5.02 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 severe active psoriatic arthritis in patients meeting certain criteria.

2 Requested listing

2.1 The submission sought the following listing with suggestions proposed by the Secretariat to the requested listing shown in italics and strikethrough.

Name, Restriction, Manner of administration and form	Max. Qty	№.of Rpts	Dispensed Price for Max. Qty	Proprietary Name and Manufacturer	
APREMILAST apremilast 10 mg tablet [4] (&) apremilast 20 mg tablet [4] (&) apremilast 30 mg tablet [19], 1 pack	1	0	$[redacted]	Otezla	CJ

Category / Program	GENERAL – General Schedule (Code GE)
Prescriber type:	☐Dental ☒Medical Practitioners ☐Nurse practitioners ☐Optometrists ☐Midwives
Episodicity:	-
Severity:	Severe
Condition:	active psoriatic arthritis
PBS Indication:	Severe active psoriatic arthritis
Treatment phase:	Initial
Restriction Level / Method:	☐Restricted benefit ☐Authority Required - In Writing ☐Authority Required - Telephone ☐Authority Required – Emergency ☐Authority Required - Electronic ☒Streamlined
Treatment criteria:	Patient must be ~~initiated~~ treated initially by a rheumatologist or dermatologist

Clinical criteria:	Patient must have previously received and failed to achieve an adequate response to one or more disease modifying anti-rheumatic drugs including methotrexate; OR Patient must be clinically inappropriate for treatment with one or more disease modifying anti-rheumatic drugs (including methotrexate). AND The treatment must be for dose titration purposes.

Name, Restriction, Manner of administration and form	Max. Qty	№.of Rpts	Dispensed Price for Max. Qty	Proprietary Name and Manufacturer	
APREMILAST apremilast 30 mg tablet, 56	1	5	$[redacted]	Otezla	CJ

Category / Program	GENERAL – General Schedule (Code GE)
Prescriber type:	☐Dental ☒Medical Practitioners ☐Nurse practitioners ☐Optometrists ☐Midwives
Episodicity:	-
Severity:	Severe
Condition:	active psoriatic arthritis
PBS Indication:	Severe active psoriatic arthritis
Treatment phase:	Continuing
Restriction Level / Method:	☐Restricted benefit ☐Authority Required - In Writing ☐Authority Required - Telephone ☐Authority Required – Emergency ☐Authority Required - Electronic ☒Streamlined
Treatment criteria:	Patient must be ~~initiated~~ treated initially by a rheumatologist or dermatologist
Clinical criteria:	Patient must have previously received and failed to achieve an adequate response to one or more disease modifying anti-rheumatic drugs including methotrexate; OR Patient must be clinically inappropriate for treatment with one or more disease modifying anti-rheumatic drugs (including methotrexate). AND Patient must have previously been treated with PBS-subsidised apremilast.

2.2 The requested restriction did not specify any criterion to demonstrate an adequate response to qualify for continuing treatment (such as tender or swollen joint counts, ACR20/ACR50 response), or any timeframes for making such assessments. No response criteria are specified in the existing restrictions for other DMARDs (methotrexate, leflunomide or sulfasalazine). In order for continued therapy with bDMARDs on the PBS, adequate response is defined by erythrocyte sedimentation rate (ESR) / C-reactive protein (CRP) measurements and active (tender and swollen) joint counts. The PBS continuation criteria for bDMARDs appear to be more similar to the outcome of ACR 50 response, rather than ACR 20 response.

2.3 The ESC noted that in various forms of inflammatory arthritis, treatments combined with methotrexate generally produce better outcomes than treatments that are not combined with methotrexate. A brief literature search indicated that apremilast may be used with methotrexate but whether there is an additive benefit of the two drugs was unclear.

2.4 The PBAC noted that the requested restriction allowed prescribing by dermatologists. The PBAC considered that limiting prescribing to rheumatologists for this condition would be more appropriate.

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

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 plaque psoriasis was also considered at the March 2015 PBAC meeting (agenda item 5.01).

