

**7.01 APREMILAST
tablets, 10 mg, 20 mg, 30 mg
Otezla®, Celgene Pty Ltd.**

1 Purpose of Application

1.1 The resubmission requested an authority required listing for apremilast for treatment of severe active psoriatic arthritis (PsA).

2 Requested listing

2.1 An abridged version of the Secretariat suggested listing is shown below. Changes to the requested restriction proposed by the secretariat are in italics:

Name, Restriction, Manner of administration and form	Max. Qty	No. 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
APREMILAST Tablets, 30 mg	56	3/5 ^a	\$ [REDACTED]	

^a number of repeats = 3 (initial) and 5 (continuing)

Category / Program	GENERAL – General Schedule (Code GE)
Prescriber type:	<input type="checkbox"/> Dental <input checked="" type="checkbox"/> Medical Practitioners <input type="checkbox"/> Nurse practitioners <input type="checkbox"/> Optometrists <input type="checkbox"/> Midwives
PBS Indication:	Severe psoriatic arthritis
Treatment phase:	Initial treatment – Initial 1 (new patient or patient recommencing treatment after a break of 5 years or more)
Restriction Level:	<input checked="" type="checkbox"/> Authority Required - In Writing
Treatment criteria:	Must be <i>treated</i> by a rheumatologist; OR Must be treated by a clinical immunologist with expertise in the management of psoriatic arthritis.
Clinical criteria:	Patient must have severe active psoriatic arthritis, <i>AND</i> <i>Patient must have received no prior PBS-subsidised treatment with this drug for this condition; OR</i> <i>Patient must have received no prior PBS-subsidised treatment with a biological agent for this condition; OR</i> <i>Patient must have received no PBS-subsidised treatment for this drug for at least 5 years if they have previously received PBS-subsidised treatment with this drug for this condition; OR</i> <i>Patient must have received no PBS-subsidised treatment with a biological agent</i>

Public Summary Document – November 2015 PBAC Meeting

	<p>for at least 5 years if they have previously received PBS-subsidised treatment with a biological agent for this condition; AND</p> <p>Patient must have failed to achieve an adequate response to methotrexate at a dose of at least 20 mg weekly for a minimum period of 3 months, AND</p> <p>Patient must have failed to achieve an adequate response to sulfasalazine at a dose of at least 2 g per day for a minimum period of 3 months; OR</p> <p>Patient must have failed to achieve an adequate response to leflunomide at a dose of up to 20 mg daily for a minimum period of 3 months, AND</p> <p><i>Patient must not receive more than 2 weeks of titration dose; AND</i></p> <p>Patient must not receive more than 18 weeks of treatment under this restriction.</p>
--	---

Category / Program	GENERAL – General Schedule (Code GE)
Prescriber type:	<input type="checkbox"/> Dental <input checked="" type="checkbox"/> Medical Practitioners <input type="checkbox"/> Nurse practitioners <input type="checkbox"/> Optometrists <input type="checkbox"/> Midwives
PBS Indication:	Severe psoriatic arthritis
Treatment phase:	Initial treatment – Initial 2 (change or recommencement of treatment)
Restriction Level:	<input checked="" type="checkbox"/> Authority Required - In Writing
Treatment criteria:	<p>Must be treated by a rheumatologist; OR</p> <p>Must be treated by a clinical immunologist with expertise in the management of psoriatic arthritis.</p>
Clinical criteria:	<p>Patient must have a documented history of severe active psoriatic arthritis, AND</p> <p>Patient must have received prior PBS-subsidised treatment with this drug for this condition in this Treatment Cycle, OR</p> <p><i>Patient must have received prior PBS-subsidised treatment with a biological agent for this condition in this Treatment Cycle; AND</i></p> <p>Patient must not have failed, or ceased to respond to, PBS-subsidised treatment with this drug within this Treatment Cycle, OR</p> <p><i>Patient must not have already failed, or ceased to respond to, PBS-subsidised treatment with 3 biological agents or 2 biological agents and this drug within this Treatment Cycle; AND</i></p> <p><i>Patient must not receive more than 2 weeks of titration dose; AND</i></p> <p>Patient must not receive more than 18 weeks of treatment under this restriction.</p>

Category / Program	GENERAL – General Schedule (Code GE)
Prescriber type:	<input type="checkbox"/> Dental <input checked="" type="checkbox"/> Medical Practitioners <input type="checkbox"/> Nurse practitioners <input type="checkbox"/> Optometrists <input type="checkbox"/> Midwives
PBS Indication:	Severe psoriatic arthritis
Treatment phase:	Continuing treatment

Restriction Level:	<input checked="" type="checkbox"/> Authority Required - In Writing
Treatment criteria:	Must be treated by a rheumatologist; OR Must be treated by a clinical immunologist with expertise in the management of psoriatic arthritis.
Clinical criteria:	Patient must have a documented history of severe active psoriatic arthritis; AND Patient must have received this drug as their most recent course of PBS-subsidised treatment for this condition in the current Treatment Cycle; AND Patient must demonstrate, at the time of application, an adequate response to treatment with this drug; AND Patient must not receive more than 24 weeks of treatment per continuing treatment course authorised under this restriction.

