

**7.10 APREMILAST,
Tablet 30 mg,
Pack containing 4 tablets of 10 mg , 4 tablets of 20 mg
and 19 tablets of 30 mg,
Otezla[®] ,
Amgen Australia Pty Ltd**

1 Purpose of Application

- 1.1 The minor resubmission requested a General Schedule, Authority Required (STREAMLINED) listing of apremilast for the treatment of severe plaque psoriasis in patients who have failed treatment with, or are contraindicated/intolerant to methotrexate. The resubmission proposed a new price and risk sharing arrangement (RSA).

Table 1: Key components of the clinical issue addressed by the resubmission

Component	Description
Population	Patients with severe plaque psoriasis
Intervention	Apremilast 30 mg tablet twice daily (after 5-day dose titration period)
Comparator	Cyclosporin (typically 3/mg/kg per day, dose is individually titrated)
Outcomes	Proportion of patients achieving at least a 75% reduction in psoriasis area and severity index (PASI-75) at 16 weeks.
Clinical claim	The PBAC previously considered the clinical claims of non-inferior comparative efficacy, non-inferior comparative safety in terms of adverse events and a superior safety profile were reasonable (paras 6.20, 6.21, apremilast PSD, November 2017 PBAC Meeting).

2 Background

Registration status

- 2.1 Apremilast was TGA registered on 19 March 2015 for the treatment of signs and symptoms of active psoriatic arthritis in adult patients; and the treatment of adult patients with moderate to severe plaque psoriasis who are candidates for phototherapy or systemic therapy.
- 2.2 Apremilast was originally sponsored by Celgene Pty Ltd. Following the acquisition of Celgene by Bristol-Myers Squibb in 2019, Amgen became the sponsor of apremilast in March 2020.

Previous PBAC consideration

- 2.3 This is the sixth submission for PBS listing of apremilast for plaque psoriasis. A summary of prior PBAC considerations is provided in Table 2.

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Table 2: Previous PBAC considerations

Meeting date	Request	Outcome	Detail
March 2015	Streamlined authority listing for moderate-severe plaque psoriasis on the basis of non-inferior efficacy/superior safety to cyclosporin and cost-utility analysis of delay to initiation of biologics.	Rejected	Cost-effectiveness to cyclosporin not adequately established; incremental benefit not evident, therefore not appropriate to require patients to trial an additional line of therapy prior to biologics (paragraph 7.1)
November 2016	Streamlined authority listing for moderate-severe plaque psoriasis based on superior efficacy and safety to cyclosporin.	Rejected	The evidence presented did not support the claims of superior comparative efficacy or safety versus cyclosporin (paragraph 7.1).
March 2017	Streamlined authority listing for moderate-severe psoriasis in patients who have failed to achieve an adequate response to or are contraindicated to methotrexate.	Rejected	The resubmission did not address issues identified in its November 2016 consideration of apremilast (paragraph 7.2).
November 2017	Streamlined authority listing for moderate-severe psoriasis on a cost-minimisation basis with cyclosporin.	Deferred	The PBAC deferred making a recommendation on whether apremilast should be listed on the PBS to allow further work to establish a price that could be considered cost effective (paragraph 7.1).
March 2018	Price and RSA proposal to achieve cost effective listing of apremilast.	Rejected	The PBAC considered the RSA proposed by the sponsor was unlikely to achieve an overall price per patient for apremilast within the range the PBAC considered cost effective at its November 2017 meeting (paragraph 7.1).

Source: Compiled by the Secretariat. Paragraph references for March 2015, November 2016, March 2017, November 2017 and March 2018 refer to apremilast public summary documents (PSDs).

2.4 A summary of the November 2017 and March 2018 submissions along with the current minor resubmission is provided in the table below.

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Table 3: Summary of recent previous submissions and the current resubmission

	November 2017 submission	March 2018	Current resubmission
Requested PBS listing	General Schedule, Authority Required (STREAMLINED) listing for moderate-severe plaque psoriasis in patients who have failed to achieve an adequate response to or are contraindicated to methotrexate.	Unchanged	Unchanged (The term 'moderate' was removed from the proposed restriction to align the proposed indication with the PBS listing of cyclosporin).
Requested effective DPMQs	Titration pack: \$ [REDACTED] Maintenance pack: \$ [REDACTED]	Unchanged	Titration pack: \$ [REDACTED]* Maintenance pack: \$ [REDACTED]* *[REDACTED]% lower than November 2017
Comparator	Cyclosporin The PBAC recalled it previously accepted cyclosporin as the appropriate comparator (paragraph 7.5).	Unchanged	Unchanged
Clinical evidence	Five apremilast vs. placebo trials One cyclosporin vs. methotrexate trial One methotrexate vs. placebo trial (Comparison was two-step meta-analysed indirect comparison)	Unchanged	Unchanged
Key effectiveness data	Primary outcome: Proportion of patients achieving PASI-75. Results of the meta-analysed indirect comparison: Risk Difference apremilast vs. cyclosporin = -1.0% (95% CI -26.0%, 24.0%, p=0.939) Heterogeneity test Q(df=4) = 4.6, p=0.333, I ² = 12.8%	Unchanged	Unchanged
Clinical claim	The PBAC noted the clinical heterogeneity of the trials included in the network meta-analysis, and on balance considered the claim of non-inferior comparative effectiveness was likely to be reasonable (paragraph 7.6). The PBAC considered that the claim of non-inferior comparative safety in terms of adverse events was reasonable. The PBAC considered that the superiority claim for safety profile was not well supported by the clinical evidence provided. However, noting the well documented cumulative toxicity of cyclosporin and the limitations of its therapeutic use in psoriasis to no more than two years, the PBAC considered that the safety profile of apremilast was likely to be superior to cyclosporin (paragraph 7.7).	Unchanged	Unchanged