3.3 This submission was made under TGA/PBAC parallel process provisions. At the time of PBAC consideration, apremilast had been approved by the Advisory Committee on Prescription Medicines (ACPM) in February 2015 for the following indication:

- *Treatment 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.*

4 Clinical place for the proposed therapy

4.1 The submission proposed that apremilast would be used as a subsequent treatment to methotrexate, but before leflunomide or sulfasalazine, for patients with psoriatic arthritis. The requested restriction for apremilast implied that patients must have trialled and failed at least one disease modifying anti-rheumatic drug (DMARD), for which no rationale is provided. This limitation on use is narrower than the proposed TGA indication which does not necessarily restrict use to treatment naïve or treatment experienced patients and 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 have represented use outside of the proposed PBS restriction.

4.2 The submission stated that apremilast is not expected to directly substitute for any currently listed drugs, but rather displace existing therapies and extend the pre-bDMARD treatment phase in psoriatic arthritis. Specifically, the submission suggested that should apremilast be listed on the PBS, patients with psoriatic arthritis will undergo treatment with 3 of 4 of the following treatments before bDMARD therapy: methotrexate, leflunomide, sulfasalazine or apremilast. The submission provided no data to support the contention that the treatment algorithm for psoriatic arthritis should change upon listing of apremilast. Expert opinion was sought during the evaluation and 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. The ESC was therefore of the view that apremilast is more likely to substitute for an existing DMARD (methotrexate, leflunomide, sulfasalazine) than add a further line of therapy.

4.3 The ESC further questioned whether a potential delay in the access of bDMARD therapy resulting from the introduction of apremilast is clinically appropriate. It is unclear whether it is clinically appropriate to require a patient to trial and fail treatment with 3 therapies prior to bDMARD therapy particularly in the context of the lack of evidence of apremilast's 'disease modifying' action.

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

5 Comparator

5.1 The submission nominated leflunomide as the comparator.

5.2 The evaluation considered that leflunomide is not the only appropriate comparator. The evaluation noted that if apremilast is likely to be used following methotrexate, sulfasalazine would also be a relevant comparator. If apremilast was used as an alternative to the current DMARDs, then methotrexate, leflunomide and sulfasalazine would be the appropriate comparators. The ESC agreed with this view and as noted above, was of the view that the latter scenario would be more likely.

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 The PBAC noted that no consumer comments were received for this item.

Clinical trials

6.3 The submission was based on three pivotal head-to-head trials comparing apremilast to placebo (n=993) in DMARD-experienced patients and one head-to-head trial comparing leflunomide to placebo (n=190) in a mixed population of DMARD-experienced and -naïve patients. A further supplementary trial comparing apremilast and placebo (n=352) in DMARD-naïve patients was also presented.

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/First Author	Protocol title/ Publication title	Publication citation
Direct randomised trials		
PALACE 1	CC-10004-PSA-002. A phase 3, multicentre, randomised, double-blind, placebo-controlled, parallel-group, efficacy and safety study of two doses of apremilast (CC-10004) in subjects with active psoriatic arthritis.	Clinical Study Report CC-10004-PSA-002. September 2013.
PALACE 2	CC-10004-PSA-003. A phase 3, multicentre, randomised, double-blind, placebo-controlled, parallel-group, efficacy and safety study of two doses of apremilast (CC-10004) in subjects with active psoriatic arthritis.	Clinical Study Report CC-10004-PSA-003. September 2013.
PALACE 3	CC-10004-PSA-004. A phase 3, multicentre, randomised, double-blind, placebo-controlled, parallel-group, efficacy and safety study of two doses of apremilast (CC-10004) in subjects with active psoriatic arthritis and a qualifying psoriasis lesion	Clinical Study Report CC-10004-PSA-004. September 2013.
TOPAS	Kaltwasser JP et al. Efficacy and safety of leflunomide in the treatment of psoriatic arthritis and psoriasis. Nash P et al. Leflunomide improves psoriasis in patients with psoriatic arthritis: An in-depth analysis of data from the TOPAS study.	Arthritis and Rheumatism, 2004; 50(6):1939-1950. Dermatology, 2006; 212: 238-249.
Supplementary randomised trial		
PALACE 4	CC-10004-PSA-005. A phase 3, multicentre, randomised, double-blind, placebo-controlled, parallel-group, efficacy and safety study of two doses of apremilast (CC-10004) in subjects with active psoriatic arthritis who have not been previously treated with disease-modifying antirheumatic drugs.	Clinical Study Report CC-10004-PSA-005. December 2013.

Source: Table B.4, pp37-38 of the submission.

