pbo	98	15%	NR	16%	-0.3 (0.1)	NR

ARC 20 = reduction in American College of Rheumatology score of 20%; CPP = chronic plaque psoriasis; DLQI = Dermatology Life Quality Index; Etan = etanercept; HAQ DI = Health Assessment Questionnaire Disability Index; Inf = infliximab; IV = intravenous; NR = not reported; PASI 75 = reduction in Psoriasis Area and Severity Index score of 75%; PI = Product Information; Pbo = placebo; PsA = psoriatic arthritis; PsARC = Psoriatic Arthritis Response Criteria; SC = subcutaneous; SD = standard deviation; Sec = secukinumab

[1*] Etanercept 25 mg SC twice weekly (PI recommended dose)

[2*] Etanercept 50 mg SC once weekly (PI recommended dose)

[3] Etanercept 50 mg SC twice weekly

[4*] Infliximab 5 mg/kg IV at Weeks 0, 2, 6; then every 8 weeks (PI recommended dose)

[5] Secukinumab 75 mg SC at Weeks 0, 1, 2, 3, 4; then every 4 weeks

[6*] Secukinumab 150 mg SC at Weeks 0, 1, 2, 3, 4; then every 4 weeks (PI recommended dose, PsA)

[7*] Secukinumab 300 mg SC at Weeks 0, 1, 2, 3, 4; then every 4 weeks (PI recommended dose, CPP)

Although ToR2 focussed on the effectiveness of the PBS-listed biologics on PsA, some safety data was identified in the systematic literature review. Overall, the safety results from these trials were similar to those in the severe CPP trials.

Children

Of the PBS-listed biologics for the treatment of severe CPP in adults, only etanercept is listed on the PBS for the treatment of severe CPP in children. The systematic literature review identified three trials, with five related publications, relating to the use of the PBS-listed biologics for the treatment of severe CPP in children: one trial each considering adalimumab, etanercept and ustekinumab. Each trial demonstrated that the biologics were better than placebo at reaching PASI 75.

Table ES.16: Biologics in children and adolescents: efficacy results

Trial	Time horizon	Age	Arm	N	PASI 75; n (%)	Δ CDLQI; mean (SD)
Adalimumab versus methotrexate						
Papp (2017)	16 weeks	4 to 17 years	Ada[1]	39	17 (44%)	-4.9 (6.2)
			Ada[2]	38	22 (58%)	-6.6 (6.2)
			Mtx	37	12 (32%)	-5.0 (7.1)
Etanercept versus placebo						
Paller (2008)	12 weeks	4 to 17 years	Etan[3*]	106	57%	-52%
			Pbo	105	11%	-18%
Ustekinumab versus placebo						
CADMUS	12 weeks	12 to 17 years	Ust[4]	37	29 (78%)	-5.6 (6.4)
			Ust[5]	36	29 (81%)	-6.7 (5.6)
			Pbo	37	4 (11%)	-1.5 (3.2)

Ada = adalimumab; CDLQI = Children's Dermatology Life Quality Index; Etan = etanercept; Mtx = methotrexate; PASI 50, 75, 90, 100 = reduction in Psoriasis Area and Severity Index score of 50%, 75%, 90% or 100%; Pbo = placebo; SC = subcutaneous; SD = standard deviation; Ust = ustekinumab; *Italics = percentage change in CDLQI*

[1] Adalimumab 0.4 mg/kg SC every other week

[2] Adalimumab 0.8 mg/kg SC every other week

[3*] Etanercept 0.8 mg/kg SC once weekly (PI recommended dose)

[4] Ustekinumab 0.375 mg/kg if ≤ 60 kg or 22.5 mg if 60-100 kg or 45 mg if > 100 kg SC at Weeks 0, 4

[5] Ustekinumab 0.75 mg/kg if ≤ 60 kg or 45 mg if 60-100 kg or 90 mg if > 100 kg SC at Weeks 0, 4

Efficacy of biologicals in specific sites on the body

e) Consider evidence on comparative effectiveness of classes of biologic agents in populations with hand/face/feet (or genital) psoriasis.

There was limited evidence for the treatment of hand/face/feet psoriasis. In the systematic review one small trial each for adalimumab, infliximab and secukinumab was identified. Two trials (of general severe CPP population from above) for secukinumab also provided sub-group analysis of palmoplantar involvement.

The trials and subgroup analysis that were identified included palmoplantar and fingernail involvement. No trials were identified that considered the effect of the PBS-listed biologics on CPP specifically focused on face or genital involvement.

Each trial assessed the proportion of patients achieving a score of clear or almost clear on the hand and/or feet Physician's Global Assessment tool. Each drug appeared to have some effect compared to placebo (Table ES.17).

Table ES.17: CPP with hands and/or feet involvement trials: efficacy results

Trial	Time horizon	Arm	N	m-PPPASI 50, %	m-PPPASI 75, %	hf PGA of 0 or 1, %	PASI 75, %
Adalimumab							
REACH	16 weeks	Ada[1]	49	NR	NR	31%	NR
		Pbo	23	NR	NR	4%	NR
Infliximab							
Bissonnette (2011)	14 weeks	Inf[2]	12	67%	33%	25%	NR
		Pbo	12	8%	8%	8%	NR
Secukinumab							
GESTURE	16 weeks	Sec[3]	68	NR	NR	22%	NR
		Sec[4]	69	NR	NR	33%	NR
		Pbo	68	NR	NR	2%	NR
Rich (2013)	12 weeks	Sec[5]	41	NR	NR	39%	32%
		Sec[6]	47	NR	NR	54%	50%
		Pbo	27	NR	NR	19%	4%
Papp (2013)	12 weeks	Sec[5]	7	NR	NR	71%	100%
		Pbo	5	NR	NR	20%	0

Ada = adalimumab; CPP = chronic plaque psoriasis; hf PGA = hands and/or feet Physician's Global Assessment; Inf = infliximab; IV = intravenous; m-PPPASI 50, 75 = reduction in modified-Palmoplantar Psoriasis Area and Severity Index score of 50% or 75%; NR = not reported; PASI 75 = reduction in Psoriasis Area and Severity Index score of 75%; PI = Product Information; SC = subcutaneous; Sec = secukinumab

[a] Baseline characteristics for patients receiving secukinumab 150 mg SC at Week 0 were not included in the comparison

[b] Baseline characteristics for patients receiving secukinumab 25 mg SC at Week 0; 25 mg SC at Weeks 0, 4, 8; and 75 mg SC at Weeks 0, 4, 8 were not included in the comparison

[1] Adalimumab 80 mg SC Week 0; then 40 mg every other week from Week 1 (PI recommended dose)

[2] Infliximab 5 mg/kg IV at Weeks 0, 2, 6 (PI recommended dose)

[3] Secukinumab 150 mg SC at Weeks 0, 1, 2, 3, 4; then every 4 weeks

[4] Secukinumab 300 mg SC at Weeks 0, 1, 2, 3, 4; then every 4 weeks

[5] Secukinumab 150 mg SC at Weeks 0, 4, 8

[6] Secukinumab 150 mg SC at Weeks 0, 1, 2, 4

The longer-term safety and efficacy of the PBS-listed biologics

f) Identify and describe any recent findings concerning safety associated with longer term use of biologics

There were a number of long term safety (≥1 year) studies available based on extension studies of primary RCTs. Study follow ranged up to five years (Table ES.18). Overall, the longer-term use of currently listed biologics (up to three years) for the treatment of CPP appears relatively safe, with approximately 10% of patients experiencing a severe adverse event. The incidence of cardiovascular disease, serious infection and malignancy was consistently very low across all studies.

