5.01 APREMILAST tablets, 10 mg, 20 mg and 30 mg; Otezla®; Celgene Pty Ltd

1 Purpose of Application

1.1 The major submission sought an Authority Required (STREAMLINED) listing for the treatment of moderate-to-severe plaque psoriasis in patients meeting certain criteria.

2 Requested listing

2.1 The requested listing is shown below:

Name, Restriction, Manner of administration and form	Max. Qty	№.of Rpts	Dispensed Price for Max. Qty	Proprietary Name and Manufacturer	
APREMILAST					
Tablets, titration pack (10 mg x4, 20 mg x4, 30 mg x19)	27	0	$[redacted]	Otezla®	Celgene Pty Ltd
Tablets, 30 mg	56	5	$[redacted]		

PBS category / program	General Schedule – Code (GE)
Episodicity:	-----
Severity:	Moderate-to-severe
Condition:	Plaque psoriasis
PBS indication:	Moderate to severe plaque psoriasis
Restriction level/method:	Authority Required (STREAMLINED)
Treatment phase:	Initial and continuing
Treatment criteria:	Must be initiated by a dermatologist or rheumatologist
Clinical criteria:	Patient must have previously received and failed to achieve an adequate response to one or more systemic therapies, including methotrexate; OR Patient must be clinically inappropriate for treatment with one or more systemic therapies, including methotrexate.

3 Background

3.1 Apremilast had not previously been considered by the PBAC for any indication.

3.2 A submission seeking listing of apremilast for use in psoriatic arthritis was also considered at the March 2015 PBAC meeting (agenda item 5.02).

3.3 This submission was made under TGA/PBAC parallel process provisions.

3.4 The first round assessment contained in the Clinical Evaluation Report recommended approval of apremilast for the treatment of psoriatic arthritis.

3.5 The TGA Delegate's Advice contained the pre-ACPM preliminary assessment that the Delegate had no reason to say that the application for apremilast for psoriatic arthritis should not be approved for registration, but restricted to specialist physicians only.

3.6 At the time of ESC and PBAC consideration, the outcome of the February 2015 ACPM consideration was unknown.

4 Clinical place for the proposed therapy

4.1 The submission proposed that apremilast would be used as a subsequent treatment to phototherapy and methotrexate, but before cyclosporin or acitretin for moderate-to-severe psoriasis. The requested restriction for apremilast implied that patients must have trialled and failed at least one systemic therapy. This limitation on use was within the proposed TGA indication which sought to make treatment available to both naïve or treatment experienced patients. Given the trials presented in the submission included treatment naïve and treatment experienced patients, prescribers may wish to prescribe apremilast in treatment naïve patients which would represent use outside of the proposed PBS restriction.

4.2 The submission claimed that apremilast is not expected to directly substitute for any currently listed drugs, but rather displace existing therapies and extend the treatment sequence in plaque psoriasis prior to the commencement of a biological disease modifying anti-rheumatic drug (bDMARD). Specifically, the submission expected that if apremilast was listed on the PBS, patients with moderate-to-severe plaque psoriasis would undergo treatment with 4 of 5 the following treatments before biologic therapy: phototherapy, methotrexate, cyclosporin, acitretin or apremilast. The current PBS restrictions for bDMARDs in severe plaque psoriasis (defined as PASI >15) require a preceding trial of 3 of 4 therapies (phototherapy and/or systemic therapy with either methotrexate, acitretin or cyclosporin). Data provided in the submission indicated that the majority of patients (>70%) currently only trial up to two non-bDMARD systemic therapies, with the proportion receiving phototherapy unknown. This evidence of widespread use of bDMARDs in patients before they have trialled and failed at least 3 of the 4 above mentioned therapies was noted to be inconsistent with the PBS restrictions for treatment of severe plaque psoriasis. The submission provided no data to support the contention that the treatment algorithm for moderate-to-severe psoriasis would change upon listing of apremilast. Expert opinion sought during the evaluation indicated that (i) the use of DMARDs was sometimes a means

to an end for eligibility for bDMARDs (except in cases of adequate response); and (ii) that increasing the number of treatments that need to be trialled and failed prior to eligibility for bDMARDs would not be well received by clinicians.

For more detail on PBAC's view, see section 7 "PBAC outcome".