6.5 The key features of the randomised trials are summarised in the table below.

Key features of the included evidence – indirect comparison

Trial	N	Design / duration	Risk of bias	Patient population	Outcome(s)	Use in modelled evaluation
PALACE 1	336	Three arm, two phase trial. • Phase one: (1:1:1) R,DB,PC	Phase 1: low	PsA (≥3 swollen and ≥3 tender joints despite prior or current use of DMARDs)	1°: ACR20 (wk16) 2°: HAQ-DI, modified PsARC, PASI;	Initial response: ACR20 (16wk), pooled; Utility: EQ-5D pooled
PALACE 2	321					
PALACE 3	336					

Trial	N	Design / duration	Risk of bias	Patient population	Outcome(s)	Use in modelled evaluation
PALACE 4	352	(24wk) • Phase two: active treatment / long-term safety (236wk)		PsA (≥3 swollen and ≥3 tender joints); not previously treated with DMARDs	QoL	Not used
TOPAS	190	Two arm R,DB,PC trial (24wk)	Phase 1: low	PsA (≥ 3 swollen and ≥ 3 tender joints)	1°: PsARC (wk24) 2°: ACR20, PASI, QoL	Not used.

Abbreviations: ACR = American College of Rheumatology; HAQ-DI=Health Assessment Questionnaire – Disability Index; PASI=Psoriasis area and severity index; PsARC=Psoriatic Arthritis Response Criteria; R=randomised; DB=double blind; PC=placebo controlled; PsA=psoriatic arthritis; OL=open label; QoL=quality of life
Source: compiled during the evaluation

6.6 All of the apremilast trials had multiple phases and the first phase of each trial incorporated a randomised, double-blind, placebo-controlled design.

Comparative effectiveness

6.7 No response criteria were specified in the requested restriction for apremilast or in the existing restrictions for other DMARDs (methotrexate, leflunomide or sulfasalazine). The evaluation advised that it may not be reasonable to assume that an ACR20 response would be applicable to a PBS population, given that in order to qualify for continued treatment with bDMARDs on the PBS, adequate response is defined by erythrocyte sedimentation rate (ESR)/C-reactive protein (CRP) measurements and active (tender and swollen) joint counts, which is more in keeping with ACR50 criteria. ACR20 response was measured in all of the included trials, as the primary outcome at 16 weeks in the apremilast trials, and as a secondary outcome at 24 weeks in the leflunomide trial.

6.8 The results of ACR 20 response assessed at 24 weeks in the apremilast and leflunomide trials are presented in the table below.

Summary of results of the indirect comparison of ACR 20 response at 24 weeks on apremilast versus ACR 20 response at 24 weeks on leflunomide

Trial	Apremilast			Leflunomide				Indirect RR[c] (95% CI)	Indirect RD[c] (95% CI)
	RD[a] (95% CI)	RR[a] (95% CI)	APR n /N (%)	PBO n /N (%)	LEF n /N (%)	RR[b] (95% CI)	RD[b] (95% CI)		
PALACE 1	**0.22 (0.13, 0.31)**	**2.68 (1.73, 4.17)**	59/168 (35.1)	22/168 (13.1)	–	–	–	–	–
PALACE 2	**0.09 (0.00, 0.18)**	**1.57 (1.00, 2.46)**	40/162 (24.7)	25/159 (15.7)	–	–	–	–	–
PALACE 3	**0.16 (0.07, 0.25)**	**2.02 (1.33, 3.08)**	52/167 (31.1)	26/169 (15.4)	–	–	–	–	–
PALACE 4	**0.11 (0.03, 0.19)**	**1.87 (1.18, 2.97)**	43/176 (24.4)	23/176 (13.1)					
TOPAS	–	–	–	16/91 (17.6)	29/95 (30.5)	**1.74 (1.01, 2.97)**	**0.13 (0.01, 0.25)**	–	–
Pooled[d] (1-3)	**0.16 (0.08, 0.23)**	**2.05 (1.52, 2.76)**	–	–	–	**1.74 (1.01, 2.97)**	**0.13 (0.01, 0.25)**	1.18 (0.64, 2.18)	0.03 (-0.11, 0.17)
Pooled[e] (1-4)	**0.14 (0.09, 0.20)**	**2.01 (1.61, 2.50)**	–	–	–	**1.74 (1.01, 2.97)**	**0.13 (0.01, 0.25)**	1.16 (0.65, 2.07)	0.01 (-0.12, 0.14)

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

Source: p83 of the submission; p5, Appendix 1 of the submission.

