

**6.02 APREMILAST,
Pack containing 4 tablets 10 mg, 4 tablets 20 mg and
19 tablets 30 mg,
Tablet 30 mg,
Otezla[®],
AMGEN AUSTRALIA PTY LIMITED**

1 Purpose of Submission

1.1 The Category 3 submission requested the following changes to the treatment criteria of apremilast (Otezla[®]) for the treatment of severe chronic plaque psoriasis (CPP) in patients who have failed treatment with, or who are contraindicated or intolerant, to methotrexate:

- To allow rheumatologists, general physicians and general practitioners (GPs) experienced in the treatment of psoriasis to initiate treatment.
- To allow medical practitioners or dermatology registrars who have consulted a dermatologist, rheumatologist, general physician or GP experienced in the treatment of psoriasis to initiate treatment.

1.2 The submission's requests were based on the following rationale:

- a. Workforce shortage and rural and remote challenges faced by patients with psoriasis
- b. Socioeconomic status in access to specialty care
- c. Rheumatologists, general physicians and GPs experienced in the treatment of psoriasis would be appropriate medical practitioners to initiate treatment with apremilast due to several reasons (see Section 4)
- d. Reasonable safety profile and clinical evidence

2 Background

Registration status

2.1 Apremilast was TGA registered on 19 March 2015 for the following indications:

- The treatment of signs and symptoms of active psoriatic arthritis in adult patients.
- The treatment of adult patients with moderate to severe plaque psoriasis who are candidates for phototherapy or systemic therapy.

Previous PBAC consideration

- 2.2 At the July 2020 PBAC meeting, apremilast was recommended for severe CPP in patients who have failed treatment with, or who are contraindicated or intolerant to, methotrexate. Apremilast was PBS-listed on 1 January 2021.
- 2.3 At its March 2022 meeting, the PBAC recommended the following amendments to the treatment criteria for apremilast, which were implemented on 1 September 2022.
- dermatology registrars, in consultation with a dermatologist, to initiate or continue treatment, and
 - GPs to prescribe maintenance treatment in consultation with a dermatologist or dermatology registrar.

3 Requested listing

- 3.1 The submission requested the following changes to the existing treatment criteria for apremilast.
- 3.2 PBS item 12218C (titration pack) and PBS item 12223H (maintenance pack)

	Treatment criteria:
New	Must be treated by a medical practitioner who is either: (i) a dermatologist, (ii) a rheumatologist, (iii) a general physician, (iv) a general practitioner experienced in the treatment of psoriasis; OR Must be treated by a medical practitioner or dermatology registrar who has consulted one of the above practitioner types.

- 3.3 The full restriction is shown below with proposed additions in *italics* and deletions in strikethrough.

MEDICINAL PRODUCT medicinal product pack	PBS item code	Max. qty packs	Max. qty units	№.of Rpts	Available brands
APREMILAST					
apremilast 10 mg tablet [4] (&) apremilast 20 mg tablet [4] (&) apremilast 30 mg tablet [19], 27	12218C	1	27	0	Otezla Titration Pack
apremilast 30 mg tablet, 56	12223H	1	56	5	Otezla

Restriction Summary / Authority Required: Streamlined	
	Category / Program: GENERAL – General Schedule (Code GE)
	Prescriber type: Medical Practitioners
	Restriction type: Authority Required – Streamlined
	Administrative Advice: <i>No increase in the maximum quantity or number of units may be authorised.</i>
	Administrative Advice: <i>No increase in the maximum number of repeats may be authorised.</i>
	Administrative Advice: <i>Special pricing arrangements apply.</i>
	Indication: Severe chronic plaque psoriasis
	Clinical criteria:
	Patient must have failed to achieve an adequate response after at least 6 weeks of treatment with methotrexate prior to initiating treatment with this drug; or
	Patient must have a contraindication to methotrexate according to the Therapeutic Goods Administration (TGA) approved Product Information; or

	Patient must have demonstrated severe intolerance of, or toxicity due to, methotrexate
	AND
	Clinical criteria:
	The condition must have caused significant interference with quality of life
	AND
	Clinical criteria:
	The treatment must not be used in combination with a PBS-subsidised biological medicine for severe chronic plaque psoriasis. Patient must not be undergoing concurrent PBS-subsidised treatment for psoriasis with each of: (i) a biological medicine, (ii) ciclosporin
	Treatment criteria:
	Must be treated by a medical practitioner who is either a: (i) a dermatologist, (ii) an accredited dermatology registrar in consultation with a dermatologist, (ii) rheumatologist, (iii) general physician, (iv) general practitioner experienced in the treatment of psoriasis; OR
	Must be treated by a general practitioner who has been directed to continue treatment (not initiated treatment) by one of the above practitioner types medical practitioner or dermatology registrar who has consulted one of the above practitioner types.
	Population criteria:
	Patient must be aged 18 years or older

3.4 The submission proposed not to have a definition for “*general practitioner experienced in the treatment of psoriasis*”, consistent with the treatment criteria presented in the ‘General Statement for Drugs for the Treatment of Hepatitis C’ (below). However, the submission noted that, should there be any changes to the treatment criteria to include GPs, the sponsor will work with the clinical community and professional organisations to ensure changes can be safely and effectively implemented (see Section 6).

	Treatment criteria:
	Must be treated by a medical practitioner or an authorised nurse practitioner experienced in the treatment of chronic hepatitis C infection; or in consultation with a gastroenterologist, hepatologist or infectious diseases physician experienced in the treatment of chronic hepatitis C infection.

Source: General Statement for Drugs for the Treatment of Hepatitis C ([PBS Website](#)).

3.5 The Secretariat noted that the proposed treatment criterion allows all medical practitioners to prescribe in consultation with the listed practitioner types.

3.6 The current restriction for initial treatment of biologic medicines in the treatment of severe CPP requires a patient to demonstrate a failure to achieve an adequate response to at least 2 prior treatments, including with apremilast. This is demonstrated using a Psoriasis Area and Severity Index (PASI) assessment performed whilst on treatment or no more than 4 weeks after completion of course. Currently, only dermatologists are able to prescribe biologics for this indication. The PBAC noted that other prescribers may not be aware that, if a patient does not achieve an adequate response on apremilast, a PASI assessment needs to occur for the patient to continue onto biologic treatment. The pre-PBAC response was supportive of including the following new Prescribing Instruction regarding the PASI assessment.