Table ES.18: Longer-term safety of biologics in the treatment of CPP (% of patients affected)

Trial	Time horizon	Arm	N	AEs	SAEs	Death	Infection	Serious infection	Malignancy	CVD	Liver disease
Adalimumab											
Gordon (2015)	52 weeks	Ada[1*]	38	61%	3%	NR	37%	3%	0	0	NR
Gordon (2006)	60 weeks	Ada[1*]	92	78%	2%	0	NR	0	1%	0	NR
		Ada[2]	50	78%	14%	2%	NR	0	6%	8%	NR
REVEAL	Year 1	Ada[3]	1,159	*3,174*	5%	0	NR	2%	< 1%	< 1%	NR
	Year 2		621	*978*	6%	0	NR	< 1%	1%	< 1%	NR
	Year 3		443	*857*	11%	0	NR	2%	1%	1%	NR
Asahina (2015)	220 weeks	Ada[3]	163	*2,851*	25%	0	NR	4%	2%	3%	59%
Etanercept											
CRYSTAL	54 weeks	Etan[4*]	357	79%	6%	0	NR	1%	1%	NR	NR
		Etan[5]	363	75%	9%	1%	NR	1%	2%	NR	NR
Elewski (2007)	72 weeks	Etan[6]	912	NR	8%	< 1%	NR	2%	7%	NR	NR
Tyring (2006)	84 weeks	Etan[7]	618	NR	NR	< 1%	NR	2%	2%	NR	NR
Luger (2016)	3 years	Etan[8]	926	30%	6%	< 1%	9%	< 1%	1%	NR	NR
OBSERVE-5	3 years	Etan[8]	2,511	NR	12%	1%	NR	3%	3%	1%	NR
Infliximab											
Torii (2010)	72 weeks	Inf[9*]	50	100%	12%	0	86%	2%	NR	NR	NR
RESTORE	124 weeks	Inf[9*]	222	73%	11%	0	NR	5%	1%	0	NR
		Inf[10]	219	71%	11%	1%	NR	1%	< 1%	< 1%	NR
Ixekizumab											
Leonardi (2012)	52 weeks	Ixe[11]	120	67%	8%	NR	NR	2%	1%	3%	NR
Ustekinumab											
PHOENIX 1	3 years	Ust[12*]	378	92%	8%	0	76%	1%	4%	1%	NR
		Ust[13]	375	91%	10%	1%	77%	3%	1%	< 1%	NR
	5 years	Ust[12*]	289	NR	NR	< 1%	NR	5%	3%	3%	NR

Trial	Time horizon	Arm	N	AEs	SAEs	Death	Infection	Serious infection	Malignancy	CVD	Liver disease
		Ust[13]	254	NR	NR	2%	NR	7%	2%	1%	NR

Ada = adalimumab; AE = adverse event; CVD = cardiovascular disease; Inf = infliximab; IV = intravenous; NR = not reported; PI = Product Information; SAE = serious adverse event; SC = subcutaneous; Ust = ustekinumab; *Italics = number of events*

[1*] Adalimumab 80 mg SC Week 0; then 40 mg every other week (PI recommended dose)
[2] Adalimumab 80 mg SC Week 0; then 40 mg every week
[3] Adalimumab – all patients who had received a dose
[4*] Etanercept 25 mg SC twice weekly (PI recommended dose)
[5] Etanercept 50 mg SC twice weekly until response; pause until relapse; 25 mg twice weekly until response; pause until relapse
[6] Etanercept 50 mg SC once or twice weekly
[7] Etanercept 50 mg SC twice weekly
[8] Etanercept SC – dose determined by study investigator
[9*] Infliximab 5 mg/kg IV every 8 weeks (PI recommended dose)
[10] Infliximab 5 mg/kg IV when required
[11] Ixekizumab 120 mg SC every 4 weeks
[12*] Ustekinumab 45 mg SC every 12 weeks (PI recommended dose)
[13] Ustekinumab 90 mg SC every 12 weeks

Again, the differing time horizons and dosing regimens utilised made it difficult to compare the longer-term efficacy of each PBS-listed biologic. However, in terms of the proportions of patients continuing to achieve a PASI 75 response, it appeared that the biologics continued to have an efficacious effect beyond one year (Table ES.22). Ustekinumab appeared to retain some efficacy for up to five years.

g) Include a quality assessment and description of the limitations of included trials or observational studies

The major limitations of the identified trials and studies were the varying double-blind time periods and the use of non-PI approved dosing regimens. This made accurate comparisons difficult.

In addition, the majority of participants in the trials had severe disease despite the majority of trials having cut-off points of PASI either greater than 10 or 12. The pooled mean PASI scores were high for most biologic trials which made it difficult to interpret their role and efficacy in less severe CPP.

Table ES.19: Pooled mean baseline severity scores of the included trials in the systematic review of efficacy in severe CPP

Biologic	BSA	PASI	DLQI
adalimumab	31%	20.5	12.4
etanercept	28%	19.3	12.4
infliximab	31%	21.3	13.2
ixekizumab	27%	20.1	12.2
secukinumab	33%	22.6	11.9
ustekinumab	29%	20.6	12.3

BSA = body surface area; CPP = chronic plaque psoriasis; DLQI = Dermatology Life Quality Index; PASI = Psoriasis Area and Severity Index

Stakeholder views (Public consultation and stakeholder forum)

- Some clinicians noted that there are efficacy differences between biologics and individual patient variations with respect to biologic efficacy:
    - The IL-17 class of biologics (e.g. ixekizumab) consistently achieves a PASI 90 response in 60 to 80% of patients, while the TNF-α inhibitor class (e.g. adalimumab, etanercept and infliximab) consistently achieves a PASI 75 response in 60 to 80% of patients.
    - The difference to patients may not be large and they may be happy with a PASI 75 response. However, most patients say they want the best response.
    - New drug classes may be more effective.
    - Etanercept has a particular role due to its long-term safety data, short half-life and use in paediatric populations.
- There are very limited options for treating psoriasis in children and this is a group with high unmet need.
- Consumers expressed concerns about waning effectiveness of biologics over time.
- It was noted that the lower the baseline PASI score (e.g. PASI 10-12), the harder it is to achieve a 75% reduction in PASI score (PASI 75). This creates issues with using PASI 75 as a measure of treatment response in these patients.
- Biologics were considered to be generally well tolerated, with adverse events such as infections consistent with those reported in the clinical trials. It was noted that psoriasis and comorbidities can be sufficiently severe that many patients are willing to accept any risk for successful treatment.

