

**7.02 APREMILAST,
Pack containing 4 tablets 10 mg, 4 tablets 20 mg and 19
tablets 30 mg; Tablet 30 mg
Otezla®,
Celgene Pty Ltd.**

1 Purpose of Application

1.1 Resubmission to request Authority Required (STREAMLINED) listing for apremilast for the treatment of moderate-to-severe plaque psoriasis.

2 Requested listing

2.1 Suggestions and additions proposed by the Secretariat are added in italics and suggested deletions are crossed out with strikethrough.

Name, Restriction, Manner of administration and form	Max. Qty	No. of Rpts	DPMQ	Proprietary Name and Manufacturer
APREMILAST Tablets, titration pack (10 mg x 4, 20 mg x 4, 30 mg x 19) Tablets, 30mg	1 56	0 5	\$ [REDACTED] (effective: \$ [REDACTED])* \$ [REDACTED] (effective: \$ [REDACTED])*	Otezla® Celgene Pty Ltd

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
Episodicity:	<i>Chronic</i>
Severity:	Moderate to severe
Condition:	Plaque psoriasis
PBS Indication:	Moderate to severe plaque psoriasis
Treatment phase:	Initial and continuing
Restriction Level / Method:	<input type="checkbox"/> Restricted benefit <input type="checkbox"/> Authority Required - In Writing <input type="checkbox"/> Authority Required - Telephone <input type="checkbox"/> Authority Required - Emergency <input type="checkbox"/> Authority Required - Electronic <input checked="" type="checkbox"/> Streamlined
Treatment criteria:	Must be treated by a dermatologist, OR <i>Must be treated by a general physician with expertise in the management of plaque psoriasis.</i>
Clinical criteria:	Patient must have moderate to severe disease

Administrative Advice	<p>No increase in the maximum number of repeats may be authorised.</p> <p>No increase in the maximum quantity or number of units may be authorised.</p> <p>Special Pricing Arrangements apply.</p>
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*Effective DPMQs calculated in the evaluation differed from the proposed effective DPMQs in the submission and the PSCR. Based on the proposed effective AEMPs in the PSCR, the evaluation calculated effective DPMQs of \$ [REDACTED] for the titration pack and \$ [REDACTED] for the standard pack.

- 2.2 The requested basis for listing was a cost-utility analysis, based on the premise that apremilast is superior to cyclosporin in terms of effectiveness and safety from non-randomised claims (persistence) data from the United States (US).
- 2.3 The requested basis for listing in the previous submission considered at the March 2015 PBAC meeting 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 systemic therapies for psoriasis and delay the commencement of biologics.
- 2.4 The DUSC noted that the requested restriction only requires that eligible patients must have moderate to severe disease. This criterion is broader than the approved indication where a patient must be an adult and be a candidate for phototherapy or systemic therapy. The DUSC further noted that the restriction does not preclude access to patients who have received prior therapy with biologics.

3 Background

- 3.1 **TGA status at time of PBAC consideration:** Apremilast was TGA registered on 19 March 2015 for the treatment of adult patients with moderate-to-severe plaque psoriasis who are candidates for phototherapy or systemic therapy.
- 3.2 The PBAC previously considered apremilast for plaque psoriasis at the March 2015 meeting. A summary of the comparison of the March 2015 submission and this resubmission is outlined in Table 1.

Table 1: Summary of the previous submission and current resubmission

	March 2015 submission	Current resubmission
Requested PBS listing	Moderate-to-severe plaque psoriasis, where other systemic therapies (including methotrexate) are ineffective or inappropriate. PBAC Comment: (paragraph 7.2). The PBAC expressed concerns over the potential delay in prescribers being able to initiate bDMARD therapy.	Moderate-to-severe plaque psoriasis
Requested price (DPMQs)	<ul style="list-style-type: none"> • Apremilast (10mg x 4, 20mg x 4, 30mg x 19): \$ [REDACTED] • Apremilast 30 mg (56): \$ [REDACTED] 	Unchanged published price, but propose effective prices: <ul style="list-style-type: none"> • Apremilast (10mg x 4, 20mg x 4, 30mg x 19): \$ [REDACTED] • Apremilast 30 mg (56): \$ [REDACTED]
Clinical evidence	<ul style="list-style-type: none"> • Apremilast versus placebo: 3 pivotal trials • Cyclosporin versus placebo: 1 pivotal trial PBAC Comment: (paragraphs 6.17; 7.4) The fixed	<ul style="list-style-type: none"> • Randomised evidence: Apremilast versus placebo: 3 trials, plus 1 inappropriately excluded trial. • Non-randomised evidence: Apremilast versus

and methotrexate, but before cyclosporin or acitretin for moderate-to-severe psoriasis (displacing existing therapies and extending the treatment sequence with systemic therapies in plaque psoriasis).

- 4.2 The resubmission stated that apremilast would be expected to directly substitute cyclosporin and displace the use of methotrexate and acitretin in clinical practice.
- 4.3 The resubmission proposed that apremilast be added to the ‘Conditions and criteria’ for the PBS authority application for PBS subsidised treatment with a biological agent for severe chronic plaque psoriasis. It was proposed (changes are underlined) that apremilast be included such that patients seeking to access PBS subsidised treatment with a biological agent for severe plaque psoriasis be required to have failed to achieve an adequate response to three of the following five (currently four) treatments: phototherapy, methotrexate, cyclosporin, acitretin, and apremilast.
- 4.4 The pre-PBAC response noted that apremilast is currently reimbursed for the treatment of plaque psoriasis in 23 countries, including the United Kingdom (UK). The PBAC noted the UK’s National Institute for Health Care Excellence (NICE) currently recommends apremilast as a treatment option for chronic plaque psoriasis in adults whose disease has not responded to other systemic therapies, including cyclosporin, methotrexate, and phototherapy¹.

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

5 Comparator

- 5.1 As per the previous submission, the current resubmission nominated cyclosporin as the main comparator. In March 2015, the PBAC accepted this, but noted that acitretin would also be a relevant comparator (apremilast PSD (plaque psoriasis) March 2015). As the requested listing no longer requires patients to ‘have previously received and failed to achieve an adequate response to one or more systemic therapies, including methotrexate’, the evaluation considered that methotrexate was also a relevant comparator.
- 5.2 The Pre-Sub-Committee Response (PSCR) (p3) argued that methotrexate and acitretin were not appropriate comparators as they would only be displaced and not replaced in practice. The ESC considered that based on the clinical place requested in the resubmission, cyclosporin, methotrexate and acitretin were all relevant comparators.
- 5.3 The PSCR requested that if the PBAC considered methotrexate to be an appropriate comparator, that the requested PBS listing be amended to restrict apremilast to patients who had previously failed treatment with methotrexate.
- 5.4 The DUSC further considered that cyclosporin may not be an appropriate main comparator as it is generally used for short periods of time to treat disease flare-ups

¹ Apremilast for treating moderate to severe plaque psoriasis, NICE Technology appraisal guidance [TA419] Published date: 23 November 2016. <https://www.nice.org.uk/guidance/TA419/chapter/1-recommendations>.

rather than for use as continuing therapy as expected for apremilast. The pre-PBAC response (p2) argued that short-term pulsing of cyclosporin was not appropriate as it “places patients at risk of severe rebound,” and that “cyclosporin is not used intentionally for short-term durations, rather that the high rate of discontinuation is a result of safety considerations requiring intense laboratory and clinical monitoring leading to high treatment burden”.

