

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

1 Purpose of submission

- 1.1 The Standard Re-entry submission requested an Authority Required (STREAMLINED) listing for apremilast for the treatment of severe active psoriatic arthritis (PsA).
- 1.2 Listing was requested on the basis of a cost-utility analysis versus placebo plus best supportive care (BSC).

Table 1: Key components of the clinical issue addressed by the submission (as stated in the submission)

Component	Description
Population	Severe active psoriatic arthritis patients who: <ul style="list-style-type: none"> • have previously received, and failed to achieve an adequate response to, methotrexate, sulfasalazine, and leflunomide unless clinically inappropriate for treatment with one or more of these agents; AND • are inappropriate for treatment with a biologic medicine for this condition ^a
Intervention	Apremilast, an oral inhibitor of phosphodiesterase 4 (PDE4), 30 mg tablet twice daily
Comparator	Placebo plus BSC ^b
Outcomes	Improvement in accepted measures of response (ACR20, ACR50); and physical function (HAQ-DI) ^c
Clinical claim	<ul style="list-style-type: none"> • In terms of clinical efficacy, apremilast is superior to placebo plus BSC • In terms of safety, apremilast has inferior short-term safety compared to placebo plus BSC ^d

Source: Table 1-1, p4 of the submission; paragraphs 2.1 & 3.3, apremilast, Public Summary Document (PSD), November 2015 PBAC meeting; apremilast submission for the November 2015 PBAC meeting.

ACR20 = Modified American College of Rheumatology 20% response; ACR50 = Modified American College of Rheumatology 50% response; BSC = best supportive care; bDMARD = biologic disease modifying antirheumatic drug; EQ-5D = EuroQol 5 Dimensions Questionnaire; HAQ-DI = Health Assessment Questionnaire Disability Index; PBS = Pharmaceutical Benefits Scheme; PBAC = Pharmaceutical Benefits Advisory Committee; PASI 75 = Psoriasis Area and Severity Index 75% response; PsA = psoriatic arthritis; PsARC = Psoriatic Arthritis Response Criteria; SF-36 = 36-item Short Form Health Survey.

^a Population in the November 2015 submission described as "Severe active PsA, where (methotrexate AND sulfasalazine OR leflunomide), are ineffective, OR contra-indicated or cannot tolerate methotrexate, sulfasalazine or leflunomide." (i.e., no discussion of bDMARDs)

^b Comparator in the November 2015 submission was adalimumab

^c Outcomes in the November 2015 submission were ACR50, ACR20, Modified PsARC response, PASI75, HAQ-DI, SF-36, and EQ-5D

^d Clinical claim in the November 2015 submission was "Apremilast is inferior in terms of comparative effectiveness and noninferior in terms of comparative safety over adalimumab."

2 Background

Registration status

- 2.1 Apremilast was included on the Australian Register of Therapeutic Goods in March 2015 and is currently TGA registered for the following indications:

- The treatment of signs and symptoms of active PsA in adult patients.

- The treatment of adult patients with moderate to severe plaque psoriasis (PsO) who are candidates for phototherapy or systemic therapy.

Previous PBAC consideration

2.2 Table 2 summarises the key matters of concern highlighted at the March 2015 and November 2015 PBAC meetings.

Table 2: Summary of key matters of concern

Component	Matter of concern (March 2015 submission)	Matter of concern (November 2015 submission)	How the resubmission addresses it
Positioning	<p>Requested PBS listing: severe active PsA, where other DMARDS, including methotrexate, are ineffective or inappropriate (para. 3.3, March 2015 PSD).</p> <p>PBAC advice: 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 (para 7.2, March 2015 PSD).</p>	<p>Requested PBS listing: Severe active PsA, where (methotrexate AND sulfasalazine OR leflunomide), are ineffective, OR contra-indicated or cannot tolerate methotrexate, sulfasalazine or leflunomide.</p> <p>PBAC advice: The proposed place of apremilast in the clinical management algorithm was deemed inappropriate (para. 7.1, November 2015 PSD). Apremilast should be one option used before 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 (para. 7.1, November 2015 PSD).</p>	<p>Requested PBS listing: Severe active PsA, where csDMARDs are clinically inappropriate and bDMARDs are inaccessible through the PBS or inappropriate due to contraindication or intolerance to treatment (i.e., last line).</p> <p>Proposed a revised place in therapy; identified a niche population that addresses unmet need in clinical practice and does not impact access to the existing PBS reimbursed therapies used to manage severe active PsA nor delay access to bDMARD therapy.</p>
Comparator	<p>The submission's nominated comparator was leflunomide. The PBAC accepted this but also considered that sulfasalazine was an appropriate secondary comparator (para. 7.3, March 2015 PSD).</p>	<p>The PBAC considered that adalimumab, or any bDMARD for the treatment of PsA, is not an appropriate comparator (para. 7.4, November 2015 PSD). The PBAC reiterated that leflunomide, or another DMARD used to treat PsA, is an appropriate comparator (para. 7.4, November 2015 PSD).</p>	<p>Consistent with the revised positioning proposed, BSC has been nominated as the comparator.</p>

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Component	Matter of concern (March 2015 submission)	Matter of concern (November 2015 submission)	How the resubmission addresses it
Economic evaluation	Cost-utility analysis based on the premise that the listing of apremilast will delay the commencement of bDMARDs (para. 6.24, March 2015 PSD) The submission's economic analysis modelled a treatment scenario that is unlikely to be realised in practice (para. 7.6, March 2015 PSD).	Given the unclear patient population likely to use apremilast, the economic 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 (para. 7.7, November 2015 PSD). A cost-minimisation analysis compared to leflunomide would be a more appropriate economic evaluation (para. 7.7, November 2015 PSD).	The submission stated cost-minimisation approach compared to leflunomide is an unviable option. A revised and simplified model, with a markedly reduced price compared to previous submissions, demonstrates cost-effectiveness of apremilast versus placebo plus BSC in the proposed population.

Source: Table 1-8, pp11-12 of the submission; paragraphs 7.1, 7.4 & 7.7, apremilast, PSD, November 2015 PBAC meeting.
bDMARD = biologic disease modifying antirheumatic drug; BSC = best supportive care; csDMARD = conventional synthetic disease modifying antirheumatic drug; ES = executive summary; PBAC = Pharmaceutical Benefits Advisory Committee; PBS = Pharmaceutical Benefits Scheme; PsA = psoriatic arthritis; PSD = Public Summary Document.

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

3 Requested listing

MEDICINAL PRODUCT medicinal product pack	Dispensed Price for Max. Qty	Max. qty packs	Max. qty units	No. of Rpts	Available brands
APREMILAST					
apremilast 10mg tablet, 4 & 20 mg tablet, 4 & 30 mg tablet, 19	\$272.35 published price \$ effective price	1	27	0	Otezla
apremilast 30 mg tablet, 56	\$652.86 published price \$ effective price	1	56	5	Otezla
Category / Program: General Schedule					
Prescriber type: <input type="checkbox"/> Dental <input checked="" type="checkbox"/> Medical Practitioners <input type="checkbox"/> Nurse practitioners <input type="checkbox"/> Optometrists <input type="checkbox"/>					
Restriction type: <input checked="" type="checkbox"/> Authority Required (STREAMLINED)					
Condition: Psoriatic arthritis					
Indication: Severe active psoriatic arthritis					
Treatment Phase: All					
Clinical criteria:					
Patient must have previously received, and failed to achieve an adequate response to, methotrexate, sulfasalazine, and leflunomide unless clinically inappropriate for treatment with one or more of these agents;					
AND					
Clinical criteria:					
Patient must be ineligible for PBS-subsidised treatment with a biologic medicine for this condition; OR Patient must be clinically inappropriate for treatment with a biologic medicine for this condition;					
AND					
Clinical criteria:					
The treatment must be the sole PBS-subsidised disease-modifying antirheumatic agent for psoriatic arthritis.					
Treatment criteria:					

<p>Must be treated by a medical practitioner who is either: (i) a rheumatologist, (ii) an accredited rheumatology registrar in consultation with a rheumatologist, (iii) clinical immunologist with expertise in the management of psoriatic arthritis, (iv) general physician; OR Must be treated by a general practitioner who has been directed to continue treatment (not initiate treatment) by one of the above practitioner types.</p>
<p>Population criteria:</p>
<p>Patient must be aged 18 years or older.</p>
<p>Notes:</p>
<p>No increase in the maximum number of repeats may be authorised. No increase in the maximum quantity or number of units may be authorised. Special Pricing Arrangements apply.</p>

- 3.1 The proposed effective price is the same as the current effective AEMP for the severe chronic plaque PsO indication.
- 3.2 The requested restriction was narrower than the TGA indication, which does not specify that patients must fail to achieve an adequate response to conventional synthetic disease modifying antirheumatic drugs (csDMARDs) or be ineligible, contraindicated, or intolerant to biologic or targeted synthetic disease modifying antirheumatic drugs (bDMARDs/tsDMARD).
- 3.3 The requested restriction is not consistent with the clinical evidence presented, as the trials presented did not require participants to have received and failed multiple lines of csDMARD therapy prior to receiving apremilast. Some trials presented also permitted prior bDMARD therapy and did not require apremilast to be the only DMARD treatment administered.
- 3.4 The ESC noted reference to ‘clinically inappropriate’ in the proposed restriction would likely not result in the same population as ‘contraindicated or stopped treatment due to side effects’ without further clarification what population this is intended to capture.

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

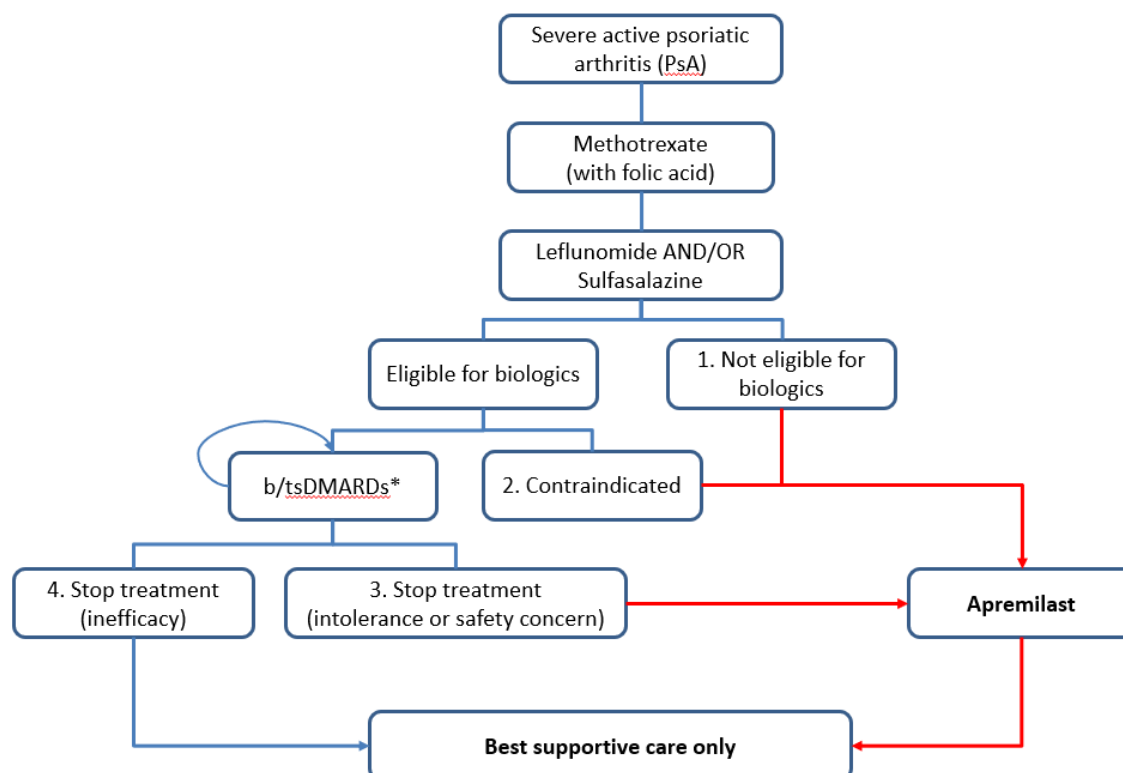
4 Population and disease

- 4.1 PsA is a chronic, inflammatory disease with a diverse clinical spectrum characterised by six core domains: peripheral arthritis, axial disease, enthesitis (inflammation where tendons or ligaments attach to bone), dactylitis (inflammation of an entire digit), and skin and nail psoriasis. Initially, PsA typically presents as an oligoarticular (involving up to five peripheral joints) and mild disease. However, with time PsA becomes polyarticular (involving more than five peripheral joints), and it is a severe disease in at least 20% of patients.
- 4.2 For many patients, the impact of PsA goes beyond standard skin and joint involvement, and hard to treat domains like enthesitis and dactylitis are common. Active chronic PsA is also associated with cardiovascular, psychological, and metabolic

comorbidities, which, together with the musculoskeletal manifestations, impose a significant patient burden with impact on quality of life and accelerated mortality.