- 2.2 The wording of the restriction was consistent with, but not identical to that for adalimumab for PsA.
- 2.3 The requested basis for listing was a cost-consequence analysis of apremilast and adalimumab, based on the premise that apremilast is inferior to adalimumab in terms of effectiveness and non-inferior in terms of safety.
- 2.4 The requested basis for listing in the previous March 2015 submission was a cost-utility analysis based on the unsupported premise that the listing of apremilast would extend the period of time patients would be treated with DMARDs for psoriatic arthritis and delay the commencement of biologics. The change to the proposed clinical positioning of apremilast in this resubmission is that apremilast would represent an alternative treatment with a different mechanism of action and mode of administration to the currently PBS-listed bDMARDs. The Pre-Sub-Committee Response (PSCR, p1) clarified that apremilast is intended to be considered as one of the three treatment options in a cycle of therapy, followed by a five year break. The ESC considered that limiting patients to two bDMARDs in a cycle of therapy may not be appropriate.

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

3 Background

- 3.1 Apremilast was TGA registered on 19 March 2015 for the following indications:
- Treatment of signs and symptoms of active psoriatic arthritis (PsA) in adult patients; and
 - Treatment of adult patients with moderate-to-severe plaque psoriasis who are candidates for phototherapy or systemic therapy.
- 3.2 PBAC previously considered apremilast for PsA at the March 2015 meeting.
- 3.3 A summary of the comparison of the previous submission considered in March 2015 and this resubmission is outlined below.

Summary of the previous submission and current resubmission

	Apremilast March 2015 submission	Current resubmission
Requested PBS listing	<ul style="list-style-type: none"> Severe active PsA, where other DMARDs, including methotrexate, are ineffective or inappropriate <p>PBAC Comment: (paragraph 7.2, Mar 2015 PBAC Minutes) The PBAC did not consider it to be clinically appropriate to potentially delay the time in commencing bDMARD therapy by requiring patients to have trialed methotrexate, apremilast and either leflunomide or sulfasalazine prior to the bDMARDs.</p>	<ul style="list-style-type: none"> Severe active PsA, where (methotrexate AND sulfasalazine OR leflunomide), are ineffective, OR contra-indicated or cannot tolerate methotrexate, sulfasalazine or leflunomide.
Main comparator	<ul style="list-style-type: none"> Leflunomide <p>PBAC Comment: (paragraph 7.3, Mar 2015 PBAC Minutes) The PBAC accepted this but also considered that sulfasalazine was an appropriate secondary comparator.</p>	<ul style="list-style-type: none"> Adalimumab <p>All bDMARDs would represent appropriate comparators.</p>
Clinical evidence	<ul style="list-style-type: none"> Apremilast versus placebo:3 pivotal trials <ul style="list-style-type: none"> PALACE -1 (N=336) PALACE-2 (N=321) PALACE-3 (N=336) Leflunomide versus placebo:1 pivotal trials <ul style="list-style-type: none"> TOPAS (N=190) <p>PBAC Comment: none</p>	<ul style="list-style-type: none"> Apremilast versus placebo:3 trials <ul style="list-style-type: none"> PALACE -1 (N=336) PALACE-2 (N=321) PALACE-3 (N=336) Adalimumab versus placebo:2 trials <ul style="list-style-type: none"> Mease 2005 (N=315) Genovese 2007 (N=102)
Clinical claim	<p>Apremilast is non-inferior in terms of comparative effectiveness and superior in terms of safety over leflunomide.</p> <p>PBAC Comment: (paragraph 7.4, Mar 2015 PBAC Minutes) The submission's clinical claim of non-inferiority in terms of comparative effectiveness versus leflunomide had not been convincingly established.</p> <p>(paragraph 7.5, Mar 2015 PBAC Minutes) the PBAC did not consider the submission's claim of superior safety to have been adequately supported... Any claims of superior safety over leflunomide would need to be supported by further long term comparative safety data.</p>	<p>Apremilast is inferior in terms of comparative effectiveness and non-inferior in terms of comparative safety over adalimumab.</p>
Economic evaluation	<p>The submission presented a modelled economic analysis based on an assumption that apremilast will <u>expand</u> the treatment sequence for PsA, but this is deemed to be uninformative.</p> <p>PBAC Comment: (paragraph 7.6, Mar 2015 PBAC Minutes) 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.</p>	<p>The model in the resubmission is deemed to be only partially informative as it does not inform on the cost-effectiveness of apremilast in those unwilling to take bDMARDs. The resubmission compares the costs and consequences of apremilast and adalimumab.</p>
PBAC decision	<ul style="list-style-type: none"> Reject. <p>(paragraph 7.6, Mar 2015 PBAC Minutes) The PBAC rejected the submission on the basis of unacceptable</p>	-

	Apremilast March 2015 submission	Current resubmission
	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.	

