Pharmaceutical Benefits Scheme

Post-market Review

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

Report to PBAC

Term of Reference 4

FINAL REPORT

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Abbreviations

Abbreviation	Full Name / Wording
AQoL	Assessment Of Quality Of Life
BSA	Body Surface Area
CNS	Central Nervous System
CPP	Chronic Plaque Psoriasis
CUA	Cost-Utility Analysis
DLQI	Dermatology Life Quality Index
DMARD	Disease Modifying Anti-Rheumatic Drug
EQ-5D	The Euroqol Five Dimensions Questionnaire
GP	General Practitioner
Hep	Hepatitis
HIV	Human Immunodeficiency Virus;
ICER	Incremental Cost-Effectiveness Ratio
IV	Intravenous
NSAID	Non-Steroidal Anti-Inflammatory Drug
PASI	Psoriasis Area And Severity Index
PBAC	Pharmaceutical Benefits Advisory Committee
PBS	Pharmaceutical Benefits Scheme
PGA	Physician's Global Assessment
PsA	Psoriatic Arthritis
PUVA	Psoralen And Ultraviolet A
QALY	Quality Adjusted Life Year
SC	Subcutaneous
sCPP	Severe Chronic Plaque Psoriasis
TB	Tuberculosis
TNF	Tumour Necrosis Factor
ToR	Term Of Reference
UV	Ultraviolet

Section 4: Terms of Reference (ToR) 4
Cost-effectiveness review

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 (CPP).

4.1 Key findings of ToR 4

Summary of issues highlighted in TOR 1-3 that potentially impact the cost-effective use of PBS biologics in CPP

According to the evidence and stakeholder input for ToR 1, 2 and 3 and the review of the previously seen cost-effectiveness analyses conducted under ToR 4, there are a number of issues that may need to be addressed in further cost effectiveness assessments. These include:

a) Evaluation of the cost-effectiveness of biologics according to the current PBS restriction including all available comparative evidence and long-term data on actual PBS utilisation.

b) A cost-effectiveness evaluation that considers the impact of any recommended changes/broadening of the current PBS restriction recommended by PBAC such as:
   - Reducing the number of prior systemic treatments that need to be trialled, from three to two, before being allowed to progress to a biologic, and
   - Increasing the population to include:
     - Patients with a PASI >10 and DLQI >10, and
     - Patients with CPP that have genital involvement.

Summary of cost- effectiveness models for CPP previously submitted to the PBAC

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

Seven models were identified from the submissions that used cost-utility analyses in adults with severe CPP. Of these, the PBAC recommended listing based on cost-effectiveness over a comparator for three comparisons (efalizumab vs placebo, infliximab vs efalizumab or etanercept, and ustekinumab vs etanercept).

The nominated comparator was either another PBS listed biologic or placebo, and this tended to be associated with the year of the submission (early models used placebo), and the population group (milder disease and children used placebo). Overall, these comparators were considered appropriate.

All seven models used a Markov model 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.

PASI 75 response was considered the most appropriate outcome to assess transition probabilities in the cost-utility models. Most models had three health states: responder, non-responder, and discontinued, with utility values assigned to each of these health states.

Depending on the source or method of calculation, the utilities assigned to the health states between each model varied considerably [redacted] Models were determined to be highly sensitive to the utilities assigned to each health state and hence the choice of utility values could be a large source of uncertainty in the models.

Few studies had response data available beyond 12 to 24 weeks and therefore required various techniques to extrapolate transition probabilities beyond the 24-week period.

Costs included in each of the models were 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).

Options for a cost-effectiveness analysis

To address the issues highlighted above, an economic model could be constructed to allow testing of multiple scenarios to assess the effects on cost-utility of the biologicals. The model would allow for the sequence of treatments using different biologicals, continuation and suspension (stand-down) rules, as well as analyses of different pricing policies to be explored.

A number of options are available to the PBAC to determine cost-effectiveness for the proposed scenarios.

a) Evaluation of the current setting to include all available comparative evidence and incorporating long-term utilisation data on continuation of treatment. A cost-utility analysis could be developed to address this scenario using a number of data sources, including:

- efficacy and safety data identified in Section 2 of the report;
- continued utilisations data identified in Section 3 of the report; and
- other data sources for utilities, background mortality, costs etc.

b) Evaluation of modifying/broadening the current restriction to include all available comparative evidence. A number of possibilities could be developed to address these scenarios using a number of different data sources, including:

- A cost-utility analysis could be developed based on the above model that would include interaction with industry to develop and obtain sub-group analysis of clinical trials in the specific populations of interest;
- A proposal for pharmaceutical companies to put forward industry based submissions for these scenarios; and
- A weighted cost per responder analysis.

The impact on total cost to government could also be presented according to different cost and utilisation assumptions.