- 4.3 The proposed populations eligible for apremilast have severe active PsA and have failed at least three csDMARDs, unless contraindicated or intolerant. Three distinct subpopulations have been identified for whom bDMARDs are not an option:
- Failed csDMARDs and PBS ineligible for bDMARDs (subpopulation 1).
 - Failed csDMARDs and contraindicated to treatment with bDMARDs (subpopulation 2).
 - Failed csDMARDs and stopped treatment with bDMARDs due to side effects (subpopulation 3).
- 4.4 The ESC noted the PBAC has previously advised that leflunomide, or another csDMARD used for the treatment of PsA, would be the appropriate comparator for apremilast. The ESC considered this remained the most appropriate place in therapy for apremilast in PsA but acknowledged the sponsor's concerns regarding this issue (see paragraph 5.3).
- 4.5 There are currently 11 listed bDMARDs for PsA covering a variety of pharmacological classes. The ESC noted patients would need to be contraindicated to, or trial and discontinue due to side effects, 11 bDMARDs before entering subpopulation 2 or 3, respectively. The ESC considered the clinical relevance of the subpopulations was uncertain, and likely reflected only a very small proportion of patients with PsA, given the number of contraindications and/or intolerances that would be required to qualify.
- 4.6 Apremilast is a small-molecule inhibitor of the phosphodiesterase type 4 (PDE4) enzyme, which works intracellularly to modulate a network of pro-inflammatory and anti-inflammatory mediators. Inhibition of PDE4 elevates intracellular cyclic adenosine monophosphate (cAMP) levels, which in turn down-regulates the inflammatory response by modulating the expression of tumour necrosis factor alpha (TNF- α), interleukin 17 (IL-17), IL-23, and other inflammatory cytokines. Elevation of cAMP also modulates the production of anti-inflammatory cytokines such as IL-10.
- 4.7 The proposed clinical management algorithm for the intended use of apremilast as a treatment for severe active PsA is provided in Figure 1. The numbered boxes in the figure correspond to: (1) subpopulation 1; (2) subpopulation 2 and (3) subpopulation 3.

Figure 1: Proposed severe active PsA management algorithm including apremilast



Source: Figure 1-2, page 14 of the resubmission

4.8 The ESC considered there was a potential risk of use of apremilast in patients that would otherwise be appropriate for, and without contraindication, to csDMARDs (some of whom would be on the pathway to bDMARDs). In this population apremilast would effectively be used as a second line therapy, and therefore for these patients the proposed comparator (BSC) would no longer be appropriate.

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

5 Comparator

5.1 The submission nominated placebo plus BSC as the comparator. The main argument provided in support of this nomination was that patients in the proposed population had no other treatment options.

5.2 The submission stated that BSC represents no active treatment and constitutes a range of pharmacological and non-pharmacological management strategies (e.g., oral corticosteroids, non-steroidal anti-inflammatory drugs, phototherapy, medical and allied health consultations).

5.3 The ESC noted the submission stated (and the Pre-Sub-Committee Response (PSCR) reiterated) that the ideal position of apremilast in the management of PsA would be as an alternate second line agent, analogous to the position of apremilast in treating

plaque PsO; however, the low-cost second line comparators in PsA made this unviable. Apremilast was listed for PsO on a cost minimisation basis with ciclosporin, accounting for differential adverse events and drug monitoring costs amounting to an 1% price premium over the AEMP (paragraph 6.2, apremilast Public Summary Document (PSD), July 2020 PBAC meeting).

6 Consideration of the evidence

Sponsor hearing

- 6.1 The sponsor requested a hearing for this item. The clinicians considered the proposed place in therapy for apremilast was reasonable, however noted a preferred positioning would be after a patient failed or was ineligible for methotrexate (i.e. similar to the current listing of leflunomide). The clinicians stated there was a need for additional treatment options for the three cohorts of patients identified in the resubmission, as there was limited evidence for sulfasalazine and leflunomide across all domains or manifestations of PsA symptoms, and patients with a high number of co-morbidities may be ineligible or intolerant for the range of bDMARDs available for PsA.

Consumer comments

- 6.2 The PBAC noted and welcomed the input from health care professionals (6) and organisations (2) via the Consumer Comments facility on the PBS website. The comments described the effectiveness of apremilast in PsA and highlighted current conventional DMARD options including methotrexate, sulfasalazine and leflunomide are often not highly effective for patients and the clinical experience with apremilast is that it is a safe and effective treatment option. The comments noted the gap in treatment options experienced by individuals who do not meet the criteria for treatment with bDMARDs/ tsDMARDs.
- 6.3 The PBAC noted the advice received from Musculoskeletal Australia, which outlined that access to apremilast would provide clinicians with more options for the treatment of patients with severe disease that are unresponsive to existing conventional options, and highlighted the favourable safety and tolerability profile compared to some of the alternative treatments.
- 6.4 The PBAC noted advice from the Australian Rheumatology Association (ARA), which outlined the novel mechanism of action of apremilast, its favourable safety profile and highlighted the quality of data in PsA from clinical trials was stronger than many of the conventional DMARDs. The ARA noted treatment guidelines stated that, whenever possible, a drug that is effective for a patient's skin and joint disease should be used. The ARA stated that good arthritis control is important, even in patients with only one or two affected joints, because PsA can be destructive. The ARA noted that since apremilast is already listed on the PBS for the management of severe CPP, it would be of additional value for it to also be listed for PsA.

Clinical trials

- 6.5 The resubmission was based on five randomised controlled trials of apremilast (30 mg twice daily) compared to placebo: ACTIVE, PALACE 1, PALACE 2, PALACE 3 and PALACE 4.
- 6.6 The ACTIVE trial, completed in November 2016, has not been considered by the PBAC. The PALACE 1-4 trials were considered by the PBAC in the March and November 2015 submissions for apremilast in this indication.
- 6.7 This submission presented extended follow-up data for the PALACE 1-4 trials (until week 260 for the PALACE 1-3 trials and until week 208 for the PALACE 4 trial). The November 2015 PBAC submission included data for the PALACE 1 and 3 trials until week 104 and the PALACE 2 trial until week 52.
- 6.8 The submission also presented subgroup analyses for prior csDMARDs exposure and baseline disease activity in the ACTIVE trial, prior csDMARDs and bDMARD exposure in the PALACE 1-3 trials.
- 6.9 Details of the trials presented in the submission are provided in Table 3.

Table 3: Trials and associated reports presented in the submission

Trial ID	Protocol title/ Publication title	Publication citation
ACTIVE NCT01925768	CC-10004-PSA-006 A phase 3b, multicenter, randomized, double-blind, placebo-controlled, parallel-group study to evaluate the efficacy and safety of apremilast (cc-10004) monotherapy in subjects with active psoriatic arthritis	CSR, 13 June 2017
	Nash P, Ohson K, Walsh J et al. Early and sustained efficacy with apremilast monotherapy in biological-naïve patients with psoriatic arthritis: a phase IIIB, randomised controlled trial (ACTIVE).	Ann Rheum Dis. 2018; 77(5):690-698
	Nash P, Richter S, Jardon S et al. Probability of achieving treatment targets with apremilast monotherapy in biologic-naïve psoriatic arthritis patients in ACTIVE with moderate and high baseline disease activity.	Annals of the Rheumatic Diseases 2021; 80:1310-1311.
PALACE 1 NCT01172938	CC-10004-PSA-002 A phase 3, multicenter, randomized, double-blind, placebo-controlled, parallel-group, efficacy and safety study of two doses of apremilast (CC-10004) in subjects with active psoriatic arthritis	CSR, 26 September 2013
	Kavanaugh A, Mease PJ, Gomez-Reino JJ et al. Treatment of psoriatic arthritis in a phase 3 randomised, placebo-controlled trial with apremilast, an oral phosphodiesterase 4 inhibitor.	Ann Rheum Dis. 2014; 73(6):1020-6
	Kavanaugh A, Mease PJ, Gomez-Reino JJ et al. Longterm (52-week) results of a phase III randomized, controlled trial of apremilast in patients with psoriatic arthritis	J Rheumatol. 2015; 42(3):479-88
PALACE 2 NCT01212757	CC-10004-PSA-003 A phase 3, multicenter, randomized, double-blind, placebo-controlled, parallel-group, efficacy and safety study of two doses of apremilast (CC-10004) in subjects with active psoriatic arthritis	CSR, 30 September 2013
	Cutolo M, Myerson GE, Fleischmann RM et al. A Phase III, Randomized, Controlled Trial of Apremilast in Patients with Psoriatic Arthritis: Results of the PALACE 2 Trial.	J Rheumatol. 2016; 43(9):1724-34

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Trial ID	Protocol title/ Publication title	Publication citation
PALACE 3 NCT01212770	CC-10004-PSA-004 A phase 3, multicenter, randomized, 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	CSR, 26 September 2013
	Edwards CJ, Blanco FJ, Crowley J et al. Apremilast, an oral phosphodiesterase 4 inhibitor, in patients with psoriatic arthritis and current skin involvement: a phase III, randomised, controlled trial (PALACE 3).	Ann Rheum Dis. 2016; 75(6):1065-73
PALACE 4 NCT01307423	CC-10004-PSA-005 A phase 3, multicenter, randomized, 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	CSR, 11 December 2013
	Wells AF, Edwards CJ, Kivitz AJ et al. Apremilast monotherapy in DMARD-naïve psoriatic arthritis patients: results of the randomized, placebo-controlled PALACE 4 trial. Wells AF, Edwards CJ, Kivitz AJ et al. Apremilast monotherapy for long-term treatment of active psoriatic arthritis in DMARD-naïve patients.	Rheumatology (Oxford) 2018; 57(7):1253-1263 Rheumatology (Oxford) 2022; 61(3):1035-1043
PALACE 1-3 Pooled analyses	Gladman DD, Kavanaugh A, Gómez-Reino JJ et al. Therapeutic benefit of apremilast on enthesitis and dactylitis in patients with psoriatic arthritis: a pooled analysis of the PALACE 1-3 studies.	RMD Open 2018; 4(1):e000669
	Kavanaugh A, Gladman DD, Edwards CJ et al. Long-term experience with apremilast in patients with psoriatic arthritis: 5-year results from a PALACE 1-3 pooled analysis.	Arthritis Res Ther. 2019; 21(1):118
	Mease PJ, Gladman DD, Kavanaugh A et al. Articular and Extra-Articular Benefits in ACR20 Non-responders at Week 104 Treated With Apremilast: Pooled Analysis of Three Randomized Controlled Trials.	Rheumatol Ther. 2021; 8(4):1677-1691
	Mease PJ, Gladman DD, Ogdie A et al. Treatment-to-Target With Apremilast in Psoriatic Arthritis: The Probability of Achieving Targets and Comprehensive Control of Disease Manifestations	Arthritis Care Res (Hoboken). 2020; 72(6):814-821
	Mease PJ, Gladman DD, Gomez-Reino JJ et al. Long-Term Safety and Tolerability of Apremilast Versus Placebo in Psoriatic Arthritis: A Pooled Safety Analysis of Three Phase III, Randomized, Controlled Trials.	ACR open rheumatology 2020; 2(8):459–470

Source: Table 2-4, pp20-22 of the submission; ACTIVE CSR; PALACE 1 CSR; PALACE 2 CSR; PALACE 3 CSR; PALACE 4 CSR.