5 Comparator

5.1 The submission nominated cyclosporin as the comparator.

5.2 The evaluation noted that cyclosporin may not be the only appropriate comparator. If apremilast is likely to be used subsequent to phototherapy and methotrexate, acitretin would also be a relevant comparator. If apremilast is used as an alternative to the current systemic therapies and phototherapy in the treatment of moderate-to-severe psoriasis, then phototherapy, methotrexate, cyclosporin and acitretin would all be appropriate comparators.

For more detail on PBAC's view, see section 7 "PBAC outcome".

6 Consideration of the evidence

Sponsor hearing

6.1 There was no hearing for this item.

Consumer comments

6.2 No consumer comments were received for this item.

Clinical trials

6.3 The submission was based on three head-to-head trials comparing apremilast to placebo (n=1,609) and one head-to-head trial comparing cyclosporin to placebo (n=128).

6.4 Details of the trials presented in the submission are provided in the table below.

Trials and associated reports presented in the submission

Trial ID	Protocol title/ Publication title	Publication citation
Direct randomised trials		
ESTEEM-1	CC-10004-PSOR-008. A Phase 3, multicentre, randomised, double-blind, placebo-controlled, efficacy and safety study of apremilast (CC-10004) in subjects with moderate to severe plaque psoriasis.	Clinical Study Report CC-10004-PSOR-008. July 2013.
ESTEEM-2	CC-10004-PSOR-009. A Phase 3, multicentre, randomised, double-blind, placebo-controlled, efficacy and safety study of apremilast (CC-10004) in subjects with moderate to severe plaque psoriasis.	Clinical Study Report CC-10004-PSOR-009. July 2013.

Trial ID	Protocol title/ Publication title	Publication citation
Direct randomised trials		
PSOR-005	CC-10004-PSOR-005-E-LTE. A Phase 2B, multicentre, randomised, double-blind, placebo-controlled, dose-ranging, efficacy and safety study of apremilast (CC-10004) in subjects with moderate-to-severe plaque-type psoriasis (PSOR-005) and two extension studies (PSOR-005E & PSOR-005LTE)	Clinical Study Report CC-10004-PSOR-005-E-LTE. December 2012.
Meffert 1997	Low-dose (1.25mg/kg) Cyclosporin A: Treatment of Psoriasis and Investigation of the Influence on Lipid Profile.	*Acta Derm Venerol (Stockh)* 1997; 77: 137-141.

Source: Table B.4, pp38-39 of the submission

6.5 The key features of the direct randomised trials are summarised in the table below. All trials had multiple phases and the first phase of each trial incorporated a randomised, double-blind, placebo-controlled design.

Key features of ESTEEM-1, ESTEEM-2, PSOR-005 and Meffert 1997

Trial	N	Design / duration	Risk of bias	Patient population	Outcome(s)	Use in modelled evaluation
ESTEEM-1	844	Two arm, four phase trial. Phase one: (2:1) R,DB,PC (16wk) Phase two: PX maintenance (16wk) Phase three: re-randomisation PASI75 treatment withdrawal (20wk) Phase four: OL extension (to 4yrs)	Phase one: low	Plaque psoriasis (PASI≥12 + BSA≥10% + sPGA≥3)	1°: PASI75 (wk16) 2°: PASI change/ response, QoL	Initial response: PASI50 (16wk), pooled ESTEEM-1 & ESTEEM-2; Cont. response: PASI50(wk52)|PASI75(wk32), ESTEEM-1; Utility: EQ-5D-3L, pooled ESTEEM-1 & ESTEEM-2;
ESTEEM-2	413	Two arm, four phase trial. Phase one: (2:1) R,DB,PC (16wk) Phase two: PX maintenance (16wk) Phase three: re-randomisation PASI50 treatment withdrawal (20wk) Phase four: OL extension (to 4yrs)				
PSOR-005	352	Four arm, three phase trial. Phase one: (1:1:1:1) R,BD,PC (16wk) + PX dose-B (8wk) Phase two: dose-B extension (28wk) Phase three: OL extension (to 4yrs)	Phase one: low	Plaque psoriasis (PASI≥12 + BSA≥10%, ≥6months)	1°: PASI75 (wk16) 2°: PASI change/ response, QoL	Not used.
Meffert 1997	128	Three arm, two phase trial. Phase one: R,BD,PC (10wk) Phase two: OL PX active (12wk)	Phase one: unclear	Plaque psoriasis (8≤PASI≤25)	1°: Change in PASI (wk10) 2°: PASI75 (wk10)	Not used.