Insert New PI	Prescribing Instruction: <i>For patients who do not demonstrate an adequate response to apremilast, a Psoriasis Area and Severity Index (PASI) assessment must be completed, preferably while on treatment, but no longer than 4 weeks following the cessation of treatment. This assessment will be required for patients who transition to 'biological medicines' for the treatment of 'severe chronic plaque psoriasis'.</i> <i>This assessment must be documented in the patient's medical records.</i>
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- 3.7 The submission claimed that apremilast is more suitable for broader prescribing than ciclosporin and deucravacitinib due to the safety concerns of these drugs and the need for careful patient monitoring (see paragraph 4.11 and Table 2). The pre-PBAC response noted that, in its March 2022 recommendation for apremilast, the PBAC did not recommend that GP continuation of apremilast be flowed onto ciclosporin (paragraph 5.5, apremilast Public Summary Document [PSD], March 2022 PBAC Meeting). The pre-PBAC also noted that, in its March 2023 recommendation for deucravacitinib, the PBAC considered that the claim of non-inferior comparative safety of deucravacitinib to apremilast was reasonable, however noted there was a lack of long-term safety data for deucravacitinib (deucravacitinib PSD, March 2023 PBAC Meeting). The pre-PBAC response therefore was not supportive of flowing on the GP initiation of apremilast to ciclosporin and deucravacitinib.

4 Consideration of the evidence

Sponsor hearing

- 4.1 There was no hearing for this item.

Consumer comments

- 4.2 The PBAC noted and welcomed the input from health care professionals (10) and organisations (2) via the Consumer Comments facility on the PBS website. The comments from health care professionals described a range of benefits of treatment with apremilast for CPP, including its effectiveness in individuals where other treatments have failed or are contraindicated, reduction in the need for prescribing biological disease modifying anti-rheumatic drugs (bDMARDs), and utility in treating both psoriatic arthritis and CPP. The comments were in overall agreement that apremilast is a relatively safe medicine, but highlighted that prescribers should be aware of the side effects of apremilast. Comments also highlighted that the shortage of specialists and high cost of seeing a specialist creates an access barrier for patients, especially in rural and remote areas. Other comments were generally in support of GPs initiating apremilast treatment, but one comment raised the risk of apremilast being prescribed by GPs who are not experienced in the treatment of psoriasis.
- 4.3 The PBAC noted the comments received from Creaky Joints Australia - Global Healthy Living Foundation Australia (CJA-GHLFA) which was supportive of adding rheumatologists and general physicians as additional prescribers, noting that patients with both psoriatic arthritis and CPP could be managed by one specialist only, therefore reducing costs and improving access to treatment. CJA-GHLFA was generally

supportive of GPs initiating apremilast for patients with CPP but raised concerns over the lack of specificity in the proposed restriction change for ‘GPs who are experienced in the treatment of psoriasis’ may increase the risk of inappropriate prescribing and there would be lack the awareness of apremilast’s side effects and contraindications.

- 4.4 The PBAC noted the advice received from The Australasian College of Dermatologists (ACD), which was not supportive of the proposed changes. The ACD commented that accurate diagnosis and assessment of the severity of the disease is a critical element in psoriasis treatment selection. The ACD considered that initial prescribing of apremilast should remain with dermatologists, and this will minimise treatment of patients with apremilast outside the restriction for severe CPP.

Rationale for request

Workforce shortages and rural and remote challenges faced by patients with psoriasis.

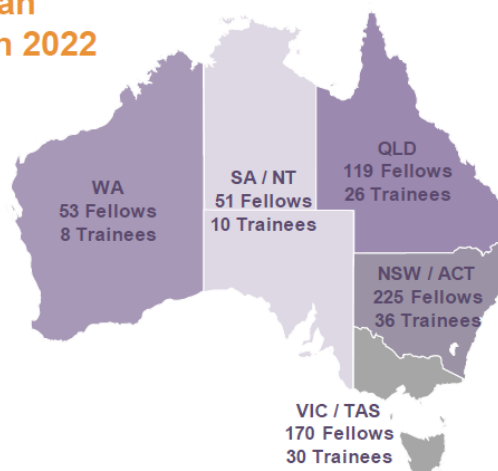
- 4.5 The submission stated that there are only 600 dermatologists to meet the needs of nearly 26 million Australians, which equates to approximately 1 dermatologist for every 43,000 Australians (see Figure 1). The submission claimed that the shortage of dermatologists creates an access barrier to timely, safe and geographically convenient care, resulting in long wait times, especially in rural and remote areas. The submission noted that the average wait time for a dermatology appointment in a Victoria public hospital is over 1.5 years¹. The submission stated that the access barrier impacts the quality of patient care which forces some patients to resort to online consultations with unknown dermatologists. The submission also stated that GPs are forced to prolong high-potency topical steroid treatments until patients are seen by a dermatologist. Consequently, the quality of life of patients with chronic skin, hair and nail conditions is further exacerbated.

¹ University of Melbourne. PODCAST INNOVATION IN MEDICAL EDUCATION By Dr Anneliese Willems and Associate Professor Alvin Chong, University of Melbourne, Skin Health Institute and St Vincent’s Hospital. Access ed 15/06/2023; available: <https://pursuit.unimelb.edu.au/articles/podcast-innovation-in-medical-education>

Figure 1: A breakdown by state of the current Australian dermatologist workforce in 2022².

A snapshot of the Australian dermatologist workforce in 2022

There are only just over 600 dermatologists* to meet the skin health needs of nearly 26 million Australians.



- 4.6 The submission stated that patients with psoriasis living in rural and remote areas of Australia have difficulty accessing dermatologists due to 1) shortage of dermatologists with 6% practising outside of metropolitan centres¹ and 2) having to travel long distances to access specialty care, resulting in additional costs and time away from work or family responsibilities. The submission further added that patients in rural and remote areas often have delayed diagnosis and sub-optimal treatment because of the limited access to the latest treatments, clinical trials and support groups.
- 4.7 To further support this claim, the submission presented a survey from eight advisory board members (four GPs and four dermatologists). The survey focused on what proportions of patients with psoriasis are undertreated in urban, regional, rural and remote areas. Respondents were given seven options to select – from “no patients affected” to a maximum of “40% of more” (see raw data in Table 1 below). The submission noted the responses below highlighted the challenges faced by patients living outside urban centres of Australia where often there is no dermatologist available at all.