Source: Compiled during the evaluation

4 Clinical place for the proposed therapy

- 4.1 The resubmission proposed that apremilast would be used as a subsequent treatment to methotrexate and leflunomide or sulfasalazine, according to the existing eligibility criteria for treatment with a bDMARD, for psoriatic arthritis. This differed from the previous submission, which proposed that apremilast would be used as a subsequent treatment to methotrexate, but before leflunomide or sulfasalazine.
- 4.2 The resubmission proposed that apremilast would represent an alternative treatment with a different mechanism of action and mode of administration to the currently PBS-listed bDMARDs. The EULAR Guidelines recommend consideration of apremilast in patients who have experience with at least one conventional synthetic DMARD, where bDMARD treatment is not appropriate.
- 4.3 The PSCR (p2) identified two patient populations who may access apremilast; those who are currently treated with bDMARDs but would prefer an oral therapy if it were available, and those who are currently appropriate and eligible for bDMARD therapy but unwilling to commence this. The ESC considered that there may be a clinical place for apremilast due to the improved adverse effect profile and oral mode of administration, however uncertainties remained as there is no evidence for the suggested “eligible but unwilling” population, and this is not incorporated into the economic model.
- 4.4 The ESC reaffirmed the previous advice from March 2015 that any potential delay in the access of bDMARD therapy resulting from the introduction of apremilast is clinically inappropriate.

For more detail on PBAC’s view, see Section 7 “PBAC outcome”.

5 Comparator

- 5.1 Adalimumab. The evaluation considered that this is not the only appropriate comparator. All bDMARDs currently PBS-listed for the treatment of PsA would also be relevant comparators. The PSCR (p1) considered that adalimumab is still the most appropriate comparator, and is a reasonable proxy for etanercept and golimumab.
- 5.2 The ESC noted the PBAC recommendation from March 2015, which accepted leflunomide as an appropriate comparator. The PBAC further stated “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 resubmission 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.” (Paragraph 7.7, Apremilast PSD for PsA, March 2015).

For more detail on PBAC’s view, see Section 7 “PBAC outcome”.

6 Consideration of the evidence

Sponsor hearing

6.1 The Sponsor requested a hearing for this item. The clinician described the place in therapy of apremilast in patients for whom the potential harms associated with bDMARD use, particularly in relation to increased risk of infection and elderly patients with comorbidities, may outweigh the benefits of treatment. These are therefore patients who are unlikely to be treated with a bDMARD. The PBAC noted that the hearing did not support the place in therapy as proposed by the resubmission.

Consumer comments

6.2 The PBAC noted and welcomed the input from health care professionals (2) via the Consumer Comments facility on the PBS website. The comments described the place in therapy of apremilast as an effective alternative to methotrexate and/or leflunomide for patients who do not qualify for bDMARDs, or as an alternative to bDMARDs in non-responding patients, valuing the benign safety profile of apremilast. The PBAC noted that this did not support the place in therapy as proposed by the resubmission.

Clinical trials

6.3 No head-to-head trials of apremilast versus any treatment in patients with PsA are available. The resubmission was based on three head-to-head trials comparing apremilast to placebo (n=993), and two head-to-head trials comparing adalimumab to placebo (n=417). These three apremilast trials were presented in the previous submission. The two adalimumab trials were previously considered by the PBAC as the primary source of evidence presented in the adalimumab March 2006 PsA submission.

6.4 Details of the trials presented in the resubmission are provided in Table 1.

Table 1: Trials and associated reports presented in the resubmission

Trial ID	Protocol title/ Publication title	Publication citation
Randomised trials of apremilast versus placebo		
DMARD-experienced		
PALACE 1	<p>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.</p> <p>Kavanaugh A et al. Treatment of psoriatic arthritis in a phase 3 randomised, placebo-controlled trial with apremilast, an oral phosphodiesterase 4 inhibitor.</p> <p>Kavanaugh A et al. Apremilast, an oral phosphodiesterase 4 inhibitor, is associated with long-term (104-week) improvements in patients with psoriatic arthritis: Results from a phase 3, randomised, controlled trial.</p> <p>Mease P et al. Long-term (104-week) safety profile of apremilast, an oral phosphodiesterase 4 inhibitor, in patients with psoriatic arthritis: Pooled safety analysis of three phase 3, randomized, controlled trials.</p> <p>Kavanaugh A et al. Long-term (52-week) results of a phase III randomized, controlled trial of apremilast in patients with psoriatic arthritis.</p> <p>Schafer P et al. The pharmacodynamics impact of apremilast, an oral phosphodiesterase 4 inhibitor, on circulating levels of inflammatory biomarkers on patients with psoriatic arthritis: Substudy results from a phase III, randomized, placebo-controlled trial (PALACE 1).</p>	<p>Clinical Study Report CC-10004- PSA-002. September 2013.</p> <p><i>Annals of the Rheumatic Diseases</i>, 2014; 73 (6): 1020-1026.</p> <p>Poster presented at: the 2014 ACR/ARHP Annual Meeting; November 15-19, 2014; Boston, MA [No. 1590]</p> <p>Poster presented at: Annual European Congress of Rheumatology EULAR 2015; 10-13 June 2015; Rome, Italy [No. THU0432]</p> <p><i>Journal of Rheumatology</i>, 2015; 42 : 479-488.</p> <p><i>Journal of Immunology Research</i>, 2015. Article ID 906349. http://dx.doi.org/10.1155/2015/906349</p>
PALACE 2	<p>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.</p> <p>Mease P et al. Long-term (104-week) safety profile of apremilast, an oral phosphodiesterase 4 inhibitor, in patients with psoriatic arthritis: Pooled safety analysis of three phase 3, randomized, controlled trials.</p>	<p>Clinical Study Report CC-10004-PSA-003. September 2013.</p> <p>Poster presented at: Annual European Congress of Rheumatology EULAR 2015; 10-13 June 2015; Rome, Italy [No. THU0432]</p>
PALACE 3	<p>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.</p> <p>Mease P et al. Long-term (104-week) safety profile of apremilast, an oral phosphodiesterase 4 inhibitor, in patients with psoriatic arthritis: Pooled safety analysis of three phase 3, randomized, controlled trials.</p> <p>Edwards et al. 2015. Disease activity and safety during long-term (104-week) treatment with apremilast, an oral phosphodiesterase 4 inhibitor, in patients with psoriatic arthritis: Results from a phase III, randomized, controlled trial and open-label extension (PALACE 3).</p>	<p>Clinical Study Report CC-10004-PSA-004. September 2013.</p> <p>Poster presented at: Annual European Congress of Rheumatology EULAR 2015; 10-13 June 2015; Rome, Italy [No. THU0432]</p> <p><i>Ann Rheum Dis</i>, 2015; 74 (Suppl2): 348.</p>