6.10 The key features of the direct randomised trials are summarised in Table 4.

Table 4: Key features of the included evidence

Trial	N	Design/ duration	Risk of bias	Patient population	Outcome(s)	Use in modelled evaluation
Apremilast vs. placebo						
ACTIVE	219	R, MC, DB (24 wk) ^a followed by APR phase (28 wk) and OL extension (1yr)	Low	PsA ≥3 mo, ≥3 swollen AND ≥3 tender joints, high sensitivity CRP ≥ 0.2 mg/dL, biologic naïve, monotherapy	Primary: ACR20 at 16 wk Secondary: ACR50, HAQ-DI (health assessment – disability), GEI (enthesitis), SF-36, DAS-28 (disease activity), safety	ACR20 at 24 wk, HAQ-DI at 16 and 24 wk
PALACE 1	336	R, MC, DB (24 wk) ^a followed by APR phase (28 wk) and OL extension (4 yr)	Low	PsA ≥6 mo, ≥3 swollen AND ≥3 tender joints, combination therapy (e.g., methotrexate) allowed	Primary: ACR20 at 16 wk Secondary: ACR50, HAQ-DI, MASES (enthesitis) ^b , dactylitis count, PASI, SF-36, EQ-5D, safety	PASI at baseline
PALACE 2	321		Low			
PALACE 3	336		Low	PsA ≥6 mo, ≥3 swollen AND ≥3 tender joints, at least 1 plaque psoriasis lesion ≥2cm, combination therapy allowed		
PALACE 4	352		Low	PsA ≥6 mo, ≥3 swollen AND ≥3 tender joints, treatment naïve, monotherapy		

Source: Tables 2-5, 2-6, 2-7, 2-11, 2-12, 2-19 & 2-20, pp23-24, 27, 30-31 & 39-44 of the submission; Figures 2-3 & 2-4, p26 of the submission; pp22-23 of the submission.

ACR20 = Modified American College of Rheumatology 20% response; ACR50 = Modified American College of Rheumatology 50% response; APR = apremilast; CRP = C-reactive protein; DAS-28 = 28-Joint Disease Activity Score; DB = double blind; EQ-5D = EuroQol 5 Dimensions Questionnaire; GEI = Gladman Enthesitis Index; HAQ-DI = Health Assessment Questionnaire-Disability Index; MASES = Maastricht Ankylosing Spondylitis Enthesitis Score; MC = multi-centre; mo = month; OL = open label; PASI = Psoriasis Area and Severity Index; PsA = psoriatic arthritis; R = randomised; SF-36 = Short Form Health Survey – 36 item; wk = week; yr = year.

^a The primary outcomes were assessed at week 16. After the primary outcome was assessed, participants who achieved in insufficient response were eligible for early escape to active treatment. Further clinical assessments at week 24 including participants in early escape were conducted without breaking the blind.

^b PALACE 1-3 trials only

Comparative effectiveness

Whole trial analysis

6.11 Table 5 compares the primary outcome (ACR20) and secondary outcome (ACR50) at week 16 across all trials.

Table 5: ACR20 and ACR50 response at Week 16 in the ACTIVE and PALACE 1-4 trials (FAS; NRI)

Trial ID	Apremilast n/N (%)	Placebo n/N (%)	Relative risk (95% CI) ^a	Risk difference (95% CI) ^a
ACR 20				
ACTIVE	42/110 (38.2)	22/109 (20.2)	1.89 (1.22, 2.95)	0.18 (0.06, 0.30)
PALACE 1	64/168 (38.1)	32/168 (19.0)	2.00 (1.39, 2.89)	0.19 (0.10, 0.28)
PALACE 2	52/162 (32.1)	30/159 (18.9)	1.70 (1.15, 2.52)	0.13 (0.04, 0.23)
PALACE 3	68/167 (40.7)	31/169 (18.3)	2.22 (1.54, 3.20)	0.22 (0.13, 0.32)
PALACE 4	54/176 (30.7)	28/176 (15.9)	1.93 (1.29, 2.89)	0.15 (0.06, 0.23)
ACR50				
ACTIVE	20/110 (18.2)	5/109 (4.6)	3.96 (1.54, 10.18)	0.14 (0.05, 0.22)
PALACE 1	27/168 (16.1)	10/168 (6.0)	2.70 (1.35, 5.40)	0.10 (0.04, 0.17)
PALACE 2	17/162 (10.5)	8/159 (5.0)	2.09 (0.93, 4.69)	0.05 (-0.00, 0.11)
PALACE 3	25/167 (15.0)	14/169 (8.3)	1.81 (0.97, 3.35)	0.07 (-0.00, 0.14)
PALACE 4	20/176 (11.4)	8/176 (4.5)	2.50 (1.13, 5.52)	0.07 (0.01, 0.12) ^b

Source: Table 2-21, p45 of the submission. **Bold** indicates statistically significant results (p<0.05).

ACR20 = Modified American College of Rheumatology 20% response; ACR50 = Modified American College of Rheumatology 50% response; CI = confidence interval; FAS = full analysis set; HAQ-DI = Health Assessment Questionnaire-Disability Index; n = number of participants with event; N = total participants in group; NRI = non-responder imputation.

^a calculated during the evaluation by entering the dichotomous outcome data in RevMan 5.4.1

^b The p-value was considered nominally significant, as hierarchical testing was stopped before this outcome was assessed for statistical significance.

- 6.12 A statistically significant greater proportion of participants treated with apremilast compared to placebo achieved an ACR20 at week 16 in all trials.
- 6.13 A greater proportion of participants treated with apremilast compared to placebo achieved an ACR50 response at week 16 in all trials. However, the difference was not statistically significant in the PALACE 2 or PALACE 3 trials. The ACR50 results in the ACTIVE, PALACE 1 and PALACE 4 trials are considered nominally significant due to the hierarchical testing process.
- 6.14 Table 6 compares the change in HAQ-DI from baseline to week 16 in all trials.

Table 6: Change from baseline in HAQ-DI at week 16 in the ACTIVE (FAS; MMRM) and PALACE 1-4 trials (FAS; LOCF)^a

Trial ID	Apremilast			Placebo			LS Mean difference	p-value
	mean baseline (SD)	mean wk 16 (SD)	LS mean change (SE)	mean baseline (SD)	mean wk 16 (SD)	LS mean change (SE)		
ACTIVE								
n(APR)=109 n(PBO)=109	1.253	0.957	-0.205 (0.0523)	1.198	1.157	-0.055 (0.0513)	-0.150	0.0229 ^b
PALACE 1								
n(APR)=159 n(PBO)=165	1.231	0.972	-0.244 (0.0364)	1.206	1.110	-0.086 (0.0360)	-0.159	0.0017
PALACE 2								
n(APR)=154 n(PBO)=153	1.222	0.995	-0.193 (0.0354)	1.147	1.078	-0.053 (0.0358)	-0.140	0.0042
PALACE 3								
n(APR)=160 n(PBO)=163	1.160	0.965	-0.192 (0.0339)	1.160	1.091	-0.065 (0.0335)	-0.127	0.0073
PALACE 4								
n(APR)=167 n(PBO)=167	1.083	0.876	-0.205 (0.0350)	1.020	1.048	0.012 (0.0350)	-0.217	<0.0001

Source: Table 2-22, p48 of the submission. **Bold** indicates statistically significant results (p<0.05).

APR = apremilast; CI = confidence interval; FAS = full analysis set; HAQ-DI = Health Assessment Questionnaire-Disability Index; LOCF = last observation carried forward; LS = least squares; MMRM = mixed-effects model of repeated measures; PBO = placebo; SD = standard deviation; SE = standard error.

^a Analyses conducted for all participants with a baseline value and at least 1 post-baseline value.

^b P-value nominally significant; however hierarchical testing was stopped after the first secondary endpoint (HAQ-DI at 24 weeks).

- 6.15 Participants treated with apremilast achieved improvements in HAQ-DI at Week 16, compared with placebo. The p-value observed for the ACTIVE trial is nominally significant, however hierarchical statistical testing was stopped after the first secondary endpoint (HAQ-DI at 24 weeks).
- 6.16 The least squares mean difference in HAQ-DI change exceeded the MCID of 0.13 specified by Kwok et al (2010) in all trials except PALACE 3. The MCID of 0.30 specified by Mease et. al (2004) was not reached in any of the included trials.
- 6.17 Additional data from the ACTIVE trial used in the economic evaluation is presented in Table 7.

Table 7: ACR20 response, ACR50 response, and change in HAQ-DI at Week 24 in the ACTIVE trial (FAS)

Trial ID	Apremilast n/N (%)		Placebo n/N (%)		Difference in proportions (95% CI)	p-value	
ACR20 (NRI)							
ACTIVE	48/110 (43.6)		27/109 (24.8)		18.5 (6.3, 30.6)	0.0040 ^a	
ACR50 (NRI)							
ACTIVE	22/110 (20.0)		12/109 (11.0)		8.5 (-0.8, 17.7)	0.0820	
HAQ-DI: change from baseline to week 24 (MMRM)							
	Apremilast			Placebo			LS mean difference: APR vs PBO
	N	LS mean Δ	SE	N	LS mean Δ	SE	
ACTIVE	109	-0.273	0.0572	109	-0.169	0.0581	-0.103

Source: Tables 24 & 41 of the ACTIVE CSR.

ACR20 = Modified American College of Rheumatology 20% response; ACR50 = Modified American College of Rheumatology 50% response; APR = apremilast; CI = confidence interval; FAS = full analysis set; HAQ-DI = Health Assessment Questionnaire-Disability Index; LS = least squares; MMRM = mixed-effects model of repeated measures; n = number of participants with event; N = total participants in group; NRI = non-responder imputation; PBO = placebo; SE = standard error.

^a The p-value was considered nominally significant, as hierarchical testing was stopped before this outcome was assessed for statistical significance.

6.18 Table 8 compares PASI50 and PASI75 response at week 16 in the PALACE trials. PASI was not assessed in the ACTIVE trial. Pooled baseline PASI score from the PALACE 1-3 trials was used to estimate utilities in the economic model.

Table 8: PASI50 and PASI75 response at Week 16 (FAS; LOCF)

Trial ID	Apremilast n/N (%)	Placebo n/N (%)	p-value	Relative risk (95% CI) ^a	Risk difference (95% CI) ^a
PASI50					
PALACE 1	36/82 (43.9)	11/68 (16.2)	0.0003 ^b	2.71 (1.50, 4.91)	0.28 (0.14, 0.42)
PALACE 2	33/77 (42.9)	10/74 (13.5)	≤ 0.005 ^c	3.17 (1.69, 5.96)	0.29 (0.16, 0.43)
PALACE 3	38/90 (42.2)	22/89 (24.7)	< 0.05 ^b	1.71 (1.10, 2.64)	0.18 (0.04, 0.31)
PALACE 4	51/109 (46.8)	18/93 (19.4)	≤ 0.0001 ^b	2.42 (1.53, 3.83)	0.27 (0.15, 0.40)
PASI75					
PALACE 1	18/82 (22.0)	3/68 (4.4)	0.0022 ^b	4.98 (1.53, 16.18)	0.18 (0.07, 0.28)
PALACE 2	17/77 (22.1)	2/74 (2.7)	≤ 0.005 ^c	8.17 (1.95, 34.14)	0.19 (0.09, 0.29)
PALACE 3	20/90 (22.2)	7/89 (8)	< 0.05 ^b	2.83 (1.26, 6.35)	0.14 (0.04, 0.25)
PALACE 4	29/109 (26.6)	10/93 (10.8)	< 0.05 ^b	2.47 (1.27, 4.80)	0.16 (0.05, 0.26)

Source: Table 2-30, p55 of the submission; Kavanaugh 2014; Cutolo 2016; Edwards 2016; Wells 2018; Table 44 of the PALACE 1, 2 & 3 CSRs Table 37 of the PALACE 4 CSR. Additional information was added during the evaluation (n/N and p-values identified in the PALACE 1-4 CSRs, RR and RD calculated during the evaluation).