- 5.5 The pre-PBAC response (p1-2) argued that acitretin is not an appropriate comparator as it is seldom used to control inflammatory psoriasis. The sponsor claimed that acitretin is used in patients with severe recalcitrant skin disease and hyperkeratotic palmoplantar psoriasis; as such, apremilast may not be a clinically appropriate treatment options for these patients.

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 presented clinical case studies and discussed the natural history of the disease, how apremilast would be used in practice, noting the clinical need for an ongoing treatment option. The clinician further discussed issues relating to the safety profiles of other systemic therapies for psoriasis (including the limitation of cyclosporin for short-term use due to toxicity concerns) and addressed other matters in response to the Committee’s questions.

Consumer comments

- 6.2 The PBAC noted and welcomed the input from individuals (27), health care professionals (62) and organisations (3) via the Consumer Comments facility on the PBS website. The comments (including those compiled by Psoriasis Australia) described a range of benefits of treatment with apremilast including improvements psoriasis symptoms, quality of life, fewer side effects, and reduced burden of additional clinician attendances, compared with alternative treatments.
- 6.3 The PBAC also noted the advice received from the Australian College of Dermatologists (ACD) and the Queensland Institute of Dermatology clarifying the likely use of apremilast in clinical practice. The PBAC specifically noted the advice from the ACD that there is currently an unmet need in patients with moderate psoriasis and that apremilast has “moderate efficacy approximately equivalent to higher doses of cyclosporin” and is relatively non-toxic and requires fewer consultations and pathology investigations, compared with other systemic therapies. The ACD also described the use of phototherapy, cyclosporin, acitretin and methotrexate in clinical practice.

Clinical trials

- 6.4 Randomised evidence: The resubmission presented three head-to-head trials comparing apremilast to placebo (ESTEEM-1, ESTEEM-2, LIBERATE; n=1,424).

One excluded trial, CORE (n=352), was included during the evaluation as the justification for its exclusion was deemed inadequate. Two of the three included trials (ESTEEM-1 and ESTEEM-2), and the excluded CORE trial, were presented in the previous submission. The previous submission also included an indirect comparison versus cyclosporin using the Meffert 1997 trial and placebo as the common reference. The resubmission did not present an indirect comparison of apremilast and cyclosporin, as the Meffert 1997 trial was excluded by the resubmission.

- 6.5 Non-randomised evidence (longitudinal claims data): The resubmission was largely based on one pivotal real-world US study of claims data comparing apremilast to cyclosporin (US MarketScan® databases; n=5,592), and three supportive apremilast single-arm studies (Australian Otezla® Product Familiarisation Program, German IMS longitudinal prescription tracking, and Canadian ez Start program; n=3,296).
- 6.6 Details of the trials and non-randomised studies presented in the resubmission are provided in Table 2.

Table 2: Trials and non-randomised studies and associated reports presented in the resubmission

Trial ID	Protocol title/ Publication title^a	Publication citation
Randomised trials of apremilast versus placebo		
ESTEEM-1	CC-10004-PSOR-008. A Phase 3, multicentre, randomised, double-blind, placebo-controlled, efficacy and safety study of apremilast (CC-10004) in subjects with moderate to severe plaque psoriasis.	Clinical Study Report CC-10004-PSOR-008. July 2013.
	Papp K et al. Apremilast, an oral phosphodiesterase 4 inhibitor, in patients with moderate to severe plaque psoriasis: Results of a phase III, randomized, controlled trial (efficacy and safety trial evaluating the effects of apremilast in psoriasis [ESTEEM] 1).	Journal of the American Academy of Dermatology, 2015; 73(1): 37-49.
ESTEEM-2	CC-10004-PSOR-009. A Phase 3, multicentre, randomised, double-blind, placebo-controlled, efficacy and safety study of apremilast (CC-10004) in subjects with moderate to severe plaque psoriasis.	Clinical Study Report CC-10004-PSOR-009. July 2013.
	Paul C et al. Efficacy and safety of apremilast, an oral phosphodiesterase 4 inhibitor, in patients with moderate-to-severe plaque psoriasis over 52 weeks: A phase III, randomized controlled trial (ESTEEM-2).	British Journal of Dermatology, 2015; 173(6): 1387-1399.
LIBERATE	CC-10004-PSOR-010. A Phase 3b, multicentre, randomised, placebo-controlled, double-blind, double-dummy, study of the efficacy and safety of apremilast (CC-10004), etanercept and placebo, in subjects with moderate to severe plaque psoriasis.	Clinical Study Report CC-10004-PSOR-010. October 2014.
CORE	CC-10004-PSOR-005-E-LTE. A Phase 2B, multicentre, randomised, double-blind, placebo-controlled, dose-ranging, efficacy and safety study of apremilast (CC-10004) in subjects with moderate-to-severe plaque-type psoriasis (PSOR-005) and two extension studies (PSOR-005E & PSOR-005LTE).	Clinical Study Report CC-10004-PSOR-005-E-LTE. December 2012.
	Papp K et al. Efficacy of apremilast in the treatment of moderate to severe psoriasis: A randomised controlled trial.	The Lancet, 2012; 380(9843): 738-746.
Non-randomised studies and associated reports presented in the resubmission		
US MarketScan® databases	Apremilast Study – Cyclosporine – Data Update March 2016	Not published
Australian Otezla® PFP	Otezla PFP Summary Data (EXCEL file)	Not published
German longitudinal prescriptions	Persistence Germany May 2016	Not published
Canadian ezStart program	Patient Persistence on Therapy_CAN	Not published

Source: Table B-4, p43 of the submission

^a It is noted that there are a number of conference abstracts associated with the apremilast trials but these have not been reported in Table 1.