Trial ID	Protocol title/ Publication title	Publication citation
Randomised trials of adalimumab versus placebo		
Mease 2005	<p>Mease P et al. Adalimumab for the treatment of patients with moderately to severely active psoriatic arthritis: Results of a double-blind, randomized, placebo-controlled trial.</p> <p>Gladman D et al. Adalimumab for long-term treatment of psoriatic arthritis: Forty-eight week data from the Adalimumab Effectiveness in Psoriatic Arthritis trial.</p> <p>Gladman D et al. Adalimumab improves joint-related and skin-related functional impairment in patients with psoriatic arthritis: Patient reported outcomes of the Adalimumab Effectiveness in Psoriatic Arthritis Trial.</p> <p>Mease P et al. Adalimumab for long-term treatment of psoriatic arthritis: 2-year data from the Adalimumab Effectiveness in Psoriatic Arthritis Trial (ADEPT).</p> <p>Mease P et al. Application and modifications of minimal disease activity measures for patients with psoriatic arthritis treated with adalimumab: Subanalyses of ADEPT.</p> <p>Gladman D et al. Risk factors for radiographic progression in psoriatic arthritis: Subanalysis of the randomized controlled trial ADEPT.</p>	<p><i>Arthritis & Rheumatism</i>, 2005; 52(10): 3279-3289.</p> <p><i>Arthritis & Rheumatism</i>, 2007; 56(2): 476-488.</p> <p><i>Ann Rheum Dis</i>, 2007; 66: 163-168.</p> <p><i>Ann Rheum Dis</i>, 2009; 68: 702-709.</p> <p><i>Journal of Rheumatology</i>, 2013; 40: 647-652.</p> <p><i>Arthritis Research & Therapy</i>, 2010; 12: R113.</p>
Genovese 2007	Genovese M et al. Safety and efficacy of adalimumab in treatment of patients with psoriatic arthritis who had failed disease modifying antirheumatic drug therapy.	<p><i>Journal of Rheumatology</i>, 2007; 34(5): 1040-1050. (erratum: <i>Journal of Rheumatology</i>, 2007; 34(6):1439.)</p>

Source: Table B-5, p40 of the resubmission.

6.5 The key features of the randomised trials are summarised in Table 2.

Table 2: Key features of the included evidence – indirect comparison

Trial	N	Design / duration	Risk of bias	Patient population	Outcome(s)	Use in modelled evaluation
Apremilast vs. placebo						
PALACE 1	336	Three arm, two phase trial. • Phase one: (1:1:1) R,DB,PC (24wk) • Phase two: active treatment / long-term safety (236wk)	Phase 1: low	PsA (≥ 3 swollen and ≥ 3 tender joints)	1°: ACR20 (wk16) 2°: ACR20 (wk 24), ACR50, ACR70, HAQ-DI, modified PsARC, PASI; QoL	Initial response: ACR50 (16wk) pooled Utility: EQ-5D pooled
PALACE 2	321					
PALACE 3	336					
Adalimumab vs. placebo						
Mease 2005	315	Two arm, two phase trial. • Phase one: R,DB,PC (24wk) • Phase two: OL active treatment (120wks)	Phase 1: Low	PsA (≥ 3 swollen and ≥ 3 tender joints)	1°: ACR20 (wk12); modified total Sharp score (wk 24) 2°: ACR20 (wk 24), ACR50, ACR70, PsARC, PASI, QoL	Initial response: ACR50 (12wk) pooled
Genovese 2007	102	Two arm, two phase trial. • Phase one: R,DB,PC (12wk) • Phase two: OL active treatment (12wk)	Phase 1: low	PsA (≥ 3 swollen and ≥ 3 tender joints)	1°: ACR20 (wk12) 2°: ACR50, ACR70, PsARC, QoL	

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

Comparative effectiveness

- 6.6 The PBAC (paragraph 7.4, Apremilast PSD for PsA, March 2015) agreed with the evaluation's suggestion that use of ACR50 may be more relevant to a PBS population and noted that ACR50 response was a secondary outcome in the apremilast trials.
- 6.7 The results of ACR50 response in the apremilast and adalimumab trials are presented in Table 3.