CI = confidence interval; FAS = full analysis set; LOCF = last observation carried forward; n = number of participants with event; N = total participants in group; PASI50 = Psoriasis Area and Severity Index 50% response; PASI75 = Psoriasis Area and Severity Index 75% response.

^a Calculated during the evaluation by entering the dichotomous outcome data from the CSRs in RevMan 5.4.1

^b P-values are ≤ 0.050 and considered nominally significant, as there was no adjustment for multiplicity based on hierarchical testing.

^c The p-value was considered nominally significant, as hierarchical testing was stopped before this outcome was assessed for statistical significance.

6.19 A greater proportion of participants treated with apremilast compared to placebo achieved a PASI50 and/or PASI75 response at week 16 in all trials.

Subgroup analysis

6.20 A subgroup analysis comparing ACR20 based on prior csDMARD treatment in the ACTIVE trial is presented in Table 9.

Table 9: Results of subgroup analysis with whole trial population results and complement results in the ACTIVE trial at week 16

Population	Apremilast	Placebo	RR (95% CI) ^a	RD (95% CI) ^a
ACR20, n/N (%)				
Whole trial population	42/110 (38.2)	22/109 (20.2)	1.89 (1.22, 2.95)	0.18 (0.06, 0.30)
Prior csDMARD use	29/74 (39.2)	16/78 (20.5)	1.91 (1.13, 3.22)	0.19 (0.04, 0.33)
Complement of subgroup	NR	NR	-	-

Source: Table 2-53, p69 of the submission. **Bold** indicates statistically significant results (p<0.05).

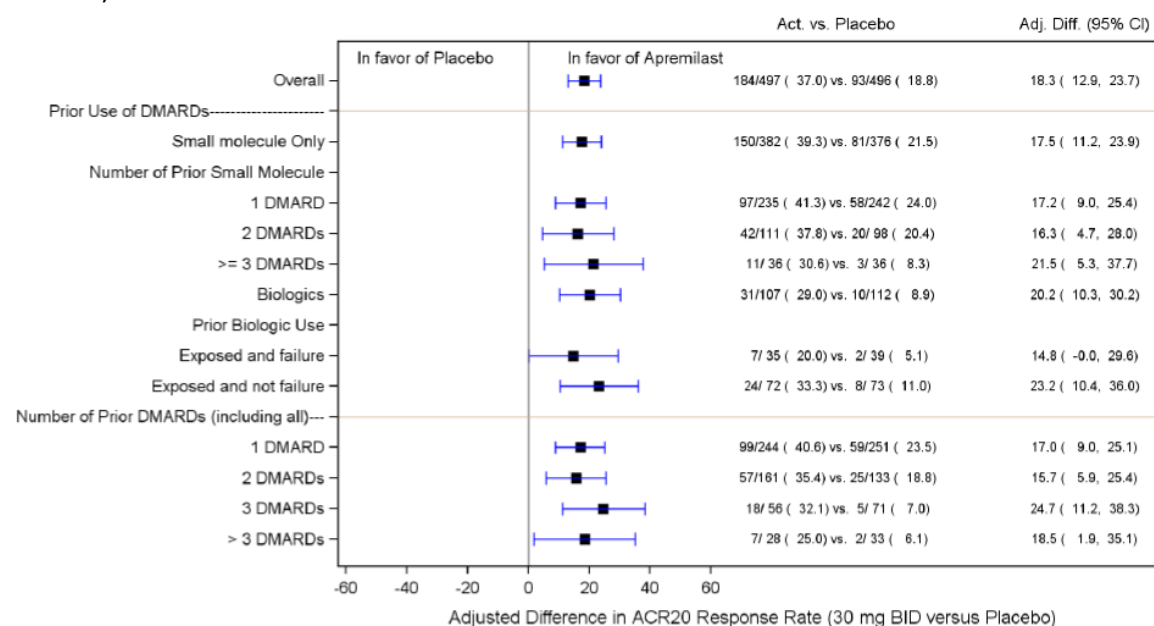
ACR20 = Modified American College of Rheumatology 20% response; CI = confidence interval; csDMARD = conventional synthetic disease modifying antirheumatic drug; n = number of participants reporting data; N = total participants in group; NE = not estimated; NR = not reported; RD = risk difference; RR = relative risk

^a calculated during the evaluation by entering the dichotomous outcome data in RevMan 5.4.1

6.21 The results observed in participants who have received prior csDMARD therapy appear similar to those for the whole trial population. Results for the complementary subgroup were not presented and no statistical tests for treatment interaction were presented within the submission.

6.22 Figure 2 shows the subgroup analysis comparing ACR20 response based on prior csDMARD and bDMARD use in the PALACE 1-3 trials.

Figure 2: ACR20 response rate at week 16 by prior use of csDMARDs and bDMARDs (pooled data from the PALACE 1-3 trials)



Source: Figure 2-11 p70 of the submission.

ACR20 = Modified American College of Rheumatology 20% response; BID = twice daily; bDMARD = biologic disease modifying antirheumatic drug; CI = confidence interval; csDMARD = conventional synthetic disease modifying antirheumatic drug; DMARD = disease modifying antirheumatic drug.

6.23 The pre-planned subgroup analysis of ACR20 response demonstrated a consistent treatment effect regardless of prior treatment, excluding participants who have failed bDMARD treatment (who were also excluded from the proposed PBS population). No statistical tests for treatment interaction were presented.

6.24 The statistical analyses presented for the subgroup analyses are insufficient to draw conclusions regarding the impact of prior treatment or baseline disease activity on the treatment effect of apremilast. Although the results show no large differences between subgroups, the trials were not designed, powered or analysed to detect a difference based on prior treatment or baseline disease activity.

Quality of life assessment

6.25 EQ-5D results for PALACE-1 and PALACE-3 are presented in Table 10. Although collected in the trials, EQ-5D data were not in the PALACE 2 and 4 CSRs provided with the resubmission.

Table 10: Change from baseline in EQ-5D at week 16 in the PALACE 1 & 3 trials (FAS; LOCF) ^a

Trial ID	Apremilast			Placebo		
	mean baseline (SD)	mean wk 16 (SD)	mean change (95% CI)	mean baseline (SD)	mean wk 16 (SD)	mean change (95% CI)
PALACE 1						
n(APR)=159	0.6621	0.7127	0.0506	0.6467	0.6908	0.0441
n(PBO)=162	(0.16552)	(0.17924)	(0.0209, 0.0803)	(0.19394)	(0.16121)	(0.0143, 0.0739)
PALACE 3						
n(APR)=160	0.6380	0.7088	0.0708	0.6544	0.6596	0.0052
n(PBO)=161	(0.19047)	(0.15655)	(0.0450, 0.0966)	(0.18441)	(0.19639)	(-0.0209, 0.0313)

Source: Table 14.2.39.1 of the PALACE 1 CSR; Table 14.2.40.1 of the PALACE 3 CSR.

APR = apremilast; CI = confidence interval; FAS = full analysis set; LOCF = last observation carried forward; PBO = placebo; SD = standard deviation.

^a Analysis conducted as last observation carried forward for all participants with a baseline value and at least 1 post-baseline value.

6.26 Quality of life assessed through the EQ-5D improved for participants in both treatment arms in the PALACE 1 and 3 trials and the improvements were larger for participants who received apremilast compared with placebo.

6.27 The SF-36 questionnaire was used in the ACTIVE and PALACE 1-4 trials, which can be converted to SF-6D to create utility values for an economic model. Only the SF-36 physical functioning domain score in the ACTIVE trial was presented in the resubmission. The evaluation noted no utility values were created using this approach.

Comparative harms

6.28 The results of key safety outcomes for apremilast and placebo during the placebo controlled phase are presented in Table 11. This data has been previously considered by the PBAC.

Table 11: 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		

Source: paragraph 6.12, apremilast, PSD, March 2015 PBAC meeting

SAE = severe adverse events; TEAE = treatment emergent adverse events

6.29 The results of key safety outcomes for apremilast and placebo during the placebo controlled phase and for the apremilast exposure period (week 0 to 104) of the ACTIVE trial are presented in Table 12.

Table 12: Summary of key adverse events in the ACTIVE trial

	Phase 1 (week 0 to 24), Safety population				Apremilast exposure period (week 0 to 104), ART population	
	Apremilast N = 109 Subject years = 43.7		Placebo N = 109 Subject years = 41.8		Apremilast N = 206 Subject years = 289.6	
	n with event (%)	EAIR per 100 SY ^a	n with event (%)	EAIR per 100 SY ^a	n with event (%)	EAIR per 100 SY ^a
Summary events						
TEAE	73 (67.0)	336.4	69 (63.3)	299.7	157 (76.2)	134.9
Drug related TEAE	30 (27.5)	80.7	18 (16.5)	48.7	52 (25.2)	21.4
Severe TEAE	2 (1.8)	4.6	4 (3.7)	9.7	8 (3.9)	2.8
Serious TEAE (SAE)	3 (2.8)	7.0	5 (4.6)	12.2	15 (7.3)	5.4
Drug related serious TEAE	0 (0.0)	0.0	0 (0.0)	0.0	0 (0.0)	0.0
TEAE leading to dose interruption	10 (9.2)	23.9	7 (6.4)	17.5	28 (13.6)	10.6
TEAE leading to drug withdrawal	10 (9.2)	23.3	5 (4.6)	12.0	17 (8.3)	5.9
Fatal TEAE	0 (0.0)	0.0	0 (0.0)	0.0	1 (0.5)	0.3
Frequently reported AEs, AEs and vital signs of interest						
Diarrhoea	16 (14.7)	39.7	12 (11.0)	31.1	34 (16.5)	13.0
Nasopharyngitis	9 (8.3)	21.9	7 (6.4)	17.4	17 (8.3)	6.3
Nausea	9 (8.3)	21.8	2 (1.8)	4.8	18 (8.7)	6.6
Headache	8 (7.3)	19.3	4 (3.7)	9.9	13 (6.3)	4.7
Hypertension	7 (6.4)	16.9	7 (6.4)	17.2	13 (6.3)	4.8
URTI	5 (4.6)	11.9	11 (10.1)	27.8	17 (8.3)	6.3
Bronchitis	5 (4.6)	11.9	3 (2.8)	7.2	11 (5.3)	4.0
Depression	2 (1.8)	4.6	0 (0.0)	0	6 (2.9)	2.1
Weight loss >5%	12 (11.0)	NR	1 (0.9)	NR	39 (18.9)	NR

Source: Tables 2-33 & 2-34, pp59-60 of the submission; Tables 78, 79, 14.3.1.3.1.1 & 14.3.1.3.1.3 of the ACTIVE CSR, pp181-182 of the ACTIVE CSR.

AE = adverse event; ART = Apremilast Participants as Randomized or Transitioned Population; CI = confidence interval; EAIR = exposure adjusted incidence rate; n = number of participants reporting data; N = total participants in group; SY = subject-years; TEAE = treatment emergent adverse event; URTI = upper respiratory tract infection.

^a The EAIR per 100 subject-years = 100 x (number of participants reporting the event/subject-years of exposure [up to the first event start date for each subject reporting the event]).

6.30 The apremilast product information includes special warnings for weight decrease; depression and/or suicidal thoughts or behaviour; and diarrhoea, nausea, and vomiting. The TGA risk management plan stated that routine risk minimisation measures are sufficient to manage the safety concerns of apremilast.

