Stakeholder Forum Summary

Post-market Review of the Use of Biologics in the Treatment of Severe Chronic Plaque Psoriasis

University of Melbourne

Parkville, Victoria

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This document is intended to provide a broad summary of the views expressed by stakeholders and only information provided at the Forum has been included. No attempt was made to reach consensus.

Abbreviations

ACD	Australasian College of Dermatologists
CPP	chronic plaque psoriasis
CSP	cyclosporine
DLQI	dermatology life quality index
MTX	methotrexate
PASI	psoriasis area and severity index
PBAC	Pharmaceutical Benefits Advisory Committee
PBS	Pharmaceutical Benefit Scheme
RCT	Randomised controlled trial
TGA	Therapeutic Goods Administration
ToR	Terms of Reference

Purpose and Context

The aim of the Stakeholder Forum is to ensure that the Report of Pharmaceutical Benefits Scheme (PBS) *Post-market Review of the use of biologics in the treatment of severe chronic plaque psoriasis* includes the views of a wide range of stakeholders and that these views inform the discussions about future options for the Pharmaceutical Benefits Advisory Committee (PBAC) to consider. Consumers and clinicians who have an interest in chronic plaque psoriasis (CPP) and pharmaceutical sponsors who have a current PBS medicine listing for biologics for this condition were invited to participate in the Forum.

The Review is being conducted under the Australian Government's Post-market Review Program for PBS-listed medicines. A Reference Group has been established to provide independent expert advice to the Review, and includes clinicians, technical experts, consumers and industry representation. A summary of the stakeholder input received at the Forum will be included in the Review's Report to the PBAC. The PBAC is an independent, expert committee that makes recommendations to the Government on the subsidy of medicines on the PBS.

Prior to the meeting, attendees were provided with a background discussion paper that included information on the Review Terms of Reference (ToR) and identified key issues and questions for the Forum.

Summary of Key Discussion Points Raised by Stakeholders

- Inclusion of a quality of life measure such as the Dermatology Life Quality Index (DLQI) for both initial severity assessment to initiate biologics and as an ongoing progress measurement for continuing therapy was considered very important by both patients and clinicians. Clearing psoriasis has a significant impact on patients' mental health and wellbeing, social interactions, work opportunities, productivity and self-confidence. Involvement of certain areas of the body (such as the genitals or scalp), despite the size of the area affected, have a significant impact on patients' quality of life and should be considered as part of the disease severity classification.
- The PBS requirement to fail prior therapies is a challenge for patients and clinicians with many patients suffering significant side-effects from methotrexate, cyclosporine and acitretin. A review of the number of therapies required to be trialled, with consideration given to their contraindications and toxicity criteria is required. A review of the rules relating to breaks in therapy and the requirements to retrial previous failed therapies is also required.
- A review of the current rule that three failures results in exclusion for access to PBS subsidised biologics for 5 years requires review. Some patients who are amongst the most severe and were prescribed biologics early in their availability have failed efalizumab (first PBS-listed biologic for psoriasis), which is no longer available, possibly twice, and etanercept (second PBS-listed biologic, initially restricted to 12 weeks on, minimum 12 weeks off), which is generally considered the least efficacious biologic (in the short term) for psoriasis.
- Lack of awareness of treatment options by patients and general practitioners may mean some patients who could benefit from biologics may not be optimally managed. Education, information and better communication is required to ensure the best possible management CPP and any comorbidities.
- Getting access to treatment with biologics is an issue. The approval process is complicated and stressful for patients and clinicians. Getting access to dermatologists experienced in biologics can be a limiting step for patients and this can be expensive and involve significant travel for rural patients. Biologics have changed the lives of many patients with CPP and are an important part of the treatment options available. Ensuring that patients who will benefit most have access is important.

Summary of Stakeholder Responses to Focus Questions

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.

Question 1.1: PBS restrictions and current clinical guidance on treatment and severity of CPP are not aligned. How is this managed in clinical practice?