Table 3: Results of the indirect comparison of ACR50 response at 16 weeks on apremilast versus ACR50 response at 12 weeks on adalimumab

Trial	Apremilast			Adalimumab				Indirect RR ^c (95% CI)	Indirect RD ^c (95% CI)
	RD ^a (95% CI)	RR ^a (95% CI)	APR n/N (%)	PBO n/N (%)	ADA n/N (%)	RR ^b (95% CI)	RD ^b (95% CI)		
PALACE 1	0.10 (0.04, 0.17)	2.70 (1.35, 5.40)	27/168 (16.1)	10/168 (6.0)	-	-	-	-	-
PALACE 2	0.05 (0.00, 0.11)	2.09 (0.93, 4.69)	17/162 (10.5)	8/159 (5.0)	-	-	-	-	-
PALACE 3	0.07 (0.00, 0.14)	1.81 (0.97, 3.35)	25/167 (15.0)	14/169 (8.3)	-	-	-	-	-
Mease 2005	-	-	-	6/162 (4)	54/153 ^d (35)	9.53 (4.22, 21.5)	0.32 (0.23, 0.40)	-	-
Genovese 2007	-	-	-	1/51 ^e (2)	13/51 (25)	13.00 (1.77, 95.7)	0.24 (0.11, 0.36)	-	-
Pooled	0.07 (0.04, 0.11)	2.14 (1.43, 3.20)	69/497 (13.9)		67/202 (33.2)	9.96 (4.69, 21.2)	0.29 (0.22, 0.36)	0.22 (0.09, 0.51)	-0.22 (-0.30, -0.14)

Source: Tables B-46-B-48, p72 of the resubmission.

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

^a apremilast over placebo

^b adalimumab over placebo

^c inferred as apremilast over adalimumab

^d the resubmission used 151 patients treated instead of 153 patients randomised to the placebo arm in the trial (Figure 1, p3282 of the Mease 2005 publication)

^e the resubmission used 49 patients treated instead of 51 patients randomised to the placebo arm in the trial (Figure 1, p1043 of the Genovese 2007 publication)

Comparative harms

- 6.8 In the apremilast trials, the incidence of AEs, serious AEs, severe AEs and AEs leading to drug withdrawal were less frequent during Weeks 52 to ≤104 relative to Weeks 0 to ≤52. Weight loss >5% was observed in 13.9% subjects in the Week 0 to ≤52 period and 23.8% subjects in the Week 52 to ≤104 period. Mean weight changes were -0.92 kg and -1.32 kg across the two time periods respectively. In the adalimumab trials, the incidence of AEs, serious AEs, severe AEs and AEs leading to drug withdrawal were more frequent during the longer-term adalimumab exposure period relative to the initial double-blind, placebo-controlled phase. Infections were also more frequent during the longer-term exposure period relative to the initial placebo-controlled phase.
- 6.9 The resubmission did not conduct a formal indirect treatment comparison for safety because safety outcomes were measured differently in the trials and at different time

points. The naïve indirect comparison of long-term safety presented by the resubmission is based on open-label non-comparative safety data.

- 6.10 The ESC noted an increased risk of depression and suicidal ideation in the apremilast trials. Table 4 below summarises these adverse events experience by patients treated with apremilast over the 104-week apremilast exposure period, pooled across PALACE 1-3.

Table 4: Summary of adverse events of depression and suicidal ideation in the apremilast trials (pooled)

Trial	Weeks 0-≤52	Weeks 52-≤104
	APR; n (%)	APR; n (%)
PALACE 1-3		
Depression	24 (1.7)	15(1.5)
Suicidal ideation	1 (0.07)	1 (0.10)
Attempted suicide ^a	1 (0.07)	1 (01.0)

Source: p81 of the resubmission.

^a In both cases of attempted suicide, the patients had plausible major confounding factors and explanation.

Benefits/harms

- 6.11 A summary of the comparative benefits (ACR50 response) for apremilast versus placebo and adalimumab versus placebo is presented in Table 5.

Table 5: Summary of comparative benefits for apremilast and adalimumab/placebo

% ACR50 response: indirect comparison								
Trial	APR	PBO	ADA	RR (95% CI)	Event rate/100 patients*			RD (95% CI)
					APR	PBO	ADA	
PALACE 1	27/168	10/168	-	2.70 (1.35, 5.40)	16	6	-	0.10 (0.04, 0.17)
PALACE 2	17/162	8/159	-	2.09 (0.93, 4.69)	11	5	-	0.05 (0.00, 0.11)
PALACE 3	25/167	14/169	-	1.81 (0.97, 3.35)	15	8	-	0.07 (0.00, 0.14)
Pooled – apremilast trials				2.14 (1.43, 3.20)	14	6	-	0.07 (0.04, 0.11)
Mease 2005	-	6/162	54/153	9.53 (4.22, 21.5)	-	4	36	0.32 (0.23, 0.40)
Genovese 2007	-	1/51	13/51	13.00 (1.77, 95.7)	-	2	25	0.24 (0.11, 0.36)
Pooled – adalimumab trials				9.96 (4.69, 21.2)	-	3	33	0.29 (0.22, 0.36)
Indirect comparison: Pooled apremilast trials versus Pooled adalimumab trials				0.22 (0.09, 0.51)	-			-0.22 (-0.30, -0.14)