Conclusion

Overall, the efficacy of biologicals compared to placebo demonstrated that biologics provide patients with clinically meaningful improvements in their psoriasis severity. There was some variation in the efficacy and safety results between different biologics. Of the currently PBS-listed biologics, while having similar pooled results, ixekizumab seemed most likely to result in a response, but also most likely to result in an adverse event when compared to placebo. When compared to each other, infliximab was most likely to result in an adverse event; ustekinumab and etanercept demonstrated the lowest point estimates. Most of the open-label extension studies had adverse event rates, which were comparable with the short-term comparator-controlled RCTs

The review identified a substantial amount of evidence that has not been presented to the PBAC prior to this review, but the new evidence tended to agree with that seen by the PBAC previously. The quality of the RCTs was generally high for methods but most trials would have had an unclear or high risk of bias. The blinding of outcome assessors was not described in a number of the studies, making this the area of most uncertainty. The other issue in terms of bias was that pharmaceutical companies funded the trials, with the exception of one infliximab trial.

There is very little data available for biologics in the mild-moderate (PASI >10 but <15) disease category, even though the consensus from international and Australian guidelines was that biologics can and should be used in this disease category. 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. Also, there was limited data for severe CPP with concomitant PsA. The trials that addressed concomitant PsA and CPP tended to have lower inclusion criteria for PASI. Therefore, to enable an analysis in the review, a lower cut off PASI score 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 disease severity). 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.

ToR 3: Prevalence and utilisation of PBS listed biologics for CPP

Estimating the prevalence of chronic plaque psoriasis

Q1. Summarise the most recent estimates of incidence and prevalence of severe CPP in Australia or other similar populations.

Q2. Provide any published estimates on the prevalence of patients with psoriatic arthritis within the patient population with CPP.

A systematic review was undertaken to identify estimates of the incidence and prevalence of severe CPP in Australia, or estimates that may be applicable to the Australian context. The systematic review also aimed to identify any estimates published on the prevalence of patients with PsA within the patient population with CPP.

The literature review focussed on epidemiological estimates from Australia as well as the following: New Zealand, United Kingdom (UK), United States of America (USA), Canada, and Europe. The literature review did not identify estimates for the prevalence of severe CPP in Australia or overseas. Therefore, the prevalence of severe CPP had to be calculated using a number of estimates from different disease categories. The prevalence of severe CPP was calculated using i) the prevalence of psoriasis in Australia, ii) the prevalence of CPP in patients with psoriasis, and iii) the prevalence of severe psoriasis within the CPP population.

Prevalence of CPP

There is considerable uncertainty around the prevalence of severe chronic plaque psoriasis in Australia. With a paucity of data and no Australian-wide evidence to guide estimates, we used a number of Australian and international sources to estimate the prevalence. The best estimate of the prevalence of severe CPP (PASI >15) in Australia was 19,000 people (range 7,000 to 360,000) (Table ES.20).

Table ES.20: Prevalence of severe CPP in Australia

Parameter	Best estimate	Lower estimate	Upper estimate	Source (best estimate)	Source (lower estimate)	Source (upper estimate)
Australian adult population	18,717,575			ABS Australian Demographic Statistics, September 2016		
Psoriasis prevalence	2.60%	2.40%	6.60%	ABS NHS 2014-15	ABS NHS 2011-12	Plunkett (1999)
Proportion CPP	79%	57.78%	94%	Icen (2009)	Schafer (2011)	Papadavid (2017)
Proportion PASI >15	5%	3%	31%	Mallbris 2005 (upper estimate)	Mallbris 2005 (lower estimate)	Piaserico (2016)
Proportion PASI ≥10	13%	13%	53%	Eder (2016)	Eder (2016)	Piaserico (2016)
Prevalence CPP with PASI >15	19,223	7,787	359,984	Calculated		
Prevalence CPP with PASI ≥10	49,980	33,743	615,456	Calculated		

ABS = Australian Bureau of Statistics; CPP = chronic plaque psoriasis; NHS = National Health Survey; PASI = Psoriasis Area and Severity Index

During the second reference group meeting and as a response to the stakeholder engagement, it was considered that options to explore the number of patients with moderate to severe CPP (PASI 10 to 15) should be considered and how this would differ from the current setting. The most likely estimate for the prevalence of CPP with a PASI 10 or greater was 50,000 people with lower and upper estimates between 33,000 and 616,000 affected people (Table ES.20; Figure ES.5). This would increase the population pool for biologics treatment by 31,000 people; with lower and upper estimates between 26,000 and 256,000 people (Table ES.20; Figure ES.5).

Q2. Provide any published estimates on the prevalence of patients with psoriatic arthritis within the patient population with CPP.

Again, there was evidence lacking on the proportion of people with PsA. Using a combination of different sources we provide a best estimate of the prevalence of patients with PsA within the moderate to severe CPP. In Australia, it was estimated that about 30% of the patients with CPP (with a PASI ≥ 10) or between 10,000 and 160,000 people would have PsA.

Utilisation of PBS listed biologics for chronic plaque psoriasis

An analysis of the utilisation of biologics for severe CPP was undertaken using prescription data from the Department of Human Services Supplied Prescriptions Database. Dispensed prescription data for biologics listed on the Pharmaceutical Benefits Scheme (PBS) for severe CPP were exacted for the period from 1 July 2013 to 31 December 2016 based on the date of dispensing. The data were extracted in May 2017. The supplied data file comprised of 119,933 dispensing records.

Overall utilisation of biologics to treat severe CPP through the PBS

Q3. Describe the overall utilisation in terms of prescriptions dispensed and government benefits paid for PBS listed biologics to treat severe CPP using unit record level PBS data.

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. Adalimumab and secukinumab are the next most commonly used biologics, with approximately 20% of patients having had at least one dispensing for adalimumab and/or secukinumab in 2016. Etanercept and infliximab have low patient numbers, with fewer than 6% of patients having used these biologics in 2016 (Figure ES.5).