Benefits/harms

6.31 A summary of the comparative benefits and harms for apremilast versus placebo is presented in Table 13.

Table 13: Summary of comparative benefits and harms for apremilast and placebo

Trial	Apremilast n/N	Placebo n/N	RR (95% CI)	Event rate/100 patients		RD (95% CI) ^a	
				Apremilast	Placebo		
Benefits							
ACR20 at week 16							
ACTIVE	42/110	22/109	1.89 (1.22, 2.95)	38.2	20.2	0.18 (0.06, 0.30)	
PALACE 1	64/168	32/168	2.00 (1.39, 2.89)	38.1	19.0	0.19 (0.10, 0.28)	
PALACE 2	52/162	30/159	1.70 (1.15, 2.52)	32.1	18.9	0.13 (0.04, 0.23)	
PALACE 3	68/167	31/169	2.22 (1.54, 3.20)	40.7	18.3	0.22 (0.13, 0.32)	
PALACE 4	54/176	28/176 ^b	1.93 (1.29, 2.89) ^c	30.7	15.9	0.15 (0.06, 0.23) ^c	
ACR50 at week 16							
ACTIVE	20/110	5/109	13.3 (5.1, 21.4)	18.2	4.6	0.14 (0.05, 0.22)	
PALACE 1	27/168	10/168	10.3 (3.7, 16.8)	16.1	6.0	0.10 (0.04, 0.17)	
PALACE 2	17/162	8/159	5.6 (-0.2, 11.3)	10.5	5.0	0.05 (-0.00, 0.11)	
PALACE 3	25/167	14/169	6.8 (0.0, 13.5)	15.0	8.3	0.07 (-0.00, 0.14)	
PALACE 4	20/176	8/176	6.8 (1.2, 12.4)	11.4	4.5	0.07 (0.01, 0.12)	
HAQ-DI: change from baseline to week 16							
	Apremilast			Placebo			LS mean difference: APR vs PBO
	N	LS mean Δ	SE	N	LS mean Δ	SE	
ACTIVE	109	-0.205	0.0523	109	-0.055	0.0513	-0.150
PALACE 1	159	-0.244	0.0364	165	-0.086	0.0360	-0.159
PALACE 2	154	-0.193	0.0354	153	-0.053	0.0358	-0.140
PALACE 3	160	-0.192	0.0339	163	-0.065	0.0335	-0.127
PALACE 4	167	-0.205	0.0350	167	0.012	0.0350	-0.217
Harms							
Diarrhoea to week 24							
ACTIVE	16/109	12/109	1.33 (0.66, 2.68)	15	11	0.04 (-0.05, 0.13)	
PALACE 1	32/168	4/168	8.00 (2.89, 22.12)	19	2	0.17 (0.10, 0.23)	
PALACE 2	24/162	8/159	2.94 (1.36, 6.36)	15	5	0.10 (0.03, 0.16)	
PALACE 3	26/167	3/168	8.72 (2.69, 28.25)	16	2	0.14 (0.08, 0.20)	
PALACE 4	21/175	3/176	7.04 (2.14, 23.18)	12	2	0.10 (0.05, 0.15)	
Weight loss >5% to week 24							
ACTIVE	12/109	1/109	12.00 (1.59, 90.70)	11	1	0.10 (0.04, 0.16)	
PALACE 1	15/168	7/168	2.14 (0.90, 5.12)	9	4	0.05 (-0.01, 0.10)	
PALACE 2	20/162	6/159	3.27 (1.35, 7.93)	12	4	0.09 (0.03, 0.14)	
PALACE 3	19/167	6/168	3.19 (1.30, 7.78)	11	4	0.08 (0.02, 0.13)	
PALACE 4	19/175	1/176	19.11 (2.59, 141.19)	11	1	0.10 (0.06, 0.15)	
Depression to week 24							
ACTIVE	2/109	0/109	5.00 (0.24, 102.95)	2	0	0.02 (-0.01, 0.05)	
PALACE 1	1/168	1/168	1.00 (0.06, 15.86)	1	1	0.00 (-0.02, 0.02)	
PALACE 2	NR	NR	-	-	-	-	
PALACE 3	3/167	1/168	3.02 (0.32, 28.72)	2	1	0.01 (-0.01, 0.04)	
PALACE 4	NR	NR	-	-	-	-	

Source: Tables 2-21, 2-22, 2-34, 2-38, 2-42, 2-46 & 2-50, pp45, 48, 59-60, 62, 64, 66 & 67-68 of the submission; Tables 78 & 14.3.1.3.1.3 of the ACTIVE CSR; Tables 68 & 108 of the PALACE 1 CSR; Table 108 of the PALACE 2 CSR; Table 108 & 14.3.1.4.1.1 of the PALACE 3 CSR; Table 78 of the PALACE 4 CSR.

ACR20 = Modified American College of Rheumatology 20% response; ACR50 = Modified American College of Rheumatology 50% response; APR = apremilast; CI = confidence interval; HAQ-DI = Health Assessment Questionnaire-Disability Index; LS = least squares; n = number of participants with event; N = total participants in group; PBO = placebo; RD = risk difference; RR = relative risk.

^a calculated during the evaluation by entering the dichotomous outcome data in RevMan 5.4.1

^b The PALACE 4 CSR stated that 28 participants in the placebo arm achieved an ACR20 response (p93 of the CSR).

^c RR and RD calculated based on 28/176 participants achieving and ACR20 response.

- 6.32 On the basis of direct evidence presented by the submission, for every 100 patients treated with apremilast in comparison with placebo over 16 weeks:
- Between 13 and 22 additional patients would achieve an ACR20 response.
 - Between 5 and 14 additional patients would achieve an ACR50 response.
- 6.33 On the basis of direct evidence presented by the submission, the comparison of apremilast and placebo resulted in:
- Between a 0.127 and 0.217 reduction in HAQ-DI score over 16 weeks. The submission stated that a reduction of 0.13 is clinically meaningful.
- 6.34 On the basis of direct evidence presented by the submission, for every 100 patients treated with apremilast in comparison with placebo over 24 weeks:
- Between 4 and 17 additional patients would experience diarrhoea.
 - Between 5 and 10 additional patients would experience weight loss >5%.
 - Between 0 and 2 additional patients would experience depression.

Clinical claim

- 6.35 The resubmission described apremilast as superior in terms of effectiveness compared to placebo based on the outcomes of ACR20, ACR50 and HAQ-DI. The ESC considered this claim was adequately supported. Apremilast demonstrated superior efficacy in terms of the primary outcome (ACR20) in all included trials. Apremilast also demonstrated superior efficacy in terms of ACR50 in the ACTIVE, PALACE 1, PALACE 3 and PALACE 4 trials and HAQ-DI in all the included trials. Long term efficacy data for the PALACE 1-4 trials suggest treatment response measured by ACR20 and ACR50 is maintained up to five years.
- 6.36 The submission described apremilast as inferior in terms of safety compared to placebo but with acceptable long term safety with no requirement for routine monitoring. The ESC considered this claim was adequately supported. Overall, the adverse event profile of apremilast is worse than placebo, however most events have mild or moderate severity and there appears to be no evidence of an increased incidence of adverse events with longer apremilast use.
- 6.37 However, the evaluation considered the applicability of the trial evidence to the proposed Australian population is uncertain because:
- None of the included trials had eligibility criteria that aligned with the proposed PBS restriction. The PALACE 1-3 trials permitted prior treatment with bDMARDs, which is not aligned with the proposed PBS restriction and treatment algorithm. The PALACE 1-3 trials also permitted concomitant csDMARD treatment, which was prohibited in the proposed PBS restriction.
 - No comparison of baseline disease characteristics between the ACTIVE trial and proposed PBS population was available during the evaluation. Approximately 30%

of participants in the ACTIVE trial had no prior treatment with csDMARDs and approximately 40% had not been treated with methotrexate. The impact of differences in baseline characteristics and prior treatments between the trial and proposed Australian population on treatment outcomes is uncertain.

- There is also likely to be substantial overlap between participants in the ACTIVE trial and Australian participants eligible for PBS funded treatment with bDMARDs. That is, some participants in the ACTIVE trial may have had characteristics that would make them eligible for bDMARDs in Australia.
- 6.38 The ESC considered that, while the trial populations likely only contained a small proportion of patients meeting the proposed PBS restriction criteria, the evidence presented supported apremilast being of superior effectiveness and inferior safety compared to BSC.
- 6.39 The PBAC considered that, although the applicability of the evidence to the requested PBS population was uncertain, the claim of superior comparative effectiveness to placebo + BSC was likely to be reasonable.
- 6.40 The PBAC considered that the claim of inferior comparative safety to placebo + BSC, with acceptable long-term safety, was reasonable.

Economic analysis

- 6.41 The submission presented a cost-utility analysis based on the ACTIVE trial. This was implemented using a Markov model with three health states (apremilast, BSC, and dead). This is consistent with the clinical claim of superior effectiveness.
- 6.42 Table 14 summarises the model structure, key inputs, and rationale. Although the economic models considered in March 2015 and November 2015 were based on different clinical positioning (and therefore different comparators, see Table 2), a comparison to the economic model in the resubmission is presented in Table 14.

Table 14: Summary of model structure, key inputs and rationale

Component	Summary	March 2015	November 2015
Treatments	Apremilast vs BSC	Apremilast vs leflunomide	Apremilast vs adalimumab
Time horizon	Five years in the model base case versus the ACTIVE trial that was blinded until week 24, then followed up participants over two years.	11 years.	Five years.
Outcomes	QALYs. This is appropriate.	QALYs.	QALYs.
Methods used to generate results	Markov model.	Cohort expected value analysis.	Cohort expected value analysis.
Health states	BSC Apremilast (+BSC) Dead The model structure assumed that patients do not become eligible for and receive bDMARDs later. This is consistent with the proposed clinical management algorithm but is not appropriate for Subpopulation 1 as they could become eligible for bDMARDs if their disease progresses.	Apremilast Leflunomide Adalimumab Etanercept Golimumab BSC Dead	Apremilast Adalimumab Etanercept Golimumab BSC
Cycle length	Year/13 (28.0962 days). Allows for changes in treatment status, aligns with the ACTIVE trial outcomes and apremilast packs.	28 days (4 weeks).	28 days (4 weeks).
Transition probabilities	ACTIVE trial, Ali (2007) et al., and Australian life tables. The eligibility criteria of the ACTIVE trial were not aligned with the proposed PBS population hindering its applicability.	PALACE 1-3 trials and PBS data.	PALACE 1-3 trials, pooled analysis for adalimumab, network meta-analysis conducted in the submission, PBS data, Rodgers et al. 2011.
Health-related quality of life	York Assessment Group regression model applied to baseline and change in HAQ-DI from the ACTIVE trial and baseline PASI from the PALACE 1-3 trials. The submission estimated utility decline for BSC based on estimates from the Norfolk Arthritis Register also presented in the York Assessment Group model.	EQ-5D from PALACE 1-3 trials.	EQ-5D from PALACE 1-3 trials.
Costs	Estimated from an advisory board and broader rheumatologist survey. Patients in the apremilast health state were assumed to have decreased costs compared to BSC. The accuracy of expert opinion is uncertain, given the methods for collecting expert opinion were not presented in the submission. The submission presented evidence of apremilast impact on concomitant medications at 104 weeks. However, this compared costs for the apremilast arm for weeks 0-24 with the unblinded period of weeks 24-104, i.e., it is not comparative data. No evidence was provided for other services or times longer than 104 weeks.	Survey of Australian rheumatologists and assumptions.	Survey of Australian rheumatologists and assumptions.

Source: Table 3-1, p82 of the submission; pp22, 82, 83, 85, 92, 103 of the submission. Table D3.3.1 & Figure D3.1, p58 of the Commentary on the March apremilast 2015 submission. Figure D.3.1, Table D.3.1, Table D.4.2, Table D.4.3 pp53, 54,56, 57 of the Commentary on the November 2015 apremilast submission.