[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

6.9 No statistically significant difference in the proportion of patients achieving an ACR 20 response at Week 24 were observed in an indirect comparison of apremilast 30 mg twice daily and leflunomide 20 mg once daily. This was consistent across DMARD-experienced patients treated with apremilast (PALACE 1-3) and both DMARD-experienced and DMARD-naïve patients treated with apremilast (PALACE 1-4). The comparison also demonstrated that apremilast met the non-inferiority criteria (i.e. the lower boundary of the 95% confidence interval of the relative risk of ACR 20 response was greater than 0.46 (golimumab Public Summary Document 2010)).

6.10 The PBS continuation criteria for bDMARDs are more similar to the ACR 50 response outcome in the PALACE trials, at least in terms of measuring active joint counts. For this reason, the ACR 50 outcome in the trials was considered important by the evaluation, more so than the primary trial outcome of ACR 20. ACR 50 response was a secondary outcome in the apremilast trials. ACR 50 response was not measured in the leflunomide trial. The tables below present the result of ACR 50 response for apremilast at week 16 and week 24.

Results of ACR 50 response at Week 16 across the randomised trials – apremilast

Trial	Apremilast 30 n/N (%)	Placebo n/N (%)	RD (95% CI)	NNT (95% CI)	RR (95% CI)
PALACE 1	27/168 (16.1)	10/168 (6.0)	**0.10 (0.04, 0.17)**	**10 (6, 25)**	**2.70 (1.35, 5.40)**
PALACE 2	17/162 (10.5)	8/159 (5.0)	0.05 (0.00, 0.11)	NA	2.09 (0.93, 4.69)
PALACE 3	25/167 (15.0)	14/169 (8.3)	0.07 (0.00, 0.14)	NA	1.81 (0.97, 3.35)
		Pooled result (1-3)	**0.07 (0.04, 0.11)**	**14 (9, 25)**	**2.14 (1.43, 3.20)**
PALACE 4	20/176 (11.4)	8/176 (4.5)	**0.07 (0.01, 0.12)**	**14 (8, 100)**	**2.50 (1.13, 5.52)**
		Pooled result (1-4)	**0.07 (0.04, 0.10)**	**14 (10, 25)**	**2.21 (1.54, 3.16)**

NNT calculated during the evaluation as 1/RD

Source: Table 27 of PALACE 1; Table 27 of PALACE 2; Table 27 of PALACE 3; Table 22 of PALACE 4 CSRs.

Results of ACR 50 response at Week 24 across the randomised trials – apremilast

Trial	Apremilast 30 n/N (%)	Placebo n/N (%)	RD (95% CI)	NNT (95% CI)	RR (95% CI)
PALACE 1	32/168 (19.0)	7/168 (4.2)	**0.15 (0.08, 0.22)**	**6 (5, 13)**	**4.57 (2.08, 10.07)**
PALACE 2	19/162 (11.7)	14/159 (8.8)	0.03 (-0.04, 0.10)	NA	1.33 (0.69, 2.56)
PALACE 3	27/167 (16.2)	13/169 (7.7)	**0.08 (0.02, 0.15)**	**13 (6, 50)**	**2.10 (1.12, 3.93)**
		Pooled result (1-3)	**0.09 (0.02, 0.16)**	**11 (6, 50)**	**2.27 (1.16, 4.41)**
PALACE 4	22/176 (12.5)	11/176 (6.3)	**0.06 (0.00, 0.12)**	**17 (8, NE)**	**2.00 (1.00, 4.00)**
		Pooled result (1-4)	**0.08 (0.03, 0.13)**	**13 (8, 33)**	**2.17 (1.36, 3.49)**

NNT calculated during the evaluation as 1/RD

Source: Table 27 of PALACE 1; Table 27 of PALACE 2; Table 27 of PALACE 3 and Table 22 of PALACE 4 CSRs.

6.11 The results demonstrated the following:

- A significantly greater proportion of patients treated with apremilast 30 mg twice daily in the pivotal PALACE-1 trial and supplementary PALACE-4 trial achieved an ACR 50 response at Week 16 and Week 24, compared to placebo.
- A significantly greater proportion of patients treated with apremilast 30 mg twice daily in the pivotal PALACE-3 trial achieved an ACR 50 response at Week 24, compared to placebo.
- No significant differences in the proportion of patients achieving an ACR 50 response were observed at 16 weeks in PALACE-2 and -3 or at 24 weeks in PALACE-2 amongst those treated with apremilast or placebo.