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	November 2017 submission	March 2018	Current resubmission
Economic evaluation	<p>Cost-minimisation to cyclosporin, with substantial modelled offsets for use of Medicare Benefits Schedule items for routine monitoring of cyclosporin and costs of adverse events management, including hospitalisations.</p> <p>The PBAC considered a reasonable cost offsets model included █ extra specialist visits and █ additional creatine tests for cyclosporin, HCG (pregnancy) testing for both cyclosporin and apremilast and the submission's estimate of adverse event costs over a 16 week period applies over a 2 year period without adjustment, or these costs are doubled (paragraph 6.33).</p> <p>On balance, the PBAC considered with a premium in the range of █% over the cost of cyclosporin, apremilast would likely be acceptably cost-effective for the purposes of the <i>National Health Act 1953</i> (Table 16, Table 17 and paragraph 6.35).</p>	<p>Unchanged</p> <p>An RSA was instead proposed to achieve an overall price per patient.</p>	<p>Cost-minimisation to cyclosporin with cost offsets for routine monitoring and adverse events consistent with those recommended by the PBAC in November 2017, with a cost equivalent to an █% premium over the drug costs of cyclosporin at the AEMP level.</p>
Number of patients	<p>Year 1: █ (█ scripts)</p> <p>Year 6: █ (█ scripts)</p> <p>The DUSC considered the proposed restriction was open to clinical interpretation, the size of the eligible population was uncertain and likely underestimated, the uptake was likely underestimated and the proportion of eligible patients treated by a dermatologist was underestimated (paragraph 6.41).</p>	<p>Year 1: █ (█ scripts)</p> <p>Year 6: █ (█ scripts)</p>	<p>Based on the tier 2 utilisation estimates in the resubmission, which include adjustment for some factors considered appropriate by the DUSC.</p> <p>Year 1: █ (█ scripts)</p> <p>Year 6: █ (█ scripts)</p> <p>The resubmission argued the November 2017 submission overestimated the number of scripts per patient assuming 100% compliance. Based on DUSC advice (November 2017) this has been reduced to 85%.</p>
Estimated net cost to PBS/RPBS	<p>Year 1: \$ █</p> <p>Year 6: \$ █</p>	<p>Year 1: -\$ █</p> <p>Year 6: \$ █</p>	<p>Based on the tier 2 utilisation estimates in the resubmission.</p> <p>Year 1: \$ █</p> <p>Year 6: \$ █</p> <p>Estimates after replacement or substitution of other PBS listed therapies.</p>

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	November 2017 submission	March 2018	Current resubmission
Risk sharing arrangement	The PBAC recommended a three-tier RSA proposal (paragraph 6.45): Tier 1: Up to submission estimates, the appropriate cost-effective apremilast price applies; Tier 2: Up to Pre-PBAC response to DUSC advice estimates, cyclosporin price applies; Tier 3: [REDACTED] rebate beyond tier 2.	The sponsor proposed a multi-tiered RSA different to that recommended by the PBAC in November 2017.	Three-tier RSA proposal based on number of services in updated utilisation estimates: Tier 1: Apremilast price (based on cyclosporin + [REDACTED]% at AEMP) up to the base case utilisation estimates (see Table 11) Tier 2: Cyclosporin price up to the utilisation estimates with assumptions considered reasonable by the DUSC (see Table 12) Tier 3: [REDACTED] rebate beyond tier 2.
PBAC decision	Defer	Rejected	-

Source: Compiled by the Secretariat. Paragraph references for November 2017 refer to the apremilast PSD.

Abbreviations: PASI = psoriasis area and severity index; CI = confidence interval, Q = Cochran's Q heterogeneity score; df = degrees of freedom; I² = measure of heterogeneity derived from Q; HCG = human chorionic gonadotrophin

Table 4: PBAC matters of concern in previous consideration (November 2017/March 2018)

Matters of concern	How the resubmission addresses it
Proposed price and cost-minimisation model	The resubmission proposed a Special Pricing Arrangement (SPA) with an effective price at an [REDACTED]% premium to cyclosporin (based on drug costs) over 104 weeks of treatment, modelled to be cost-minimised to cyclosporin when accounting for differential monitoring and adverse event costs.
Utilisation and financial estimates	The resubmission provided minor changes to the utilisation and financial estimates based on the November 2017 submission and modified some assumptions based on prior DUSC advice.
Risk Sharing Arrangement proposal	Same structure as that recommended by the PBAC in November 2017, with updated figures based on the revised utilisation and financial estimates.