6.7 The key features of the randomised controlled trials are presented in Table 3.

Table 3: Key features of ESTEEM-1, ESTEEM-2, LIBERATE and CORE

Trial	N	Design / duration	Risk of bias	Patient population	Outcome(s)	Use in modelled evaluation ^a
Apremilast versus placebo						
ESTEEM-1	844	Two arm, four phase trial. Phase one: (2:1) R,DB,PC (16wk) Phase two: PX maintenance (16wk) Phase three: re-randomisation PASI75 treatment withdrawal (20wk) Phase four: OL extension (to 4yrs)	Phase one: low	Plaque psoriasis (PASI \geq 12 + BSA \geq 10% + sPGA \geq 3)	1°: PASI75 (wk16) 2°: sPGA \leq 1, PASI change/ response, QoL	Not used
ESTEEM-2	413	Two arm, four phase trial. Phase one: (2:1) R,DB,PC (16wk) Phase two: PX maintenance (16wk) Phase three: re-randomisation PASI50 treatment withdrawal (20wk) Phase four: OL extension (to 4yrs)				
LIBERATE	167	Three arm, two phase trial. Phase one: (1:1:1) R,DB,PC (16wk) Phase two: PX maintenance (88wk)	Phase one: low	Plaque psoriasis (PASI \geq 12 + BSA \geq 10% + sPGA \geq 3)	1°: PASI75 (wk16) 2°: sPGA \leq 1, QoL	Not used
CORE	352	Four arm, three phase trial. Phase one: (1:1:1:1) R,BD,PC (16wk) + PX dose-B (8wk) Phase two: dose-B extension (28wk) Phase three: OL extension (to 4yrs)	Phase one: low	Plaque psoriasis (PASI \geq 12 + BSA \geq 10%, \geq 6months)	1°: PASI75 (wk16) 2°: PASI change/ response, QoL	Not used

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

Source: compiled during the evaluation

^a Outcomes in the model based on persistence rates from the non-randomised US persistence analysis.

6.8 The key features of the non-randomised studies are summarised in Table 4.

Table 4: Key features of the included non-randomised evidence (longitudinal claims data)

	US MarketScan® databases	Australian Otezla® PFP	German IMS	Canadian ez Start program
Inclusion criteria				
Starting date ^a	March 2014	August 2015	February 2015	December 2014
Males & females	Yes	Yes	Yes	Yes
Age	≥18 years	≥18 years	≥18 years	≥18 years
Psoriasis	Yes	Yes (moderate-to-severe)	Yes	Yes (moderate-to-severe)
Disease severity	NR	PASI ≥12; OR BSA ≥10% or sPGA ≥3 (if PASI <12)	NR	NR
Candidate for treatment	-	Phototherapy and/or systemic therapy	-	-
Restrictions	-	Inappropriate for, intolerant or has failed methotrexate therapy. No concomitant oral systemics or biologics.	-	Failed a topical agent, or at least one systemic agent ^b
Criteria for continuing treatment	-	16 weeks: No worsening in disease (PASI) from baseline. Week 28, 40, 52: Maintenance of response. All above timepoints: No addition of concomitant oral systemic therapy or biologic therapy ^c .	-	No standard criteria (assessments varying from 6mths to 1yr)
Other	Patients were continuously enrolled in their health plan for ≥6 months prior to and after the psoriasis treatment initiation.	-	-	Private and public insurance markets
Exclusion criteria				
Exclusion criteria	-	-	Samples/free of charge (titration packs); in-hospital prescriptions/initiations; private health insurance prescriptions	Dispensing of apremilast not from a Specialty Pharmacy; dispensing from a retail pharmacy

Abbreviations: PASI=Psoriasis Area Severity Index; BSA=Body Surface Area Involvement; sPGA= Static Physician Global Assessment, PFP = product familiarisation program. Source: pp64-69, 95 of the resubmission.

^a for patients initiating treatment (apremilast or cyclosporin)

^b For private insurance patients. There is no standard criteria for access to apremilast, however this criteria applies to the majority of payers. For public insurance patients

^c Refer Figure B-2, p67 of the resubmission

Comparative effectiveness

6.9 Randomised evidence: The results of the apremilast trials are presented in Table 5.

Table 5: Results of PASI 75 and PASI 50 response at the end of the controlled, double-blind phase (16 weeks) of the randomised trials

Trial ID	Apremilast n/N (%)	Comparator n/N (%)	RD (95% CI)	RR (95% CI)	Indirect RR (95% CI)
PASI 75 at 16 weeks: apremilast versus placebo					
ESTEEM-1	186/562 (33.1)	15/282 (5.3)	0.28 (0.23, 0.32)	6.22 (3.75, 10.32)	
ESTEEM-2	79/274 (28.8)	8/137 (5.8)	0.23 (0.16, 0.30)	4.94 (2.46, 9.92)	
LIBERATE	33/83 (39.8)	10/84 (11.9)	0.28 (0.15, 0.40)	3.34 (1.76, 6.33)	
CORE	36/88 (40.1)	5/88 (5.7)	0.35 (0.24, 0.47)	7.20 (2.96, 17.49)	
Meta-analysis			0.27 (0.23, 0.31)	5.16 (3.74, 7.12)	0.81 (0.19, 3.52) ^a
Meta-analysis (excluding CORE)			0.26 (0.23, 0.30)	4.87 (3.34, 7.08)	0.77 (0.18, 3.36) ^a
Meta-analysis (excluding LIBERATE)			0.27 (0.22, 0.33)	5.98 (4.12, 8.67)	0.94 (0.22, 4.12) ^a
PASI 50 at 16 weeks: apremilast versus placebo					
ESTEEM-1	330/562 (58.7)	48/282 (17.0)	0.42 (0.36, 0.48)	3.45 (2.64, 4.50)	
ESTEEM-2	152/274 (55.5)	27/137 (19.7)	0.36 (0.27, 0.45)	2.81 (1.98, 4.01)	
LIBERATE	52/83 (62.7)	28/84 (33.3)	0.29 (0.15, 0.44)	1.88 (1.33, 2.65)	
CORE	53/88 (60.2)	22/88 (25.0)	0.35 (0.22, 0.49)	2.41 (1.62, 3.59)	
Meta-analysis			0.38 (0.33, 0.43)	2.61 (1.97, 3.46)	0.41 (0.15, 1.12) ^b
Meta-analysis (excluding CORE)			0.38 (0.31, 0.44)	2.66 (1.84, 3.84)	0.42 (0.15, 1.18) ^b
Meta-analysis (excluding LIBERATE)			0.39 (0.35, 0.44)	2.98 (2.42, 3.67)	0.47 (0.18, 1.26) ^b
PASI 75 at 16 weeks: apremilast versus etanercept					
LIBERATE	33/83 (39.8)	40/83 (48.2)	-0.08 (-0.23, 0.07)	0.82 (0.58, 1.17)	N/A
PASI 50 at 16 weeks: apremilast versus etanercept					
LIBERATE	52/83 (62.7)	69/83 (83.1)	-0.20 (-0.34, -0.07)	0.75 (0.62, 0.91)	N/A

^a Meffert 1997 reported a RR=6.35 (95% CI: 1.52, 26.5) for PASI 75 response at 10 weeks

^b Meffert 1997 reported a RR=6.35 (95% CI: 2.42, 16.7) for PASI 50 response at 10 weeks

Source: Tables B.12-13, p50 and Tables B.14-15, p51 of the resubmission, Apremilast March 2015 PSD and Table 18, p87 and Table 28, p98 of the LIBERATE CSR