Comparative harms

6.12 The adverse events reported in the apremilast trials up to week 24 are summarised in the table below.

Summary of adverse events in PALACE trials to 24 weeks (placebo-controlled phase)

Trial ID	Apremilast n/N (%)	Placebo n/N (%)	RD (95% CI)	RR (95% CI)
PALACE 1				
TEAE	103/168 (61.3)	81/168 (48.2)	**0.13 (0.03, 0.24)**	**1.27 (1.04, 1.55)**
Drug-related TEAE	70/168 (41.7)	32/168 (19.0)	**0.23 (0.13, 0.32)**	**2.19 (1.53, 3.13)**
Severe TEAE	11/168 (6.5)	6/168 (3.6)	0.03 (-0.02, 0.08)	1.83 (0.69, 4.84)
Serious TEAE (SAE)	9/168 (5.4)	7/168 (4.2)	0.01 (-0.03, 0.06)	1.29 (0.49, 3.37)
Drug-related SAE	3/168 (1.8)	2/168 (1.2)	0.01 (-0.02, 0.03)	1.50 (0.25, 8.86)
TEAE leading to drug withdrawal	12/168 (7.1)	8/168 (4.8)	0.02 (-0.03, 0.07)	1.50 (0.63, 3.58)
TEAE leading to death	0	0		
PALACE 2				
TEAE	96/162 (59.3)	72/159 (45.3)	**0.14 (0.03, 0.25)**	**1.31 (1.06, 1.62)**
Drug-related TEAE	57/162 (35.2)	28/159 (17.6)	**0.18 (0.08, 0.27)**	**2.00 (1.34, 2.97)**
Severe TEAE	11/162 (6.8)	5/159 (3.1)	0.04 (-0.01, 0.08)	2.16 (0.77, 6.07)
Serious TEAE (SAE)	4/162 (2.5)	3/159 (1.9)	0.01 (-0.03, 0.04)	1.31 (0.30, 5.75)
Drug-related SAE	1/162 (0.6)	0	0.01 (-0.01, 0.02)	2.94 (0.12, 71.75)
TEAE leading to drug withdrawal	12/162 (7.4)	3/159 (1.9)	**0.06 (0.01, 0.10)**	**3.93 (1.13, 13.65)**
TEAE leading to death	0	0		
PALACE 3				
TEAE	104/167 (62.3)	83/168 (49.4)	**0.13 (0.02, 0.23)**	**1.26 (1.04, 1.53)**
Drug-related TEAE	62/167 (37.1)	33/168 (19.6)	**0.17 (0.08, 0.27)**	**1.89 (1.31, 2.72)**
Severe TEAE	10/167 (6.0)	8/168 (4.8)	0.01 (-0.04, 0.06)	1.26 (0.51, 3.11)
Serious TEAE (SAE)	6/167 (3.6)	9/168 (5.4)	-0.02 (-0.06, 0.03)	0.67 (0.24, 1.84)
Drug-related SAE	0	2/168 (1.2)	-0.01 (-0.03, 0.01)	0.20 (0.01, 4.16)
TEAE leading to drug withdrawal	12/167 (7.2)	10/168 (6.0)	0.01 (-0.04, 0.07)	1.21 (0.54, 2.72)
TEAE leading to death	0	0		
PALACE 4				
TEAE	99/175 (56.6)	73/176 (41.5)	**0.15 (0.05, 0.25)**	**1.36 (1.10, 1.70)**
Drug-related TEAE	58/175 (33.1)	25/176 (14.2)	**0.19 (0.10, 0.28)**	**2.33 (1.53, 3.55)**
Severe TEAE	2/175 (1.1)	6/176 (3.4)	-0.02 (-0.05, 0.01)	0.34 (0.07, 1.64)
Serious TEAE (SAE)	1/175 (0.6)	5/176 (2.8)	-0.02 (-0.05, 0.00)	0.20 (0.02, 1.70)
Drug-related SAE	1/175 (0.6)	0	0.01 (-0.01, 0.02)	3.02 (0.12, 73.56)
TEAE leading to drug withdrawal	6/175 (3.4)	4/176 (2.3)	0.01 (-0.02, 0.05)	1.51 (0.43, 5.25)
TEAE leading to death	0	0		
Trial ID	**Leflunomide n/N (%)**	**Placebo n/N (%)**	**RD (95% CI)**	**RR (95% CI)**
TOPAS				
TEAE	82/96 (85.4)	70/92 (76.1)	0.09 (-0.02, 0.21)	1.12 (0.97, 1.29)
Drug-related AE	61/96 (63.5)	37/92 (40.2)	**0.23 (0.09, 0.37)**	**1.58 (1.18, 2.11)**
SAE	13/96 (13.5)	5/92 (5.4)	0.08 (0.00, 0.16)	2.49 (0.92, 6.71)
TEAE leading to drug withdrawal	10/96 (10.4)	2/92 (2.2)	**0.08 (0.01, 0.15)**	**4.79 (1.08, 21.28)**
TEAE leading to death	0	0		