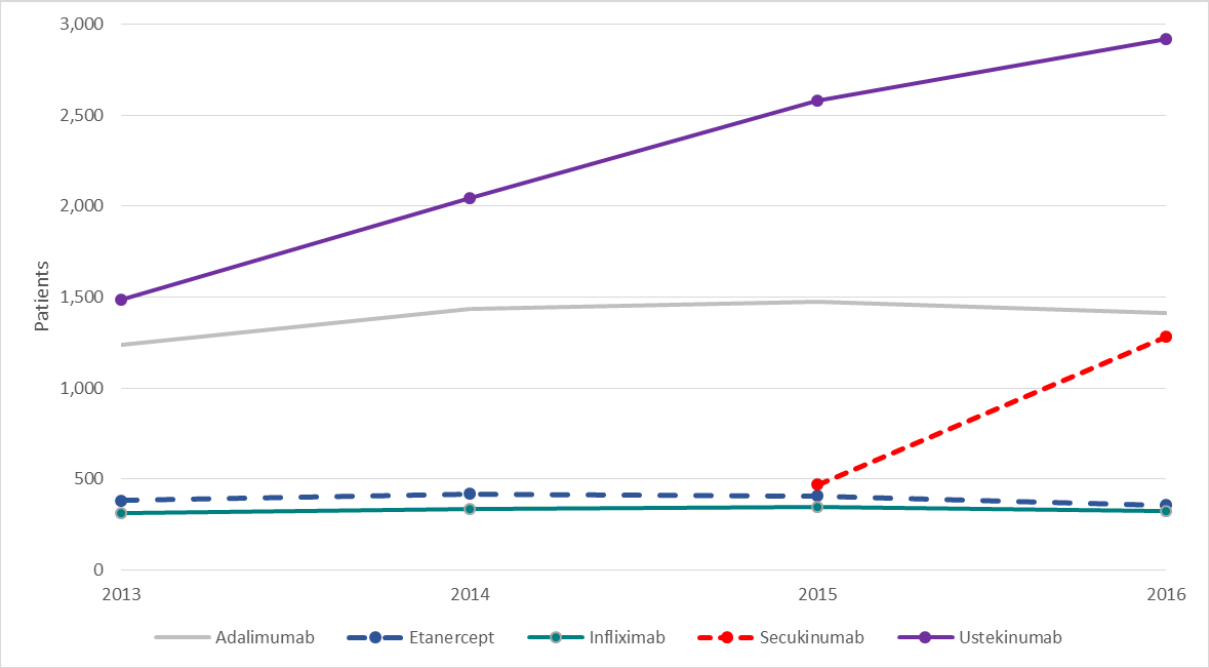

Figure ES.5: Number of patients receiving biologics for severe CPP by drug

Source: DHS Supplied prescriptions database (date of supply), extracted May 2017
Note: Secukinumab was listed on the PBS on 1 September 2015.

CPP = chronic plaque psoriasis

In line with the number of patients being treated; prescription numbers show an increase since 2013. Secukinumab has had a rapid increase since its PBS-listing in September 2015, with ustekinumab showing slightly less of an increase (Figure ES.6).

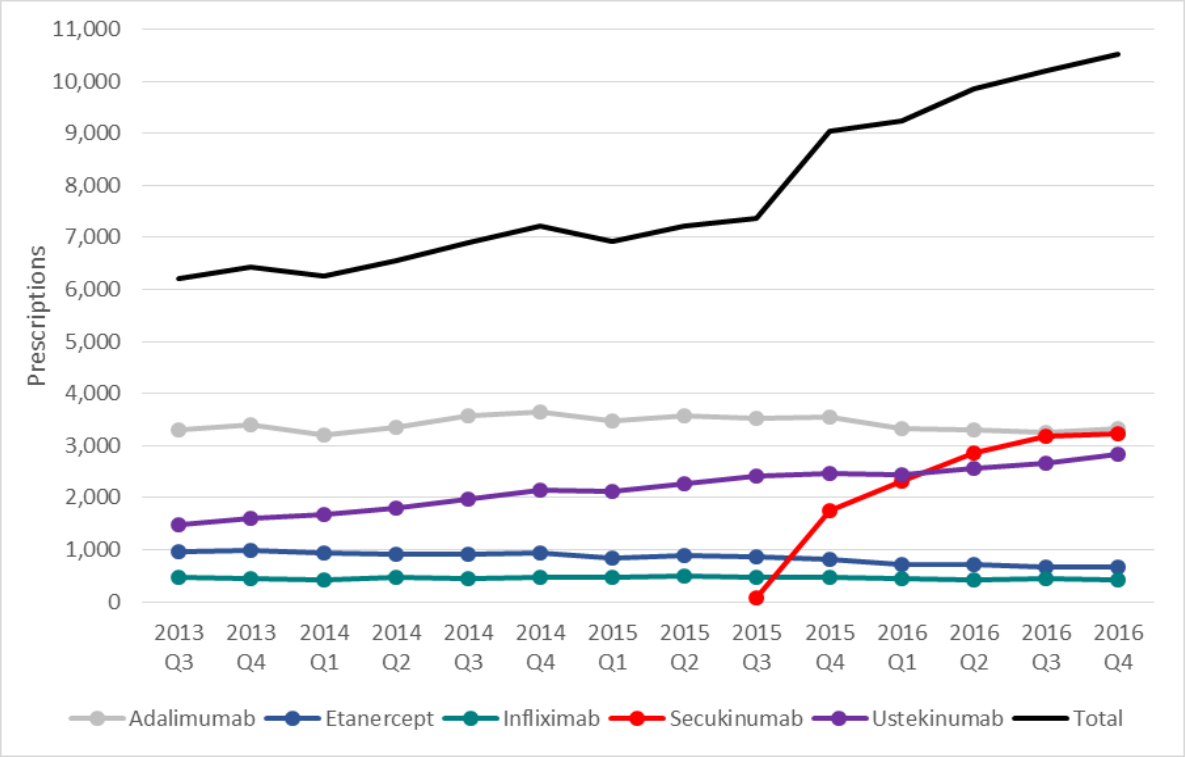

Figure ES.6: Biologic prescriptions for severe CPP, 2013-2016

Source: DHS Supplied prescriptions database (date of supply), extracted May 2017
Note: Secukinumab was listed on the PBS on 1 September 2015.
CPP = chronic plaque psoriasis

Across the state and territory capital cities there appeared to be a trend towards higher biologic utilisation in cities further south of the equator (Figure ES.7). For example, the rate of utilisation in Hobart was three times greater than Brisbane and twice the rate of Sydney. This was in line with the findings from the epidemiology estimates.