4.2 Summarise issues highlighted in ToR 1 to ToR 3 of the report that would need to be addressed using cost-effectiveness analysis

Term of reference 1

While there are some inconsistencies between the PBS restrictions and the Australian consensus concerning the clinical measures 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 taking into consideration the evidence and cost-effectiveness of biologics in the less severe population. 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 on the PBS restrictions.

Term of reference 2

Overall, the efficacy of biological compared to placebo demonstrated that biologics provide patients with clinically meaningful improvements in their psoriasis severity. There was some variation in the efficacy between different biologics, but these differences tended to be minor overall. 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 randomised control trials (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 were generally high for methods but most trials 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 only biologics where trials were conducted that included patients with PASI <15 were for adalimumab and etanercept (Table 1 and Table 2).

Table 1: Adalimumab trials: inclusion and exclusion criteria

Trial	Inclusion criteria	Exclusion criteria
CHAMPION (versus methotrexate versus placebo)	- ≥ 18 years; - moderate-to-severe psoriasis; - plaque psoriasis for ≥ 1 year, stable for ≥ 2 months; - BSA ≥ 10%, PASI ≥ 10; - candidates for systemic or phototherapy; - active psoriasis despite topical agents	- concomitant therapies; - active TB; - clinically significant haematological, renal or liver disease; - demyelinating disease, cancer or lymphoproliferative disease; - immunocompromised patients
BELIEVE (versus adalimumab plus calcipotriol/betamethasone ointment)	- ≥ 18 years; - CPP (concomitant psoriasis palmaris and/or plantaris permitted) for ≥ 6 months; - previously failed/intolerant of/contraindicated to ≥ 2 different systemic, biologic or non-biologic therapies (one must have been cyclosporin, methotrexate or oral psoralen and UV-A); - must meet 2 of 3 severity criteria: PASI ≥ 10 OR BSA ≥ 10% OR DQLI ≥ 10	- exposure to adalimumab; - systemic or topical corticosteroids within 2-4 weeks, biologics within 3 weeks to 65 days, known overexposure to UV-A/UV-B; - coexisting skin disease; - pregnancy or breastfeeding; - poorly controlled medical conditions; - history of opportunistic/chronic infections/ immunocompromising conditions/active TB

BSA = body surface area; CPP = chronic plaque psoriasis; DLQI = Dermatology Life Quality Index; PASI = Psoriasis Area and Severity Index; TB = tuberculosis; TNF = tumour necrosis factor; UV = ultraviolet

Table 2: Etanercept trials: inclusion and exclusion criteria

Trial	Inclusion criteria	Exclusion criteria
Leonardi (2003) (versus placebo)	- ≥ 18 years; - active but stable plaque psoriasis; - BSA ≥ 10%, PASI ≥ 10; - previous phototherapy or systemic therapy	- guttate, erythrodermic or pustular psoriasis; - active skin conditions; - previous etanercept or TNF antibody; - anti-CD4 antibodies or IL-2-diphtheria toxin fusion protein within 6 months
Papp (2005) (versus placebo)	- ≥ 18 years; - active, clinically stable plaque psoriasis; - BSA ≥ 10%, PASI ≥ 10; - received or were candidate for prior systemic or phototherapy; - adequate haematological, renal and hepatic function	- active guttate, erythrodermic or pustular psoriasis; - other skin conditions; - antibiotics within 1 week; - active severe infection within 4 weeks;
van de Kerkhof (2008) (versus placebo)	- ≥ 18 years; - clinically stable plaque psoriasis; - BSA ≥ 10%; PASI ≥ 10; - failed to respond/were intolerant/were contraindicated to systemic or phototherapy	- guttate, erythrodermic or pustular psoriasis; - other active skin conditions; - serious infection within one month; - BMI > 38 kg/m^2; - previous etanercept
Tyring (2006) (versus placebo)	- ≥ 18 years; - active, clinically stable plaque psoriasis; - BSA ≥ 10%; PASI ≥ 10; - received/been a candidate for systemic or phototherapy; - adequate haematological, renal and hepatic function	- guttate, erythrodermic or pustular psoriasis; - other skin conditions; - history of psychiatric disease
PRISTINE (versus placebo)	- ≥ 18 years; - active, clinically stable CPP; - BSA ≥ 10%; PASI ≥ 10; - failed/intolerant/contraindicated/not a candidate for methotrexate, cyclosporine, PUVA	- other skin conditions; - rheumatologic disease; - severe comorbidities; - recent serious infection, TB
Gottlieb (2012) (versus etanercept plus methotrexate)	- ≥ 18 years; - stable moderate-to-severe plaque psoriasis for ≥ 6 months; - BSA ≥ 10%, PASI ≥ 10; - candidate for systemic or phototherapy; - adequate/normal blood levels	- guttate, erythrodermic or pustular psoriasis; - other skin conditions; - concurrent significant medical conditions