Source: Compiled during the evaluation. Paragraph references refer to the November 2017 and March 2018 PSDs.

For more detail on PBAC's view, see section 6 PBAC outcome.

3 Requested listing

3.1 The resubmission requested the following new listings of apremilast.

Secretariat suggested additions are in italics and deletions are in strikethrough.

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Name, Restriction, Manner of administration and form	PBS item code	Max. qty packs	Max. qty units	№.of Rpts	Dispensed price Max Qty	Available brands
APREMILAST apremilast 10 mg tablet [4] (& apremilast 20 mg tablet [4] (& apremilast 30 mg tablet [19], 27	NEW	1	27	0	Published \$266.60 Effective \$ [REDACTED]	Otezla Titration Pack
apremilast 30 mg tablet, 56	NEW	1	56	5	Published \$641.67 Effective \$ [REDACTED]	Otezla

Category / Program: GENERAL – General Schedule (Code GE)
Prescriber type: <input checked="" type="checkbox"/> Medical Practitioners
Restriction type / Method: <input checked="" type="checkbox"/> Authority Required – Streamlined [new code]
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.
Episodicity: [blank]
Severity: Severe
Condition: <i>chronic</i> plaque psoriasis
Indication: Severe <i>chronic</i> plaque psoriasis
Treatment Phase: Initial treatment [blank]
Clinical criteria: Patient must have failed to achieve an adequate response to methotrexate <i>prior to initiating treatment with this drug; or unless contraindicated or not tolerated according to the Therapeutic Goods Administration (TGA) approved Product Information.</i> <i>Patient must have a contraindication to methotrexate according to the Therapeutic Goods Administration (TGA) approved Product Information; or</i> <i>Patient must have experienced an intolerance to methotrexate of a severity necessitating permanent treatment withdrawal</i>
Treatment criteria: Must be treated by a dermatologist; or <i>Must be treated by a general physician with expertise in the management of plaque psoriasis.</i>
AND
Population criteria: Patient must be aged 18 years or older

Category / Program: GENERAL – General Schedule (Code GE)
Prescriber type: <input checked="" type="checkbox"/> Medical Practitioners
Restriction type / Method: <input checked="" type="checkbox"/> 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.
Episodicity:
Severity: Severe
Condition: Plaque psoriasis
Indication: Severe plaque psoriasis
Treatment Phase: Continuing treatment [The Secretariat suggested continuing treatment be accessed through the above listing]
Clinical criteria: Patient must have previously received PBS-subsidised treatment with this drug for this condition.

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Category / Program: GENERAL – General Schedule (Code GE)
Prescriber type: <input checked="" type="checkbox"/> Medical Practitioners
Restriction type / Method: <input checked="" type="checkbox"/> 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.
Episodicity:
Severity: Severe
Condition: Plaque psoriasis
Indication: Severe plaque psoriasis
Treatment Phase: Grandfather treatment <i>[The Secretariat suggested such patients access treatment through the regular listing]</i>
Clinical criteria: Patient must have previously received <i>been receiving</i> non-PBS subsidised treatment with this drug for this condition prior to <i>[listing date]</i> .
AND
Prior to initiation of this drug, patient must have failed to achieve an adequate response to methotrexate unless contraindicated or not tolerated according to the Therapeutic Goods Administration (TGA) approved Product Information.
Treatment criteria: Must be treated by a dermatologist OR Must be treated by a general physician with expertise in the management of plaque psoriasis.
AND
Population criteria: Patient must be aged 18 years or older

- 3.2 The pre-PBAC response stated that the Secretariat proposed revisions to the listing are acceptable to the sponsor. In addition, the pre-PBAC response confirmed that the product familiarisation program was no longer in operation. The pre-PBAC response stated the sponsor estimated that less than 10,000 Australians receive apremilast through private script and it is not known what percentage of these would qualify for apremilast on the PBS. For equity reasons, the PBAC was of the view that if such patients could not meet the recommended PBS restrictions, then PBS eligibility should not extend to these patients.
- 3.3 The PBAC noted that, consistent with its November 2017 recommendation (paragraph 7.11, apremilast PSD, November 2017 PBAC Meeting), the proposed PBS indication had changed to ‘severe plaque psoriasis’ from ‘moderate to severe plaque psoriasis’ compared to previous submissions.
- 3.4 The PBAC noted the apremilast treatment criteria allowed prescribing by either a dermatologist or a general physician with expertise in the management of plaque psoriasis while the cyclosporin listing for severe psoriasis is limited to dermatologists only. The PBAC considered that the treatment criteria for apremilast should match that of cyclosporin and hence be limited to dermatologists only.
- 3.5 The PBAC noted the apremilast Product Information states that it has not been studied in combination with cyclosporin or biologic therapies. As such the PBAC considered the apremilast restriction should include statements that use must not be in

combination with either cyclosporin or a biological medicine for severe chronic plaque psoriasis.