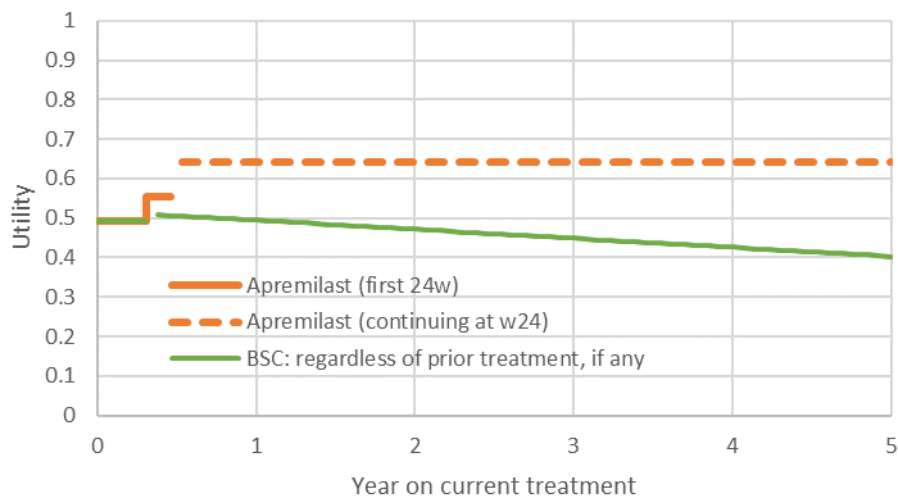
BSC = best supportive care; HAQ-DI = Health Assessment Questionnaire-Disability Index score; PASI = Psoriasis Area and Severity Index; PBAC = Pharmaceutical Benefits Advisory Committee; PBS = Pharmaceutical Benefits Schedule; PsA = psoriatic arthritis.

6.43 The model structure was based on the ACTIVE trial and did not directly address PsA health states such as the six core domains peripheral arthritis, axial disease, enthesitis, dactylitis, and skin and nail psoriasis. Further, the model structure is not appropriate

for subpopulation 1 as these patients could later become eligible for bDMARDs due to disease progression, which is not represented in the model.

- 6.44 The proportion of participants who continued apremilast after the first 24 weeks of treatment was assumed to be the proportion of participants in the apremilast treatment arm who were ACR20 responders at week 24 in the ACTIVE trial including two participants in early escape (50/110=45.45%). This approach is not reasonable as it will overestimate the response rate for apremilast as (i) it includes patients in early escape and (ii) it does not account for the placebo response. The ESC noted using the placebo-adjusted difference (18%) increased the ICER from \$25,000 to < \$35,000/QALY to \$25,000 to < \$35,000/QALY.
- 6.45 The submission mapped HAQ-DI scores from the ACTIVE trial and baseline PASI scores from the PALACE 1-3 trials to EQ-5D utilities using the York Assessment Group regression equations. HAQ-DI captures physical functioning, whereas the PASI score represents dermatologic symptoms. Neither capture other attributes relevant to health-related quality of life, such as mental health.
- 6.46 Changes in utility were inferred from changes in HAQ-DI, ignoring changes in PASI because it was not collected in the ACTIVE trial. This makes the accuracy of derived utility estimates uncertain. The impact of this uncertainty cannot be determined. Baseline PASI scores from the PALACE 1-3 trials may not apply to the ACTIVE trial or the proposed PBS population. The impact of applying baseline estimates from two different datasets on the derived utilities is uncertain.
- 6.47 The ACTIVE trial reported the SF-36 physical function scale score and the physical component summary score. The ACTIVE trial CSR stated that Version 2 of the SF-36 was administered. The CSR did not report mental health components, and whether these were measured is unclear. The evaluation considered the full SF-36 would have been preferred as it would consider other attributes important to health-related quality of life, such as mental health.
- 6.48 Figure 3 presents utilities by health state over the model's time horizon.

Figure 3: Utility by health state over the model's time horizon



Source: Figure 3-2, p95 of the submission.
BSC = best supportive care; W = weeks.

- 6.49 The submission assumed that HAQ-DI in the BSC health state would increase (i.e., decreasing utilities) after week 16. The submission estimated HAQ-DI increase in the BSC health state from the Norfolk Arthritis Register. The Norfolk Arthritis Register included participants with three tender joints and three swollen joints, and previous use of two or more DMARDs or were still using two DMARDs for at least 30 days. These criteria were designed to assess patients eligible for bDMARDs in the United Kingdom. The applicability of this data to the Australian setting is uncertain.
- 6.50 The submission assumed that HAQ-DI for patients in the apremilast arm after week 24 would remain unchanged, i.e., it did not consider disease progression. This might not be appropriate. Disease progression could also apply to patients taking apremilast, as the Norfolk Arthritis Register included patients still using two DMARDs (not biologics) for at least 30 days, showing deterioration after five years. Excluding disease progression in the apremilast health state if disease progression exists, overestimates utilities in the apremilast arm.
- 6.51 The model considered utility decrements in the BSC health state according to the cycle and the transitions of apremilast to BSC health states. When a non-responder transitioned from apremilast to BSC, utilities from cycle one in the BSC arm were applied, regardless of the cycle when the transition occurred. This overestimates utilities in the apremilast arm.
- 6.52 The model assumed that every participant starting in the apremilast arm stayed in the apremilast health state from week 1 (cycle 1) until week 24 (cycle 6). It also assumed all participants in the apremilast arm experienced an increase in their utility from week 16 (cycle 4) to week 24 (cycle 6) compared to BSC. While some participants in the apremilast arm were non responders, the model assumed these non-responders also experienced an increase in their utility from week 16 (cycle 4) to week 24 (cycle 6).

Utilities for non-responders were therefore overestimated between week 16 (cycle 4) to week 24 (cycle 6). The model also assumed non responders in the apremilast arm experienced the same decrease in BSC costs as responders between week 1 (cycle 1) to week 24 (cycle 6). This underestimates BSC costs in the apremilast arm.

- 6.53 The PSCR stated the model uses a regression equation that estimates utility from HAQ-DI and PASI scores, however the model assumes no change in PASI score, so the change in utility depends only on change in HAQ-DI, as measured in the ACTIVE trial. The PSCR stated that for mathematical convenience, a baseline utility was required, however it has no effect on the calculated ICER and the assumption of no change in PASI score was likely to bias the model to higher ICER values, as apremilast is likely to lead to improvement in PASI score in responders. Furthermore, the PSCR also stated the utility between week 16 and 24 was estimated from the HAQ-DI of all apremilast patients at week 16, which therefore accounts for non-responders.
- 6.54 The submission estimated costs from a survey to an advisory board and Australian rheumatologists. It is appropriate to consult expert opinion due to the lack of Australian published data. However, results should be interpreted with caution as their accuracy is unclear, and methods were not presented.
- 6.55 The submission assumed that costs for BSC in the apremilast health state were lower than the BSC health state due to the effect of apremilast. It is uncertain whether the assumption of lower costs for BSC in the apremilast health state is valid.
- 6.56 A summary of the key drivers of the model is provided in Table 15.

Table 15: Key drivers of the model

Description	Method/Value	Impact
		Base case: \$ ¹ /QALY gained
Time horizon	5 years (compared to 2 years follow up in ACTIVE trial).	High, favours apremilast. ICER at 24 weeks (blinded period allowing for early escape) was \$ ¹ /QALY gained. ICER at 3 years was \$ ² /QALY gained.
Response rate	Absolute apremilast response at 24 weeks (45%)	Moderate, favours apremilast: An 18% response rate (accounting for placebo response) increased the ICER to \$ ¹ /QALY gained.
Utilities	Change in HAQ-DI at 24 weeks used to estimate utilities in the apremilast health state.	Moderate, favours apremilast: Applying 75% of the base case change in HAQ-DI increased the ICER to \$ ¹ /QALY gained.
	Change in HAQ-DI for BSC after 16 weeks	Moderate, favours apremilast: Applying lower CI change in HAQ-DI increased the ICER to \$ ¹ /QALY gained.
	A utility decrement applied to the apremilast health state was not applied.	Moderate, favours apremilast: Applying a utility decrement increased the ICER to \$ ¹ /QALY gained.
	Utility change per variation of HAQ-DI in the BSC health state.	Moderate, favours apremilast: Applying 83.3% increased the ICER to \$ ¹ /QALY gained.

Source: Compiled during the evaluation from 'Appendix 3.2_Apremilast_PsA_Economic_Model'.

ACR50 = 50% improvement in American College of Rheumatology criteria; BSC = best supportive care; CI = confidence interval; HAQ-DI = health assessment questionnaire disability index; ICER = incremental cost-effectiveness ratio; QALY = quality-adjusted life years.

The redacted values correspond to the following ranges:

¹ \$255,000 to < \$355,000

² \$25,000 to < \$35,000

6.57 The submission stated that a stepped analysis was not presented because the cost per HAQ-DI-week could not be readily interpreted. Results considering the ACTIVE trial study design was conducted during the evaluation and is presented in Table 16.

Table 16: Results of the economic evaluation

Step and component	Apremilast	BSC	Increment
Step 1: ACTIVE trial blinded period (16 weeks)			
Costs (\$)		\$295	
QALY	0.151	0.151	0
Incremental cost/extra QALY gained			Undefined
Step 2: ACTIVE trial blinded period allowing for early escape (24 weeks)			
Costs (\$)		\$433	
QALY	0.236	0.229	0.007
Incremental cost/extra QALY gained			¹
Step 3: ACTIVE trial active treatment phase (1 year)			
Costs (\$)		\$959	
QALY	0.540	0.498	0.042
Incremental cost/extra QALY gained			²
Step 4: ACTIVE trial open-label extension phase (2 years)			
Costs (\$)		\$1,915	
QALY	1.093	0.980	0.113
Incremental cost/extra QALY gained			³
Step 5: model time horizon (5 years)			
Costs (\$)		\$4,761	
QALYs	2.628	2.288	0.340
Incremental cost/extra QALY gained			⁴
Step 6: discounting (5%) included			
Costs (\$)		\$4,330	
QALYs	2.396	2.089	0.306
Incremental cost/extra QALY gained (base case)			⁴

Source: Table 3-9, p109 of the submission. Table D5.5, p63 of the Commentary on the March 2015 PBAC submission; Table D5.5, p58 of the Commentary on the November 2015 PBAC submission.

BSC = best supportive care; QALY = quality-adjusted life year.

The redacted values correspond to the following ranges:

¹ \$255,000 to < \$355,000

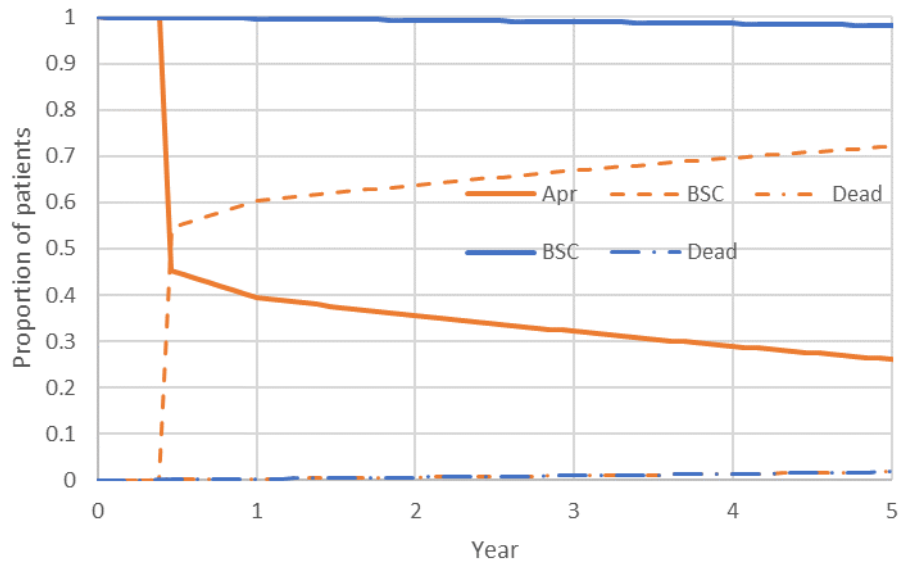
² \$55,000 to < \$75,000

³ \$35,000 to < \$45,000

⁴ \$25,000 to < \$35,000

6.58 Figure 4 presents the Markov traces produced by the model.

Figure 4: Markov traces presented by the submission



Source: Figure 3-3, p108 of the submission.
Apr = apremilast; BSC = best supportive care.