Abbreviations: SAE = severe adverse events; TEAE = treatment emergent adverse events
Source: Table B.78, B.82, B.86, B.90; pp91, 93, 95, 97, 99 of the submission

6.13 With longer exposure to apremilast, the incidence of treatment-emergent adverse events (TEAEs) and serious TEAEs did not notably increase.

6.14 The submission did not present an indirect comparison between apremilast and leflunomide for safety outcomes.

6.15 Significantly greater 'any TEAEs' and drug-related TEAEs were reported with apremilast compared with placebo, across all the apremilast trials. Significantly

greater drug-related AEs and TEAEs leading to drug withdrawal occurred with leflunomide compared with placebo, in the TOPAS trial.

6.16 TEAEs relating to diarrhoea and nausea were reported more frequently by patients treated with apremilast compared to placebo. In the leflunomide trial, higher proportions of leflunomide patients had diarrhoea, ALT increase and tiredness/lethargy compared to the placebo patients.

Benefits/harms

6.17 A summary of the comparative benefits for apremilast versus placebo is presented in the table below. For a summary of harms, refer to the above table.

Summary of comparative efficacy for apremilast and leflunomide/placebo

Trial	APR	LEF/PBO	RR (95% CI)	Event rate/100 patients*		RD (95% CI)
				APR	LEF/PBO	
Benefits						
Dichotomous Outcome: ACR20 response at 24 weeks						

	APR	PBO	LEF	RR (95% CI)	Event rate/100 patients*			RD (95% CI)
					APR	PBO	LEF	
PALACE 1	59/168	22/168	-	**2.68 (1.73, 4.17)**	35.	13	-	**0.22 (0.13, 0.31)**
PALACE 2	40/162	25/159	-	**1.57 (1.00, 2.46)**	25	16	-	**0.09 (0.00, 0.18)**
PALACE 3	52/167	26/169	-	**2.02 (1.33, 3.08)**	31	15	-	**0.16 (0.07, 0.25)**
Pooled (PALACE 1-3)				**2.05 (1.52, 2.76)**	30	15	-	**0.16 (0.08, 0.23)**
PALACE 4	43/176	23/176		**1.87 (1.18, 2.97)**	24	13	-	**0.11 (0.03, 0.19)**
Pooled (PALACE 1-4)				**2.01 (1.61, 2.50)**	29	14	-	**0.14 (0.09, 0.20)**
TOPAS	-	16/91	29/95	**1.74 (1.01, 2.97)**	-	18	31	**0.13 (0.01, 0.25)**
Indirect comparison: Pooled (PALACE 1-3) versus TOPAS				1.18 (0.64, 2.18)	-			0.03 (-0.11, 0.17)
Indirect comparison: Pooled (PALACE 1-4) versus TOPAS				1.16 (0.65, 2.07)	-			0.01 (-0.12, 0.14)

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

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

- Approximately 15 additional patients would have ACR20 response over 24 weeks of treatment.

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

- Approximately 13 additional patients would achieve ACR20 response over 24 weeks of treatment.

6.20 There were no statistically significant differences in the number of patients achieving ACR20 response in those treated with apremilast or leflunomide over 24 weeks.

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

Clinical claim

6.21 The submission described apremilast as non-inferior in terms of comparative effectiveness and superior in terms of safety ("equivalent" in terms of short-term safety but "superior" in terms of long-term safety), over leflunomide.

6.22 The data presented in the submission supported the claim of non-inferior effectiveness of apremilast 30 mg twice daily (including titration) compared with leflunomide 20 mg daily (including loading doses) over 24 weeks in terms of ACR20 response.