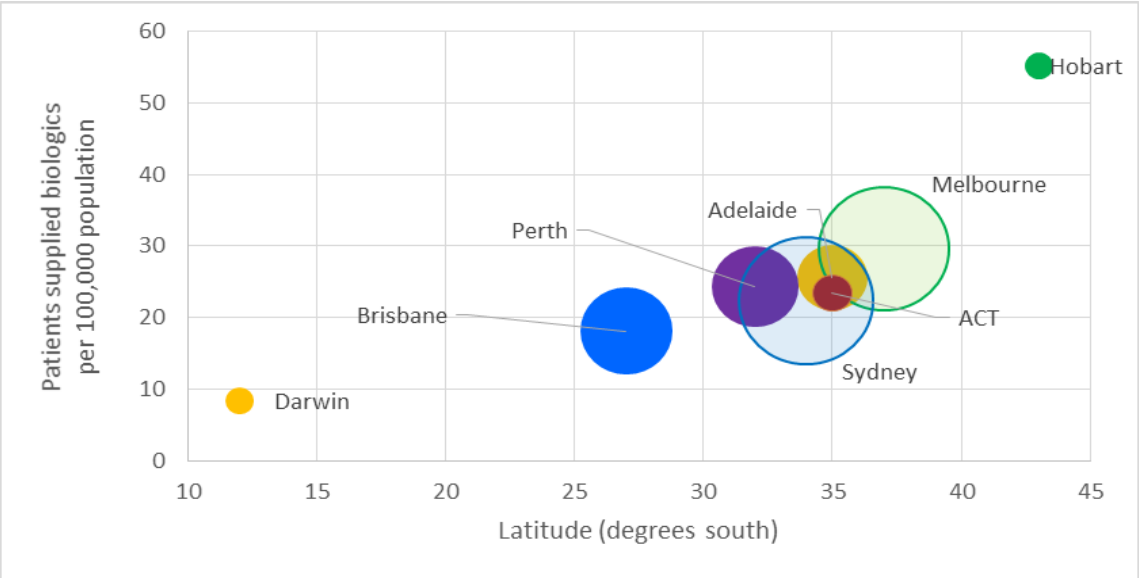

Figure ES.7: Utilisation by latitude for capital cities (age-adjusted)

Source: DHS Supplied prescriptions database (date of supply), extracted May 2017, ABS Regional Population Growth, Australia (March 2017 release), ABS Postcode 2016 to SA4 2016 Correspondence table.
Note: The size of the circles represent the size of the greater capital city population.

Because of the increase in the patients being treated with biologicals, the Commonwealth expenditure has nearly doubled, from approximately $79 million in 2014 to approximately $121 million in 2016. Prescriptions for ustekinumab accounted for over half of total expenditure and was the most commonly prescribed biologic between 2014 and 2016.

Table ES.21 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. Total expenditure on biologics for CPP has increased substantially from $79 million in 2014, (the first full year of data) to over $121 million in 2016.

Table ES.21: Biologic expenditure for severe CPP

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

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

[a] These figures are for the months July to December only

[b] Special pricing arrangements

Treatment length or persistence for PBS listed biologic in CPP

Q4. Determine length of treatment or persistence on PBS listed biologic agents for the treatment of severe CPP. Provide an estimate of the length of treatment by drug and overall continuous length of treatment on any biologic. Present results of patients' individual length of treatment using Kaplan Meier survival techniques.

Time-to-event analyses (survival analyses) were performed to understand the length of time patients spend on continuous treatment with biologics prior to discontinuing treatment or switching to a different biologic. These analyses were performed on a cohort of biologic naïve patients who had their first biologic dispensing for severe CPP between 1 July 2014 and 30 June 2015;

Persistence rates with biologics was high:

- 83% of biologic naïve patients remained on continuous treatment with their *first* biologic for at least 6 months
- 80% of biologic naive patients remained on continuous treatment with any biologic for at least 18 months

There were some differences between the proportion of patients persisting on treatment with biologics in the PBS data (which assumes a prolonged PASI 75 response) and the PASI

75 response seen in trials. Persistence to treatment was much higher for infliximab and ustekinumab in the PBS data than the response rate reported in the clinical trials (Table ES.22).

Table ES.22: Persistence of 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% [b] -70%[c] (24 weeks)	62%	67% [b] (48 weeks)
Etanercept	21% [d]	44% - 62% (24 weeks) [f]	16%	-
Infliximab	100%	77%- 82% (24 weeks) [g]	93%	55% (50 weeks) [h]
Ustekinumab	97%	≈80% [i] (24 weeks)	88%	≈70% [i] (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

[a] Proportion of patients who received a continuing authority approval for the same biologic or a different biologic

[b] Gordon (2012) Cohort D

[c] Ashina (2010)

[d] Includes only adult patients

[e] Leonardi (2003) and PRESTA trial

[f] EXPRESS and RESTORE trials

[g] Menter (2007) (5mg/kg every 8 weeks dosing)

[h] Kimball (2012)

Treatment breaks/holidays

Q5. Report on breaks in biologic medicine coverage that could be considered treatment holidays or discontinuation due to sustained remission of the disease.

The frequency of treatment holidays from biologic medicines was rare, with only 5% of biologic naïve patients having had treatment holidays during the 18-month follow-up period in the prescription data. The PBS prescription data does not contain clinical information about the reason a patient discontinues or recommences treatment. Therefore, it was not possible, from the data, to determine why patients had taken a treatment holiday. Treatment holidays could be due to sustained remission of CPP, drug toxicity or other reasons.

Treatment switching

Q6. Examine the rate individual patients switch between biologics for the treatment of CPP.

Patients who initiated biologics with adalimumab and etanercept had higher rates of switching to other biologics and lower rates of persistence than patients who initiated biologics with infliximab and ustekinumab. Of biologic naïve patients who switched biologics, most switched to secukinumab or ustekinumab (Table ES.23).

Table ES.23: Most common biologic sequences for CPP

Rank	Biologic Sequence	n (%)
1	Ustekinumab only	378 (49%)
2	Adalimumab only	154 (20%)
3	Etanercept only	65 (8%)
4	Ustekinumab -> Secukinumab	53 (7%)
5	Adalimumab -> Ustekinumab	42 (5%)
6	Adalimumab -> Secukinumab	27 (3%)
7	Any 3 biologics	20 (3%)
8	Infliximab only	10 (1%)
9	Ustekinumab -> Adalimumab	9 (1%)
10	Etanercept -> Ustekinumab	5 (1%)
11	Infliximab -> Ustekinumab	5 (1%)
12	Any 4 or more biologics	<5[1]

Source: DHS Supplied prescriptions database (date of supply), extracted May 2017
Note: Values in the table do not add to 100%
[1] Patient numbers lower than five were suppressed to protect patient privacy

Consistence of current utilisation with clinical guidelines and PBS restrictions

Q7. Examine the prior use of non-biologic medicines before switching to biologics.