^a RR and RD interpreted as apremilast versus placebo (apremilast trials), adalimumab versus placebo (adalimumab trials) and apremilast versus adalimumab (indirect comparison)

^b Timepoint at which ACR50 response measured: apremilast trials = 16 weeks; adalimumab trials = 12 weeks

Abbreviations: ADA = adalimumab; APR = apremilast; PBO = placebo; RD = risk difference; RR = risk ratio

Source: Compiled during the evaluation

- 6.12 On the basis of direct evidence presented by the resubmission, for every 100 patients treated with apremilast in comparison to placebo:
- Approximately 8 additional patients would have an ACR50 response over 16 weeks of treatment.

- 6.13 On the basis of direct evidence presented by the resubmission, for every 100 patients treated with adalimumab in comparison to placebo:
- Approximately 30 additional patients would have an ACR50 response over 12 weeks of treatment.
- 6.14 On the basis of an indirect comparison presented by the resubmission, for every 100 patients treated with adalimumab in comparison with apremilast:
- Approximately 22 additional patients would have an ACR50 response over 12 to 16 weeks of treatment.

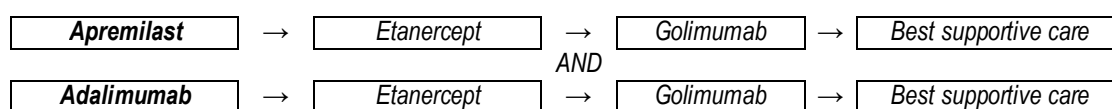
Clinical claim

- 6.15 The resubmission described apremilast as inferior in terms of comparative effectiveness and non-inferior in terms of safety (“equivalent” in terms of short-term safety but “superior” in terms of long-term safety), over adalimumab. The ESC considered that the clinical claim was reasonable.
- 6.16 The data presented in the resubmission supported the claim of inferior effectiveness at 16 weeks of apremilast compared with the effectiveness at 12 weeks of adalimumab, in terms of ACR50 and ACR20 response, PsARC response and PASI 75 response.
- 6.17 The PBAC considered that the claim of inferior comparative effectiveness was reasonably supported by the data.
- 6.18 The PBAC considered that the claim of non-inferior short-term safety and superior long-term safety was reasonably supported by the data.

For more detail on PBAC’s view, see section 7 “PBAC outcome”.

Economic analysis

- 6.19 The resubmission presented a modelled evaluation of apremilast versus adalimumab, specifically:



- 6.20 The PSCR (p3) acknowledged that a more appropriate model would have been apremilast > adalimumab > etanercept > best supportive care, and this was incorporated into a revised economic model.
- 6.21 Although the resubmission identified an “eligible but unwilling” population in Section A of the resubmission, and accounted for the potential use of apremilast in this population in its financial estimates in Section E of the resubmission (assuming they are currently untreated), the modelled economic evaluation did not inform the cost-effectiveness of apremilast in this group who are unable or unlikely to be treated with bDMARDs. The PSCR (pp. 2-3) suggested a considerable majority of prospective apremilast patients would otherwise receive a bDMARD and moreover, for those prospective patients who are truly “eligible but unwilling” a bDMARD would represent

a clinically optimal and acceptably cost effective therapy; albeit one which is bypassed for various individual and patient-specific reasons. The ESC considered that a model that does not inform the cost effectiveness of those patients unable or unwilling to be treated with bDMARDs was problematic as the economic evaluation presented was only for a subset of patients, and therefore considered that this may not be sufficient for decision making.

- 6.22 The resubmission compared the costs and consequences of apremilast to adalimumab in patients who have undergone and failed therapy with methotrexate and leflunomide or sulfasalazine.

Table 6: Summary of model structure and rationale

Component	Summary
Time horizon	5 years in the model base case versus 24 weeks in trial
Outcomes	QALYs
Methods used to generate results	cohort expected value analysis
Health states	First-line treatment, Second-line treatment, Third-line treatment, Best Supportive Care, Dead
Cycle length	28 days (4 weeks)
Transition probabilities	See Section D.4

Source: compiled during the evaluation

- 6.23 The difference in short-term relapse between adalimumab and apremilast, difference in utility between baseline and responder, difference in initial response rates (ACR50) between apremilast and adalimumab, and assumed treatment sequence were found to be driving the model.

Table 7: Key drivers of the model

Description	Method/Value	Impact
Difference in short-term relapse rates between adalimumab and apremilast	2.6% (6.5%-3.9%); adalimumab relapse derived from 10% longitudinal PBS sample	High
Difference in utility between baseline and responder	0.25 (0.77 – 0.52); UK valuation algorithm from the pooled apremilast trials	High, favours adalimumab
Difference in initial ACR50 response rates between apremilast and adalimumab	19.1% (33% - 13.9%); ACR50 response rates pooled across apremilast and adalimumab trials, respectively.	Moderate
Treatment sequence	Apremilast → Etanercept → Golimumab → BSC	Moderate, favours apremilast

Source: compiled during the evaluation

- 6.24 The results of the cost-utility analysis are summarised in Table 8. Table 8 shows that an average reduction in cost of \$ [REDACTED] per patient, and an average loss of 0.06 QALYs per patient, treated with apremilast compared with adalimumab over 5 years. The ICER was estimated to be \$105,000/QALY - \$200,000/QALY foregone assuming that apremilast would replace one of three bDMARDs in a treatment cycle. This was updated in the PSCR (p4) to \$75,000/QALY - \$105,000/QALY foregone reflecting decreased costs of \$ [REDACTED] and decreased effectiveness of 0.093 QALYs for apremilast compared to adalimumab. The ESC considered that a step-wise modification of the base case would have been more informative than simply the presentation of a new ICER.