For more detail on PBAC's view, see section 6 PBAC outcome.

4 Comparator

- 4.1 Consistent with previous submissions, cyclosporin was nominated as the main comparator. In November 2016, the PBAC accepted that cyclosporin was the appropriate main comparator if apremilast was restricted to patients who have failed treatment with methotrexate (paragraph 7.5, apremilast PSD, November 2016 PBAC Meeting).

5 Consideration of the evidence

Sponsor hearing

- 5.1 There was no hearing for this item as it was a minor submission.

Consumer comments

- 5.2 The PBAC noted and welcomed the input from health care professionals (1) via the Consumer Comments facility on the PBS website. The comment described the long-term durability of patient responses to apremilast treatment and highlighted the overall low rates of adverse events after the initial titration period.

Economic analysis

- 5.3 The November 2017 submission presented the following equi-effective doses based on clinical data from an indirect network meta-analysis:

- Apremilast 30 mg BID after an initial titration period over 6 days and cyclosporin 3.29 mg/kg/day are equi-effective over 16 weeks (paragraph 6.24, apremilast PSD, November 2017 PBAC Meeting).

- 5.4 At that time, the PBAC considered the following approach to a cost-minimisation analysis of apremilast versus cyclosporin would be appropriate (paragraph 6.33, apremilast PSD, November 2017 PBAC Meeting).

Step 1: correct price per mg of cyclosporin to \$0.0455 mg. In the November 2017 resubmission an average weight of 92.2 kg for cyclosporin treated patients was assumed. This is unchanged in the current resubmission.

Step 2: Monitoring and adverse event costs adjusted to assume:

- [REDACTED] extra specialist visits over 2 years are assumed for cyclosporin treated patients compared with apremilast treated patients;
- [REDACTED] extra creatinine tests are conducted over 2 years for cyclosporin treated patients ([REDACTED] pre-treatment, then one every [REDACTED] weeks for [REDACTED] months,

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then one every ■ or ■ months for ■ months; apremilast patients receive ■ creatinine test pre-treatment and ■ per year for 2 years; and ■ renal function test pre-treatment);

- the same proportions of apremilast and cyclosporin patients are assumed to require pregnancy testing;
- no differences in other routine monitoring costs; and
- the submission’s estimate of adverse event costs over a 16 week period applies over a 2 year period without adjustment, or these costs are doubled. In November 2017 the submission assumed the adverse event cost over 16 weeks was \$■ for cyclosporin and \$■ for apremilast.

5.5 The minor resubmission re-presented the cost-minimisation analysis from the November 2017 submission, updated to include the cyclosporin price (Table 5), cost offsets for monitoring (Table 6) and adverse events consistent with those recommended by the PBAC at that time (see paragraph 5.4). Cyclosporin drug and monitoring/adverse event costs were calculated over 2 years to determine the total cost of treatment. The cost-minimised price of 2 years treatment with apremilast was then calculated with offsets for monitoring (Table 6) and adverse events to achieve an equivalent price over the same duration.

Table 5: Cyclosporin drug costs

	Value	Source
AEMP Cyclosporin 100mg; 30 capsules	\$136.60	PBS; http://www.pbs.gov.au/info/industry/pricing/ex-manufacturer-price
Ex-manufacturer price per mg	\$0.0455	Calculated
Average patient weight, kg	92.29	Apremilast trials
Average daily dose (mg/kg/day)	3.2	Heydendael 2003
Total mg per day per patient	296.66	Calculated
Average cost per patient per 104 weeks	\$9,833.80	Calculated

Source: Table 1, pg. 4 of the resubmission.

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Table 6: Monitoring costs for apremilast and cyclosporin

Item description	Cost per item ^a	MBS item number	Cyclosporin			Apremilast	
			Pre-treatment	Week 1-104 (minimum)	Week 1-104 (maximum)	Pre-treatment	Week 1-104
Specialist consultation (subsequent)	\$43.00	105	█	█	█	█	█
Full blood examination	\$16.95	65070	█	█		█	█
Liver function tests, Lipid studies, Urea, Electrolytes, Creatinine	\$17.70	66512	█	█	█	█	█
Urinalysis (microscopy)	\$12.50	69300	█	█		█	█
Serology – HIV	\$15.65	69384	█	█		█	█
Serology – hepatitis	\$15.65	69384	█	█		█	█
HCG (pregnancy)	\$39.75	66750	█	█		█	█
Tuberculosis	\$34.90	69471	█	█		█	█
Total			\$█	\$█	\$█	\$█	\$█

Source: Table 2, pg. 5 of the resubmission. MBS item 105 cost not updated in the resubmission.