6.23 The ESC considered that the claim of non-inferior comparative effectiveness was reasonable. However, the ESC noted that while leflunomide's safety profile is well known, US prescribing information on apremilast provides warnings and precautions on depression and weight decrease and lists diarrhoea, nausea and headache as the most common adverse events (≥5%) in psoriatic arthritis patients. 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

6.24 The submission presented a cost-utility analysis based on the premise that the listing of apremilast will extend the period of time patients would be treated with DMARDs for psoriatic arthritis and delay the commencement of bDMARDs.

6.25 The submission presented a modelled comparison of:

- the "current treatment algorithm (without apremilast)" in which patients receive 1 line of DMARDs prior to biologic treatment, and
- the "proposed treatment algorithm (with apremilast)" in which patients receive 2 lines of DMARDs prior to biologic treatment in patients who are assumed to have undergone and failed therapy with methotrexate.

6.26 The results of the modelled economic evaluation presented by the submission claim that the "proposed algorithm (with apremilast) is less costly and more effective than the current algorithm. The model is driven by the addition of a DMARD to the "proposed algorithm", regardless of whether that drug is apremilast or one of the other currently listed DMARDs.

6.27 The economic analysis presented in the submission was considered by the evaluation to be uninformative as the evaluation considered that should apremilast be listed on the PBS, it would represent an alternative therapy to DMARD therapy prior to commencement of treatment with bDMARDs as opposed to adding a further line of therapy.

6.28 The ESC noted the following issues in the economic modelling presented by the submission:

- The cost saving result is highly sensitive to the time horizon employed by the model, and is maximised at the 10 year mark. If the horizon modelled is below 7 or above 14 years, the saving becomes a positive cost. This is illustrated in the figure below that graphs the annual cost-savings per patient over time.

Annual cost-savings per patient over time

- The transition matrix employed in the submission was relatively simple, and may have over-estimated the cost-saving and QALY gain associated with listing apremilast. Specifically, it was assumed that the discontinuation rate for each drug was independent of the line of therapy. If prior failure on apremilast affects (for example) the failure rate of other DMARDs (or bDMARDs), then the delay in reaching bDMARDs and then of exhausting treatment options would be reduced;
- The method to estimate QALYs was not well described or justified. Utility values derived using the EQ-5D-3L instrument were used in preference to utility values derived from the SF-6D instrument which could have been derived from the SF-36 data available in the trials presented in the submission. Additionally, the algorithm employed to generate utility weights is the US one, a selection neither explained nor appropriate; and

- The submission used the trial-derived absolute change in utility ([redacted]) rather than the incremental change (relative to placebo) ([redacted]), which meant the QALY gained was over-estimated.

6.29 A cost-minimisation analysis performed by the evaluation and based on the assumption that apremilast over 24 weeks (including titration) is non-inferior to leflunomide over 24 weeks in terms of efficacy and safety, is presented in the table below.

Cost-minimisation analysis based on the conclusion that apremilast over 24 weeks (including titration) is non-inferior to leflunomide over 24 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
Leflunomide	20mg (30)	$83.05*	$64.50	$0.1075	100mg/day	3days	5	300mg	$32.25	$387.00
	20mg (30)	$83.05*	$64.50	$0.1075	20mg/day	24wks	1	3300mg	$354.75	
Apremilast	Titration (27)	$[redacted]	$[redacted]	$[redacted]	Titration	2wks	1 -> 2[b]	690mg	$[redacted]	
	30mg (56)	$[redacted]	$[redacted]		60mg/day	22wks	2	9240mg	$[redacted]	

* PBS item 5450W

[a] calculated as ex-man price + wholesaler mark-up (7.52%), + pharmacy mark-up of 15% (up to and including $30.00) OR 10% ($45.01-$180.00) + dispensing fee ($6.76)

[b] titration schedule

6.30 The ESC considered the cost-minimisation analysis informative, but noted that it was based on the premise that apremilast is non inferior in both efficacy and safety to leflunomide and that it is leflunomide that would be replaced by apremilast should it be listed.

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

Drug cost/patient/course/year:

6.31 $[redacted] based on the requested price and assuming one initiation and 12 maintenance scripts per year. This compares 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 leflunomide 20 mg/day for 24 weeks. This also compares with a cost of $[redacted] for leflunomide, assuming 13 scripts per year.