6.59 The results of key univariate sensitivity analyses are summarised in Table 17.

Table 17: Results of key sensitivity analyses

Analyses	Incremental cost (\$)	Incremental QALY	ICER	% change to ICER
Base case		0.306	1	
Discount rate (base case: 5%)				
0%		0.340	1	-3%
3.5%		0.316	1	-1%
Time horizon (base case: 5 years)				
3 years		0.177	1	27%
Response rate (base case: 45.45%, absolute ACR20 response at 24 weeks)				
Placebo-adjusted difference at 24 weeks (18.5%)		0.149	1	14%
0% at 24 weeks		0.041	2	83%
Utility decrement from BSC applied to apremilast from week 24 (base case did not apply a decrement)^a				
0.0016505		0.248	1	24%
Change in HAQ-DI for ACR20 responders after 24 weeks (base case: -0.548)^b				
50% of change in HAQ-DI		0.193	4	59%
75% of change in HAQ-DI		0.249	1	23%
125% of change in HAQ-DI		0.363	3	-16%
Change in HAQ-DI for BSC at 16 weeks (base case: -0.055)				
Upper CI (0.0456)		0.359	3	-15%
Lower CI (-0.156)		0.253	1	21%
Utility change per variation of HAQ-DI (base case: -0.298)				
83.3% of utility per change in HAQ-DI		0.255	1	20%
120% of utility per change in HAQ-DI		0.367	3	-17%

Source: Table 3-11, p114 of the submission; Tables 24 & 41 of the ACTIVE CSR; 'Appendix 3.2_Apremilast_PsA_Economic_Model' of the submission.

ACR50 = 50% improvement in American College of Rheumatology criteria; CI = confidence interval; HAQ-DI = health assessment questionnaire disability index; QALY = quality-adjusted life year.

^a Changes made to cells X101:230 'Model' sheet.

^b Changes made to cell E27 'Model' sheet.

The redacted values correspond to the following ranges:

¹ \$25,000 to < \$35,000

² \$45,000 to < \$55,000

³ \$15,000 to < \$25,000

⁴ \$35,000 to < \$45,000

6.60 The evaluation noted that assuming a 0% response rate at 24 weeks for apremilast resulted in an ICER of \$45,000 to < \$55,000. The PSCR clarified the change described in the evaluation does not represent a 0% response rate for apremilast, as implied; rather, the scenario described would examine how the ICER changes if all patients on apremilast have the benefits modelled from the ACTIVE trial for 24 weeks, followed by discontinuation of apremilast, with accompanying utility immediately reverting to baseline.

6.61 The ESC considered there were a number of key issues with the economic model, including:

- The use of treatments as health states (rather than health outcomes) does not capture the health benefits of BSC and therefore overestimates the health benefits of apremilast.

- SF-36 data was collected in the trials but not presented or used in the model. The ESC considered that using trial-based utilities was likely to be more reliable than utilities modelled by applying an equation combining HAQ-DI from the ACTIVE trial and PASI outcomes from the PALACE trials.
 - The ESC considered the validity of the approach of combining HAQ-DI scores, which are a measure of physical function, and PASI score, which is a measure of dermatological symptoms, into a single utility weight, was uncertain.
 - There were differences in the populations in the PALACE and ACTIVE trials, which further undermined the validity of the approach of pooling these to generate a single treatment utility weight.
 - The assumption of constant utilities in the apremilast state, but linear decline in the BSC state was poorly justified.
 - The model made no assumptions about patients subsequently becoming eligible for bDMARDs at some point in the future, which the ESC considered was unrealistic for at least a subset of patients.
 - Costs were estimated from an advisory board and broader rheumatologist survey, and the methods for the survey were not presented.
- 6.62 Overall, the ESC considered the economic model was unlikely to be reliable for decision-making.
- 6.63 The Pre-PBAC Response stated the model structure used in the submission was based on the model used in the UK application to NICE, and argued the model is a simplified version of a model that allows comparison with several sequences of treatments followed by BSC, and an important aspect of it is the expected decline in utility over time for patients on BSC. The PBAC noted the economic model in the resubmission did not allow for patients subsequently becoming eligible for bDMARDs and modelling this would impact the utility decline over time in the BSC health state. The PBAC noted that while the model structure in the resubmission may have been similar to the model considered by NICE, it is not clear if the assumptions underpinning the models were similar.

Apremilast cost/patient/year

- 6.64 Apremilast cost per patient per year is presented in Table 18. Costs are presented for the initiating year and year 2 to represent differences in inputs from the trial, model, and financial estimates.

Table 18: Drug cost per patient for apremilast

	Apremilast Trial dose and duration	Apremilast Model	Apremilast Financial estimates
Mean dose [A]	1 titration pack, then 60 mg/day	60 mg/day	1 titration pack, then 60 mg/day
Compliance year 1 [B]	97.5% ^a	94.10% ^b	Titration pack 100% Maintenance pack 90% ^c
Compliance year 2 [C]	97.5% ^a	100%	90% ^c
Continuers year 1 [D]	100% ^d	69.01% ^e	72.50% ^f
Continuers year 2 [E] (C-52)	43.75% ^g	34.88% ^h	68.88% ⁱ
Cost/patient/year 1 [F] (A x B x D x effective price)	\$	\$	\$
Cost/patient/year 2 [G] A x C x E x effective price)	\$	\$	\$

Source: Tables 4-10, and 4-12, pp99, 108, 128, and 129 of the submission. Tables 14.1.13.4 and 14.1.12.4 of the ACTIVE trial CSR.

^a Table 14.1.13.4 of the ACTIVE CSR, treatment compliance through week 104, apremilast arm.

^b 87.21% first 24 weeks, then 100% weighted average.

^c Additional compliance factor.

^d Considers treatment duration through week 104, apremilast arm Table 14.1.12.4 of the ACTIVE CSR. Treatment duration was 74.72 weeks.

^e 100% first 24 weeks, 45% at week 24, then 1.96% each cycle (1/13 of a year) weighted average.

^f 100% first six months, then 45% for the next six months weighted average.

^g Estimated by weeks in year 2: 74.72 weeks – 52 weeks in a year = 22.75. Then, the proportion was estimated as 22.75/52 = 0.4375.

^h 0.76% stopping each cycle (1/13 of a year) applied to continuers year 1 (69.01%) weighted average.

ⁱ 68.88% first six months as per year 1, then 90% the last six months weighted average.

6.65 The difference in the cost per patient between the economic and financial model in Year 2 was largely driven by the difference in the percentage of continuers (35% vs 69%). The PBAC considered the different assumptions for the economic model and financial estimates was not adequately justified in the submission.

Estimated PBS usage & financial implications

6.66 This submission was not considered by DUSC. The submission adopted an epidemiological approach to estimate the financial impact of listing apremilast on the PBS/ RPBS for treating severe active PSA. Table 19 presents key inputs for the financial estimates.

Table 19: Key inputs for financial estimates

Parameter	Value applied and source	Comment
Incident/prevalent population	<p>bDMARD discontinuers: incident population = ██████¹ in Year 1 increasing to ██████¹ in Year 6, prevalent population = ██████². Based on 10% PBS sample for bDMARDs in 2018 and ██████% growth.</p> <p>csDMARD discontinuers: incident population = ██████² in Year 1 increasing to ██████² in Year 6, prevalent population = ██████². Based on 10% PBS sample for sulfasalazine, methotrexate and leflunomide in 2018 and ██████% growth.</p> <p>Prevalent patients in 2023 were estimated by adding 2021 and 2022 estimates.</p>	<p>10% PBS sample data was used. Information regarding the data supplier, PBS codes, or whether the date of supply or processing was used, were not provided in the resubmission but were provided with the PSCR. Using extrapolated values from 2018 PBS 10% sample data might underestimate incident and prevalent populations as 2018 values are lower than for 2021 PBS 10% sample data.</p>
Growth rate	5% (assumption).	
Uptake rate	<p>bDMARD discontinuers: incident population = ██████% in Year 1 increasing to ██████% in Year 3 and beyond, prevalent population = ██████%</p> <p>csDMARD continuers: incident population = ██████% in Year 1 increasing to ██████% in Year 4 and beyond, prevalent population = ██████%.</p> <p>Based on a survey of an advisory board and Australian rheumatologists who specialise in managing PsA.</p>	<p>The accuracy of expert opinion is uncertain, and the method to elicit responses was not provided.</p>
Compliance rate	<p>Titration pack: 100% (assumption).</p> <p>Maintenance pack initiating year continuers: 45% (ACTIVE).</p> <p>Maintenance pack continuing year continuers: 90% (assumption).</p> <p>Additional compliance factor: 90% (assumption).</p>	<p>Maintenance pack data is consistent with the ACTIVE trial.</p> <p>Apremilast maintenance pack continuation was double counted in the Financial Workbook when estimating patients and scripts.</p>
Grandfathered patients	Considered in the prevalent population.	This is reasonable.
Dose/duration	Every patient starts with a titration pack. Then continues with maintenance packs until discontinuation.	
Offsets for comparator/subsequent therapies	Paracetamol, meloxicam and triamcinolone.	These offsets were not applied in the model.
MBS item	Specialist, GP and physiotherapy visits, image-guided steroid injections.	These offsets were not included in the estimates.

Source: Tables 4-2, 4-3, 4-4, 4-5, 4-9 & 4-10, pp119, 121, 123, 127 & 129-132 of the submission.

bDMARD = biologic disease-modifying antirheumatic drugs; csDMARD = conventional synthetic disease-modifying antirheumatic drugs; GP = general practitioner; MBS = Medicare Benefits Schedule; PBS = Pharmaceutical Benefits Scheme; PsA = psoriatic arthritis.

The redacted values correspond to the following ranges:

¹ < 500

² 500 to < 5000

6.67 Table 20 presents the estimated use and financial implications of listing apremilast for treating severe active PsA. Cost offsets for other medicines and MBS costs were not estimated in the financial model.

Table 20: Estimated use and financial implications (effective PBS price)

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
Estimated extent of use						
Initiating patients						
Subpopulation 1	■ ¹	■ ¹	■ ²	■ ²	■ ²	■ ²
Subpopulation 2	■ ¹	■ ¹	■ ¹	■ ¹	■ ¹	■ ¹
Subpopulation 3	■ ¹	-	-	-	-	-
Total initiating patients	■ ²	■ ²	■ ²	■ ²	■ ²	■ ²
Total number of patients treated	■ ²	■ ²	■ ²	■ ²	■ ²	■ ²
Number of scripts dispensed	■ ³	■ ³	■ ⁴	■ ⁴	■ ⁵	■ ⁵
Net financial implications						
Net cost to PBS/RPBS	■ ⁶	■ ⁶	■ ⁶	■ ⁶	■ ⁷	■ ⁷
Previous submission March 2015						
Net cost to PBS/RPBS	■ ⁶	■ ⁶	■ ⁷	■ ⁷	■ ⁸	Not reported
Previous submission November 2015						
Net cost to PBS/RPBS	■ ⁶	■ ⁶	■ ⁶	■ ⁶	■ ⁶	Not reported

Source: Tables 4-11 & 4-14, pp128 & 129, and Section 4 workbook, Appendix 4 of the submission; Table E.4.1, p73 of the Commentary on the March 2015 PBAC submission; Table E.4.1, p68 of the Commentary on the November 2015 PBAC submission.