Trial	Inclusion criteria	Exclusion criteria
Lebwohl (2013) (versus etanercept plus clobetasol ointment)	- ≥ 18 years; - stable moderate-to-severe plaque psoriasis for ≥ 6 months; - BSA ≥ 10%, PASI ≥ 10; - failed topical corticosteroid therapy	- guttate, erythrodermic or pustular psoriasis; - medication-induced or medication-exacerbated psoriasis; - active infection within 30 days; - significant concurrent medical conditions
EGALITY (Biosimilar trial)	- ≥ 18 years; - active, stable CPP for ≥ 6 months; - BSA ≥ 10%, PASI ≥ 10; PGA ≥ 3; - previous systemic or phototherapy	- previous etanercept, TNF antagonists or other biological immune-modulating agents in 6 months prior; - ongoing use of prohibited psoriasis treatments (topical corticosteroids, UV therapy); - presence of active systemic infections in 2 weeks prior or latent TB
Gisondi (2008) (Mild-to-moderate psoriasis versus Etanercept + acitretin or Acitretin)	- ≥ 18 years; - active, but stable, moderate-to-severe plaque psoriasis (no minimum PASI score or BSA)	- psoriatic arthritis or other type of psoriasis (guttate, erythrodermic or pustular); - active or chronic infections including HIV, Hep B/C, latent TB; - previous malignancies; - severe haematological, renal or hepatic disorders, severe CHF or demyelinating disease; - previous biologics

BMI = body mass index; BSA = body surface area; CD4 = cluster of differentiation 4 (glycoprotein); CHF = congestive heart failure; CPP = chronic plaque psoriasis; Hep = hepatitis; HIV = human immunodeficiency virus; IL = interleukin; PASI = Psoriasis Area and Severity Index; PGA = Physician's Global Assessment; PUVA = psoralen and ultraviolet A photochemotherapy; TB = tuberculosis; TNF = tumour necrosis factor; UV = ultraviolet

While these trials included patients with less severe disease than other trials, the mean baseline severity (BSA, PASI and DLQI) did not vary much from other trials that incorporated more severe disease (Appendix B; [redacted]Table 8 and Table 9).

Overall, 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 (See Terms of Reference 2, Section 2.7). Also, there was limited data for severe CPP with concomitant psoriatic arthritis (PsA). The trials that addressed concomitant PsA and CPP tended to have lower severity in the inclusion criteria for PASI. Overall, 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, which may be due to the lower severity inclusion criteria. 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 tested biologics have some effect in treating CPP of the hands and/or feet, but genital areas were not specifically assessed.

Term of reference 3

Noting the limitations of PBS prescription data, utilisation appears to be broadly consistent with PBS restrictions; however, the length of time that patients remain on treatment was higher than would have been expected based on the efficacy (PASI 75 response rate) seen in the clinical trials.

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 in submissions. In general, most submissions accounted for a reduction in 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 is presented in the cost-utility analysis models (PBS prescription data), 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. Also, no prior models considered treatment switching. In the current PBS setting, a patient with severe CPP is able to use three biologics prior to being considered to have exhausted all treatment options.

4.3 Review of the cost-effectiveness analyses submitted for consideration to the PBAC

A review of the Public Summary Documents for biologics in CPP was undertaken to identify submissions that carried out cost-effectiveness analysis. We identified ten submission/resubmissions that presented cost effectiveness analysis (all in the form of cost-utility models and some as repeated models with cost changes only), for decision making for the use of biologics in the treatment of severe CPP (n = 9) and moderate-severe CPP (n = 1). Models presented in submissions requesting PBS restriction changes that were not relevant to the current or proposed cost-effectiveness analysis, were excluded. Table 3 presents the key features of the seven models of each biologic that used cost-utility analysis (see appendix A [redacted] for a more detailed comparison) in the comparisons of interest in this review.

Table 3: 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 sCPP	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

CUA = cost-utility analysis; PBAC= Pharmaceutical Benefits Advisory Committee; QALY = quality adjusted life year; sCPP = severe chronic plaque psoriasis

Economic models of biologics presented to the PBAC:

Efalizumab

Three submissions were presented (November 2004, July 2005 and November 2005) for efalizumab that carried out cost-effectiveness analysis in severe CPP.

The July 2005 resubmission addressed the November 2004 submission issues of an unacceptably high incremental cost-effectiveness ratio (ICER) by offering a price reduction, and presenting a revised economic evaluation and economic model. The November 2005 model adjusted a number of key parameters including using a criterion for response of PASI ≥ 75% rather than PASI ≥ 50% after 12 weeks of initial treatment.

The model:

[redacted]

[redacted]

1. [redacted]

These issues resulted in the PBAC rejecting the application (July 2005), concluding that the resulting modelled ICER was high and unacceptable.

The November 2005 resubmission presented a further updated economic evaluation where the definition of a responder was changed to PASI 75. This resulted in the PBAC recommending listing on the basis of an acceptable cost-effectiveness.