- 6.25 The cost savings are likely to be overestimated. Available data from the trials suggested that █% of Week 16 ACR 50 responders lose response by Week 24, with a further █% losing ACR50 response by Week 52. The model, however, assumed a constant discontinuation rate per cycle over the first year of treatment with apremilast (based on the data reported above). The effect of this in the modelled economic evaluation was that patients remained on apremilast for longer, accruing benefits (utility associated with ACR50 response) and lower treatment costs (given apremilast costs were estimated to be lower than those for the bDMARDs) before switching to bDMARD treatment in the model. The ESC agreed that the issues identified in the model were likely to overestimate cost savings.
- 6.26 Although fewer QALYs are accrued among those treated with apremilast (0.43) compared with adalimumab (0.69) while they are treated with these therapies in the model, the apremilast arm of the model “catches-up” with accrual of QALYs when moving on to subsequent treatment with bDMARDs and best supportive care therapy (see Table 8).

Table 8: Results of the stepped economic evaluation

Step and component	Apremilast	Adalimumab	Increment
Costs			
	\$ █	\$63,837	-\$ █
Apremilast	\$ █	\$0	\$ █
Adalimumab	\$0	\$22,897.37	-\$22,897.37
Etanercept	\$ █	\$22,835.25	\$ █
Golimumab	\$ █	\$15,820.23	\$ █
Best supportive care	\$ █	\$2,284.56	\$ █
QALYs	2.86	2.91	-0.06
Apremilast	0.43	-	0.43
Adalimumab	-	0.69	-0.69
Etanercept	0.77	0.71	0.06
Golimumab	0.53	0.48	0.04
Best supportive care	1.13	1.03	0.10
Incremental saving/extra QALY forgone			\$ █

Source: Table D-4, p121 of the resubmission

- 6.27 The ESC advised that the ICER shown in Table 8 above needed to be interpreted as an incremental saving per QALY forgone. The ESC further advised that the interpretation of ICERs in the south-west quadrant of the cost-effectiveness plane is not the same as ICERs in the north-east quadrant as reduced effectiveness may require a greater than equal reduction in price and consideration is required regarding how much of a cost saving would be required to compensate for the reduced effectiveness of apremilast compared with adalimumab (and all other bDMARDs). A loss of QALYs may not be acceptable, even in the face of potential cost savings (the magnitude of which is uncertain). As such, this resubmission was effectively proposing, by proxy, for patients to pay (in terms of QALY loss) for convenience (mode of administration).
- 6.28 The ESC advised that an ICER in the south-west quadrant for this apremilast resubmission was difficult to interpret given the proposed positioning of apremilast would inappropriately limit patients to two bDMARDs in a cycle of therapy, and the “eligible but unwilling” population were not factored into the clinical or economic considerations. Additionally, consideration would be required regarding the

opportunity costs, and whether the cost savings are reasonable, because they may allow for accumulation of QALYs among patients other than those with PsA, rather than optimising QALY gains among PsA patients.

- 6.29 Due to the unclear clinical place of apremilast and the issues associated with the model, the ESC considered that a cost-minimisation analysis compared to leflunomide may be a more appropriate economic evaluation, noting that apremilast should replace the use of a DMARD (sulfasalazine or leflunomide) and not be an additional line of therapy that may delay treatment with bDMARDs.
- 6.30 Univariate sensitivity analyses showed that that the model in the resubmission was most sensitive to the assumption that no patients go onto best supportive care (treatment cycling), the short-term relapse rates for adalimumab versus apremilast, the utility value of best supportive care, the incremental utility of responder vs. non-responder and responder vs. baseline/BSC, and the incremental ACR50 initial response rates for adalimumab vs. apremilast.

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

Drug cost/patient/year: \$ [REDACTED].

- 6.31 \$ [REDACTED] per patient per year based on the requested price and assuming one initiation and 12 maintenance scripts per year. This compares with a cost of \$ [REDACTED] for adalimumab, assuming the July 2015 PBS price of \$ [REDACTED], and 12.5 scripts per year. The savings per patient per year would be \$ [REDACTED].

Estimated PBS usage & financial implications

- 6.32 This resubmission was not considered by DUSC. The resubmission used a market-based approach, based on current PBS prescription data of bDMARDs for PsA, and results of the expert clinician survey. There was no appropriately worded question in the survey from which to derive the proportion of untreated patients who are eligible but not treated with bDMARDs.
- 6.33 Table 9 summarises the estimated use and financial implications of listing apremilast on the PBS. The net cost to the PBS estimated in the current resubmission is much lower than that estimated in the previous submission (see last row of the table).