Analyses of medicine/phototherapy utilisation prior to commencing biologic therapies was not conducted. It is not possible to determine from PBS and MBS data whether patients were contraindicated to or failed these therapies.

Q8. Consider to what extent current utilisation of PBS listed biologics is consistent with clinical guidelines and PBS restrictions.

The extent to which current utilisation of biologics was consistent with the clinical guidelines and PBS restrictions could not be fully assessed with the available data. Continued use was broadly consistent with treatment guidelines that recommend continuous treatment if an adequate response is achieved. However, persistence with ustekinumab and infliximab in the PBS data was much higher than the proportion of patients who achieved a PASI 75 response in the clinical studies at both 6 and 12 months (Table ES.22). These results suggest that patients may be using biologics beyond the PASI 75 response which would be outside

the suggested continuation restriction. Also, if this is the case, the cost-effectiveness estimates used by the PBAC for the decision making on listing of these drugs would have been overestimated.

The majority of patients appeared to use biologics persistently. A very small number of patients used more than three biologics. However, this may not be outside the PBS restriction because patients are able to trial more than three biologics as long as they do not fail treatment with more than three biologics in a treatment cycle.

Conclusion

Prevalence data for CPP and PsA are limited in Australia and the estimates from available data were wide ranging suggesting there is considerable uncertainty of the true population with CPP and PsA. The review of prevalence data and the prescription utilisation data suggest that the prevalence of CPP is affected by latitude and a population estimate based on local observational studies could over or underestimate (depending on the location of the study) the prevalence of CPP.

Prescription utilisation was broadly consistent with treatment guidelines and PBS restrictions; however, the length that patients remained on treatment was higher than would have been expected, based on the efficacy (PASI 75 response) seen in the clinical trials.

Stakeholder views (Public consultation and stakeholder forum)

- 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 lack of awareness or access to dermatologists, and issues with prior therapies.
- Patients using biologics in Australia may have had psoriasis for longer without treatment than those in clinical trial populations and, in effect, have worse psoriasis on commencement. This may influence continuation rates.
- Time to diagnosis could influence uptake rates, utilisation and outcomes. Patients who are difficult to diagnose may end up with a late diagnosis and a treatment course dependent on comorbidities. Those with an early diagnosis may have a higher number of treatments over their disease course and improved management of comorbidities.
- Uptake was slow when biologics were first available, with prescribers initially hesitant to use them. Additionally, it takes a long time for patients to become eligible for biologics.
- There were conflicting views from stakeholders as to whether the retention rate of biologics is higher on the PBS than was predicted in studies.
- The real-life treatment goal is to maintain the treatment effect and to optimise patient outcomes.
- Some stakeholders considered that general practitioners are not well equipped to treat severe CPP, only prescribing topical therapy until the patient is referred to a dermatologist.

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

Q1. Summarise issues highlighted in ToR 1 to ToR 3 of the report that could impact the cost-effectiveness of biologics for CPP.

From the findings for TOR 1-3, there are a number of possible modifications to the PBS restrictions for biologics that need to be explored. 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; and
- Increasing the population with severe CPP (PASI >15) to include;
    - Patients with a PASI >10 and a DLQI >10, and
    - Patients with CPP that have genital involvement.

There were some differences between the long term clinical efficacy data and the PBS prescription continuation data. Patients in the PBS prescription data were continuing treatment for longer than would have been expected based on the data provided to the PBAC during submissions (Table ES.22). In general, most submissions accounted for a reduction in clinical response over time that would have led to discontinuation of treatment and an appropriate reduction in costs in the model. However, in practice, patients are continuing for longer than seen in the cost-utility analysis (CUA) models, leading to higher costs without an understanding of how this long term treatment is affecting patient response and toxicity, and in turn, the cost-effectiveness of the biologic. In addition, no prior models considered treatment switching. Under the current PBS setting, a patient with severe CPP is able to use three biologics prior to being considered to have exhausted treatment options.

Q2. Summarise previous cost-effectiveness analyses for CCP seen by the PBAC.

A review of previously submitted and evaluated cost effectiveness analyses for the treatment of severe CPP with biologics was undertaken. The review identified eleven submissions/resubmissions that used cost-effectiveness analysis for the treatment of CPP with biologics that were presented to the PBAC. Models evaluated the following biologics: efalizumab, etanercept, infliximab, ustekinumab, and adalimumab.

Only one submission (adalimumab 2013) evaluated the cost-effectiveness for patients with moderate CPP, all others were in patients with severe CPP. Only one submission was for children (etanercept 2012) and this submission was based on a cost per responder analysis, not a cost-utility analysis. Seven models were identified from the submissions that used cost-utility analysis in adults with severe CPP (some resubmissions used similar models with only minor changes and were considered as one model in the review) (Table ES.24).

Table ES.24: Comparison of CUA models for biologics presented to the PBAC

Component	Type of analysis	Population	Comparator	Time horizon	Cost per QALY PBAC outcome
Efalizumab 2005	Cost-utility analysis	Adults sCPP	Placebo	[redacted]	Recommended on a cost-effectiveness basis to placebo within the range of $45,000 - $75,000/QALY gain
Etanercept 2006	Cost-utility analysis	Adults sCPP	Placebo	10 years	Rejected based on cost-effectiveness to placebo but recommended on a cost-minimisation basis with efalizumab
Infliximab 2006	Cost-utility analysis	Adults sCPP	Efalizumab	254 weeks (4.9 years)	Rejected the submission's claim of cost-effectiveness over efalizumab on the grounds of a high incremental cost-effectiveness ratio
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Ustekinumab 2009	Cost-utility analysis	Adults sCPP	Infliximab or etanercept	5 years	Recommended based on acceptable cost-effectiveness compared with etanercept within the range of $15,000 - $45,000/QALY gain
Adalimumab 2009	Cost-utility analysis	Adults sCPP	Efalizumab, and infliximab	5 years	Rejected based on cost-effectiveness but recommended on a cost-minimisation basis with efalizumab or etanercept
Adalimumab 2013	Cost-utility analysis	Adults mCPP	Placebo or standard care	10 years	Rejected the submission's claim of cost-effectiveness over standard care on the grounds of a high incremental cost-effectiveness ratio

ALOS = average length of stay; BSA = body surface area; CsA = cyclosporin; DLQI = dermatology life quality index; GP = general practitioner; IV = intravenous; mCPP = moderate chronic plaque psoriasis; PASI = psoriasis area severity index; PUVA = psoralen and ultraviolet A photochemotherapy; QALY = quality-adjusted life-year; SC = subcutaneous; sCPP = severe chronic plaque psoriasis

All seven models used a Markov modelling approach with time horizons between two and 10 years (four of the seven used five years) and treatment cycles between 12 and 24 weeks. Models generally used 12 weeks as the time to first response assessment and then determined continuation (response) at 24-week cycles thereafter.