Etanercept

The etanercept 2006 resubmission followed a PBAC rejection of the July 2005 submission. The two submissions have an identically structured economic model with some differences in some of the assumptions and transition probabilities.

The model:

[redacted]

1. [redacted]

[redacted]

The PBAC approved the listing of etanercept on a cost-minimisation basis with efalizumab.

Infliximab

Two submissions were presented (July 2006 & March 2007) for infliximab that carried out cost-utility analysis in severe CPP. The July 2006 submission was the first submission to the PBAC for infliximab.

The model:

[redacted]

[redacted]

Ustekinumab

The ustekinumab submission presented to the PBAC in July 2009 carried out a cost-utility analysis in severe CPP.

The model:

[redacted]

[redacted]

Adalimumab

The July 2008 submission presented a cost-minimisation with infliximab as the main comparator and efalizumab as a secondary comparator. The 2008 submission was rejected on the grounds of uncertain clinical effectiveness and the resulting uncertain cost-effectiveness of adalimumab when compared with efalizumab. The first resubmission was presented to the PBAC in March 2009. In this resubmission the sponsor presented a cost-utility analysis with efalizumab as the main comparator and infliximab and etanercept as secondary comparators.

The 2009 model:

[redacted]

[redacted]

The PBAC recommended listing of adalimumab on the PBS for the treatment of severe chronic plaque psoriasis on a cost-minimisation basis with efalizumab or etanercept.

The 2013 model:

At the time of the application, biologic therapy in Australia was only subsidised for patients with a PASI >15 (severe psoriasis). Therefore, a treatment gap existed for patients with a baseline PASI or DLQI >10 but PASI ≤15 (moderate psoriasis). The adalimumab model attempted to describe the cost-utility associated with broadening the PBS eligibility criteria to moderate CPP.

Given that no biologic for CPP was indicated for use with moderate CPP the nominated comparator for this submission was placebo. This was accepted by the PBAC as reasonable.

The model:

[redacted]

[redacted]

Therefore, based on an uncertain cost-effectiveness, the PBAC rejected the submission requesting extension of the current listing for adalimumab to include patients with moderate plaque psoriasis.

Summary of the models:

Population

All but the final Adalimumab submission (2013) evaluated the cost-effectiveness of biologics for patients with severe chronic plaque psoriasis (CPP). Only the adalimumab 2013 submission presented an economic model to evaluate its effectiveness in a moderate severity CPP population (but was unsuccessful). All models evaluated the biologics in an adult population (≥ 18 years). Etanercept provided a cost-effectiveness model (cost per responder) for a paediatric population.

Comparator

The success of the 2007 infliximab resubmission was based on acceptable cost-effectiveness against efalizumab, which was delisted due to toxicity concerns. In turn, the success of the 2009 ustekinumab submission, and to some extent the adalimumab 2009 submission, was based on acceptable cost-benefit against infliximab, though adalimumab was listed based on cost-minimisation following a cost-utility analysis submission.

The etanercept 2006 model identified placebo as the appropriate comparator despite the recent listing of efalizumab. This resulted in the PBAC rejecting the model but accepting listing of etanercept in a cost-minimisation comparison with efalizumab.

Both the efalizumab 2005 and adalimumab 2013 submission defined placebo as the primary comparator but did so for slightly different reasons. The efalizumab submission had no other PBS listed biologics to act as comparators in patients with severe CPP while in the adalimumab submission, no biologics were listed for the treatment of patients with moderate CPP. The PBAC accepted placebo as the logical comparator in both instances.

Time horizon

The 2005 efalizumab submission used a two-year time horizon and the adalimumab 2013 submission used a 10-year time horizon. The commentary determined that the ICER in the adalimumab 2013 model changed minimally between years five and 10. The commentary for etanercept suggested that the 10-year time horizon unfairly advantaged etanercept. All other models used a five-year time horizon.

Response

All models, except for the efalizumab 2005 model, defined a response to biologic treatment as PASI 75 (i.e. a 75% improvement in PASI score from pre-treatment). The efalizumab 2005 submission was rejected primarily based on the use of a PASI 50. In the successful minor resubmission in 2006, the efalizumab model defined a response as PASI 75.

Cycle length

[redacted]

Transition probabilities and discontinuation rates

The data behind transition probabilities and discontinuation rates was a major weakness of all models. Transition probabilities were generally only available from observed data up to the first assessment period (i.e. 10 or 12 weeks), whereas the models had on average, five-year time horizons with 24 weekly assessments of response. That is, all other assessment periods in the model used transition probabilities that were calculated/extrapolated from the observed data.

[redacted]

Efalizumab:

[redacted]

Etanercept:

[redacted]

Infliximab:

[redacted]

Ustekinumab:

[redacted]

Adalimumab:

[redacted]

[redacted]

Utilities

The models used a number of different sources and/or methods to determine utilities associated with response and non-response to biologics for the treatment of CPP. This resulted

in a wide variation in the utility scores used in the models to represent essentially the same health states: responders and non-responders (Figure 1).