Abbreviations: R=randomised; DB=double blind; PC=placebo controlled; OL=open label; PX=placebo crossover; dose-B=dose-blinded; PASI=psoriasis area severity index; BSA=body surface area; sPGA=static physician's global assessment; QoL=quality of life

Source: compiled during the evaluation

Comparative effectiveness

6.6 While no response criteria were specified in the requested restriction for apremilast or in the existing restrictions for other systemic therapies (methotrexate, acitretin or cyclosporin), the evaluation considered that it may reasonable to asses response to treatment using a PASI 75 response, given this is the response rate that this required in order for continued therapy with bDMARDs on the PBS. PASI 75 was measured in all of the included trials, as the primary outcome at 16 weeks in ESTEEM-1, ESTEEM-2 and PSOR-005, and as a secondary outcome at 10 weeks in Meffert 1997. The submission claimed that the relevant outcome to assess response in moderate-to-severe plaque psoriasis is PASI 50 (i.e. 50% improvement from the baseline PASI score). However, as the premise of the submission was that the treatment algorithm would change upon listing apremilast, such that patients would delay commencement of biologic therapy, accepting a PASI 50 response would require acceptance that patients would be willing to forego the potential for additional improvement in their condition from bDMARD treatment. Using a more stringent criterion for response to apremilast (e.g. PASI 75) would reduce the time spent receiving apremilast, but therefore also reduce the reported QALY gains and cost savings.

6.7 The results of PASI 75 response assessed at 16 weeks in the apremilast trials and assessed at 10 weeks in the cyclosporin trial are presented in the table below.

Summary of results of the indirect comparison of PASI 75 response at 16 weeks on apremilast versus PASI 75 response at 10 weeks on cyclosporin

	Apremilast				Cyclosporin			Indirect RR[c] (95% CI)	Indirect RD[c] (95% CI)
	RD[a] (95% CI)	RR[a] (95% CI)	APR *n* /*N* (%)	PBO *n* /*N* (%)	CSP *n* /*N* (%)	RR[b] (95% CI)	RD[b] (95% CI)		
ESTEEM-1*	**0.28 (0.23, 0.32)**	**6.22 (3.75, 10.3)**	186/562 (33.1)	15/282 (5.3)	–	–	–	–	–
ESTEEM-2*	**0.23 (0.16, 0.30)**	**4.94 (2.46, 9.92)**	79/274 (28.8)	8/137 (5.8)	–	–	–	–	–
PSOR-005*	**0.35 (0.24, 0.47)**	**7.20 (2.96, 17.5)**	36/88 (40.1)	5/88 (5.7)	–	–	–	–	–
Meffert 1997	–	–	–	2/43 (4.7)	13/44 (30.0)	**6.35 (1.52, 26.5)**	**0.25 (0.10, 0.40)**	–	–
Pooled[d]	***0.27 (0.22, 0.33)***	***5.98 (4.12, 8.67)***	–	–	–	**6.35 (1.52, 26.5)**	**0.25 (0.10, 0.40)**	*0.94 (0.22, 4.12)*	*0.02 (-0.14, 0.18)*

Abbreviations: CI = confidence interval; *n* = number with event; *N* = number in group; RR = relative risk

* LOCF analysis

[a] proposed drug over common reference

[b] main comparator over common reference

[c] inferred as proposed drug over main comparator

[d] pooled using the random effects model

Source: Tables B.22, B.32 and B.47, pp61, 67 and 75

6.8 The cyclosporin outcomes above had wide confidence intervals around the relative risk (RR) and risk difference (RD), which contributed to wide confidence intervals in the indirect comparison. Therefore, the assertion of non-inferiority was sensitive to small changes in event rates in the cyclosporin group.

Comparative harms

6.9 The adverse events reported in the apremilast trials up to week 16 are summarised in the table below.

Summary of adverse events in ESTEEM-1, ESTEEM-2 and PSOR-005 to 16 weeks (placebo-controlled phase)