5.6 Two scenarios for the cost-minimisation analysis were presented, a ‘minimum’ (Table 7) and a ‘maximum’ (Table 8) scenario based on the range of monitoring costs and adverse event scenarios the PBAC considered reasonable in November 2017 (see paragraph 5.4). The only differences between the scenarios was the number of specialist consultations (█ in the ‘minimum’ versus █ in the ‘maximum’) and liver function tests (█ versus █) over the 2 year period and a doubling of adverse event costs in the ‘maximum’ model.

Table 7: Cost minimised price of apremilast over 2 years (minimum)

	Total cost of treatment per 104 weeks	Adverse event costs	Monitoring costs	PBS costs (AEMP)	Premium
Cyclosporin	\$█	\$█	\$█	\$9,833.80	
Apremilast	\$█	\$█	\$█	\$█	█%
Difference	\$█	(\$█)	(\$█)	\$█	

Source: Table 3, pg. 5 of the resubmission

Table 8: Cost minimised price of apremilast over 2 years (maximum)

	Total cost of treatment per 104 weeks	Adverse event costs	Monitoring costs	PBS costs (AEMP)	Premium
Cyclosporin	\$█	\$█	\$█	\$9,833.80	
Apremilast	\$█	\$█	\$█	\$█	█%
Difference	\$█	(\$█)	(\$█)	\$█	

Source: Table 4, pg 5 of the resubmission.

5.7 The resubmission stated that the costs scenarios match those in Table 16 and Table 17 of the November 2017 PSD with some small differences due to rounding. In November 2017 the PBAC considered that, with a premium within the range of █%

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over the drug cost of cyclosporin, apremilast would likely be acceptably cost-effective for the purposes of the National Health Act 1953 (paragraph 6.35, apremilast PSD, November 2017 PBAC Meeting).

- 5.8 Based on an assumption of 2 years of treatment on maintenance therapy (i.e. not including a 5-day titration period), the cost-minimised AEMP for the apremilast maintenance pack (28 days therapy, 26 four-week periods) would be in the range of \$ [REDACTED] - \$ [REDACTED]. The resubmission requested an effective AEMP of the apremilast continuing pack of \$ [REDACTED], at the upper limit of this range.
- 5.9 The resubmission requested listing of the titration pack at the same price per mg (\$ [REDACTED]/mg) as the maintenance pack. The resubmission also requested a Special Pricing Arrangement (SPA) with published and effective prices as outlined in the table below.

Table 9: Proposed effective and published prices of apremilast titration and maintenance packs

	Effective		Published	
	AEMP	DPMQ	AEMP	DPMQ
Maintenance pack - 56 x 30mg; 28-day supply	\$ [REDACTED]	\$ [REDACTED]	\$571.96	\$641.67
Titration pack	\$ [REDACTED]	\$ [REDACTED]	\$234.91	\$266.60

Source: Table 5, pg. 5 of the resubmission.

Effective AEMPs are consistent with the [REDACTED]% price premium outlined in Table 4 (maintenance pack) and derived per mg price (titration pack).

Drug cost/patient/year: \$8,367.38 (published), \$ [REDACTED] (effective)

- 5.10 The estimated drug cost per patient per year would be \$8,367.38 at published prices based on the proposed maintenance pack dispensed price for maximum quantity (DPMQ \$641.67) and 13.04 prescriptions per year (28 days' treatment per script).

Estimated PBS usage & financial implications

- 5.11 The minor resubmission presented two utilisation models with assumptions of use up to the Tier 1 and Tier 2 caps in the proposed RSA. The proposed utilisation models and RSA tiers were based on utilisation models in the November 2017 submission (Tier 1) and new utilisation estimates which include some re-specified assumptions recommended by the Drug Utilisation Sub-Committee (DUSC) in November 2017 (Tier 2). A comparison of the utilisation model assumptions are outlined in the table below.

Table 10: Key elements of utilisation and financial estimates models

Parameter	Tier 1 model	Tier 2 model	Comment
Projected Australian adult population (years in model)	2020-2025		Updated to projected Australian adult population estimates for period 2020-2025 (ABS Series B population projections included in Department Utilisation and Financial Estimates Workbook). Original submission used 2017-2022 from same resource.
Prevalence of plaque psoriasis	3.3%	2.64%	Addressed - Tier 2 reduced by 20%. DUSC considered the population-level prevalence should be reduced 10-20% to account for the proportion of psoriasis that is