[redacted]

Efalizumab

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

Infliximab

[redacted]

[redacted]

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Adalimumab

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- [redacted]
- [redacted]
- [redacted]

[redacted]

[redacted]

The York model:

In a systematic review of cost-effectiveness models for CPP, Woolcott et al in 2008 determined that; of the cost-effectiveness models evaluated from the literature it was apparent that they suffered from many weaknesses. The key was that the models failed to consider all relevant treatment options. Therefore, the authors found it necessary to develop a “de novo” cost-effectiveness model (referred to as ‘the York Model’). At the time of the modelling only efalizumab and etanercept were available for the treatment of CPP.

The model was very basic in its construction, essentially comparing the costs and consequences of responders and non-responders to each treatment being considered over a specified period. Therefore, the model required information on the proportion of patients responding to treatments, and the costs, effects and total duration of treatment for both responders and non-responders.

In the base case of the model, the treatments compared were 25 mg and 50 mg etanercept, efalizumab and standard care. The model also attempted to determine which treatment sequence (providing these three treatments,) would be the most cost-effective.

Costs included in the model were the cost of drugs, drug administration, cost of monitoring, and outpatient and inpatient hospital stays. Only non-responders were assumed to experience hospital stays (average length of stay of 19.6 days). No other adverse events were applied to the model due to the absence of quality data. The model discounted costs at 6% per annum.

Utilities were determined from a relationship with the reported DLQI experienced for patients with different levels of PASI improvement and reported as utility gains.

Table 5: Gains in utility based on PASI response category

PASI	Mean (SE)
< 50	0.05 (0.01)
≥50 and < 75	0.17 (0.04)
≥ 75 and < 90	0.19 (0.04)
≥ 90	0.21 (0.05)

Source: Table 48, p63, Woolacott 2006
PASI = psoriasis area and severity index; SE = standard error

The model assumed that there was no difference in mortality between treatments and that there was a dropout rate of 20% per annum for responding patients. Discounting of outcomes was set at 1.5% per annum.

The base case of the model showed that inclusion of the drugs etanercept and efalizumab into the treatment sequence in any order after supportive care, resulted in unacceptably high ICERs.

4.4 Develop options for cost-effectiveness to be re-established in:

Models proposed for the currently listed PBS biologics for CPP

Considering the issues highlighted in ToR 1 to 3, and in the above review of previous cost-effectiveness models, it may be appropriate to consider the following economic evaluations:

a) An economic evaluation of currently PBS-listed biologics at the current restriction, incorporating the systematic review and efficacy data from the network meta-analysis which compared all currently PBS-listed biologics for severe CPP, incorporating;
    a. long term usage from the utilisation data; and
    b. treatment switching from the utilisation data.
b) An economic evaluation exploring the cost-effectiveness for changes in PBS restrictions that incorporates;
    a. Reducing the number of prior treatments (from three to two out of four prior therapies);
    b. Increasing the population to include patients with a PASI >10 and DLQI >10; and

c. Increasing the population to include patients with CPP that have genital or other specific area involvement.

An economic evaluation of currently PBS listed biologics at the current restriction

It is proposed that a cost-utility model using data obtained from ToR 1, 2 and 3 along with other data as needed should be conducted. The model should account for current Australian practices and consider discontinuation and switching. A model similar to the decision tree presented below (Figure 1) (or other pending consultation with the reference group) could be constructed (using TreeAge or other software) to assess the comparative cost-effectiveness of each of the main biologicals.

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 etc; and
- Assess the cost-effectiveness of current usage through the model.

Possible model for current setting

The cost-utility model would be constructed in collaboration with the reference group to ensure that the current clinical settings are considered. As an overview based on the review of previous submissions and current standards, it is proposed that a cost-utility model would be based on a comparison between the listed biologics. It is proposed that the model would have two health states: response (PASI 75) and nonresponse (PASI < 75). Patients not achieving a response can a) discontinue treatment, b) receive the next biologic, or c) continue to receive the same biologic as the patient may exhibit improvement to treatment (just not 75% improvement) and continue to be measured for response at the next assessment time point.