	ESTEEM-1		ESTEEM-2		PSOR-005	
	PBO (N=282)	APR (N=560)	PBO (N=136)	APR (N=272)	PBO (N=88)	APR (N=88)
Any TEAE	157 (55.7)	388 (69.3)	82 (60.3)	185 (68.0)	57 (64.8)	72 (81.8)
URTI[a]	21 (7.4)	57 (10.2)	-	-	4 (4.5)	14 (15.9)
Viral URTI[a]	-	-	-	-	8 (9.1)	7 (8.0)
Nasopharyngitis[a]	23 (8.2)	41 (7.3)	6 (4.4)	20 (7.4)	7 (8.0)	5 (5.7)
Gastroenteritis[a]	-	-	-	-	3 (3.4)	5 (5.7)
Tension headache[a]	12 (4.3)	41 (7.3)	2 (1.5)	20 (7.4)	7 (8.0)	14 (15.9)
Headache[a]	13 (4.6)	31 (5.5)	1 (0.7)	17 (6.3)	5 (5.7)	7 (8.0)
Diarrhoea[a]	20 (7.1)	105 (18.8)	8 (5.9)	43 (15.8)	4 (4.5)	12 (13.6)
Nausea[a]	19 (6.7)	88 (15.7)	9 (6.6)	50 (18.4)	7 (8.0)	17 (19.3)
Vomiting[a]	-	-	5 (3.7)	14 (5.1)	-	-
Dyspepsia[a]	-	-	-	-	2 (2.3)	4 (4.5)
Psoriasis[a]	-	-	7 (5.1)	4 (1.5)	-	-
Pain in extremity[a]	-	-	-	-	6 (6.8)	1 (1.1)
Any Drug-related TEAE	58 (20.6)	224 (40.0)	29 (21.3)	106 (39.0)	11 (12.5)	32 (36.4)
Any Mild TEAE	88 (31.2)	221 (39.5)	38 (27.9)	92 (33.8)	25 (28.4)	36 (40.9)
Any Moderate TEAE	60 (21.3)	147 (26.3)	38 (27.9)	81 (29.8)	29 (33.0)	29 (33.0)
Any Severe TEAE	9 (3.2)	20 (3.6)	6 (4.4)	12 (4.4)	3 (3.4)	5 (5.7)
Diarrhoea[b]	1 (0.4)	2 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Nausea[b]	1 (0.4)	2 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Headache[b]	0 (0.0)	2 (0.4)	0 (0.0)	2 (0.7)	0 (0.0)	1 (1.1)
Psoriasis[b]	1 (0.4)	2 (0.4)	1 (0.7)	0 (0.0)	1 (0.7)	0 (0.0)
Any Serious TEAE	8 (2.8)	12 (2.1)	3 (2.2)	5 (1.8)	2 (2.3)	4 (4.5)
Any Serious Drug-related TEAE	0 (0)	4 (0.7)	0 (0)	0 (0)	0 (0)	0 (0)
Any TEAE Leading to interruption	13 (4.6)	37 (6.6)	4 (2.9)	16 (5.9)	4 (4.5)	6 (6.8)
Any TEAE Leading to withdrawal	9 (3.2)	29 (5.2)	7 (5.1)	15 (5.5)	5 (5.7)	12 (13.6)a
Any TEAE Leading to death	1 (0.4)	1 (0.2)	0 (0)	0 (0)	1 (1.1)	0 (0)

[a] TEAEs that occurred in ≥5% of patients in any treatment group

[b] severe TEAE reported by ≥2 subjects

Source: Tables B.55, B.56 and B.57, pp82-83 of the submission

6.10 No new pattern of treatment-emergent adverse events (TEAEs) were observed with longer exposure to apremilast and no TEAEs or serious TEAEs indicative of a long-term cumulative toxicity were observed.

6.11 The submission did not present an indirect comparison between apremilast and cyclosporin for safety outcomes. Adverse events reported by Meffert (1997) were not adequately described with results reported as aggregated values across all treatment arms including placebo. The safety profile of cyclosporin is well known. Common adverse events reported in the cyclosporin Product Information include: hypertension, hirsutism, impaired renal function, gingival hypertrophy, gastrointestinal disturbances, tremor and fatigue, and hyperlipidaemia.

Benefits/harms

6.12 A summary of the comparative benefits and harms for apremilast versus cyclosporin is presented in the table below.

Summary of comparative benefits for apremilast and cyclosporin/placebo

Trial	APR	Cyclo/PBO	RR (95% CI)	Event rate/100 patients*		RD (95% CI)
				APR	Cyclo/PBO	
Benefits						
Dichotomous Outcome: PASI 75 response						