Bold typography indicates statistically significant differences

- 6.10 The apremilast versus placebo trials demonstrated that a statistically significantly greater proportion of patients treated with apremilast achieved PASI 75 response at 16 weeks compared with placebo.
- 6.11 Based on the approach taken in the previous submission (with an indirect comparison of apremilast versus cyclosporin (Meffert 1997), using placebo as the common reference), no statistically significant differences between apremilast and cyclosporin were observed in the proportion of patients achieving PASI 75 response at 16 weeks for apremilast versus 10 weeks for cyclosporin. The PBAC considered (paragraph 7.4, apremilast (plaque psoriasis), March 2015 PSD) that “non-inferiority in terms of comparative effectiveness [of apremilast compared with cyclosporin], had not been established”, noting that the indirect comparison of PASI 50 response at 16 weeks favoured cyclosporin and that cyclosporin dosing (fixed dose of cyclosporin 2.5 mg/kg/day for 10 weeks) in the Meffert 1997 trial may have been sub-optimal.
- 6.12 The LIBERATE trial provided a head-to-head comparison of apremilast and etanercept. Although this was not a primary comparison nominated in the trial, at 16 weeks no statistically significant differences were observed between treatments with respect to the proportion of patients achieving a PASI 75 response, however a statistically significantly lower proportion of patients treated with apremilast achieved a PASI 50 response compared with those treated with etanercept.

- 6.13 Non-randomised evidence – US MarketScan® databases: The results of comparative persistence rates in the pivotal non-randomised study (US MarketScan® databases) are presented in Table 6 and Figure 1. The resubmission considered persistence to therapy to be a highly relevant outcome measure to assess the comparative effectiveness, safety and tolerability of apremilast and cyclosporin. Data from the US MarketScan® databases indicated that a greater proportion of patients persisted with apremilast compared with cyclosporin, but the ESC noted that it did not report any final health outcomes relevant to psoriasis.

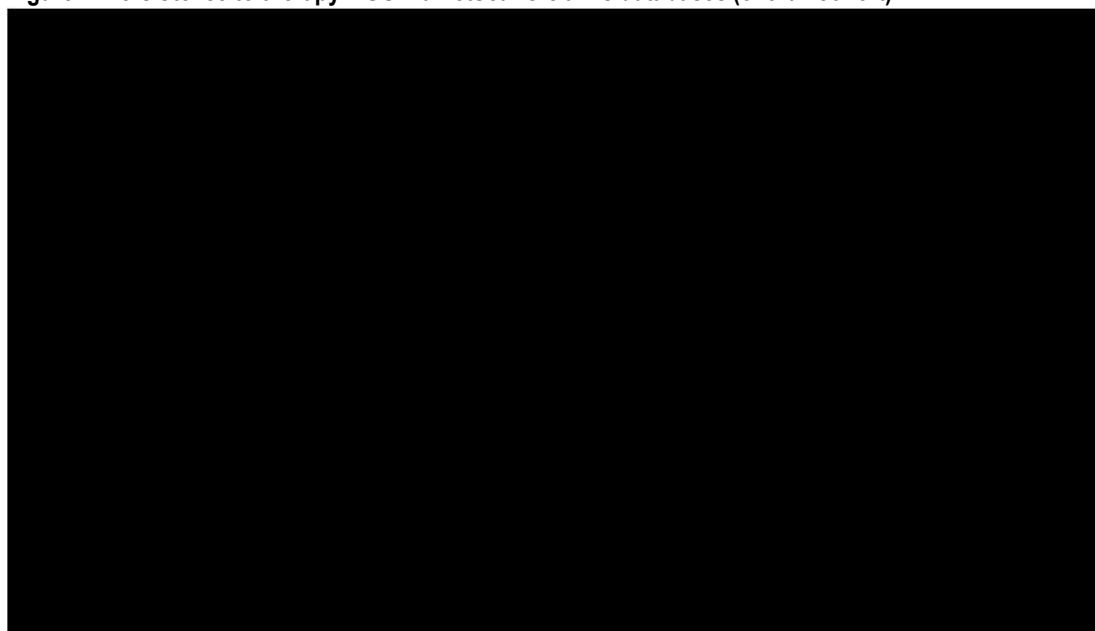
Table 6: Results of persistence rates – US MarketScan® claims databases (overall cohort)

Time (months)	Apremilast N=1902		Cyclosporin ^a N=538	
	N	Rate (95%CI)	N	Rate (95%CI)
1				
4				
6				
9				
12				

Source: Tables B-36; p73 of the resubmission.

^a The cyclosporin subgroup included patients who were initiated on cyclosporin before or after apremilast launch to increase the sample size.

Figure 1: Persistence to therapy – US MarketScan® claims databases (overall cohort)



Source: Figure 2, p8 of Executive Summary to resubmission

- 6.14 The evaluation considered that as there were no reported criteria for initiating and continuing apremilast or cyclosporin treatment in the US MarketScan® databases, it was not known whether the data are applicable to the likely PBS use of apremilast or cyclosporin. The PSCR (p2) argued that the US MarketScan® data are applicable to the Australian population, noting the FDA and TGA indications are identical for apremilast and comparable for cyclosporin. The PSCR stated that persistence with apremilast in Australia is expected to have more of a correlation with PBS initiation and continuation criteria while the US data are highly reflective of clinical

effectiveness. The ESC considered the claim that US persistence data were highly reflective of clinical effectiveness was unsubstantiated and specifically noted that apremilast was not FDA approved for plaque psoriasis until 23 September 2014², while the persistence study period began in March 2014. Accordingly, any use of apremilast for plaque psoriasis during the first six months of the persistence study was off-label.

- 6.15 The pre-PBAC response (p2) acknowledged that approximately 5% of patients treated with apremilast in the MarketScan® dataset initiated treatment for plaque psoriasis prior to the FDA approval date for that indication, but argued that it does not jeopardise the validity of the results as all patients with a diagnosis of psoriatic arthritis were excluded from the analysis.
- 6.16 The MarketScan® databases are a combination of claims databases which comprised de-identified service-level claims for inpatient and outpatient services, and outpatient prescription drugs, submitted by large employers, managed care organisations, hospitals, and Medicare programs. The evaluation considered there were difficulties in applying the MarketScan® databases to the Australian context, particularly noting the range of health care settings which may affect persistence rates (A3, p13 of Compliance to Medicines Working Group (CMWG) Report to PBAC; April 2010³). The PSCR argued that this reference to persistence relates to ‘compliance’ of which persistence is only one aspect along with ‘acceptance’ and ‘adherence’. The ESC agreed with the evaluation and noted the CMWG Report (p36) regarding the applicability of overseas studies of compliance, specifically:
- *“Descriptive studies which measure the level of compliance in different populations are unlikely to be directly transferable between countries with different health-care systems and methods of funding pharmaceuticals.*
 - *Comparative studies of compliance are likely to be informative when interpreted in light of the characteristics of the health care settings within which they were done.*
 - *Ideally, evidence on comparative compliance to medicines should be based on data collected in the Australian health care setting. Overseas studies may provide complementary evidence to some decisions.”*
- 6.17 The pre-PBAC response (p2-3) argued that the evidence presented in the resubmission is comparative, not descriptive, and that the US data is applicable to PBAC decision-making on the basis of the additional guidance in the CMWG report:
- “In some circumstances, it may be reasonable to consider results from comparative studies of compliance to medicines from other countries when evidence for a particular medicine is not available in Australia. However, the health care setting and the variables measured should be examined in detail to assess their applicability to the Australia population for whom the treatment is intended.*

² Celgene media release, 23 September 2014, <http://ir.celgene.com/release/detail.cfm?releaseid=872240>.