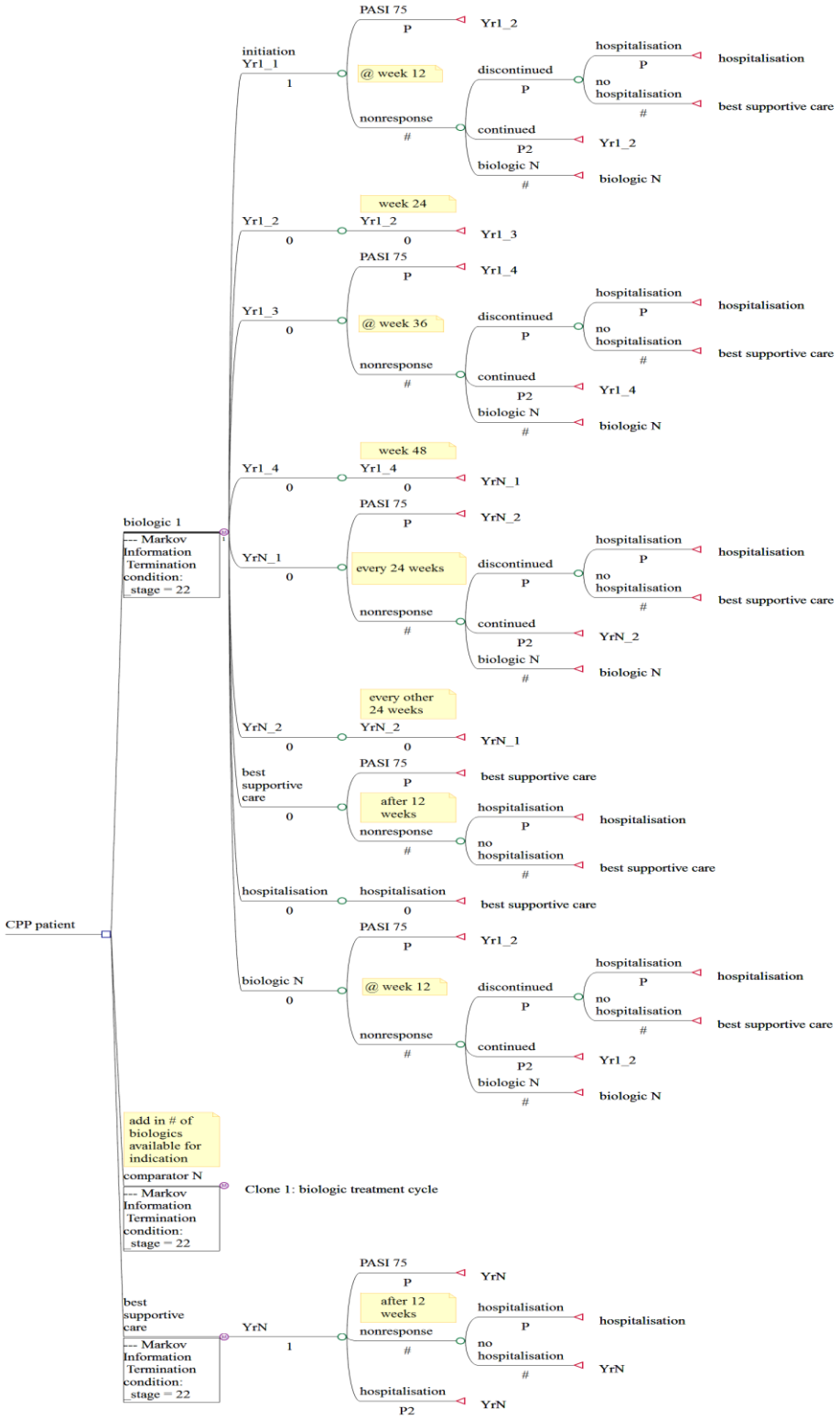

Figure 1: Proposed model for evaluating the cost-effectiveness of biologics for CPP

CPP = chronic plaque psoriasis; P = probability; PASI = psoriasis area and severity index; Yr1_1 = year one 12 week period one; Yr1_2 = year one 12 week period two; Yr1_3 = year one 12 week period three; Yr1_4 = year one 12 week period four; YrN_1 = subsequent year N 24 week period one; YrN_2 = subsequent year N 24 week period two

Based on current standards, the model assumes that patients are assessed at week 12 for initial response and then every 24 weeks thereafter to follow the continuation rule. It is assumed that monitoring would be conducted at every 12 weeks in the first year and then every 24 weeks thereafter (i.e. four times in year one and twice yearly every year after). Patients would not change medication until these time points were realised, though response could change. Transition probabilities would include:

- probability of PASI 75 response at time;
- discontinuation rate; and
- risk of hospitalisation.

Costs to consider in the model are:

- drug costs;
- drug administration costs;
- monitoring costs; and
- adverse events – hospitalisation (for patients who discontinue biologic treatment, standard care only).

Based on feedback from the reference group and the Economic Sub-Committee (ESC) of the PBAC, the time horizon could be five years, 10 years, or lifetime, though clinical evidence is lacking for long term therapy response.

Other models considered appropriate for PBAC decision-making based on options provided by the reference group

If a broader restriction is considered to include milder disease, fewer prior therapies and/or including specific body areas, the above model could be modified to incorporate the broader restriction and 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 sub-groups. However, there are a number of issues with developing a cost-effectiveness analysis for these specific sub-groups and a number of avenues may need to be explored.