	APR	PBO	Cyclo	RR (95% CI)	Event rate/100 patients*			RD (95% CI)
					APR	PBO	Cyclo	
ESTEEM-1*	186/562	15/282	-	**6.22 (3.75, 10.3)**	33	5	-	**0.28 (0.23, 0.32)**
ESTEEM-2*	79/274	8/137	-	**4.94 (2.46, 9.92)**	29	6	-	**0.23 (0.16, 0.30)**
PSOR-005*	36/88	5/88	-	**7.20 (2.96, 17.5)**	40	6	-	**0.35 (0.24, 0.47)**
			Pooled	***5.98 (4.12, 8.67)***	33	6	-	***0.27 (0.22, 0.33)***
Meffert 1997	-	2/43	13/44	**6.35 (1.52, 26.5**	-	5	30	**0.25 (0.10, 0.40)**
Indirect comparison: Pooled versus Meffert 1997				*0.94 (0.22, 4.12)*	-			*0.02 (-0.14, 0.18)*
Dichotomous Outcome: PASI 50 response								

	APR	PBO	Cyclo	RR (95% CI)	Event rate/100 patients*			RD (95% CI)
					APR	PBO	Cyclo	
ESTEEM-1*	330/562	48/282	-	**3.45 (2.64, 4.50)**	59	17	-	**0.42 (0.36, 0.48)**
ESTEEM-2*	152/274	27/137	-	**2.81 (1.98, 4.01)**	56	20	-	**0.36 (0.27, 0.45)**
PSOR-005*	53/88	22/88	-	**2.41 (1.62, 3.59)**	60	25	-	**0.35 (0.22, 0.49)**
			Pooled	***2.98 (2.42, 3.67)***	58	19	-	***0.39 (0.35, 0.44)***
Meffert 1997	-	4/43	26/44	***6.35 (2.42, 16.7)***	-	9	59	***0.50 (0.33, 0.67)***
Indirect comparison: Pooled versus Meffert 1997				*0.47 (0.18, 1.26)*	-			*-0.11 (-0.29,0.07)*

Abbreviations: APR = apremilast; PBO = placebo; Cyclo = cyclosporin; RD = risk difference; RR = risk ratio
Source: Compiled during the evaluation

6.13 On the basis of direct evidence presented by the submission, for every 100 patients treated with apremilast in comparison to placebo:

- Approximately 27 additional patients would achieve a PASI 75 improvement over 16 weeks of treatment, and

- Approximately 39 additional patients would achieve a PASI 50 improvement over 16 weeks of treatment.

On the basis of direct evidence presented by the submission, for every 100 patients treated with cyclosporin in comparison to placebo:

- Approximately 25 additional patients would achieve a PASI 75 improvement over 16 weeks of treatment, and
- Approximately 50 additional patients would achieve a PASI 50 improvement over 16 weeks of treatment.

6.14 There were no statistically significant differences in the number of patients achieving PASI 75 or PASI 50 improvement in those treated with apremilast (30 mg twice daily for 16 weeks, including titration) or cyclosporin (2.5 mg/kg for 10 weeks), and the point estimate from the indirect comparison in terms of PASI 50 tends towards inferiority.

Clinical claim

6.15 The submission described apremilast as non-inferior in terms of comparative effectiveness and superior in terms of safety ("comparable" in terms of short-term safety but "favourable" in terms of long-term safety), over cyclosporin.

6.16 The evaluation noted that the evidence presented in the submission supported the conclusion that apremilast 30 mg twice daily for 16 weeks (including a titration period of 2 weeks) is non-inferior in terms of comparative effectiveness to cyclosporin 2.5mg/kg/day for 10 weeks. However, a thorough assessment of comparative safety was not presented.

6.17 The evaluation identified that a fixed dose of cyclosporin 2.5 mg/kg/day for 10 weeks is not the recommended dose regimen in the Product Information. Thus, the comparative effectiveness (and safety) of apremilast and cyclosporin (as used in the Australian setting) is unknown. Should the dose of cyclosporin in the Australian setting be higher than 2.5 mg/kg/day, the evaluation identified the possibility that apremilast is inferior to cyclosporin could not be excluded.

6.18 The ESC considered that the claim of non-inferior comparative effectiveness was reasonable based on the trial results presented. However, the ESC noted that while cyclosporin's safety profile is well known, US prescribing information on apremilast provides warnings and precautions on depression and weight decrease. In the absence of long-term comparative safety data, it was difficult for the ESC to form an overall view on comparative safety.

For more detail on PBAC's view, see section 7 "PBAC outcome".

Economic analysis

6.19 The submission presented a cost-utility analysis based on the premise that the listing of apremilast would extend the period of time patients would be treated with systemic therapies for psoriasis and delay the commencement of more costly bDMARDs.