MBS = Medicare Benefits Schedule; PBS = Pharmaceutical Benefits Schedule; RPBS = Repatriation Pharmaceutical Benefits Schedule.

^d The Financial Workbook assumed \$30 general copayment.

The redacted values correspond to the following ranges:

¹ < 500

² 500 to < 5,000

³ 5,000 to < 10,000

⁴ 10,000 to < 20,000

⁵ 20,000 to < 30,000

⁶ \$0 to < \$10 million

⁷ \$10 million to < \$20 million

⁸ \$20 million to < \$30 million

6.68 The resubmission stated the net cost to the PBS/RPBS, net of patient copayments over six years was estimated to be \$40 million to < \$50 million based on effective prices.

6.69 The resubmission considered two severe active PsA cohorts using 10% PBS sample data of alive patients that did not receive another DMARD:

- Cohort 1: bDMARD discontinuers. This cohort represented patients who are bDMARD intolerant (subpopulation 3).
- Cohort 2: csDMARD discontinuers. This cohort represented patients who are bDMARD ineligible according to current PBS criteria (subpopulation 1) and those who are contraindicated to bDMARDs (subpopulation 2).

6.70 The resubmission defined the incident populations as those who discontinued DMARDs in the last 12 months and prevalent populations as those who discontinued DMARDs between 12 and 24 months. The submission used 2023 to start counting the incident population and added 2021 and 2022 to yield the prevalent population. It is uncertain whether the estimates accurately represent the incident and prevalent

populations. Patients could trial other bDMARDs in the future (11 bDMARDs available in Australia for PsA) to identify one with an acceptable side-effect profile (subpopulation 3) or not contraindicated (subpopulation 2). This could overestimate prevalence and incidence. On the other hand, patients potentially eligible for apremilast before 24 months were excluded from the prevalent population due to the 24 month arbitrary cut-off used to define the prevalent population. The evaluation considered this could underestimate the prevalent population.

- 6.71 The resubmission claimed that patients who discontinue bDMARD treatment and do not receive any further treatment in the PBS dataset were most likely to have stopped bDMARDs due to safety reasons (i.e., Cohort 1) as opposed to the larger pool of patients who eventually transition to another DMARD.
- 6.72 The analysis of bDMARD discontinuers (Cohort 1) presented in the submission showed 10,000 to < 20,000 prevalent patients in 2021 compared with 19,719 in the 2020/21 financial year in the DUSC analysis (Review of PBS Authority Required listings – Tranche 6, Ratified DUSC, February 2022). The submission argued that differences in methodology to ascribe indications or counting unique patients caused this discordance. DUSC reported estimates $\frac{1}{2}$ % higher than those presented in the submission.
- 6.73 The submission considered leflunomide, methotrexate and sulfasalazine in the analysis of csDMARD discontinuers (Cohort 1). Patients receiving leflunomide were identified by indication-specific PBS item code. Sulfasalazine patients were assumed to be patients with rheumatoid arthritis or PsA. The submission used $\frac{1}{2}$ % of this patient number to represent patients with PsA. The source of this ratio was not presented. The submission excluded methotrexate alone as it is prescribed for various indications. The evaluation considered this could potentially underestimate the number of patients in Cohort 2.
- 6.74 The submission assumed a $\frac{1}{2}$ % growth rate based on leflunomide PsA prescriptions growth from 2019 to 2021. The submission noted that there were $\frac{1}{2}$ % more bDMARD users in 2021 than in 2020. The evaluation noted assuming $\frac{1}{2}$ % growth could potentially underestimate patient numbers.
- 6.75 The submission estimated apremilast uptake by surveying an advisory board of eight members and six Australian rheumatologists. The accuracy of using expert opinion is uncertain. Further, Years 1 and 2 for Cohort 1 and Years 1 to 3 for Cohort 2 incident population uptake rates were not justified using expert advice.
- 6.76 The submission made the following assumptions to determine scripts:
- All patients received a titration pack in the initiating year.
 - Discontinuers received supply for six months in the discontinuation year.
 - The ACTIVE trial response rate (45%) determined discontinuers in the initiating year.

- Discontinuers in continuing years were assumed to be 10% per year.
 - An additional 90% compliance factor was applied every year.
- 6.77 Discontinuation (55% for initiating year and 10% for continuing years) was applied to estimate total patients. Then the submission applied 63.3% for initiating years and 85.5% for continuing years to estimate scripts. These percentages (63.3% and 85.5%) also considered discontinuation (55% and 10%). The evaluation considered discontinuation was double counted as it was used to estimate patient numbers and again for scripts. The net cost excluding double counted discontinuations was estimated to be \$50 million to < \$60 million over six years. The ESC noted the PSCR did not comment on the double counting of discontinuations identified by the evaluation.
- 6.78 The ESC considered the estimated number of patients that would be eligible for treatment with apremilast to be highly uncertain.

Quality Use of Medicines

- 6.79 The submission claimed that extensive education and patient support programs would be implemented.

Financial Management – Risk Sharing Arrangements

- 6.80 The submission declared willingness to agree to a financial cap arrangement based on costs estimated using the effective price presented in Table 20. The submission stated that apremilast for PsO has a two-tier financial cap where for utilisation exceeding Tier 1 cap, an additional rebate of | % applies, then above Tier 2 a | % rebate applies. The evaluation considered the existing risk sharing arrangement for apremilast in PsO may need to be adjusted to account for additional patients treated for the PsA indication.
- 6.81 The PSCR acknowledged the exact number of eligible patients was uncertain and may be underestimated, however stated the financial risk could be addressed through an RSA, and noted the suggestion in the evaluation that an adjustment to the current subsidisation caps for psoriasis could be affected to achieve this outcome. The sponsor proposed adding the cost of listing apremilast estimated in the resubmission (i.e., \$0 to < \$10 M in Year 1 and \$10 M to < \$20 M in Year 6) to the Tier 1 and Tier 2 caps currently in place for psoriasis.
- 6.82 The ESC noted expenditure on apremilast for PsO in Year 1 and Year 2 of listing was approximately | % of the Tier 1 cap. The ESC considered adding expenditure for PsA to the PsO expenditure caps would allow for cross-subsidisation across the indications and would not manage the specific risk for PsA, given PsO expenditure in Year 2 was | % of the Tier 1 cap.

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 psoriatic arthritis (PsA), in patients who have previously failed to achieve an adequate response to, or are clinically inappropriate for, conventional synthetic disease modifying anti-rheumatic drugs (csDMARDs) (i.e., methotrexate, sulfasalazine and/or leflunomide), and who are ineligible or clinically inappropriate for treatment with a biologic or targeted synthetic disease modifying anti-rheumatic drug (bDMARD/tsDMARD). The PBAC acknowledged there was likely to be a cohort of patients with severe PsA who are unable to be treated with the available treatment options who would benefit from the availability of an additional treatment option. However, the PBAC considered the proposed restriction criteria did not adequately identify the appropriate cohort of patients. The PBAC considered the cost-effectiveness of apremilast for the treatment of severe PsA was unable to be determined.
- 7.2 The PBAC noted the consumer comments highlighted that the available csDMARDs are often not effective for PsA and that apremilast is a safe and effective treatment that improves joint and skin manifestations of PsA. The PBAC also noted the comments in the sponsor hearing that the use of bDMARDs/ tsDMARDs in patients unsuitable for csDMARDs may not always be clinically appropriate. The PBAC considered there was a moderate clinical need for additional treatment options for patients with severe PsA.
- 7.3 The PBAC noted the requested restriction criteria were not consistent with the clinical evidence presented (paragraph 3.3) and may be difficult to interpret in clinical practise (paragraphs 3.4 and 4.8). Additionally, the PBAC noted some clinical trials allowed use of apremilast in combination with other DMARDs but the proposed restriction criteria required apremilast to be the sole PBS-subsidised DMARD agent.
- 7.4 The PBAC considered it was reasonable for initial prescribing to be limited to a rheumatologist, an accredited rheumatology registrar in consultation with a rheumatologist, or clinical immunologist with expertise in the management of psoriatic arthritis, with continuing prescribing able to be managed by general practitioners under the direction of these specialist physicians.
- 7.5 The PBAC considered the proposed comparator of placebo + best supportive care (BSC) was reasonable for the requested population, as this cohort of patients had either failed or were not eligible for alternative treatment options.
- 7.6 The resubmission presented five randomised controlled trials of apremilast compared to placebo. The PBAC noted it had previously considered the four PALACE trials included in the submissions for apremilast for PsA in 2015, but not the ACTIVE trial, completed in November 2016. The PBAC noted additional follow up data was provided for the PALACE trials (as outlined in paragraph 6.7). The PBAC noted none of the clinical trials presented were directly applicable to the requested population (as

discussed in paragraph 6.37).

- 7.7 The PBAC considered the available evidence supported a conclusion that apremilast is effective for the treatment of PsA and noted the results for ACR20 (Table 5) were statistically significant versus placebo for all available trials. The PBAC noted the ACR20 results for subgroups based on prior treatments (Table 9, Figure 2) were consistent with those for the whole-trial population. The PBAC noted the results for ACR50 (Table 5) and HAQ-DI scores (Table 6) also demonstrated improvements with apremilast over placebo. Overall, the PBAC considered the claim that apremilast is of superior comparative effectiveness to placebo + BSC was adequately supported.
- 7.8 The PBAC considered the available evidence supported the claim of inferior comparative safety to placebo + BSC but the long-term safety of apremilast was likely to be acceptable, noting there was no requirement for routine monitoring whilst patients were on treatment.
- 7.9 The PBAC agreed with the ESC and considered that the economic model was uninformative for assessing the cost-effectiveness of apremilast. The PBAC noted the range of issues raised by the ESC (paragraph 6.61) that related to the model structure and approach for determining the model inputs which were not able to be adequately addressed through sensitivity analyses. Overall, the PBAC considered the cost-effectiveness of apremilast for the treatment of severe PsA was unable to be determined.
- 7.10 The PBAC considered that the estimated number of patients that would be eligible for treatment with apremilast to be highly uncertain and hence it was unclear if an RSA based on these estimates would adequately manage the risk of use in patients outside of the proposed restriction where cost-effectiveness has not been demonstrated, for example use in patients suitable for csDMARDs and continued use in patients not achieving the modelled response criteria (i.e., ACR20). The PBAC considered it would be inappropriate to add the cost of listing apremilast as estimated in the resubmission to the Tier 1 and Tier 2 caps currently in place for psoriasis (as proposed by the sponsor, see paragraph 6.81) noting the lower than expected use in psoriasis would result in cross-subsidisation across the indications and hence the high risk of use in a broader PsA population would not be managed.
- 7.11 The PBAC considered a resubmission for apremilast for PsA should better define the cohort of patients with severe PsA who are unable to be treated with the available treatment options in terms of restriction criteria, present an economic model addressing the issues noted during the evaluation and by ESC, address the identified uncertainties in the financial estimates, and propose an RSA that manages the risk of use of apremilast outside of the proposed restriction.
- The resubmission may be lodged at any future standard due date for PBAC submissions using the standard re-entry pathway.
- 7.12 The PBAC noted that this submission is eligible for an Independent Review.

Outcome:

Not recommend

8 Context for Decision

The PBAC helps decide whether and, if so, how medicines should be subsidised through the Pharmaceutical Benefits Scheme (PBS) in Australia. It considers applications regarding the listing of medicines on the PBS and provides advice about other matters relating to the operation of the PBS in this context. A PBAC decision in relation to PBS listings does not necessarily represent a final PBAC view about the merits of the medicine or the circumstances in which it should be made available through the PBS. The PBAC welcomes applications containing new information at any time.

9 Sponsor's Comment

Amgen is disappointed with this outcome and will continue to work with the PBAC to provide improved access to apremilast. Amgen would like to thank all of the healthcare professionals, professional societies, patient organisations and consumers for their support of the apremilast submission.