Reducing the number of prior therapies

Considering the proposed changes, it is unlikely that a reduction from three to two, out of four prior therapies, would change the cost-effectiveness of biologics compared to other biologics as seen previously by the PBAC. This is because most of the clinical evidence used in PBAC decision making for comparing biologics with each other did not require patients to receive three prior therapies. The main issue with regards to this sub population is calculating the cost-effectiveness of the biologic compared to standard therapy that would incorporate the four therapies (cyclosporin, methotrexate, acitretin and phototherapy) that are available on the PBS for this population.

The risk of listing an early line of therapy without having a true understanding of the cost-effectiveness of these comparisons, could result in a considerable increase in the costs to the government without a real improvement in health outcomes. The evidence is limited in the comparison of biologics to non-biologics with only three RCTs having been conducted that examine the efficacy of biologics compared to any of these prior therapies for patients with severe CPP (Table 6).

Table 6: Inclusion criteria for randomised control trials that compare biologics with PBS listed prior therapies

Trial	Inclusion criteria	Exclusion criteria
CHAMPION (Adalimumab versus methotrexate versus placebo)	- ≥ 18 years; - moderate-to-severe psoriasis; - plaque psoriasis for ≥ 1 year, stable for ≥ 2 months; - BSA ≥ 10%, PASI ≥ 10; - candidates for systemic or phototherapy; - active psoriasis despite topical agents	- concomitant therapies; - active TB; - clinically significant haematological, renal or liver disease; - demyelinating disease, cancer or lymphoproliferative disease; - immunocompromised patients
Gottlieb (2012) (Etanercept versus etanercept plus methotrexate)	- ≥ 18 years; - stable moderate-to-severe plaque psoriasis for ≥ 6 months; - BSA ≥ 10%, PASI ≥ 10; - candidate for systemic or phototherapy; - adequate/normal blood levels	- guttate, erythrodermic or pustular psoriasis; - other skin conditions; - concurrent significant medical conditions
RESTORE Infliximab versus methotrexate	- 18-75 years; - moderate-to-severe plaque psoriasis for ≥ 6 months; - BSA ≥ 10%, PASI ≥ 12; - candidate for systemic or phototherapy	- previous methotrexate, biologic or TNF antagonist within 3 months; - CHF; - history of chronic/recurrent infection or TB

BSA = body surface area; CHF = congestive heart failure; PASI = Psoriasis Area and Severity Index; TB = tuberculosis; TNF = tumour necrosis factor

Conducting a cost-effectiveness model for these comparisons would require a number of indirect comparisons and assumptions to be made to enable a better understanding of this setting.

Changing the requirement for the severity of disease to include PASI >10 or genital involvement

Again, the evidence is very limited in this sub population with only two biologics (adalimumab and etanercept) having trials that include patients with a PASI >10, only one trial that has no lower limit for severity, and no clinical trial evidence that specifically looks at genital involvement. The main issue with regards to this sub-population is calculating the clinical effectiveness of biologics in this less severe category. This in turn, would lead to difficulties in determining the comparative cost-effectiveness of each biologic compared.

Also of note is identifying the correct comparator for this population. Given the above comments on reducing the number of prior treatments required, cyclosporin, methotrexate, acitretin and phototherapy would be appropriate comparators. This would need to be considered by the reference group when determining an appropriate approach.

There are a number of possibilities to address these issues in determining the cost-effectiveness of biologics in the sub-categories.

Modified cost-utility model

It may be appropriate to further expand the above cost-utility model to incorporate this milder disease population, or to specifically focus on the PASI 10 to 15 sub-category. However, clinical effectiveness data would be needed in order that it could be correctly incorporated into the model. While not ideal, it may be possible to liaise with pharmaceutical companies to obtain sub-group analysis of the larger trials to focus on the population with PASI ≤15. However, it should be considered that the majority of trials were conducted in populations with a PASI ≥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

It may be appropriate to request industry submissions from the pharmaceutical companies that focus on the PASI 10 to 15 sub-population similar to that seen in the Adalimumab in March 2013 submission, noting that the PBAC rejected this submission on the basis of highly uncertain cost-effectiveness. Other relevant points (from the Adalimumab Public Summary Document March 2013) included:

- "With regard to safety, the PBAC was particularly concerned with the use of adalimumab (and monoclonal antibodies in general) in larger patient populations to treat milder forms of disease, albeit with high health distress, insofar as it increases exposure of patients to the adverse effects associated with use of these agents, particularly infection and malignancy."
- "The PBAC considered that there was a risk that adalimumab would be used in a proportion of patients with mild disease (i.e., PASI < 10), since determination of a PASI score is to some extent subjective. Furthermore, the PBAC noted that a proportion of patients with moderate psoriasis might be currently receiving PBS subsidised adalimumab under the severe disease restriction. The PBAC requested a review of the use of adalimumab in patients with moderate disease." (Adalimumab Public Summary Document, March 2013).