² Source: The Australian College of Dermatologists (ACD) White Paper, November 2022

Table 1: Estimated proportion of “undertreated” patients with psoriasis in urban, regional, and rural and remote areas of Australia

Prescriber type	Urban	Regional	Rural/remote
GP	10 to <20%	20 to <30%	30 to <40%
Dermatologist	< 10%	'40% or more	'40% or more
GP	< 10%	30 to <40%	'40% or more
GP	20 to <30%	30 to <40%	'40% or more
Dermatologist	20 to <30%	'40% or more	'40% or more
Dermatologist	20 to <30%	30 to <40%	30 to <40%
Dermatologist	'40% or more	'40% or more	'40% or more
GP	20 to <30%	'40% or more	I do not know

Note: “undertreated” was defined as either being unable to access appropriate dermatology care or treatment

Socioeconomic status in access to specialty care

- 4.8 The submission stated that the addition of new types of medical practitioners to the treatment criteria for apremilast will help to reduce geographic and socioeconomic inequities in access to specialty care for patients from low socioeconomic backgrounds. The submission stated that studies have shown patients from low socioeconomic backgrounds may experience more severe disease due to reduced access to healthcare services, treatments and poor health literacy^{3,4}. These patients have limited access to speciality care such as dermatologists and they rely solely on primary care providers or the public healthcare system which consequently increases their risk of comorbidities associated with psoriasis (i.e. cardiovascular disease, diabetes, depression).
- 4.9 The submission noted that the proposed addition of new types of medical practitioners to the treatment criteria has the potential to improve patient access to appropriate treatment, especially for rural and remote patients.

Rationale for the additional medical practitioners to the apremilast restriction

Rheumatologists

- 4.10 The submission noted that the consumer comments received in support of the March 2023 apremilast for severe active psoriatic arthritis (PsA) submission highlighted that while apremilast has utility in treating both PsA and psoriasis, prescribing of apremilast is limited to dermatologists. The management and treatment of psoriatic diseases (PsA and psoriasis) often require specialist care by both dermatologists and rheumatologists. The submission claimed that the referral pathways between these specialties are not well established, and if a rheumatologist has a patient with predominant skin involvement (i.e. psoriasis) and low joint count,

³ Australian Institute of Health and Welfare (2022) Health across socioeconomic groups, AIHW, Australian Government, accessed 11 May 2023.

⁴ Detels, Roger and others (eds), 'Socioeconomic inequalities in health in high-income countries: The facts and the options', in Roger Detels and others (eds), Oxford Textbook of Global Public Health, 7 edn, Oxford Textbooks in Public Health (Oxford, 2021; online edn, Oxford Academic, 1 Nov. 2021), <https://doi.org/10.1093/med/9780198816805.003.0009>, accessed 11 May 2023.

the patient has to be referred to a dermatologist and wait to access PBS subsidised apremilast. The sponsor has also been made aware of instances where rheumatologists have had to refer patients first back to the GP who then has to organise a subsequent referral to a dermatologist.

- 4.11 The submission claimed that five randomised controlled trials demonstrated apremilast's broad and sustained efficacy across most of the core PsA domains⁵, one of which is psoriasis. The submission stated it is no surprise that, in some states of Australia where the dermatology workforce is particularly low, rheumatologists are already routinely managing patients with psoriasis⁶. The PBAC noted that the proposed inclusion of rheumatologist as one of the eligible medical practitioner types may result in leakage to the cohort of patients with PsA.

General physicians

- 4.12 The submission noted that general physicians are well suited to managing patients with psoriasis as they are a distinct speciality with a breadth and depth of knowledge across a variety of diseases. The submission also noted that, as general physicians are available in most public hospitals, the inclusion of general physicians as one of the medical practitioner types to initiate apremilast could improve timely access for patients with psoriasis in rural and remote areas and those who are unable to access private dermatology care due to financial constraints.

General practitioners (GPs)

- 4.13 The submission proposed that GPs experienced in the management of psoriasis can initiate apremilast, while all other GPs will have the same prescribing rights as dermatology registrars (i.e. GPs to initiate treatment in consultation with an experienced prescriber such as dermatologist, rheumatologist, general physician, or GP experienced in the management of psoriasis). The submission highlighted that GPs are usually the first point of contact for patients seeking medical treatment and tend to be heavily relied on by people living in rural and remote areas and with low socioeconomic backgrounds due to geographical and financial constraints. The submission stated that including GPs as one of the eligible prescribers to initiate apremilast would provide patients with psoriasis access to treatment in a timely manner.
- 4.14 The submission further noted that Amgen recently held an advisory board of 4 GPs and 4 dermatologists to discuss implications and identify gaps that need to be addressed should the treatment criteria of apremilast be expanded to include GPs. A central theme of the advisory board was the importance of standardised education for GPs. The majority of the advisors considered that apremilast and methotrexate

⁵ Coates, L.C., Soriano, E.R., Corp, N. et al. Group for Research and Assessment of Psoriasis and Psoriatic Arthritis (GRAPPA): updated treatment recommendations for psoriatic arthritis 2021. *Nat Rev Rheumatol* 18, 465–479 (2022). <https://doi.org/10.1038/s41584-022-00798-0>

⁶ Khosrotehrani K, Murrell D, Veysey E, Tong P, Bennett H, Mar V, Soyer HP. Training and Retaining Physician–Scientists in Dermatology: Australia. *JID Innov.* 2021 Nov 24;2(1):100074. doi: 10.1016/j.xjidi.2021.100074. PMID: 35005683; PMCID: PMC8719011.

were suitable for GP prescribing, but had reservations about GP prescribing for other oral systemic therapies (e.g. cyclosporin and acitretin) mainly related to safety.

- 4.15 At its September 2023 meeting, DUSC considered a utilisation review of apremilast for severe chronic plaque psoriasis (Item 10.03 Apremilast DUSC analysis, November 2023 PBAC meeting). The review identified that the majority of patients who initiated treatment with apremilast since PBS listing were with dermatologists (refer to Figures 11 and 12 of the Item 10.03 DUSC report). In September 2022, there was an extension of listing to allow accredited dermatology registrars to initiate treatment in consultation with a dermatologist and to allow general practitioners to prescribe maintenance treatment in consultation with a dermatologist or accredited dermatology registrar. Following the listing change in September 2022, of patients who initiated treatment with apremilast, there was a slight decrease in patients who initiated treatment with dermatologists and an increase in patients who initiated treatment with GPs, despite GPs restricted to prescribing maintenance treatment. The DUSC Secretariat conducted a further analysis of prescriber type by remote area pre- and post- the September 2022 listing changes presented in Figures 2 and 3 below. This analysis appears to indicate that prescribing by GPs in remote Australia is increasing after the listing changes.