³ Compliance to Medicines Working Group. *Compliance to Medicines Working Group Report to PBAC April 2010*. Commonwealth Department of Health. Australia: Canberra. Accessed 27 November 2016. Available at: <http://www.pbs.gov.au/info/publication/factsheets/shared/cmwg-report-to-pbac#B4>.

The results of overseas studies of compliance may also be useful when considered in conjunction with Australian findings. Indeed, overseas studies may reinforce the results of Australian studies if their findings are in the same direction, particularly where Australian studies may have been subject to biases that overseas studies have apparently been able to control because of the availability of data on potential confounding variables.”

- 6.18 The ESC considered there were substantial conceptual, translational and methodological issues in comparing persistence data for apremilast and cyclosporin and the way these data were used in the submission. The ESC noted that cyclosporin is recommended for intermittent short durations (average of 12 weeks duration)^{4,5}, and that long term continuous cyclosporin use may only be appropriate for a subgroup of patients (kept below two years whenever possible). The ESC therefore considered it was possible that the higher rates of discontinuation observed in cyclosporin patients, compared with apremilast, may be reflective of appropriate clinical practice rather than the premise of withdrawal for either efficacy or safety reasons, as argued in the submission. The ESC therefore considered that the study, by design, may be conceptually flawed and inherently favour apremilast.
- 6.19 As discussed in paragraph 5.4, the pre-PBAC response (p2) argued that short-term pulsing of cyclosporin was not appropriate as it “places patients at risk of severe rebound,” and that “cyclosporin is not used intentionally for short-term durations, rather that the high rate of discontinuation is a result of safety considerations requiring intense laboratory and clinical monitoring leading to high treatment burden”.
- 6.20 The ESC also considered that the definition of discontinuation in the study (greater than 60 days with no re-supply) was not consistent with the use of cyclosporin in practice and may have inappropriately censored cyclosporin patients given the intermittent nature of its use and that the data presented in Griffiths et al 2004 reported a median time to relapse of 109 days after the end of the first treatment period⁴.
- 6.21 The ESC considered it was difficult to assess the comparative efficacy of apremilast and cyclosporin from the presented evidence as disease severity was not known for either treatment, and patients in the apremilast arm could receive other systemic therapies whilst those in the cyclosporin arm could not.
- 6.22 Non-randomised evidence – supportive persistence studies: The results of the supportive non-randomised persistence studies (Australian Otezla® PFP, German longitudinal prescriptions and Canadian ezStart program) demonstrated a declining trend in apremilast persistence rates over time following initiation of therapy, similar to the US data in Table 6. The persistence to apremilast therapy in the Australian Otezla® PFP cohorts was greater than in the US persistence analysis. The German persistence rates were higher than those in the Australian cohorts in the initial

⁴ Griffiths, C.E.M., Dubertret, L., Ellis, C.N., Finlay, A.Y., Finzi, A.F., Ho, V.C., Johnston, A., Katsambas, A., Lison, A.-E., Naeyaert, J.M., Nakagawa, H., Paul, C. and Vanaclocha, F. (2004), Cyclosporin in psoriasis clinical practice: an international consensus statement. *British Journal of Dermatology*, 150: 11–23. doi:10.1111/j.0366-077X.2004.05949.x.

⁵ Samarasekera Eleanor, Sawyer Laura, Parnham Jill, Smith Catherine H. Assessment and management of psoriasis: summary of NICE guidance *BMJ* 2012; 345 :e6712

months of treatment, and similar to the Australian rate at 4 months (limited inference can be drawn from the German analysis beyond 4 months). The Canadian persistence rates were higher than the Australian rates and converged with the Australian rates at 9-10 months. The validity of comparing across these studies is limited due to differences in inclusion criteria (as outlined in Table 4).

- 6.23 For the Australian Otezla® PFP, outcomes of PASI 75 response and per cent mean PASI change from baseline were also reported. The resubmission stated that “the pronounced difference between the non-responder imputed (NRI) and observed data validates the a priori assumption that patients remain on therapy due to a perceived clinical benefit”. The evaluation considered that the observed correlation between persistence with apremilast and “perceived clinical benefit” observed in the Australian Otezla® PFP may in fact be a result of the aim of the program i.e., that patients “who continue to meet the eligibility criteria [no PASI worsening at week 16 or maintenance of response at assessments >16 weeks and no addition of systemics and biologics at all assessments] for ongoing treatment will be supplied apremilast for up to 3 years from commencement of therapy, or until PBS listing”.
- The PSCR (p1) stated that the correlation between persistence and PASI response was not inevitable. The PSCR also stated that continuation of treatment with apremilast under the Australian Otezla® PFP was governed by clinical judgement and patient preference, and that patients were not required to demonstrate a minimum response to treatment in order to remain on the PFP.
 - The ESC considered that this appeared to contradict what was presented in the resubmission (Figure B-2, p67 of the re-submission), which showed that that patients were deemed eligible to continue apremilast treatment at 16 weeks if the following criteria were met: no PASI worsening of disease from baseline; and no addition of concomitant oral systemic, or biologic therapy. The PASI is an objective and quantitative assessment of psoriasis lesional burden. Hence, if the PASI was used to assess response at 16 weeks, treatment continuation under the PFP was not governed by clinical judgement.
 - The pre-PBAC response (p3) acknowledged the “perceived contradiction between the resubmission and PSCR noted by the ESC”. The pre-PBAC response claimed, however, that the response criteria noted by the ESC was to “enable a degree of medical visibility of judicious prescribing” and the sponsor maintained that “the PASI is not the only final health outcome of relevance to the patient and that the decision to continue a treatment is a joint clinical decision between the clinician and the patient.”

Comparative harms

- 6.24 Treatment emergent adverse events (TEAEs) that occurred in the placebo-controlled phases (0-16 weeks) of ESTEEM-1, ESTEEM-2, LIBERATE and CORE demonstrated that a significantly greater number of any TEAEs (RR=1.21, 95% CI: 1.12, 1.31) and drug-related TEAEs (RR=1.86, 95% CI: 1.46, 2.36) were reported with apremilast compared with placebo. Most were predominately mild or moderate in severity. The most common TEAEs in either arm included headache (including tension headache), gastrointestinal events (diarrhoea and nausea), and infections (upper respiratory tract infection and nasopharyngitis).

- 6.25 No increase in rates of serious AEs and discontinuation rates due to AEs were reported with long-term exposure of apremilast.
- 6.26 The resubmission did not present any comparisons between apremilast and cyclosporin for safety outcomes. The safety profile of cyclosporin is well known. Very common adverse events reported in the TGA approved product information (PI) include: hypertension, hirsutism, impaired renal function, gingival hypertrophy, gastrointestinal disturbances, tremor and fatigue, and hyperlipidaemia.