Table 9: Estimated use and financial implications

	Year 1	Year 2	Year 3	Year 4	Year 5
Estimated extent of use					
Number initiating treatment					
Uptake rate:					
bDMARD treated	22%	22%	22%	22%	22%
Untreated, eligible but unwilling	66%	66%	66%	66%	66%
Titration packs ^a					
Continuation packs ^b					
Estimated net cost to PBS/MBS					
Net cost to PBS	\$	\$	\$	\$	\$
Net cost to MBS	-	-	-	-	-
Estimated total net cost					
Net cost PBS/MBS	\$	\$	\$	\$	\$
Net cost PBS/MBS – Mar 2015	\$	\$	\$	\$	\$

Source: Compiled during the evaluation

^a One titration pack per patient initiating treatment

^b 4 continuation packs per initial non-responder, 9 continuation packs per part-year responder, 13 continuation packs per full-year responder, 13 continuation packs per patient continuing treatment

The redacted table above shows the estimated patients to receive initiating treatment with apremilast to be less than 10,000 per year and the estimated net cost to PBS/MBS to be less than \$10 million per year.

- 6.34 These estimates were most sensitive to the proportion of untreated patients (who are eligible but currently unwilling) who were assumed to present again to their specialist for treatment should a new oral therapy become available, and the proportion of untreated patients who are eligible but currently unwilling. The estimates were also sensitive to the price of apremilast and the assumed uptake rates of apremilast.

Financial Management – Risk Sharing Arrangements

- 6.35 The PSCR (p4) noted the considerable uncertainty surrounding estimated financial implications and the potential for use beyond the proposed restriction, suggesting that a risk sharing arrangement may be appropriate.

For more detail on PBAC’s view, see section 7 “PBAC outcome”.

7 PBAC Outcome

- 7.1 The PBAC did not recommend the listing of apremilast for the treatment of severe active psoriatic arthritis on the basis that the proposed place of apremilast in the clinical management algorithm is inappropriate and the comparison to bDMARDs is also inappropriate for patients unwilling to try bDMARDs.
- 7.2 The PBAC agreed with the ESC that limiting patients to two bDMARDs in a cycle of therapy, as proposed in the resubmission, would not be appropriate, given that apremilast is a significantly less effective treatment than bDMARDs. The PBAC

reiterated its previous conclusions from March 2015 that apremilast should be one of the options to be used before the bDMARDs, but not as an additional line of therapy prior to patients being initiated on bDMARD therapy because this would unnecessarily delay the use of more effective bDMARD treatment.

- 7.3 The PBAC noted that the PSCR identified two patient populations who may access apremilast: those who are currently treated with bDMARDs, but would prefer an oral therapy and would switch if apremilast became available; and those who are currently appropriate and eligible for bDMARD therapy, but are unwilling to commence this. The PBAC noted that neither of these populations were incorporated into the economic model, which assumed patients initiate treatment with apremilast after failure of DMARDs, directly replacing the use of adalimumab. The PBAC considered that the identified “eligible but unwilling” population were not adequately defined by the resubmission, and in clinical practice are likely to be quite small. The sponsor hearing defined this population as predominantly elderly patients with significant comorbidities who are therefore unsuitable for bDMARDs. This assumed that patients would not otherwise be treated with adalimumab (or another bDMARD) after failure of DMARDs, however this is not represented by the model structure.
- 7.4 The PBAC considered that adalimumab, or any bDMARD for the treatment of PsA, is not an appropriate comparator because the more appropriate place of apremilast is earlier in the clinical management algorithm than the bDMARDs. The PBAC reiterated that leflunomide, or another DMARD used for the treatment of PsA, is the appropriate comparator.
- 7.5 The PBAC noted that, on the basis of the indirect comparison of apremilast to adalimumab, apremilast was statistically significantly inferior to adalimumab in terms of ACR50 response. Despite reliance on an indirect comparison, the PBAC was reasonably confident of inferiority, given the magnitude of the difference and the lack of clear differences in known modifiers of treatment effect (with the exception of year of study).
- 7.6 The PBAC considered the claim of non-inferior short-term safety compared to adalimumab was reasonably supported by the data. The PBAC considered that, in the absence of comparative safety data, the claim of superior long-term safety of apremilast compared to adalimumab was not robustly supported (with the exception of the rate of infections, which is likely to be greater with adalimumab).
- 7.7 The PBAC agreed with the ESC that issues identified in the model were likely to result in an overestimate of the cost savings. The PBAC noted that the ICER for apremilast lay within the south-west quadrant of the cost effectiveness plane (i.e. less effective and cheaper) compared to bDMARDs. However the PBAC considered that, given the unclear patient population likely to use apremilast, this model did not adequately assess the cost-effectiveness of apremilast in its proposed place in therapy, let alone the earlier place in therapy considered to be more appropriate. The PBAC therefore considered that a cost-minimisation analysis compared to leflunomide would be a more appropriate economic evaluation.
- 7.8 The PBAC considered that it was difficult to accurately estimate the number of patients likely to be captured by the proposed “eligible but unwilling” patient population.

7.9 The PBAC noted that this resubmission is eligible for 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.