Figure 2: Prescriber type by remote area pre- September 2022 listing changes

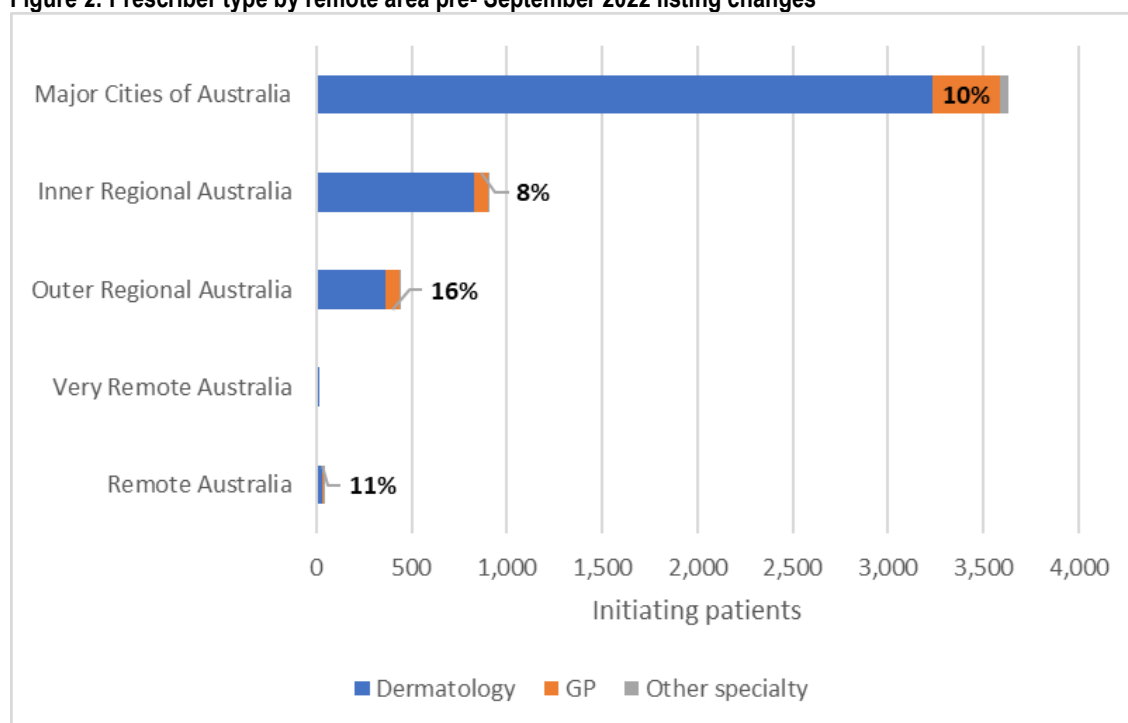
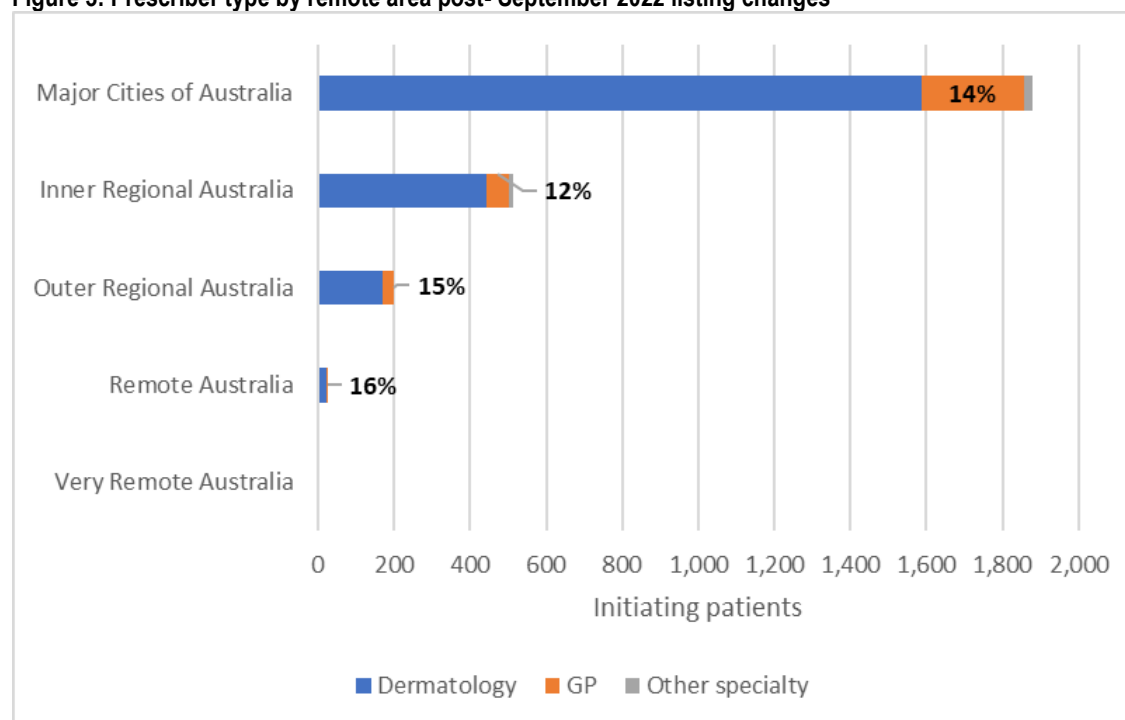


Figure 3: Prescriber type by remote area post- September 2022 listing changes



Clinical and other evidence regarding side-effect profiles, safety and comparative safety

- 4.16 The submission presented a table comparing the current oral treatments for CPP, their current PBS restrictions, and the safety or monitoring considerations for medical practitioners to consider when a patient is undergoing treatment (see Table 2). The submission proposed that, as GPs are eligible to prescribe methotrexate, which has complex safety and monitoring requirements, apremilast should also be considered appropriate for GP prescribing. The submission also proposed that apremilast is safer and requires less monitoring than acitretin (second-line option) and ciclosporin (comparator). The pre-PBAC response provided an updated table which included deucravacitinib, that was PBS listed on 1 October 2023 with the same restriction as apremilast. The pre-PBAC response noted that deucravacitinib is a newer treatment compared to apremilast and thus lacks longer-term safety data.
- 4.17 The submission noted that the TGA no longer requires the sponsor to provide Periodic Safety Update Reports (PSURs) for apremilast. The latest PSUR submitted in March 2023 found no new significant change in the risk profile of apremilast and the submission therefore concluded that the benefit-risk profile of apremilast remains favourable for the approved indications. To further support this claim, the submission

noted that a recent 5-year prospective real-world study did not identify any new safety signals for apremilast⁷.