- The Australasian College of Dermatologists (ACD) treatment goals for psoriasis are aligned with global consensus in recommending that patients with a psoriasis area and severity index (PASI) score of > 10 require systemic treatment for CPP.
- The ACD also includes quality of life indicators (Dermatology Life Quality Index - DLQI) in the assessment of disease severity and the presence of CPP in visible areas of the body including back of hands, major parts of the scalp, genitals, involvement of at least two fingernails and significant itch.
- These inclusions recognise the impact of psoriasis on quality of life and the effect of involvement of specific parts of the body. Visible areas of the body can affect employment prospects, and involvement of genitals and scalp or severe itch can significantly impact quality of life.
- When the PBS first implemented prior therapy restrictions, patients were required to fail two out of the three available therapies. With the introduction of new therapies, this was increased to three out of four, which many clinicians and patients consider to be excessive.
- There is a strong preference for altering the PBS restrictions to require patients to have failed two out of four prior therapies. There may be clinical reasons that don't match the PBS toxicity criteria as to why doctors do not want to prescribe acitretin, methotrexate (MTX) or cyclosporine (CSP).
- Acitretin, MTX or CSP have significant side-effects that can make patients unwell. Despite this, patients must have trialled them for the required timeframe before it can be considered a 'failed prior therapy' or demonstrate contraindications or intolerance of a severity to necessitate permanent withdrawal.
- Patients who have had a break of five years or more from a biologic for CPP must trial and fail the prior therapies again before commencing a biologic. This can be daunting for patients who have previously experienced side-effects to the prior therapies. This includes patients who may have failed three biologics and are ineligible to be considered for a biologic for five years.
- The baseline PASI score in most clinical trials is 10 to 12. Although a useful comparative measure, PASI was designed as a clinical trial outcome measure not as a patient clinical assessment tool.
- Current PBS restrictions require patients to have a PASI score > 15, preferably while still on a treatment, but no longer than 1 month following cessation of the most recent prior treatment. In comparison, most of the patients entering clinical trials have not received systemic treatment in the month prior to their PASI score and have much higher median PASI scores (even though baseline entry criteria is lower). As such, a 75% reduction in PASI score is much harder for the PBS patients to achieve than it is for the trial patients.

- Situations where the PASI score may not correlate with DLQI include very itchy psoriasis but in small amounts, psoriasis on scalp/face/hands/feet, genital involvement and smaller areas but with joint involvement.
- It was recognised that moving from an objective measure like the PASI to a subjective measure such as DLQI is a paradigm shift. However, the PASI is a blunt tool and at the moment some patients who should be considered for biologics are falling through the gaps. There is a need to capture less tangible impacts such as fatigue.

Question 1.2: What obstacles do the patients and clinicians experience in meeting the PBS criteria of failing 3 out of 4 specified prior treatments before commencing a biologic for CPP?

- Patients report getting onto biologics as 'hard work'.
- Side-effects with prior therapies including MTX, acitretin and CSP are distressing and concerning including hair loss, loss of feeling in hands and feet and concerns over risk in pregnancy.
- Cyclosporine is an undesirable therapy due to toxicity, particularly hypertension and effects on renal function. Current international consensus is that CSP should not be used for more than two years cumulatively over a lifetime. In the US, health insurers will only fund a maximum of one year of CSP before patients move to biologics.
- Acitretin is not an option for many females due to fertility risk.
- Phototherapy is not sustainable or practical for all patients because of the need to attend clinics frequently. Access to phototherapy is limited in rural areas.
- Some doctors suggest sunlight if there is no access to phototherapy, and other patients buy sunlamps but don't understand the lifetime limit – there are no guidelines for personal use. This is a challenge with risk and awareness of skin cancer. Sun exposure doesn't meet PBS requirements for phototherapy.

Question 1.3: What are the benefits in using biologics to treat mild to moderate CPP or where PASI scores are < 15?

- Early treatment may help manage immune-related comorbidities such as psoriatic arthritis.
- Clearing psoriasis will impact quality of life and influence mental health and wellbeing, ability to work and productivity.
- There is an outstanding question as to whether early treatment can alter the course of the disease.
- The lower the baseline PASI score (e.g. PASI 10-12), the harder it is to achieve a 75% reduction in PASI score. This creates issues with using a 75% reduction in PASI score as a measure of treatment response in these patients.

Question 1.4: What aspects of the current PBS restrictions can be improved to promote quality use of biologics for CPP?

- Quality of life assessment measures should be included in the assessment of disease severity. Dermatologists are familiar with using the DLQI to assess the patient's quality of life.
- The DLQI accommodates patients who have small areas of CPP that are in difficult areas.
- Patients don't lie on the DLQI test just to stay on a medicine that isn't working.

- Reducing the PASI score to > 10 brings it in line with international consensus.
- If DLQI can't be incorporated into the PBS assessment criteria, the ACD recommendation to include the involvement of visible areas, scalp or genitals, fingernails and significant itch as a surrogate for quality of life measurement should be considered.
- Some patients don't require the recommended dosage/frequency of the biologic to achieve and maintain a PASI 75, which may result in the patient filling their scripts less often. There needs to be a mechanism for flexibility in dosage adjustments to enable dose increases and decreases depending on patient response, without causing patients to 'fail' due to altered prescription rates.
- Streamlining and automating the approval system to a true online system will help reduce paperwork, avoid delays and improve communication.