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Parameter	Tier 1 model	Tier 2 model	Comment
			plaque psoriasis (p6, apremilast DUSC advice, November 2017 PBAC Meeting).
Proportion of patients treated by dermatologist or experienced general physician	20%	38%	Addressed - Tier 2 increased, based on DUSC position that the number of treating physicians and number of patients physicians could consult was underestimated (p6, apremilast DUSC advice, November 2017 PBAC Meeting).
Proportion of patients meeting disease severity requirement	20%	20%	Unchanged.
Proportion of patients intolerant/contraindicated to methotrexate	61%	61%	Unchanged. Given the wide confidence intervals around this estimate DUSC suggested that the submission should have considered providing sensitivity analyses (for example 50% and 70%) (p7, apremilast DUSC advice, November 2017 PBAC Meeting). Reducing the proportion of patients intolerant/contraindicated to methotrexate from 61% to 50% for both Tier 1 and Tier 2 models would reduce the utilisation estimates on which the RSA is based. The pre-PBAC response argued that a value of 61% was in the middle of DUSC's 50-70% range and was used in the utilisation estimates for the November 2017 and March 2018 submissions.
Replacement/displacement of other medicines	<p>█% of apremilast use will be new (market growth) Of the █% apremilast use that is market share:</p> <ul style="list-style-type: none"> • █% from cyclosporin • █% from acitretin • █% from biologics 		Resubmission states these were based on a dermatologist survey as in previous submissions but applied to match the full epidemiological approach in the updated analysis template. In November 2017 DUSC considered that the methods and calculations used to quantify the cost of medicines displaced by apremilast were unclear and cannot be relied on to determine the net financial impact to the PBS arising from the listing of apremilast (apremilast DUSC advice, November 2017 PBAC Meeting). No further verification of the survey was provided in the resubmission. The pre-PBAC response acknowledged that there is inherent uncertainty in determining the cost offsets based on a clinician survey but argued that this represents the best information available to the sponsor and noted that the majority of substitution is for cyclosporin rather than for a biologic.
Unit prices for MBS and PBS listings	<p><u>Cyclosporin:</u> Public - \$546.40 Private - \$546.40 (\$575.63) <u>Ustekinumab:</u> \$4,349.46 (\$3,926.23) <u>Acitretin:</u> \$207.77</p>		<p>Unchanged. Current listing prices as at June 2020 are shown in italics.</p> <p>MBS item 105 for specialist consultation has increased to \$44.35, the original cost of \$43.00 is retained.</p>

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Parameter	Tier 1 model	Tier 2 model	Comment
Apremilast uptake	Yr 1: █% Yr 5: █%	Yr 1: █% Yr 5: █%	Unchanged. DUSC considered to be an underestimate due to familiarity of many psoriasis-interested dermatologists with apremilast (due to the familiarisation program) (p7, apremilast DUSC advice, November 2017 PBAC Meeting). The pre-PBAC response stated that the product familiarisation program was no longer in operation (see paragraph 3.2).
Adherence (maintenance therapy)	85%	85%	Changed from 100% in the November 2017 submission for both Tier 1 and Tier 2. Adherence of 85% is consistent with DUSC advice that adherence of 80-90% was reasonable (apremilast DUSC advice, November 2017 PBAC Meeting).
Biologics assumptions	Ustekinumab as proxy for all biologics		<p>Submission makes an arbitrary assumption on the effective price of ustekinumab (-40% of published).</p> <p>Biologics likely to be displaced (rather than replaced) in many circumstances.</p> <p>Level of displacement/replacement uncertain as apremilast would be an additional treatment option for determining eligibility for biologics and not adding a new line of therapy.</p> <p>Table 11 and Table 12 below indicate biologics accounted for █% of cost offsets for substituted medicines in Year 6 of both the Tier 1 and Tier 2 estimates (Tier 1 biologics \$█ of a total of \$█; Tier 2 biologics \$█ of a total of \$█).</p> <p>The pre-PBAC response argued that if at some time in the future an apremilast patient were to transition to a biologic, within the timeframe construct of the financial analysis it is reasonable to account for the immediate cost offsets.</p>

Source: Compiled by the Secretariat from current resubmission and November 2017 DUSC Advice.

5.12 The resubmission used these different sets of assumptions to estimate utilisation and financial estimates models, which formed the basis of the proposed RSA tiers. Utilisation and financial estimates for each of these models (referred to as Tier 1 and Tier 2) are outlined in the tables below. Utilisation and financial estimates are presented at the proposed effective apremilast price and assumed effective ustekinumab price (\$2,600 based on a published DPMQ of \$4,349.46).

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Table 11: Estimated use and financial implications (Tier 1 estimates)

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
Estimated extent of use						
Eligible patients	16,185	16,450	16,714	16,976	17,241	17,509
Number of patients treated	█	█	█	█	█	█
Number of scripts dispensed ^a	█	█	█	█	█	█
Estimated financial implications of apremilast						
Cost to PBS/RPBS	\$ █	\$ █	\$ █	\$ █	\$ █	\$ █
Cost to PBS/RPBS less copayments	\$ █	\$ █	\$ █	\$ █	\$ █	\$ █
Substitution of other medicines (scripts)						
Cyclosporin	- █	- █	- █	- █	- █	- █
Acitretin	- █	- █	- █	- █	- █	- █
Biologics	- █	- █	- █	- █	- █	- █
Estimated financial implications for substituted medicines						
Cost to PBS/RPBS	(\$ █)	(\$ █)	(\$ █)	(\$ █)	(\$ █)	(\$ █)
- Cyclosporin	(\$ █)	(\$ █)	(\$ █)	(\$ █)	(\$ █)	(\$ █)
- Acitretin	(\$ █)	(\$ █)	(\$ █)	(\$ █)	(\$ █)	(\$ █)
- Biologics	(\$ █)	(\$ █)	(\$ █)	(\$ █)	(\$ █)	(\$ █)
Cost to PBS/RPBS less copayments	(\$ █)	(\$ █)	(\$ █)	(\$ █)	(\$ █)	(\$ █)
Net financial implications						
Net cost to PBS/RPBS	\$ █	\$ █	\$ █	\$ █	\$ █	\$ █
Net cost to MBS	(\$ █)	(\$ █)	(\$ █)	(\$ █)	(\$ █)	(\$ █)
Net cost to Government	\$ █	\$ █	\$ █	\$ █	\$ █	\$ █

^a Assuming 1 initial and 10.63 continuing scripts per patient per year as estimated by the resubmission.