- 4.18 As the effects of long-term exposure to apremilast across its approved indications have not been formally published, the submission presented a study which pooled results from 15 clinical studies with open-label extension phases⁸. The study confirmed that serious treatment-emergent adverse events (TEAEs) were low throughout use, with mild to moderate TEAEs at least 91.6% of those reported, and no new TEAEs were identified. Mean treatment duration was 84.7 weeks.
- 4.19 As a Category 3 submission, no evaluation of the clinical evidence was undertaken.

⁷ Persson R, Cordey M, Paris M, Jick S. Safety of Apremilast in Patients with Psoriasis and Psoriatic Arthritis: Findings from the UK Clinical Practice Research Datalink. *Drug Saf.* 2022 Nov;45(11):1403-1411. doi: 10.1007/s40264-022-01235-7. Epub 2022 Sep 23. PMID: 36151359; PMCID: PMC9510500.

⁸ Mease, P.J., Hatemi, G., Paris, M. et al. Apremilast Long-Term Safety Up to 5 Years from 15 Pooled Randomized, Placebo-Controlled Studies of Psoriasis, Psoriatic Arthritis, and Behçet's Syndrome. *Am J Clin Dermatol* (2023). <https://doi.org/10.1007/s40257-023-00783-7>

Table 2: PBS-Listed Oral Medications Used in CPP

Medicine	PBS restrictions on prescribing	Safety and monitoring considerations
Apremilast	<p>Authority Required (STREAMLINED) PBS treatment criteria limit prescribing to: (i) a dermatologist, (ii) an accredited dermatology registrar in consultation with a dermatologist; OR a general practitioner who has been directed to continue treatment (not initiate treatment) by one of the above practitioner types.</p>	<ul style="list-style-type: none"> • Apremilast is generally well tolerated, but increased incidences of diarrhoea and upper respiratory tract infections have been reported. • Apremilast is contraindicated during pregnancy and in nursing women; no human data are available • Precautions include worsening of depression; gastrointestinal disturbance; weight loss • Dose adjustment is necessary in those with severe renal insufficiency • Pregnancy category B3² • <i>Note:</i> The treatment criteria for apremilast were initially implemented to match the clinical comparator (ciclosporin) in the original PBAC submission; however unlike ciclosporin, there is no cautionary note recommending careful monitoring in the apremilast PBS listing
Methotrexate	<p>No restriction on prescriber type; however, the following restriction categories apply:</p> <ul style="list-style-type: none"> • Unrestricted benefit for tablets (eg 10 mg (15) and 2.5 mg (30)) • Restricted Benefit for 10 mg tablets (quantity 50) for patients requiring doses >20 mg per week <p>Authority Required (STREAMLINED) for injectable forms (eg 10 mg/0.2 mL injection) for patients unsuitable for administration of an oral form of methotrexate for severe PsO</p>	<ul style="list-style-type: none"> • Methotrexate is teratogenic—it is contraindicated in females during pregnancy, and in both males and females in the 6 months before conception. • Pregnancy category D • Hepatotoxicity (cirrhosis) can occur with long-term use • Contraindicated in case of renal insufficiency • Other side effects of concern include pneumonitis or pulmonary fibrosis; and bone marrow suppression • Methotrexate has clinically significant interactions with many other drugs, which can reduce its efficacy or increase its toxicity • The duration of methotrexate therapy should be limited because toxicity is cumulative; when the skin is clear, the dose should be gradually reduced over a few months • Regular monitoring is recommended in addition to folic acid supplementation to reduce adverse effects on haematopoiesis and the GIT
Ciclosporin	<p>Authority Required (STREAMLINED)</p> <ul style="list-style-type: none"> • PBS treatment criteria limit prescribing to: (i) a dermatologist, (ii) an accredited dermatology registrar in consultation with a dermatologist <p><i>Caution: Careful monitoring of patients is mandatory.</i></p>	<ul style="list-style-type: none"> • Treatment is limited to not more than 1 year because of the risk of irreversible nephrotoxicity • Other adverse effects include hypertension, deterioration of kidney function, hirsutism, gingival hyperplasia, lymphoma and skin cancer risks, gastrointestinal disturbances, liver dysfunction, dyslipidaemia, central nervous system effects. • Ciclosporin has several clinically significant interactions with many other drugs. • Ciclosporin is not recommended for continuous use because of long-term adverse effects; its suggested role is for short-term treatment of patients with severe plaque psoriasis or who are in crisis, and as a bridge therapy to long-term therapies such as biologics or other oral medications due to fast onset of action • Pregnancy category C

Public Summary Document – November 2023 PBAC Meeting

Medicine	PBS restrictions on prescribing	Safety and monitoring considerations
Deucravacitinib	As per the current apremilast treatment criteria	<ul style="list-style-type: none"> • It is not known whether TYK2 inhibition may be associated with the observed or potential adverse reactions of Janus Kinase (JAK) inhibition (eg sudden cardiovascular death, major adverse cardiovascular events, overall thrombosis, deep venous thrombosis, pulmonary embolism, and malignancies (excluding non-melanoma skin cancer)) • Serious infections have been reported in clinical trials; use with caution in patients with chronic infection or history of recurrent infection • Herpes virus reactivation was reported in clinical trials; the impact of deucravacitinib on chronic viral hepatitis is unknown • Prior to initiating treatment with deucravacitinib, patients should be evaluated for tuberculosis (TB) infection. Do not administer deucravacitinib to patients with active TB. • Anti-TB treatment should be considered prior to initiating deucravacitinib in patients with active TB or a past history of latent TB in whom an adequate course of treatment cannot be confirmed. Patients receiving deucravacitinib should be monitored for signs and symptoms of active TB. • Malignancies, including lymphomas, were observed in clinical trials with deucravacitinib • Non-melanoma skin cancer have been reported in patients treated with deucravacitinib. Periodic skin examination is recommended for patients who are at increased risk for skin cancer. • Prior to initiating therapy with deucravacitinib, consider completion of all age-appropriate immunisations according to current immunisation guidelines. Avoid use of live vaccines in patients being treated with deucravacitinib. The response to live or non-live vaccines has not been evaluated. • Not recommended in patients with severe hepatic impairment (Child-Pugh Class C) • The effect of deucravacitinib on human fertility has not been evaluated. Animal studies do not indicate direct or indirect harmful effects with respect to fertility (category B1) • Monitoring recommendations: <ul style="list-style-type: none"> ○ Monitor for signs of infection before initiating and during treatment ○ Pre-treatment screening for hepatitis B and C, HIV +/- tuberculosis ○ Baseline kidney function ○ Lipids ○ Liver function tests (LFTs) ○ Creatine kinase (CK) may require monitoring if myopathy is suspected. • Sotyktu (deucravacitinib) is subject to the Black Triangle Scheme, as it is a new prescription medicine and some side effects or adverse events associated with it may not be known due to limited use in the general population.
Acitretin	No restriction on prescriber type; however, the listing is Authority Required	<ul style="list-style-type: none"> • Oral acitretin is a potent teratogen; at the time of writing, Australian State and Territory law restricts prescribing of acitretin to specialist physicians and dermatologist