6.20 The submission presented a modelled comparison of:

- the "current treatment algorithm (without apremilast)" in which patients receive phototherapy + 2 lines of systemic therapy (including methotrexate) prior to biologic treatment, and
- the "proposed treatment algorithm (with apremilast)" in which patients receive phototherapy + 3 lines of systemic therapy (including methotrexate and apremilast) prior to biologic treatment.

6.21 The results of the modelled economic evaluation presented by the submission claimed that the "proposed algorithm (with apremilast) is less costly and more effective than the current algorithm.

6.22 The evaluation considered the economic modelling to be uninformative because if apremilast was PBS-listed, it would represent an alternative therapy to phototherapy, methotrexate, cyclosporin or acitretin prior to commencement of treatment with bDMARDs, thereby creating a further line of systemic therapy which may inappropriately delay treatment with bDMARD therapy. The evaluation noted that the cost savings estimated in the submission's modelled economic evaluation resulted from the addition of a systemic line of therapy to the "proposed algorithm" and delay of more costly (but more effective) bDMARD therapy, regardless of whether that drug is apremilast or one of the other currently listed systemic drugs. The evaluation noted that using the logic of the submission's economic modelling, even greater savings would result by further use of the currently listed systemic therapies given that the proposed price of apremilast was considerably higher than current systemic therapies).

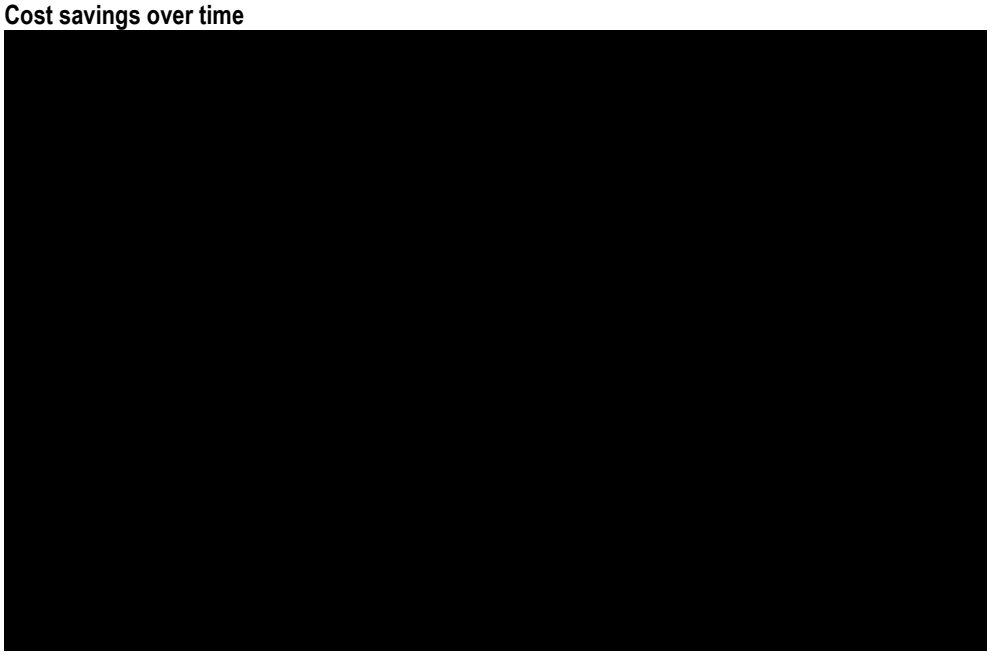
6.23 Sensitivity analyses conducted during the evaluation confirmed that the model was driven by the addition of a systemic line of therapy to the "proposed algorithm", regardless of whether that drug is apremilast or one of the other currently listed systemic drugs. Thus, by adding this line of therapy:

- Patients in the "proposed arm" are treated with systemic therapy for a longer duration of time, and therefore a greater proportion of patients are assumed to be suffering from "moderate to severe" compared to "severe" disease;
- Patients in the "proposed arm" accrue greater QALYs because "moderate to severe" disease is associated with higher quality of life compared with "severe" disease; and
- Ultimately, fewer patients in the "proposed arm" receive treatment with biologic therapy (88% v 95% by the end of the model, respectively), which is cost saving.

6.24 The ESC advised that if it was assumed that listing apremilast would extend the number of therapies required to be trialled before being eligible for bDMARD treatment, the following issues would need to be considered:

- The time horizon of the model. The model was based on ten years, but the ESC noted that the predicted cost savings are smaller, or negative, under both shorter and longer durations than 7-10 years. The figure below graphs the cost savings over time and it can be seen that savings are greatest around the 7 – 10 year mark.