Benefits/harms

- 6.27 The modelled economic evaluation and financial estimates presented in the resubmission were based on the non-randomised studies reporting persistence, drug survival and retention for apremilast and cyclosporin (primarily the US MarketScan® databases). The randomised apremilast trials are versus placebo, and an indirect comparison of apremilast versus the nominated comparator of cyclosporin was not conducted by the resubmission. Accordingly, a benefits/harms table has not been presented.

Clinical claim

- 6.28 Based on randomised evidence, the resubmission describes apremilast as superior in terms of comparative effectiveness and inferior in terms of safety, over placebo. The evaluation, ESC and the PBAC considered that this conclusion was supported in terms of randomised trial evidence up to 16 weeks.
- 6.29 The resubmission described apremilast as superior in terms of comparative effectiveness and superior in terms of comparative safety over cyclosporin, based on claims (persistence) data from the US.
- The ESC noted that this differed from the clinical claim made in the previous submission (which was based on randomised evidence) where: “The submission described apremilast as non-inferior in terms of comparative effectiveness and superior in terms of safety (comparable” in terms of short-term safety but favourable” in terms of long-term safety), over cyclosporin.”
 - The ESC considered that the resubmission’s approach to establishing a therapeutic claim of apremilast compared with cyclosporin on the basis of longitudinal claims data (which were not linked to any final health outcomes associated with plaque psoriasis) rather than on an indirect comparison of randomised controlled trials was inadequately supported in this instance (see paragraphs 6.14-6.21).
- 6.30 The PBAC considered that the claim of superior comparative effectiveness and safety was not adequately supported by the data.

Economic analysis

- 6.31 The resubmission presented a modelled evaluation of apremilast versus cyclosporin. Table 7 summarises the model structure and rationale of the economic evaluation.

Table 7: Summary of model structure and rationale

Component	Summary
Model type and structure	State transition model with two health states: 'Treatment with index agent' and 'Discontinued from index agent'. Only one possible transition to the 'Discontinued from index agent' health state. This assumption of one-directional movement appeared to be reasonable given the treatment algorithm for psoriasis and the multiple alternative treatments available; however there is no restriction on patients re-trialling any of the available therapies on the PBS. The ESC noted the model did not include an all-cause death state which may not have been appropriate, particularly given the older age of the patient population (45-50 years at the start of the model) and the 10 year time horizon.
Model population	Based on the population in the US persistence analysis without any adjustments. Overall, there is insufficient data to conclude whether patients in the US MarketScan® databases were representative of the likely PBS population who would be eligible for therapy with apremilast.
Time horizon	10 years in the model base case versus 12 months in US persistence analysis (up to 651 days and 673 days of drug survival data for apremilast and cyclosporin, respectively)
Outcomes	Patients continuing treatment and QALYs
Methods used to generate results	Cohort expected value analysis
Cycle length	One day
Treatment costs	Apremilast dosage based on PI and dosage derived from US persistence analysis; cyclosporin dosage derived from US persistence analysis. Overall, there is insufficient data to conclude whether apremilast and cyclosporin dosing for patients in the US MarketScan® databases were representative of the likely doses in the PBS population.
Adverse event and physician costs	No adverse events were included in the model and the costs of physician visits (for initiation of treatment) were omitted for apremilast in the base case. This assumption did not appear to be reasonable.
Costs of subsequent therapy	Patients discontinuing from index treatment moved onto subsequent therapy with a fixed proportion assumed to move on to particular therapies (58% of patients discontinuing cyclosporin received biologics (40% ustekinumab, 15% adalimumab, 2% etanercept, 1% infliximab) and 42% received no PBS treatment or other treatment (23%), methotrexate (12%) or acitretin (7%)) and continued with that subsequent therapy for the remainder of the time horizon of the model. This assumption did not appear to be reasonable. The data used by NostraData in arriving at these results have not been reported in sufficient detail by the resubmission.
Transition probabilities	Persistence analyses from US MarketScan® databases and parametric survival analyses. The parametric fits were extended to a 10-year follow-up. All the parametric modelling was done conditional on persisting for more than 36 days, to deal with a problem of a pronounced drop in the Kaplan-Meier curve at 30 days. The base case assumed the log-Normal model. Log-logistic and Gompertz models used in sensitivity analyses. These extrapolations are uncertain as in reality, the persistence curves could behave in a variety of ways beyond the observed follow-up times.
Discount rate	5% per annum for costs and outcomes
Software package	Excel 2010

Source: constructed during the evaluation

6.32 Table 8 summarises the key drivers of the model.

Table 8: Key drivers of the model

Description	Method/Value	Impact
Utility values	<p>Applied to patients based on the treatment received rather than a health state defined by PASI and/or DLQI.</p> <ul style="list-style-type: none"> 0.84 for apremilast and 0.73 for discontinued and on no other treatment – inappropriately using the EQ-5D results for ‘responders’ and ‘non-responders’, respectively, based on PASI response and DLQI, from the pooled ESTEEM trials. 0.76 for treatment with cyclosporin, methotrexate or acitretin; and 0.80 for treatment with biologics – Norlin et al., 2012a; 2012b. <p>The ESC queried the face validity of the relative utility scores, particularly that between the apremilast and biologics arms.</p>	High, favours apremilast
Costs of subsequent therapy	%’s derived from NostraData analysis	Moderate, favours apremilast
Prices of bDMARDs	Published prices. Special Pricing Arrangements are in place for ustekinumab, adalimumab, secukinumab and etanercept.	Moderate, favours apremilast

Source: compiled during the evaluation.

- 6.33 The results of the stepped economic evaluation in the resubmission are presented in Table 9. Multiple errors in the model were corrected during the evaluation and the ICER of \$15,000 - \$45,000 per QALY gained represents the results with these errors corrected (uncorrected ICER: less than \$15,000 per QALY gained). The ESC noted that the PSCR did not contest these corrections.

Table 9: Results of the stepped economic evaluation

Step and component	Apremilast	Cyclosporin	Increment
Step 1: trial-based costs and outcomes (undiscounted)			
16 weeks			
Costs (drug and monitoring)	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]
Probability of persistence	[REDACTED] %	[REDACTED] %	[REDACTED] %
Incremental cost/extra patient continuing treatment at 16 weeks			\$ [REDACTED]
2 years			
Costs (drug and monitoring)	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]
Probability of persistence	[REDACTED] %	[REDACTED] %	[REDACTED] %
Incremental cost/extra patient continuing treatment at 2 years			\$ [REDACTED]
Step 2: modelled evaluation (extrapolating to 10 years, transformation into QALYs and including costs of subsequent treatment) – discounted (base case)			
Costs	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]
QALYs	6.38	6.27	0.10
Incremental cost/extra QALY gained			\$ [REDACTED]

Source: Constructed during the evaluation using the “Results” and “Costs” worksheets of EXCEL model file.