Source: Table 7 and financial estimates workbook of the resubmission

5.13 For Tier 1 estimates, at Year 6 the estimated number of patients was less than 10,000 and the net cost to the PBS/RPBS would be less than \$10 million.

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Table 12: Estimated use and financial implications (Tier 2 estimates)

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
Estimated extent of use						
Eligible patients	24,601	25,004	25,406	25,803	26,206	26,613
Number of patients treated	█	█	█	█	█	█
Number of scripts dispensed ^a	█	█	█	█	█	█
Estimated financial implications of apremilast						
Cost to PBS/RPBS	\$ █	\$ █	\$ █	\$ █	\$ █	\$ █
Cost to PBS/RPBS less copayments	\$ █	\$ █	\$ █	\$ █	\$ █	\$ █
Substitution of other medicines (scripts)						
Cyclosporin	█	█	█	█	█	█
Acitretin	█	█	█	█	█	█
Biologics	█	█	█	█	█	█
Estimated financial implications for substituted medicines						
Cost to PBS/RPBS	(\$ █)	(\$ █)	(\$ █)	(\$ █)	(\$ █)	(\$ █)
- Cyclosporin	(\$ █)	(\$ █)	(\$ █)	(\$ █)	(\$ █)	(\$ █)
- Acitretin	(\$ █)	(\$ █)	(\$ █)	(\$ █)	(\$ █)	(\$ █)
- Biologics	(\$ █)	(\$ █)	(\$ █)	(\$ █)	(\$ █)	(\$ █)
Cost to PBS/RPBS less copayments	(\$ █)	(\$ █)	(\$ █)	(\$ █)	(\$ █)	(\$ █)
Net financial implications						
Net cost to PBS/RPBS	\$ █	\$ █	\$ █	\$ █	\$ █	\$ █
Net cost to {MBS/DHS/other}	(\$ █)	(\$ █)	(\$ █)	(\$ █)	(\$ █)	(\$ █)
Net cost to {PBS/RPBS/MBS/DHS}	\$ █	\$ █	\$ █	\$ █	\$ █	\$ █

^a Assuming 1 initial and 10.63 continuing scripts per patient per year as estimated by the resubmission.

Source: Table 8 and financial estimates workbook of the resubmission

5.14 For Tier 2 estimates, at Year 6 the estimated number of patients was 10,000 – 50,000 and the net cost to the PBS/RPBS would be \$10 - \$20 million.

5.15 As a minor resubmission, the financial estimates have not been independently evaluated.

Financial Management – Risk Sharing Arrangement

5.16 In November 2017 the PBAC recommended that a tiered RSA based on the patient numbers estimated by the submission be put in place if apremilast is listed on the PBS (paragraph 6.45, apremilast PSD, November 2017 PBAC Meeting). The resubmission proposed a three-tier RSA consistent with the PBAC’s November 2017 advice:

- Tier 1: Apremilast price (based on cyclosporin + █% at AEMP) up to the base case utilisation estimates (see Table 11)
- Tier 2: Cyclosporin price up to the utilisation estimates updated with some DUSC-specified assumptions (see Table 12)

- Tier 3: [REDACTED] rebate beyond tier 2.

For more detail on PBAC's view, see section 6 PBAC outcome.