Appendix A

[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
				[redacted]			
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Appendix B

Table 8: Baseline characteristics of adalimumab trials

Trial	Arm	N	BSA; mean % (SD)	PASI; mean (SD)	DLQI; mean (SD)
Adalimumab versus placebo					
CHAMPION[a]	Ada[1*]	108	34% (20)	20.2 (7.5)	11.8 (6.6)
	Pbo	53	28% (16)	19.2 (6.9)	11.7 (7.0)
Adalimumab versus adalimumab plus calcipotriol/betamethasone ointment					
BELIEVE[b]	Ada[1*] + CB	366	33% (20)	19.5 (8.6)	13.7 (7.3)
	Ada[1*]	364	33% (20)	19.5 (8.7)	14.2 (7.7)
Average of the trials with PASI ≥ 10 inclusion criteria					
N = 891	NR	NR	33% (NR)	19.6 (NR)	13.5 (NR)
AVERAGE OF ALL Trials in in Table 6, p24 of Terms of Reference 2					
N = 3,279	NR	NR	31% (NR)	20.5 (NR)	12.4 (NR)

ABP 501 = adalimumab biosimilar; Ada = adalimumab; BSA = body surface area; CB = calcipotriol/betamethasone; DLQI = Dermatology Life Quality Index; NR = not reported; PASI = Psoriasis Area and Severity Index; Pbo = placebo; PI = Product Information; SC = subcutaneous; SD = standard deviation; *Italics = median (IQR)*

[a] PASI not specified

[b] Baseline characteristics for methotrexate arm not included in the comparison

[c] must meet 2 of 3 severity criteria: PASI ≥ 10 OR BSA ≥ 10% OR DQLI ≥ 10

[d] baseline characteristics of arms presented in Table 6, p24 of Terms of Reference 2

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

[2] Adalimumab 80 mg SC Weeks 0 and 1; 40 mg every week from Week 2

Table 9: Baseline characteristics of etanercept trials

Trial	Arm	N	BSA; mean % (SD)	PASI; mean (SD)	DLQI; mean (SD)
Etanercept versus placebo					
Leonardi (2003)	Etan[1]	160	28% (2)	18.2 (0.7)	12.2 (0.5)
	Etan[2*]	162	29% (2)	18.5 (0.7)	12.7 (0.5)
	Etan[3]	164	30% (2)	18.4 (0.7)	11.3 (0.5)
	Pbo	166	29% (1)	18.3 (0.6)	12.8 (0.6)
Papp (2005)	Etan[2*]	196	29% (18)	19.1 (8.2)	11.5 (7.2)
	Etan[3]	194	29% (17)	19.5 (8.8)	11.4 (6.5)
	Pbo	193	27% (17)	18.6 (8.6)	12.2 (6.8)

Trial	Arm	N	BSA; mean % (SD)	PASI; mean (SD)	DLQI; mean (SD)
Etanercept versus placebo					
van de Kerkhof (2008)	Etan[4*]	96	27% (15)	21.4 (9.3)	13.2 (NR)
	Pbo	46	30% (18)	21.0 (8.7)	13.6 (NR)
Tyring (2006)	Etan[3]	311	27% (18)	18.3 (7.6)	12.1 (6.7)
	Pbo	307	27% (17)	18.1 (7.4)	12.5 (6.7)
Etanercept versus etanercept					
PRISTINE	Etan[4*]	137	33% (21)	20.9 (9.4)	15.0 (8.0)
	Etan[3]	136	33% (19)	21.4 (9.4)	14.1 (7.3)
Etanercept versus etanercept plus methotrexate					
Gottlieb (2012)	Etan[3]	239	24% (14)	18.3 (6.6)	NR
	Etan[3] + Mtx	239	24% (16)	18.2 (8.2)	NR
Etanercept versus etanercept plus clobetasol ointment					
Lebwohl (2013)	Etan[3]	297	24% (17)	18.2 (8.3)	NR
	Etan[3] + CP	295	26% (18)	18.9 (9.2)	NR
Biosimilar trial					
EGALITY	Etan[3]	267	31% (15)	22.5 (9.5)	NR
	GP 20153	264	31% (14)	22.5 (8.9)	NR
Average of the trials with PASI ≥ 10 inclusion criteria					
N = 3,689	-	-	31% (NR)	18.6 (NR)	11.7 (NR)
Gisondi (2008) N = 60	-	-	12% (NR)	11.1 (NR)	NR
AVERAGE OF ALL Trials in in Table 11, p34 of Terms of Reference 2					
N = 5,595	-	-	28% (NR)	19.3 (NR)	12.4 (NR)

BSA = body surface area; CP = clobetasol propionate; DLQI = Dermatology Life Quality Index; Etan = etanercept; Mtx = methotrexate; NR = not reported; PASI = Psoriasis Area and Severity Index; Pbo = placebo; PI = Product Information; SC = subcutaneous; SD = standard deviation; SE = standard error; *Italics = (SE), (range) or median (range)*

[1] Etanercept 25 mg SC once weekly

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

[3] Etanercept 50 mg SC twice weekly

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