Note: Corrected for errors during the evaluation.

- 6.34 The ESC considered that on face validity, the difference between the utility value for apremilast (0.84), compared with the more effective biologics (0.80) was questionable. The ESC noted that the UK algorithm (rather than the Australian algorithm) was applied to both sets of EQ-5D data and the impact of this was unknown. Moreover, as outlined in Table 8, applying utilities for ‘responders’ from the pooled ESTEEM trials to all continuing apremilast patients and utilities for ‘non-responders’ for those who discontinued or are on no treatment, appeared inappropriate. This is because not all apremilast patients are ‘responders’ and not all patients discontinuing from treatment or on no treatment would be ‘non-responders’

(12% of placebo patients in the LIBERATE trial achieved PASI 75 response). The ESC considered that a justification for a higher utility for apremilast could be that those patients receiving the biologics are those patients who had tried and failed apremilast and other systemic therapies, and therefore had more severe symptoms on average than those patients on apremilast, despite the superior efficacy of biologics. In this regard, the ESC considered that the submission unreasonably applied utilities to treatments rather than health states defined by PASI and/or DLQI scores. The ESC noted that this assumed that there was a constant treatment effect for all patients on apremilast regardless of symptom severity. The PSCR (p4) maintained that applying utilities to treatments was appropriate and highly relevant to the decision context.

- The ESC noted that the ICER was sensitive to the utility values; for example, assuming lower utility values for apremilast to be equivalent to the biologics (0.80) increased the ICER from \$15,000 - \$45,000 per QALY gained to \$45,000 - \$75,000 per QALY gained.
- In addition, if the apremilast utility was set to be the same as for the systemic therapies (0.76), apremilast therapy was dominated.

6.35 In addition to the utility values, the evaluation found that the ICER was very sensitive to the exclusion of costs of subsequent therapy (increased the ICER to \$105,000 - \$200,000 per QALY gained). The ICER was also sensitive to the price of apremilast with ICERs of less than \$10,000 per QALY and \$15,000 - \$45,000 per QALY gained estimated from decreasing and increasing the price by 10%, respectively.

6.36 The ESC noted the following additional issues with the model:

- The model used persistence (based on claims data, not linked to final outcomes associated with psoriasis) as an unsubstantiated proxy for the effectiveness and safety of apremilast and cyclosporin (see paragraphs 6.14-6.21).
- Limited information on patient characteristics and criteria for initiating and continuing treatment with apremilast or cyclosporin in this dataset were reported to allow for conclusions regarding the applicability of the claims (persistence) data from US MarketScan® to the likely PBS population. Additionally, extrapolation of this data was considered uncertain as ■% of patients remained on apremilast for the 10-year model period, which may be implausible.
- The costs for adverse events were not included in the model, and costs for physician visits (initiation of treatment) were omitted for apremilast. The PSCR (p4) stated that initiation of apremilast does not require an additional physician consultation over routine medical care. In the model, a pre-treatment physician visit was costed for cyclosporin, and all the assumed treatments for subsequent therapy. Therefore, it appeared inappropriate that a pre-treatment physician visit was omitted for apremilast, as apremilast has to be initiated by a dermatologist under the proposed PBS restriction.
- It was not possible to test the sensitivity of the model to a time horizon beyond 10 years. Given the model is based on displacing treatments, the ESC considered that it would have been informative to be able to increase this variable to more than the base case of 10 years.

6.37 The PBAC noted that when the effective prices of the biologics were applied to the (corrected) base case, the ICER increased substantially. The PBAC further noted that the ICER for the sensitivity analysis in which the utility for apremilast treatment

was assumed to be the same as the biologics (0.80, see paragraph 6.34) also increased substantially.

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

6.38 \$ [REDACTED] assuming one titration script (lasting for 2 weeks) at an effective DPMQ of \$ [REDACTED] and 12.5 maintenance scripts per year (lasting for a duration of 50 weeks) at an effective DPMQ of \$ [REDACTED]. The cost of cyclosporin cannot be estimated given details of the mean weight of psoriasis patients and mean dose of cyclosporin used in the Australian setting is unknown. However, the estimated cost per patient per year for cyclosporin applied in the resubmission was \$ [REDACTED] per patient per year assuming the varying dosage (mg per day) from the US MarketScan® databases (using the approach in Section D of the resubmission, but corrected for errors identified in aligning timepoints) and \$ [REDACTED] assuming a cyclosporin fixed daily dose of [REDACTED] mg per day (as in Section E of the resubmission).

Estimated PBS usage & financial implications

6.39 The submission was considered by DUSC. The re-submission used a combined epidemiological and market share approach, based on Prospection 10% Medicare sample data, to estimate the population of patients with moderate-to-severe psoriasis in Australia, and the METIS Healthcare Research Survey of 138 patients with moderate-to-severe psoriasis to estimate uptake of apremilast.

6.40 At year 5, the estimated number of new patients was less than 10,000 per year and the net cost to the PBS would be more than \$100 million per year.

Table 10: Estimated use and financial implications

	Year 1	Year 2	Year 3	Year 4	Year 5
Estimated extent of use					
Number treated	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
Uptake rate:					
Systemic naive	[REDACTED] %	[REDACTED] %	[REDACTED] %	[REDACTED] %	[REDACTED] %
Methotrexate experienced	[REDACTED] %	[REDACTED] %	[REDACTED] %	[REDACTED] %	[REDACTED] %
Substitution from patients treated with conventional tx:					
Cyclosporin	[REDACTED] %	[REDACTED] %	[REDACTED] %	[REDACTED] %	[REDACTED] %
Acitretin	[REDACTED] %	[REDACTED] %	[REDACTED] %	[REDACTED] %	[REDACTED] %
Methotrexate	[REDACTED] %	[REDACTED] %	[REDACTED] %	[REDACTED] %	[REDACTED] %
Titration packs ^a	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
Standard packs ^b	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
Total packs	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
Estimated net cost to PBS/MBS					
Net cost to PBS	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]
Net cost to MBS	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]
Estimated total net cost					
Net cost to PBS/MBS	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]

Source: Compiled during the evaluation

^a One titration pack per patient initiating treatment

^b Base case assumption that mean duration of apremilast treatment is 28.9 months (13 continuation packs in the first two years of treatment, 2.8 continuation packs in the third year of treatment).