In all but three submissions, the nominated comparator was another PBS listed biologic. These comparators were accepted by the PBAC. In the other three submissions, placebo was the nominated comparator; efalizumab 2005, because it had no other listed biologic to act as a comparator; etanercept, which was argued to be a last-line therapy with no biologic comparator; and adalimumab 2013, because it had no listed biologic for moderate CPP to compare to. In the etanercept 2006 submission, the PBAC suggested that placebo was superseded with the recent listing of efalizumab. In the other two submissions (efalizumab 2005 and adalimumab 2013), the PBAC accepted placebo as the appropriate comparator.

All models used PASI improvement from baseline as the primary outcome measure. Efalizumab 2005 submission defined a response to biologic treatment as a PASI 50 (50% improvement in PASI score from baseline). This was the basis for rejection of the efalizumab 2005 submission. The resubmission responded by using a 75% improvement in PASI score from baseline (PASI 75) as the definition for response in the model. Thereafter all models considered PASI 75 as the definition of treatment response.

Few studies had response data available from studies beyond 12 to 24 weeks and therefore required various techniques to provide transition probabilities beyond the 24-week period leading to considerable uncertainty in the models. Four of the seven models assumed that a proportion of patients would discontinue treatment with the two infliximab models assigning a discontinuation rate at each assessment time point, whereas the two models using placebo as a comparator assumed a 20% discontinuation rate per year for the drug arm only.

Costs included in each of the models was not exhaustive with the majority of the models applying costs of drugs, drug administration costs (four of six models), monitoring costs (three of six models), and hospital costs (five of six models).

Stakeholder views (Public consultation and stakeholder forum)

A number of stakeholders provided rationale in support of the cost-effectiveness of various biologics in the use of CPP.

Review Options

The Reference Group has considered the evidence review and stakeholder input, and proposes the following options for the PBAC to consider. DUSC and ESC will also provide advice on the following review options.

The Reference Group noted that any alteration to the restrictions surrounding the PBS listing of biologics for medicines would need to consider the cost-effectiveness of these medicines.

Option 1: Alter the PBS restrictions so that patients only need to have failed two of the four prior treatments (phototherapy, methotrexate, cyclosporine, acitretin).

Current restriction

The PBS restrictions require patients to have failed to achieve an adequate response to, or be contraindicated or intolerant to, at least three of the following four treatments: phototherapy; methotrexate; cyclosporin; acitretin.

Rationale for option

- The PBS requirement to fail prior therapies is challenging for patients and clinicians, with many patients suffering significant side-effects from methotrexate, cyclosporin and acitretin.
- There may be clinical reasons that don't match the toxicity criteria used by the Department of Human Services in assessing contraindications to prescribing acitretin, methotrexate or cyclosporin.
- This option is in alignment with the Australasian College of Dermatologists (ACD) Consensus Statement for the treatment of CPP.
- This option may increase access to PBS-listed biologics for psoriasis, thereby impacting the cost-effectiveness that was originally assessed by the PBAC.

Option 2: Alter the PBS restrictions to enable patients with a baseline PASI >10 to access PBS-listed biologics for CPP if their Dermatology Life Quality Index (DLQI) is > 10.

Current restriction

The current PBS restrictions require adult patients to have severe CPP of the:

- whole body (baseline PASI > 15) OR
- face, a palm of the hand or the sole of a foot (2 of 3 PASI symptom sub-scores rated as severe or very severe or 30% or more of the area is affected).

Rationale for option

- The current PBS restrictions do not consider quality of life impacts in regard to accessing biologics for CPP.
- Stakeholders considered that CPP has a significant impact on patients' mental health and wellbeing, social interactions, work opportunities, productivity and self-confidence. Consideration of a quality of life measure, such as the DLQI, was considered to be important for both initial and continuing access to biologics for CPP.
- This option would be in alignment with the Australasian College of Dermatologists' Consensus Statement for the treatment of CPP.
- This option would increase the number of people eligible for PBS-listed biologics for psoriasis, thereby impacting the cost-effectiveness that was originally assessed by the PBAC and the total cost to the PBS.

Option 3: Alter the PBS restrictions to enable patients with CPP involvement of the genitals to access PBS-listed biologics.

Current restriction

The current PBS restrictions require adult patients to have severe CPP of the:

- whole body (baseline PASI > 15) OR
- face, a palm of the hand or the sole of a foot (2 of 3 PASI symptom sub-scores rated as severe or very severe or 30% or more of the area is affected).

This option proposes to include genitalia in the restriction as per the following:

- whole body (baseline PASI > 15) OR
- face, genitalia, a palm of the hand or the sole of a foot (2 of 3 PASI symptom sub-scores rated as severe or very severe or 30% or more of the area is affected).

Rationale for option

- Stakeholders and the reference group have advised that involvement of genitalia has a significant impact on patients' quality of life and should be considered part of the eligibility criteria in the PBS restriction for biologics in psoriasis.
- 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, thus indicating the possible need for phototherapy and/or systemic treatment. The full list of features included in the Consensus Statement is:
    - involvement of visible areas
    - involvement of major parts of the scalp
    - involvement of genitals
    - involvement of palms and/or soles
    - onycholysis or onychodystrophy of at least two fingernails
    - pruritus leading to excoriation.
- This option would increase the number of people eligible to access PBS-listed biologics for psoriasis, thereby impacting the cost-effectiveness that was originally assessed by the PBAC and total cost to the PBS.

Options for cost effectiveness analysis

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.

Option 4a) review the cost-effectiveness in all PBS listed biologics according to the current PBS restriction and actual PBS utilisation and recent clinical evidence, and
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 >10 and a DLQI>10; and increasing the population to include patients with CPP that have genital involvement or other specific circumstances as recommended by the PBAC.

Clarification of Option 4a

It is proposed that a cost-utility model (analysis) using data obtained from ToR 1, 2 and 3 should be conducted. The model should account for current Australian practices and consider discontinuation and switching. The aims of the model would be to:

- Assess the cost-effectiveness of biologicals under the current PBS restrictions.
- Assess the impact of continuation rates on cost-effectiveness, including trial-based rates, PBS prescription data rates, and more recent evidence on the relative efficacy and safety of biologics for CPP.
- Assess the cost-effectiveness of current usage through the model.

Clarification of Option 4b

If a broader restriction is recommended to include milder disease, less prior therapies and/or specific body areas, the above model could be modified to incorporate the broader population and associated disease response rates. The transition probabilities from the above model and the utilities associated with response would need to be adjusted to consider the varying efficacy for these specific subgroups. However, there are a number of issues with developing a model to assess cost-effectiveness for these specific sub-groups and a number of avenues need to be explored.