Cost savings over time



- The transition probabilities for ongoing discontinuation could not be replicated by the evaluators or the ESC.
- The use of the American algorithm to derive EQ-5D-3L weights was not justified. The trials collected SF-36 utility data, and it was unclear why SF-6D weights were not reported.
- The baseline utility for patients entering third-line therapy (cyclosporin/acitretin in the intervention sequence, ustekinumab in the comparator) depended on which sequence the patient was in. This was inappropriate and exaggerated the QALY gain.

6.25 A cost-minimisation analysis performed by the evaluation and based on an assumption that apremilast 30 mg twice daily over 16 weeks (including titration) is non-inferior to cyclosporin 2.5 mg/kg/day over 10 weeks in terms of efficacy and safety, was presented and shown in the table below. Assumptions included:

- Patients weigh 90 kg (patients in the submission's model had an assumed weight of 92.62 kg based on ESTEEM-1 and ESTEEM-2), requiring a total dose of 225 mg cyclosporin per day;
- Total dosing per day is comprised on 2 x 100 mg and 1 x 25 mg cyclosporin capsules; and
- Section 100 pricing of cyclosporin was used which included initiation, stabilisation and review of therapy.

Cost-minimisation analysis based on the conclusion that apremilast 30 mg twice daily over 16 weeks (including titration) is non-inferior to cyclosporin 2.5 mg/kg/day over 10 weeks in terms of efficacy and safety

Strength (#tabs/script)	Cost (DPMQ)[a]	Cost (ex-man)	Cost (ex-man) / mg	Initiation period					
				Dose	Duration	#tabs/ day	Total mg	Cost/ total mg	Total cost
Cyclosporin									
100mg (120)	$651.08*	$651.08#	$0.054	225mg/day&	10wks	2	14000mg	$756.00	$845.25
25mg (120)	$153.56^	$153.56#	$0.051			1	1750mg	$89.25	
Apremilast									
Titration (27)	$[redacted]	$[redacted]	$[redacted]	Titration	2wks	1 -> 2[b]	690mg	$[redacted]	
30mg (56)	$[redacted]	$[redacted]		60mg/day	14wks	2	5880mg	$[redacted]	

* PBS item 5636P ^PBS item 5634M # S100 Public DPMQ = ex-manufacturer price & assuming 2.5 mg/kg/day * 90 kg

[a] calculated as ex-man price + wholesaler mark-up (7.52%), + pharmacy mark-up of 10% ($45.01-$180.00) or $18.00 ($180.01-$450.00) + dispensing fee ($6.76)

[b] see titration schedule

6.26 Whilst the above cost-minimisation analysis provided an indication of an estimated price for apremilast which is supported by the data presented in the submission, it did not consider:

- Subsequent maintenance dosing with cyclosporin under the General Schedule; where cyclosporin 25 mg x 60 capsules and 100 mg x 60 capsules have DPMQs of $97.58 and $374.78, respectively;
- All of the comparators relevant to moderate and severe psoriasis, where the therapeutic relativities of them are unknown; and
- The proportional split of likely use of each of the relevant comparators for moderate and severe psoriasis.

For more detail on PBAC's view, see section 7 "PBAC outcome".

Drug cost/patient/course/year:

6.27 $[redacted] based on the requested price and assuming one initiation and 12 maintenance scripts per year. This compared with $[redacted] based on the price estimated from the cost-minimisation analysis presented above, assuming apremilast 30 mg twice daily for 16 weeks (including a titration period of 2 weeks) is non-inferior in terms of comparative effectiveness to cyclosporin 2.5 mg/kg/day for 10 weeks. The cost of cyclosporin could not be estimated given details of the mean weight of psoriasis patients and mean dose of cyclosporin used in the Australian setting was unknown to the evaluation.

Estimated PBS usage & financial implications

6.28 This submission was not considered by DUSC.

6.29 Like the economic evaluation presented by the submission, the financial estimates provided were based on the premise that apremilast would expand the treatment sequence for plaque psoriasis. The evaluation considered these estimates to be uninformative as this was likely to be clinically inappropriate and therefore not likely to be reflective of actual use in practice.

6.30 The submission estimated that the number of patients would be less than 10,000 and the net cost to the PBS would be less than $10 million per year in Year 1. This increases in Year 5 to less than 10,000 per year patients initiating treatment (less than 10,000 per year on treatment) and the net cost to the PBS would be $30 – $60 million. The net cost is due to the addition of a line of therapy to the algorithm (which is more costly than current non-bDMARD systemic therapies, but less costly than bDMARDs) and the majority of cost-offsets being derived from reduced use of ustekinumab. The likely financial impact of listing apremilast when assuming it would replace existing therapies (phototherapy, methotrexate, cyclosporin or acitretin) was considered unknown by the evaluation.