Public Summary Document – November 2023 PBAC Meeting

Medicine	PBS restrictions on prescribing	Safety and monitoring considerations
	<p>(STREAMLINED) for severe intractable psoriasis with the following notes to the listing:</p> <ul style="list-style-type: none"> • <i>Care must be taken to comply with the provisions of State/Territory law when prescribing this drug.</i> • <i>Caution: This drug is a potent teratogen - pregnancy should be avoided during therapy and for at least three years after cessation of therapy.</i> 	<ul style="list-style-type: none"> • Pregnancy category X • Systemic retinoids can have many adverse effects, including cheilitis; dry nose, eyes and face; peeling of palms and soles; softened nails; hair loss; joint and muscle pain; headache; dyslipidaemia; photosensitivity; hepatotoxicity.

Source: Table 4, p.17 of Submission Main Body and Table 1, p.2 of the pre-PBAC Response. Details were taken from Product Information for each medicine, Therapeutic Guidelines. Psoriasis. Melbourne: Therapeutic Guidelines Limited; <https://www.tg.org.au>; and Australian Medicines Handbook 2020 (online). Adelaide: Australian Medicines Handbook Pty Ltd; 2022 July. Available from: [https://amhonline.amh.net.au/Australian Medicines Handbook. 2022](https://amhonline.amh.net.au/Australian_Medicines_Handbook_2022).

Estimated PBS usage and financial implications

4.20 The submission considered that the change to treatment criteria to include additional eligible prescribers would increase the utilisation of apremilast. A summary of the assumptions with its revision is presented in Table 3 below.

Table 3: Summary of the agreed assumptions with its revisions

Parameter	July 2020 PBAC recommendation	November 2023 PBAC submission	Source
Australian adult population (years in model)	2020-2025	2020-2025 2024-2029*	ABS
Psoriasis prevalence	3.3%	3.3%	2015 National Health Survey First results – proportion of persons aged 18 and over
Proportion of patients meeting disease severity requirement	20%	20%	(Menter, 2008) - Guidelines of care for the management of psoriasis and psoriatic arthritis, J Am Acad Dermatol, 5:826-50
Proportion of patients treated by the specified prescribers	20% (dermatologist or experienced general physician)	25% (dermatologist, rheumatologist, general physician or GP experienced in the treatment of psoriasis)	Dermatologist survey (Sponsor driven)
Proportion of patients intolerant/contraindicated to methotrexate	61%	61%	Dermatologist survey (Sponsor driven)
Apremilast uptake	Yr 1: █ % Yr 2: █ % Yr 3: █ % Yr 4: █ % Yr 5: █ % Yr 6: █ %	Year 2021 - 2026 Yr 1: █ % Yr 2: █ % Yr 3: █ % Yr 4: █ % Yr 5: █ % Yr 6: █ % Year 2024 - 2029 Yr 1: █ % Yr 2: █ % Yr 3-6: █ %	Dermatologist survey (Sponsor driven)

Shaded cells show values that are changed compared to the previously accepted estimates

Source: Apremilast PSD, July 2020 PBAC meeting, Submission Appendix 3,4 and 5..

* On request from the Department, estimates for Year 2024 to 2029 were provided

4.21 The submission estimated the proportion of patients being treated by the prescribers proposed in this submission (dermatologists, rheumatologists, general physicians or GPs experienced in the treatment of psoriasis) to be 25% from Year 2024 onwards. This is an increase from 20% proposed in the July 2020 submission, when the eligible medical practitioners were dermatologists and experienced general physicians. The submission stated that it is expected that dermatologists will still do the majority of apremilast prescribing, as the additional prescribers will only prescribe in select circumstances outlined previously (e.g. rural and remote patients). It was assumed

that the additional prescribers will account for a maximum of 20% of total apremilast prescribing, therefore an additional 5% was added to the July 2020 assumption.

- 4.22 Table 4 shows the proposed July 2020 uptake rates, actual uptake rates in Year 2021 and 2022 and revised uptake rate for 2023-2026 based on the first two years of apremilast listing. Table 4 does not include the additional medical practitioner types proposed in this submission.

Table 4: Uptake 2021-2022 (actual) and 2023-2026 (estimated, applying 2021-2022 trends)

Year	2021	2022	2023	2024	2025	2026
Estimated uptake (July 2020)	%	%	%	%	%	%
Actual uptake	%	%	NA	NA	NA	NA
Revised uptake	NA	NA	%	%	%	%

Source: Table 5, p15 Submission main body.

- 4.23 Table 5 shows the revised net cost to the PBS/RPBS from 2024-2029, using the revised uptake rates (Table 4) and incorporating the additional medical practitioner types proposed in this submission.

Table 5: Estimated use and financial implications (based on effective prices)*

Year	2024	2025	2026	2027	2028	2029
Estimates using uptake proposed in July 2020 submission						
Estimated uptake rates (July 2020 submission)	█%	█%	█%	█%	█%	█%
Proportion of patients treated by the specified prescribers (July 2020 submission)	20%	20%	20%	20%	20%	20%
Number of patients treated ^a	█ ¹	█ ¹	█ ¹	█ ¹	█ ¹	█ ¹
Estimated scripts ^a	█ ²	█ ²	█ ³	█ ³	█ ³	█ ⁹
Cost to PBS / RPBS – less co-payment ^a	\$█ ⁴	\$█ ⁴	\$█ ⁴	\$█ ⁴	\$█ ⁴	\$█ ⁴
Estimates using revised uptake rates – November 2023 submission						
Revised uptake rates	█%	█%	█%	█%	█%	█%
Number of patients treated (revised uptake) ^b (A)	█ ¹³	█ ¹	█ ¹	█ ¹	█ ¹	█ ¹
Estimated scripts (revised uptake applied) ^b (B)	█ ⁷	█ ²	█ ³	█ ³	█ ³	█ ⁹
Cost PBS / RPBS – less co-payment (revised uptake) ^b (C)	\$█ ⁵	\$█ ⁴	\$█ ⁴	\$█ ⁴	\$█ ⁴	\$█ ⁴
Estimates using revised uptake rate and proportion treated by specified prescribers – November 2023 submission						
Revised proportion of patients treated by the specified prescribers (D)	25%	25%	25%	25%	25%	25%
Number of patients treated [A + (A x D)]	█ ¹	█ ¹	█ ¹	█ ¹	█ ¹	█ ¹
Estimated scripts [B + (B x D)]	█ ³	█ ³	█ ¹⁰	█ ¹⁰	█ ¹⁰	█ ¹⁰
Cost to PBS / RPBS – less co-payment [C + (C x D)]	\$█ ⁵	\$█ ⁴	\$█ ⁶	\$█ ⁶	\$█ ⁶	\$█ ⁶
Net cost to PBS/RPBS – less co-payment	█ ¹¹	\$█ ¹²	\$█ ¹²	\$█ ¹²	\$█ ¹²	\$█ ¹²

Source: Appendix 7 PBS Apremilast vD 20201203 - SPONSOR with new prescribers from 2024.xlsx Financial estimates workbook, requested during evaluation.