Estimated PBS usage & financial implications

6.32 This submission was not considered by DUSC.

6.33 Like the economic evaluation presented by the submission, the financial estimates were based on the premise that apremilast would expand the treatment sequence for psoriatic arthritis. The evaluation therefore also considered these estimates to be uninformative as the evaluation considered that should apremilast be listed on the PBS, it would represent an alternative therapy to methotrexate, leflunomide and sulfasalazine prior to commencement of treatment with bDMARDs.

6.34 In summary, the estimates for the financial implications of listing apremilast on the PBS provided in the submission, was a net cost of less than $10 million in Year 1, increasing to $20 – $30 million in Year 5. The net cost was due to the addition of a line of therapy to the algorithm (which is more costly than current DMARD therapies, but less costly than bDMARDs) and the majority of cost-offsets being derived from reduced use of adalimumab. The likely financial impact of listing apremilast when assuming it would replace existing therapies (methotrexate, leflunomide or sulfasalazine) was unknown.

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 of unacceptable cost-effectiveness compared to leflunomide at the price proposed in the submission, and a low clinical need for a treatment that would potentially delay treatment with more effective (but more costly) bDMARD therapy.

7.2 The PBAC noted the submission's proposed clinical place in therapy for apremilast as an additional treatment to leflunomide or sulfasalazine following inadequate response to methotrexate. Given that the current PBS restrictions for bDMARD therapy for psoriatic arthritis require a patient to have trialled 2 prior DMARD therapies (i.e. methotrexate and either leflunomide or sulfasalazine) and the submission's proposed treatment algorithm required a patient to have trialled 3 prior therapies before being eligible for bDMARD therapy, the PBAC expressed concerns over the potential delay in prescribers being able to initiate bDMARD therapy. The PBAC acknowledged that treatment of this condition with DMARDs is often not successful but that treatment with bDMARDs can be very effective in many patients. The PBAC did not consider it to be clinically appropriate to potentially delay the time in commencing bDMARD therapy by requiring patients to have trialled methotrexate, apremilast and either leflunomide or sulfasalazine prior to the bDMARDs.

7.3 The submission's nominated comparator was leflunomide. The PBAC accepted this but also considered that sulfasalazine was an appropriate secondary comparator.

7.4 The PBAC noted that in the indirect comparison of apremilast to leflunomide, there was no statistically significant differences in the proportion of patients achieving an ACR 20 response at week 24 for both a DMARD-experienced group (PALACE 1-3) and a mixed (i.e. DMARD-experienced and DMARD-naïve patients; PALACE 1-4) group. However, the PBAC agreed with the evaluation's suggestion that use of ACR 50 may be more relevant to a PBS population and noted that ACR 50 response was a secondary outcome in the apremilast trials and was not measured in the leflunomide trial. When using ACR 50 as an outcome measure, the PBAC noted that no statistically significant differences in the proportion of patients achieving an ACR 50 response were observed at 16 weeks in the PALACE-2 and PALACE-3 trials or at 24 weeks in the PALACE-2 trial amongst those treated with apremilast or placebo. Additionally, based on the trial evidence, it was not clear to the PBAC what benefits apremilast has with respect to disease modification.

Therefore, in the PBAC's view, the submission's clinical claim of non-inferiority in terms of comparative effectiveness versus leflunomide had not been convincingly established.

7.5 In the absence of a formal indirect comparison between apremilast and leflunomide 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 that leflunomide's safety profile is well known. Any claims of superior safety over leflunomide would need to be supported by further long term comparative safety data.

7.6 For the reason outlined in the evaluation, the PBAC did not find the submission's economic modelling through a 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 of bDMARD therapies, the submission's economic analysis therefore modelled a treatment scenario that is unlikely to be realised in practice. In turn, the PBAC also considered the submission's estimates of patient usage and financial implications to be unreliable for the same reasons.

7.7 Given that the trial evidence did not demonstrate any significant clinical advantages in having apremilast available over leflunomide or any other DMARD therapy, the PBAC was of the view that a low clinical need exists for an additional line of treatment. In the context of the undesirability of delaying bDMARD therapy, should a re-submission be lodged, the PBAC considered that a cost-minimisation analysis against leflunomide or a mix of leflunomide and sulfasalazine may be a more feasible approach to the submission. Any re-submission should also take the form of a major submission.

7.8 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.