Question 1.5: Biologics to treat CPP are prescribed by dermatologists rather than general practitioners. What information should be communicated to general practitioners (GPs) when their patients are receiving biologics to treat their CPP?

- Many healthcare professionals have inadequate knowledge of biologics compared to the older drugs. A tool to assist GPs (e.g. with images and questions) to understand when to refer patients would be useful.
- GP management of psoriasis varies. A minority will try a range of treatments before referring, although this is variable. GPs are discouraged from prescribing methotrexate. GPs can prescribe phototherapy, but it is not usually within their clinic.
- GPs need general information about access to biologics as patients often seek specialist advice once they are aware of the biologics, only to be disappointed to discover that they need to trial prior therapies.
- Good communication is needed between a patient's dermatologist, general practitioner and other specialists to make sure they are aware that their patient has commenced a biologic and therefore to recognise infections and adverse effects of biologics. Flags in practice software could be considered.
- Better communication will potentiate better patient outcomes, in particular, recognising co-morbidities in patients with psoriasis and the underlying issues that affect the progression of the disease. Delays in treating psoriatic arthritis can lead to long-term damage as well as inability to work.
- Patients should be encouraged to receive any necessary vaccinations before commencing biologics.
- GPs need to know how to manage patients on biologics in terms of travel and pregnancy.

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.

Question 2.1: What adverse effects have patients experienced when treated with biologics for CPP?

- The Australasian Psoriasis Registry collects clinician reported data on efficacy (PASI scores), quality of life (DLQI), adverse events, pregnancy, family planning, prior therapies, concomitant therapies, comorbidities for approximately 2,000 patients.

- Biologics are generally well tolerated, with adverse events such as infections consistent with those reported in the randomised clinical trials (RCTs).
- Clinicians are getting better at managing (predicting and planning) biologic side effects, in particular for planning around times when a biologic must be stopped such pre and post-surgery and identifying patients with higher risk of infection.
- Cancer diagnoses require patients and clinicians to weigh up the risks and benefits whether to stop or continue biologics.
- Pharmaceutical industry Patient Support Programs capture adverse events and provide education. There is some scepticism from clinicians and consumers, however very few consumers say they do not want to be involved. The intended outcome is to increase compliance.
- Side-effects associated with injections are a concern for some patients, but the prospect of effective treatment outweighs the risk.
- Waning effect may mean the need to increase dose which increases the number of injection, which can impact a patient's quality of life.
- Unanswered questions include: What is the adverse effect profile if using different doses? Is the adverse effect profile different in different age groups (e.g. from young age, older people)?

Question 2.2: Are patients and clinicians concerned about the safety of long term use of biologics?

- There is now over 10 years' experience in using biologics in psoriasis. Registry data indicates no increase in malignancies in age matched cohorts.
- Common patient questions include: How long do we need to be on a biologic? Can you stop a biologic? What happens if you stop? What is the likelihood that restarting therapy will not be effective?
- Patients on biologics are not encouraged to stop to trial no treatment or take a treatment break. This is because there is limited data around re-starting biologics, and a perceived risk that the biologic may not be as effective once re-started due to the 'neutralising antibodies'. Consumers may be willing to take treatment breaks, but this is not encouraged by clinicians.
- Psoriasis and comorbidities can be so severe that many patients are willing to accept any risk for successful treatment.

Question 2.3: What patient related outcomes from the use of biologics for severe CPP are important?

- For most patients, the primary focus is clearing the psoriasis and the outcomes of this include improvement in self-confidence, workforce participation, mental health and wellbeing and social participation.
- The reduction of fatigue is an important outcome, particularly in those who also have psoriatic arthritis.
- Co-morbidities associated with psoriasis such as mental health and inflammatory conditions, cardiovascular and diabetes can impact treatment choice. Co-morbidities that are inflammatory based may improve with biologics.

- Workforce participation and productivity can be significantly impacted by psoriasis, particularly in industries such as hospitality. This also has economic impacts in absenteeism and presenteeism (i.e. present, but not focused on work).
- Choice of clothes patients wear (e.g. shorts, T-shirts, bikinis) and their employment options are influenced by successful management of their CPP.

Question 2.4: Are there quality of life issues for patients with CPP that are not well captured in the randomised clinical trials?