^a Appendix 7 PBS Apremilast vD 20201203 - SPONSOR with new prescribers from 2024.xlsx with uptake and prescriber rates applied as per July 2020

^b Appendix 7 PBS Apremilast vD 20201203 - SPONSOR with new prescribers from 2024.xlsx with uptake changed to the new rates and prescriber rates applied as per July 2020

*Note, all co-payments are the new co-payments (\$30.00 per script; \$7.30 for concession/RPBS as implemented on 1 January 2023).

The redacted values correspond to the following ranges:

¹ 5,000 to < 10,000

² 70,000 to < 80,000

³ 80,000 to < 90,000

⁴ \$30 million to < \$40 million

⁵ \$20 million to < \$30 million

⁶ \$40 million to < \$50 million

⁷ 50,000 to < 60,000

⁸ 60,000 to < 70,000

⁹ 90,000 to < 100,000

¹⁰ 100,000 to < 200,000

¹¹ Net cost saving

¹² \$0 to < \$10 million

¹³ 500 to < 5,000

4.24 The submission estimated that 50,000 to < 60,000 patients would receive treatment with apremilast over the 6 years based on the revised uptake rates and proportion of patients treated by the specified prescribers.

- 4.30 Additional resources such as a psoriasis treatment protocol and training module for primary care will also be developed to support the quality use of apremilast.

5 PBAC Outcome

- 5.1 The PBAC recommended the following changes to the treatment criteria of apremilast (Otezla®) for the treatment of severe chronic plaque psoriasis (CPP) in patients who have failed treatment with, or who are contraindicated or intolerant, to methotrexate:
- To allow rheumatologists and general physicians to initiate treatment (in addition to dermatologists).
 - To allow rheumatology registrars to initiate treatment in consultation with one of the above practitioner types (in addition to dermatology registrars).
- 5.2 The PBAC did not recommend the requested change to allow GPs to initiate treatment with apremilast (Otezla®) for the treatment of severe chronic plaque psoriasis (CPP) in patients who have failed treatment with, or who are contraindicated or intolerant, to methotrexate.
- 5.3 The PBAC noted the submission's rationale of the current workforce shortage and the difficulty in accessing specialists, especially in remote and rural areas. The PBAC considered that allowing additional medical practitioners to initiate treatment would improve patient access to apremilast, especially in rural and remote areas.
- 5.4 The PBAC noted the comments received from healthcare practitioners, Creaky Joints Australia – Global Healthy Living Foundation Australia and The Australasian College of Dermatologists. The PBAC noted the consumer comments were generally supportive of the proposed changes to the treatment criteria, but that the Australasian College of Dermatologists did not support the changes.
- 5.5 The PBAC further noted the sponsor's commitment to support quality use of apremilast in GPs by addressing gaps in GP practice regarding appropriate diagnosis and management of CPP. However, the PBAC considered that the proposed treatment criteria of 'GPs who are experienced in the treatment of psoriasis' was broad and that the required experience is not ascertainable in a manner that can be verified, and carried a risk of misdiagnosis and inappropriate prescribing. The PBAC noted that GPs are currently able to prescribe continuing treatment with apremilast where there is agreement with one of the initiating practitioner types, and considered that this remained appropriate.
- 5.6 The PBAC noted that the submission claimed that apremilast is safer and requires less monitoring than the currently available treatment options for CPP. The PBAC recalled that at its March 2022 meeting, it had considered that apremilast was well tolerated with minimal risk of severe or serious side effects (para 5.2, apremilast PSD, March 2022 PBAC meeting).

- 5.7 The PBAC noted that the submission estimated that the change in restriction would likely result in increased utilisation and a net cost to the PBS/RPBS of \$40 million to < \$50 million over the first 6 years of listing.
- 5.8 The PBAC noted that from 1 October 2023, deucravacitinib was listed on the PBS with the same criteria as apremilast for CPP, and the listing of deucravacitinib was not included as part of the submission's financial estimates. The PBAC recalled that, at its March 2023 PBAC meeting, it considered that deucravacitinib would likely replace apremilast in clinical practice given deucravacitinib had a moderate clinical benefit over apremilast (para 10.8, deucravacitinib PSD March 2023 PBAC meeting). The PBAC therefore considered that the overall utilisation of apremilast may be lower than proposed by the submission and therefore the cost to the PBS/RPBS may be overestimated. The PBAC further considered that the risk of apremilast exceeding the current caps for the existing RSA is low.
- 5.9 The PBAC recommended that the Prescribing Instruction regarding the need for prescribers to complete a Psoriasis Area and Severity Index (PASI) assessment for patients to move onto biologic treatments should be included in the restriction for apremilast and should flow on to ciclosporin and deucravacitinib.
- 5.10 The PBAC advised that the changes to the initial treatment criteria for apremilast should flow onto ciclosporin for the treatment of CPP. The PBAC recalled that, in its March 2022 recommendation for apremilast, the Committee did not recommend GP continuation to flow onto ciclosporin due to ciclosporin's safety profile and monitoring requirements. The PBAC reaffirmed its view that GPs should not be allowed to prescribe ciclosporin on the PBS.
- 5.11 The PBAC recalled that, in its March 2023 recommendation for deucravacitinib, it considered it was appropriate for the restriction criteria for deucravacitinib to be consistent with the criteria for apremilast. The PBAC also recalled that the claim of non-inferior comparative safety of deucravacitinib to apremilast was reasonable, however noted there was a lack of long-term safety data for deucravacitinib. The PBAC therefore advised that all of the recommended changes to the treatment criteria for apremilast should flow onto the listings for deucravacitinib for severe CPP.
- 5.12 The PBAC noted that, given the treatment criteria changes to Otezla® are not expected to provide a substantial and clinically relevant improvement in efficacy, or reduction of toxicity, or not expected to address a high and urgent unmet clinical need given the presence of an alternative therapy, the criteria prescribed by the *National Health (Pharmaceuticals and Vaccines – Cost Recovery) Regulations 2022* for Pricing Pathway A were not met.
- 5.13 The PBAC noted that this submission is not eligible for an Independent Review as it received a positive recommendation.