6 PBAC Outcome

- 6.1 The PBAC recommended the General Schedule, Authority Required (STREAMLINED) listing of apremilast for the treatment of severe chronic plaque psoriasis in patients who have failed treatment with or who are contraindicated or intolerant to methotrexate. In making this recommendation, the PBAC accepted that the resubmission had adequately addressed concerns raised in previous considerations, and had appropriately proposed a price and risk sharing arrangement (RSA) consistent with Committee's November 2017 advice.
- 6.2 The PBAC recommended the listing of apremilast on a cost minimisation basis with cyclosporin, accounting for differential adverse event and drug monitoring costs amounting to an [REDACTED]% price premium over the approved ex-manufacturer price (AEMP).
- 6.3 The PBAC considered the equi-effective doses were apremilast 30 mg twice daily and cyclosporin at a dose of 3.29 mg per kg of body weight per day.
- 6.4 The PBAC recalled it had previously considered there was a clinical need for an alternative therapy for psoriasis and reaffirmed its November 2017 advice that apremilast would provide some patients with a safer, longer term treatment option compared to cyclosporin, which has limitations of its therapeutic use in psoriasis to no more than two years (paragraph 7.4, apremilast PSD, November 2017 PBAC Meeting).
- 6.5 The PBAC recommended the listing of apremilast include the following elements:
- An Authority Required (STREAMLINED) restriction level;
 - An indication of 'Severe chronic plaque psoriasis';
 - A combined listing for initial and continuing treatment;
 - A statement that use must not be in combination with either cyclosporin or a biological medicine for severe chronic plaque psoriasis;
 - A statement that failure to achieve an adequate response to methotrexate must be assessed after at least 12 weeks of methotrexate therapy;
 - No grandfather restriction as the existing private patients could access treatment if the clinical criteria were met; and
 - Apremilast should be one of the therapies for determining eligibility for PBS-subsidised biological medicines for severe chronic plaque psoriasis without increasing the total number of therapies that should be trialled i.e. patients must trial at least 2 of 5 therapies comprising methotrexate, cyclosporin, acitretin, phototherapy or apremilast. The PBAC noted flow-on changes to the listings of biological medicines for the treatment of severe chronic plaque psoriasis to include apremilast in the list of eligible systemic therapies.

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- 6.6 The PBAC noted that the comparator and clinical claim were unchanged and recalled that the Committee had previously accepted these at its November 2017 meeting (see Table 3).
- 6.7 The PBAC noted the resubmission had followed the cost minimisation approach recommended by the Committee in November 2017 (see paragraph 5.4). In addition, the PBAC noted the requested price premium of █% over the AEMP of cyclosporin was within the range considered acceptable at its November 2017 meeting.
- 6.8 The PBAC recalled previous concerns that there was significant uncertainty in the utilisation estimates and the Committee’s advice that this uncertainty could be addressed through the implementation of a tiered RSA based on patient numbers (paragraph 7.10, apremilast PSD, November 2017 PBAC Meeting). The PBAC noted the amendments to the financial estimates outlined in Table 10 along with clarification from the pre-PBAC response that a product familiarisation program was no longer in operation. The PBAC considered that it was reasonable to accept the Tier 1 and Tier 2 utilisation estimates as presented in the resubmission as the basis of a RSA.
- 6.9 The PBAC noted the resubmission’s proposed 3-tiered RSA structure (see paragraph 5.16) was consistent with the approach it considered reasonable at its November 2017 meeting, and reaffirmed this approach was reasonable.
- 6.10 The PBAC advised that apremilast should not be treated as interchangeable with any other drugs.
- 6.11 The PBAC advised that apremilast is not suitable for prescribing by nurse practitioners.
- 6.12 The PBAC recommended that the Early Supply Rule should not apply.
- 6.13 The PBAC noted that its recommendation was on a cost-minimisation basis and advised that, because apremilast is not expected to provide a substantial and clinically relevant improvement in efficacy, or reduction of toxicity over cyclosporin, 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 2009 for Pricing Pathway A were not met.
- 6.14 The PBAC noted that this resubmission is not eligible for an Independent Review as it received a positive recommendation.

Outcome:

Recommended

7 Recommended listing

- 7.1 Add new medicinal product:

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Name, Restriction, Manner of administration and form	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	NEW	1	27	0	Otezla Titration Pack
apremilast 30 mg tablet, 56	NEW	1	56	5	Otezla

Restriction Summary [new] / Treatment of Concept: [new]

Category / Program: GENERAL – General Schedule (Code GE)
Prescriber type: <input checked="" type="checkbox"/> Medical Practitioners
Restriction type / Method: <input checked="" type="checkbox"/> 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.
Episodicity: [blank]
Severity: Severe
Condition: chronic plaque psoriasis
Indication: Severe chronic plaque psoriasis
Treatment Phase: [blank]
Clinical criteria: Patient must have failed to achieve an adequate response after at least 12 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.
AND
Clinical criteria: The treatment must not be used in combination with a PBS-subsidised cyclosporin for severe psoriasis.
Treatment criteria: Must be treated by a dermatologist.
AND
Population criteria: Patient must be aged 18 years or older

7.2 Flow on changes to biological medicines for severe chronic plaque psoriasis:

Add apremilast to the list of prior therapies that patients are required to trial before being eligible for PBS-subsidised biologics. An example of one of the relevant concepts (8114; attached to etanercept) is reproduced below:

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8114 - Patient must have failed to achieve an adequate response, as demonstrated by a Psoriasis Area and Severity Index (PASI) assessment, to at least 2 of the following 3 treatments: (i) phototherapy (UVB or PUVA) for 3 treatments per week for at least 6 weeks; and/or (ii) methotrexate at a dose of at least 10 mg or 10 mg per square metre weekly (whichever is lowest) for at least 6 weeks; and/or (iii) acitretin at a dose of at least 0.4 mg per kg per day for at least 6 weeks

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

8 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.

9 Sponsor's Comment

Amgen is pleased that apremilast will be made available on the PBS as an additional treatment option for patients with plaque psoriasis.