For more detail on PBAC's view, see section 7 "PBAC outcome".

7 PBAC Outcome

7.1 The PBAC rejected the submission on the basis that cost-effectiveness compared to cyclosporin treatment had not been adequately established at the price proposed in the submission. An incremental benefit in terms of comparative efficacy and safety over cyclosporin was not evident for apremilast and so it did not appear clinically appropriate to require patients to trial an additional line of therapy before being eligible for bDMARD therapy. Therefore, the cost-utility analysis approach to the economic modelling was not considered informative.

7.2 The PBAC noted the submission's proposed clinical place in therapy for apremilast as an additional treatment to cyclosporin or acitretin following inadequate response to methotrexate. Given that the current PBS restrictions for bDMARD therapy for plaque psoriasis require a patient to have trialled at least 3 treatment options from a list of 4 (phototherapy, cyclosporin, methotrexate or acitretin) and the submission's proposed treatment algorithm suggested a patient trial 4 treatment options from a list of 5 (phototherapy, cyclosporin, methotrexate, acitretin or apremilast), the PBAC expressed concerns over the potential delay in prescribers being able to initiate bDMARD therapy.

7.3 The submission's nominated comparator was cyclosporin. The PBAC accepted this, but noted that acitretin would also be a relevant comparator.

7.4 The PBAC noted that in the indirect comparison of apremilast to cyclosporin, all three individual apremilast trials demonstrated a statistically significant effect in terms of PASI 75 or PASI 50 improvement compared to placebo and that the cyclosporin trial also demonstrated a statistically significant effect for cyclosporin over placebo using the same outcome measures. However, when indirectly comparing apremilast to cyclosporin, the PASI 50 results favoured cyclosporin over apremilast. The PBAC further noted that the fixed dose of cyclosporin 2.5 mg/kg/day for 10 weeks in the Meffert (1997) trial was not the recommended dose regimen specified in the Product Information and was possibly sub-optimal. Therefore, in the PBAC's view, non-inferiority in terms of comparative effectiveness, had not been established.

7.5 In the absence of a formal indirect comparison between apremilast and cyclosporin in terms of comparative harms and the absence of long term comparative safety data

for apremilast, the PBAC did not consider the submission's claim of superior safety to have been adequately supported. The PBAC recognised cyclosporin's safety profile is well known but the PBAC also noted potential safety signals for apremilast in terms of increased risk of weight loss and possibly depression. The PBAC was of a view that claims of superior safety over cyclosporin would need to be adequately quantified and supported by further long term comparative safety data.

7.6 For the reasons outlined in the evaluation, the PBAC did not find the submission's cost-utility analysis informative. Given that it was the PBAC's view that it would be clinically inappropriate to potentially delay the commencement of more effective (but more costly) treatments in the form bDMARD therapies, the submission's economic analysis modelled a treatment scenario that is unlikely to be realised in practice. The PBAC was further of the view that the potential harm in delaying bDMARD therapy and the associated disutility of this was not adequately captured in the economic model.

7.7 The PBAC also considered the submission's estimates of patient usage and financial implications to be unreliable for the same reasons.

7.8 Given that the cost savings estimated by the submission by introducing apremilast to the DMARD phase of the treatment algorithm were not adequately supported by data, the PBAC suggested that an alternative approach to any re-submission should seek to be limited to a simple comparison of apremilast to cyclosporin in terms of comparative efficacy and safety alone. Modelling the potential harm of delaying bDMARD therapy and the associated disutility would be difficult as these data are unlikely to be available. If further data became available to establish a claim that apremilast has less toxicity than cyclosporin, then a re-submission could use a cost-utility approach to the economic analysis. The PBAC was of the view that any re-submission should be a major submission.

7.9 The PBAC noted that this submission is eligible for an Independent Review.

Outcome:
Rejected

8 Context for Decision

The PBAC helps decide whether and, if so, how medicines should be subsidised in Australia. It considers submissions in this context. A PBAC decision not to recommend listing or not to recommend changing a listing does not represent a final PBAC view about the merits of the medicine. A company can resubmit to the PBAC or seek independent review of the PBAC decision.

9 Sponsor's Comment

The Sponsor had no comment.