Outcome:

Recommended

6 Recommended listing

6.1 Amend existing listing as follows, additions in italics, deletions in strikethrough:

MEDICINAL PRODUCT medicinal product pack	PBS item code	Max. qty packs	Max. qty units	No. of Rpts	Available brands
APREMILAST					
apremilast 10 mg tablet [4] (&) apremilast 20 mg tablet [4] (&) apremilast 30 mg tablet [19], 27	12218C	1	27	0	Otezla Titration Pack
apremilast 30 mg tablet, 56	12223H	1	56	5	Otezla
Restriction Summary / Authority Required: Streamlined					
	Category / Program: GENERAL – General Schedule (Code GE)				
	Prescriber type: Medical Practitioners				
	Restriction type: Authority Required – Streamlined				
	Administrative Advice: No increase in the maximum quantity or number of units may be authorised.				
	Administrative Advice: No increase in the maximum number of repeats may be authorised.				
	Administrative Advice: Special pricing arrangements apply.				
	Indication: Severe chronic plaque psoriasis				
	Clinical criteria:				
	Patient must have failed to achieve an adequate response after at least 6 weeks of treatment with methotrexate prior to initiating treatment with this drug; or				
	Patient must have a contraindication to methotrexate according to the Therapeutic Goods Administration (TGA) approved Product Information; or				
	Patient must have demonstrated severe intolerance of, or toxicity due to, methotrexate				
	AND				
	Clinical criteria:				
	The condition must have caused significant interference with quality of life				
	AND				
	Clinical criteria:				
	Patient must not be undergoing concurrent PBS-subsidised treatment for psoriasis with each of: (i) a biological medicine, (ii) ciclosporin, (iii) deucravacitinib				
	Treatment criteria:				
	Must be treated by a medical practitioner who is either: (i) a dermatologist, (ii) a rheumatologist, (iii) general physician OR (iii) an accredited dermatology registrar in consultation with a dermatologist; OR				
	<i>Must be treated by a medical practitioner in consultation with one of the above specialist types who is either an accredited: (i) dermatology registrar, (ii) rheumatology registrar; OR</i>				
	Must be treated by a general practitioner where there is agreement who has been directed to continue treatment (not initiate treatment) by with one of the above practitioner types.				
	Population criteria:				
	Patient must be aged 18 years or older				
	Prescribing instruction				
	<i>For patients who do not demonstrate an adequate response to apremilast, a Psoriasis Area and Severity Index (PASI) assessment must be completed, preferably while on treatment, but no longer than 4 weeks following the cessation of treatment. This assessment will be required for patients who transition to 'biological medicines' for the treatment of 'severe chronic plaque psoriasis'.</i>				
	<i>This assessment must be documented in the patient's medical records.</i>				

This restriction may be subject to further review. Should there be any changes made to the restriction the Sponsor will be informed.

- 6.2 Flow-on changes to ciclosporin’s existing treatment criteria for the treatment of severe psoriasis to allow rheumatologists, general physicians and rheumatology registrars to prescribe, and to add the Prescribing Instruction for PASI assessments (PBS item codes: 5633L, 6125J, 5632K, 6232B, 5635N, 6353J, 5634M, 6352H, 5636P and 6354K).

	Treatment criteria:
	Must be treated by a medical practitioner who is either: (i) a dermatologist, (ii) a rheumatologist, (iii) general physician OR (ii) an accredited dermatology registrar in consultation with a dermatologist; OR
	Must be treated by a medical practitioner in consultation with one of the above specialist types who is either an accredited: (i) dermatology registrar, (ii) rheumatology registrar;
	Prescribing instruction
	For patients who do not demonstrate an adequate response to apremilast, a Psoriasis Area and Severity Index (PASI) assessment must be completed, preferably while on treatment, but no longer than 4 weeks following the cessation of treatment. This assessment will be required for patients who transition to ‘biological medicines’ for the treatment of ‘severe chronic plaque psoriasis’.
	This assessment must be documented in the patient’s medical records.

This restriction may be subject to further review. Should there be any changes made to the restriction the Sponsor will be informed.

- 6.3 Flow-on changes to deucravacitinib’s existing treatment criteria for the treatment of severe CPP to allow rheumatologists, general physicians and rheumatology registrars to prescribe, amend the wording for the general practitioner continuing prescriptions, and to add the Prescribing Instruction for PASI assessments (PBS item codes: 13649J).

	Treatment criteria:
	Must be treated by a medical practitioner who is either: (i) a dermatologist, (ii) a rheumatologist, (iii) general physician OR (ii) an accredited dermatology registrar in consultation with a dermatologist; OR
	Must be treated by a medical practitioner in consultation with one of the above specialist types who is either an accredited: (i) dermatology registrar, (ii) rheumatology registrar; OR
	Must be treated by a general practitioner where there is agreement who has been directed to continue treatment (not initiate treatment) by with one of the above practitioner types.
	Prescribing instruction
	For patients who do not demonstrate an adequate response to apremilast, a Psoriasis Area and Severity Index (PASI) assessment must be completed, preferably while on treatment, but no longer than 4 weeks following the cessation of treatment. This assessment will be required for patients who transition to ‘biological medicines’ for the treatment of ‘severe chronic plaque psoriasis’.
	This assessment must be documented in the patient’s medical records.

This restriction may be subject to further review. Should there be any changes made to the restriction the Sponsor will be informed.

7 Context for Decision

The PBAC helps decide whether and, if so, how medicines should be subsidised through the Pharmaceutical Benefits Scheme (PBS) in Australia. It considers applications regarding the listing of medicines on the PBS and provides advice about other matters relating to the operation of the PBS in this context. A PBAC decision in relation to PBS listings does not necessarily represent a final PBAC view about the

merits of the medicine or the circumstances in which it should be made available through the PBS. The PBAC welcomes applications containing new information at any time.

8 Sponsor's Comment

Amgen welcomes the PBAC's recommendation to change the apremilast treatment criteria and allow rheumatologists, rheumatology registrars and general physicians to prescribe apremilast on the PBS but is disappointed that the PBAC did not support GP initiation of apremilast. Amgen would like to thank all of the healthcare professionals, professional societies, patient organisations and consumers for their support of the apremilast submission.