- Most patients report that improved quality of life outweighs the risk of adverse effects with biologics.
- Mental health effects of psoriasis are significant with one patient recounting suicidal feelings before starting biologics.
- Different aspects of quality of life are captured in the DLQI measure and the alternative EQ-5D —a widely used generic (disease non-specific) quality of life instrument. However, the EQ-5D is time consuming and may not appropriate to perform in practice.
- Change in PASI and change in DLQI correlate quite well. A new paper from the ACD is about to be published regarding PASI correlation with EQ-5D.
- Situations where the PASI score may not correlate with DLQI include very itchy psoriasis but in small amounts, psoriasis on scalp, face, hands, feet, genital involvement and smaller areas with joint involvement.
- Life impacts such as 'lost life opportunity', work absenteeism and presenteeism are real issues and should be considered.

Question 2.5: Are there some biologics that seem more effective than others in the treatment of CPP?

- Different biologics have different pros and cons. Clinicians see some efficacy differences between products as well as individual patient variations.
- Clinicians report that the IL-17 class of biologics consistently achieves a PASI 90 response in 60 – 80% of patients, while the TNF inhibitor class consistently achieves a PASI 75 response in 60 – 80% of patients. The difference to patients may not be large and they may be happy with a PASI 75 response. However, when asked, most patients say they want the 'best response'. New drug classes may be more effective.
- The ideal situation is that pharmacogenomics will be used to find the best biologic to treat a patient's psoriasis. However, there is not enough research in this area to be used clinically at this stage.
- Consumers are concerned about waning effectiveness. One patient needed to increase her dose to achieve continued effectiveness after a number of years on therapy.
- There are very limited options for treating psoriasis in children and this is a group with high unmet need. There is not much data in this population. More research is required to understand if treating early influences the course of the disease.
- Etanercept has a particular role due to its long-term safety data, short half-life and use in paediatric populations.

ToR 3

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

Question 3.1: The incident and prevalent use of biologics for CPP continues to grow in Australia, despite being available on the PBS since 2006. What are the possible explanations for this?

- The retention rate of biologics is higher than predicted in studies. The real-life treatment goal is to maintain treatment effect and clinicians try to optimise patient outcomes.
- It was generally felt that biologics are not being over-utilised. Instead, there is likely to be a pool of people who have disease severe enough to treat, but who have not accessed biologics yet for a variety of reasons including awareness, access to specialists 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 is likely to influence continuation rates.
- Time to diagnosis could influence uptake rates, utilisation and outcomes. Patients who are difficult to diagnosis may end up with a late diagnosis and a treatment course dependant on comorbidities. Those with early diagnosis may have a higher number of treatments over their disease course and improved management of comorbidities.
- When biologics were first made available there was low uptake with prescribers initially hesitant to use them.
- It takes a long time for patients to become eligible for biologics. They need to have a good relationship with their dermatologist, and it is hard both physically and emotionally. Stigma contributes to difficulties engaging with health care professionals - it is a challenge to open up.
- GPs are not well equipped to treat severe psoriasis, only prescribing topical therapy until referring to a dermatologist when required. Access to dermatologists is a limiting step for many patients. In Canberra and Adelaide, it can take 3 to 4 months to see a dermatologist and in rural Victoria patients may need to travel up to 6 hours to the nearest dermatology clinic. There are 14 dermatologists in Tasmania and only one or two prescribe biologics. Private dermatologists are expensive and hard to access.
- Not all dermatologists prescribe biologics. Some dermatologists then refer to other dermatologists who will prescribe biologics, increasing the costs and time for patients. A list of specialists who can prescribe biologics (available through the College?) would be useful.
- Changing specialist demographics may improve this situation over time with younger dermatologists more aware of biologics through their training.
- It is possible that some patients who have 'failed' therapy may not be true failures e.g. patients whose dosage has been reduced due to a successful response. This may require further analysis of the data.
- Uptake may be slowed by issues including access to dermatologists who are willing to prescribe biologics; GPs not asking the questions required to prescribe; paperwork difficulties in small clinics; fear; process too long.

- Patients are interested- when a new drug becomes available in Europe, enquiries about its availability in Australia start within 24 hours.
- Social media could help patients engage with health care professionals and help navigate the system, spreading the word on dermatologists to recommend, positive experiences
- Outstanding questions include: Has the number of prescribers changed over time? What is the distribution of these prescribers across Australia?

Question 3.2: Patients are only able to receive PBS-listed biologics to treat severe CPP if they have a PASI score of greater than 15. How many more patients might access treatment with biologics for CPP if this was lowered to a PASI of 10?

- Suggestions for additional data / information include:
    - epidemiological data around who has early disease
    - hidden suffering- concern around mental health of younger patients, increased risk of depression, cardiovascular disease
    - early treatment may decrease comorbidities
    - early treatment may change course of the disease.