Modified cost-utility model

It may be appropriate to further expand the above cost-effectiveness model to incorporate the milder disease population, or to specifically focus on the PASI 10 to 15 sub category. However, clinical effectiveness data for this sub-group is required to model the cost-effective value in this population. Currently there is limited data available from one trial presented in the adalimumab submission for this sub-group. It may be possible to liaise with pharmaceutical companies to obtain sub-group analyses of the larger trials to focus on the population with PASI >10 and <15. However, it should be noted that the majority of trials were conducted in populations >12 and not >10. This could limit the pool of populations in the sub-group analysis and also undermine the estimate of clinical effectiveness in the PASI >10 but < 12 sub population.

Industry submissions

Alternatively, it may be more appropriate to request the relevant sponsor companies to provide submissions to PBAC that focus on the cost-effectiveness of biologics in CPP populations with a PASI range of 10 to 15 and DLQI >10. A similar submission from the

sponsor of adalimumab was made to PBAC in March 2013. For further information on this submission and PBAC consideration, refer to Section 4 - ToR4.

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Appendix A – Glossary of terms

Term	Explanation
Adverse event	A side effect or an unintended and sometimes harmful occurrence caused by a medicine or medical treatment. A serious adverse event is one that requires hospitalisation, causes disability or permanent damage, requires intervention to prevent disability or permanent damage, is life-threatening, causes death, results in a birth defect, or causes another serious medical event.
AGREE	The Appraisal of Guidelines for Research and Evaluation instrument is a tool used to assess the quality of clinical guidances. Only guidances assessed as having an overall quality of four or above (on a scale of one to seven) were included.
Ankylosing spondylitis	A type of arthritis that causes long term inflammation of the joints in the spine. Ankylosing spondylitis can be treated with some biologic medicines.
Biologic medicine or biopharmaceutical	Medicines produced from biological sources. Most of the biologic medicines used to treat psoriasis are monoclonal antibodies, which are identical proteins usually made in special cell cultures.
Biosimilar	A biosimilar medicine is a biologic medicine that is highly similar to a 'reference biological medicine'. They are checked for safety and to confirm they provide the same health outcomes as the reference biological medicine. Some biosimilars are 'substitutable', which means pharmacists can substitute between brands in consultation with the patient but without needing to refer back to the doctor.
Blinded study / trial	Is where the information about the medicine or placebo given in a medical study is not given to the study participant (or patient), treating clinicians or the data analyst who reports the results. This reduces the chance that one treatment is more favourably considered than the other (see risk of bias).
CASPAR criteria	The Classification Criteria for Psoriatic Arthritis are the current standard diagnostic criteria for psoriatic arthritis.
Chronic plaque psoriasis	Plaque psoriasis is the most common type of psoriasis. It causes raised red patches (plaques) with silver or white scales. It is usually an ongoing (chronic) condition.
DLQI	The Dermatology Life Quality Index is a validated questionnaire used to measure quality of life of people with skin conditions. The Children's Dermatology Life Quality Index (CDLQI) is a version of the DLQI developed for children.
Epidemiological studies / estimates	Epidemiological studies are studies that look at the patterns and causes of conditions. Epidemiological estimates in this report are estimates of the number of patients with psoriasis and patterns of psoriasis from epidemiological studies.
GRADE	Grading of Recommendations Assessment, Development, and Evaluation is a systematic way of judging scientific studies and recommendations.
Incidence	The incidence of a medical condition is the number of people who developed that condition over a particular point in time.
Minimal clinically important difference	The minimal clinically important difference is the smallest difference in a score that patients consider meaningful.
Network meta-analysis	A statistical method of bringing together the results of many studies of different treatments for a particular condition. This technique gives results that allows

Term	Explanation
	each treatment to be compared to each of the other treatments included in the analysis.
Psoriasis Area and Severity Index	The Psoriasis Area and Severity Index is a way of measuring how severe a patient's psoriasis is based on the area of the body affected by psoriasis, the level of redness, the thickness and level of scaling.
PASI 75	A 75% or greater reduction in PASI score
Persistence	In this report, treatment persistence is how long patients continue treatment without a break.
Physician's Global Assessment	An assessment of all psoriatic lesions based on redness, scale and thickness. There are many variations on how this assessment is done.
Prevalence	The prevalence of a medical condition is the total number of patients with that condition
Psoriatic arthritis	A type of inflammatory arthritis that occurs in people affected by psoriasis. It usually occurs after patients develop psoriasis of the skin. Psoriatic arthritis is more likely to affect the joints at the ends of the fingers and the lower back than other types of arthritis.
PUVA	Psoralen and ultraviolet A phototherapy. This involves using psoralens, which make the skin more sensitive to ultraviolet light, then applying ultraviolet light to treat psoriasis and other conditions.
Quality of life	An evaluation of positive and negative aspects of life. In this report, quality of life refers mostly to health-related quality of life which is related to physical, mental, emotional, and social functioning. It can be measured in many ways. For example, the Dermatology Life Quality Index is a questionnaire that is specific to measure quality of life in patients with skin conditions.
Randomised controlled trial	A type of scientific study where participants are randomly allocated to the experiment group or a placebo or standard treatment group. Randomised controlled trials are considered to be the best type of clinical trial to compare the effectiveness of medical treatments because random allocation reduces bias (see risk of bias) and there is a very similar group (placebo or standard care group) to compare the results.
Rheumatoid arthritis	A type of inflammatory arthritis that mostly affects the joints in the wrist and fingers.
Risk of bias	The risk of bias in a scientific study is the chance that an interference has happened that might make the study results differ substantially from the truth. This may be due to factors like sicker patients leaving the trial early, a newer medicine being assessed more favourably or patients with more severe psoriasis being more involved in studies of psoriasis. The risk of bias of the clinical trials was assessed using the Cochrane Collaboration's 'Risk of bias tool'. A risk of bias tool for prevalence studies was used to assess studies that estimated the number of people with psoriasis, the severity and location of psoriasis, and the number of people with psoriatic arthritis.
Standard coverage days	The number of days of treatment provided by a prescription. In this report, the time taken for half of PBS patients to have a repeat prescription dispensed (median) was the standard coverage days for the biologic.
Systematic review	A structured way to gather and analyse research papers.

Term	Explanation
Treatment holiday or drug holiday	A break from medical treatment for a period of time. In this report, treatment holidays were where patients stopped using biologic prescriptions and restarted treatment.
Utilisation or drug utilisation	The pattern of medicine use. In this report, patterns of biologic medicine use for CPP was examined using prescription dispensing data.