- 6.41 The evaluation noted that the financial implications estimated by the resubmission were most sensitive to apremilast treatment duration, proportion diagnosed by a dermatologist and uptake in the untreated/undertreated market.
- 6.42 This DUSC considered the estimates presented in the submission to be underestimated. The main issues were:
- The registered indication for apremilast requires that patients should be candidates for phototherapy. The resubmission did not attempt to estimate the number of eligible patients on phototherapy.
 - The reliability of the assumptions for the treated population based on the METIS survey were uncertain. Due to a number of limitations with the survey, there may be differences between the patients' self-reported severity of disease in the survey compared with moderate to severe plaque psoriasis as defined in the proposed PBS restriction.
 - The approach of using two steps in the estimate of eligible patients through applying an "Estimated proportion of patients diagnosed by a dermatologist" and a "Proportion of patients seen by a dermatologist in the last year" was likely to underestimate the eligible population. The assumption that only 48% of patients would be seen by a dermatologist was considered to be an underestimate noting that the METIS survey reported that 85% of respondents had seen a dermatologist. Further, other medical practitioners, such as general practitioners, can also diagnose the disease and refer to a specialist.
 - The treatment assumptions derived from the Prospection analysis of a 10% PBS sample could not be fully critiqued as insufficient information was provided regarding the methods of analysis.

Quality Use of Medicines

- 6.43 The DUSC considered the inclusion of apremilast in the treatment algorithm for chronic plaque psoriasis may replace a short-term treatment (cyclosporin) with a long-term treatment with highly uncertain comparative effectiveness and safety.
- 6.44 The pre-PBAC response (p3) disagreed with the DUSC, arguing that "cyclosporin is necessarily used short-term, not due to the intent of the treatment (i.e., to treat a psoriasis flare) but because treatment with cyclosporin is associated with significant safety and toxicity issues limiting treatment exposure. The sponsor believes that "cyclosporin, a highly toxic agent with significant safety issues limiting longer-term use will be replaced with apremilast, a highly effective and exceptionally safe agent allowing for long-term control of a complex chronic disease".

Financial Management – Risk Sharing Arrangements

- 6.45 The resubmission did not propose a risk sharing arrangement (RSA) but stated that the Sponsor accepts that an RSA which would minimise any potential uncertainties around the budgetary impact of this listing would need to be negotiated with the Department of Health/PBAC.
- 6.46 The Sponsor has requested a Special Pricing Arrangement (SPA). The PSCR clarified that the sponsor is proposing a ■■■% discount to the published AEMP.

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 moderate to severe plaque psoriasis on the basis that the evidence presented did not support the claims of superior comparative efficacy or safety versus cyclosporin and the cost effectiveness of apremilast was uncertain and unacceptable at the requested price.
- 7.2 The PBAC recalled that it previously rejected apremilast for this indication in March 2015 on the basis that cost-effectiveness compared with cyclosporin treatment had not been adequately established at the price proposed in the submission. An incremental benefit in terms of comparative efficacy and safety over cyclosporin was not evident for apremilast and so it did not appear clinically appropriate to require patients to trial an additional line of therapy before being eligible for therapy with biologics. Therefore, the cost-utility analysis approach to the economic modelling was considered to be uninformative.
- 7.3 The PBAC noted and welcomed the consumer comments received relating to this submission. The PBAC also acknowledged the correspondence from the Australian College of Dermatologists, the Queensland Institute of Dermatology and Psoriasis Australia for this submission. The PBAC recognised the support for subsidised access to apremilast.
- 7.4 The PBAC noted the resubmission's proposed clinical place in therapy as an additional treatment option in the same line of therapy as cyclosporin. The PBAC considered there was a clinical place for apremilast as an alternative treatment option for plaque psoriasis.
- 7.5 On the basis of the clinical place proposed in the resubmission, the PBAC considered that cyclosporin, methotrexate and acitretin were all relevant comparators. The PSCR (p3) requested that if methotrexate was considered to be a relevant comparator, that apremilast be restricted to patients who have failed treatment with methotrexate. In addition, the pre-PBAC response (p1-2) argued that acitretin is not an appropriate comparator as it is seldom used to control inflammatory psoriasis. In this context, the PBAC accepted cyclosporin as the main comparator.
- 7.6 The PBAC recalled that the March 2015 submission had described apremilast as non-inferior in terms of comparative effectiveness and superior in terms of comparative safety compared with cyclosporin, and that it previously considered that neither of these claims had been adequately supported.
- 7.7 The PBAC noted this resubmission revised the clinical claim to describe apremilast as superior in terms of comparative effectiveness and safety compared with cyclosporin. The revision to the clinical claim was based on a real-world, non-randomised US study of comparative persistence rates and supportive analyses of persistence from medicine access programs in Australia, Canada and Germany. The PBAC considered that the applicability of the non-randomised US persistence data presented in the submission to the likely PBS use of apremilast was unclear. Furthermore, the submission did not demonstrate that apremilast was associated

with improvements in health outcomes relevant to psoriasis (compared with cyclosporin). In this regard, the PBAC noted that the indirect comparison of clinical trial evidence suggested that there is no statistically significant difference in the proportion of patients achieving PASI 75 response at 16 weeks for apremilast versus 10 weeks for cyclosporin (see paragraph 6.11). Overall, the PBAC considered that the non-randomised persistence data was relevant supportive information, but that it was an insufficient basis to support the claim of superiority in comparative effectiveness or safety.

7.8 Given that the economic model used non-randomised persistence data as an unsubstantiated proxy for the comparative effectiveness and safety of apremilast and cyclosporin, the PBAC considered the model to be uninformative for decision making. In addition, the PBAC considered the ICER per QALY gained for apremilast was uncertain due to the following issues:

- Utilities were applied to treatment states, rather than health states defined by PASI and/or DLQI scores, which assumed that there was a constant treatment effect for all patients on apremilast regardless of symptom severity.
- The model results were sensitive to changes in utility values and the difference between the utility values for apremilast (0.84) and the biologics (0.80) lacked face validity.
- The costs for adverse events were not included in the model, and costs for physician visits (initiation of treatment) were omitted for apremilast.
- It was not possible to test the sensitivity of the model to the time horizon beyond 10 years.

Notwithstanding these issues, in its consideration of the results of the economic model using the effective prices of biologics (see paragraph 6.37), the PBAC considered that the ICER per QALY gained at the requested price for apremilast was unacceptably high.

7.9 The PBAC noted that the net cost of apremilast to government over the five years of listing was estimated to be more than \$100 million, with an estimated less than 10,000 new patients treated in year 5. The PBAC noted the substantial opportunity cost of listing apremilast for moderate to severe plaque psoriasis, particularly in the context of the uncertain treatment benefit over other systemic therapies. Furthermore, the PBAC agreed with the DUSC that the utilisation estimates were likely to be underestimated due to limitations with the METIS survey, and the assumptions used to estimate the population eligible to receive apremilast (see paragraph 6.42).

7.10 The PBAC considered that any major resubmission should ensure that presented data and economic analyses are associated with specific health outcomes compared to relevant comparator(s). A resubmission would likely require a significant price reduction in order to address uncertainties in the comparative clinical effectiveness.

7.11 The PBAC noted that the submission is eligible for an Independent Review.

Outcome:

Rejected

8 Context for Decision

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

9 Sponsor's Comment

Celgene would like to thank the Australian College of Dermatologists, the Queensland Institute of Dermatology, Psoriasis Australia and the numerous patients that provided comment for their support in helping the PBAC understand the need for subsidised access to apremilast.

Celgene is disappointed with the outcome given the acknowledged clinical place for apremilast as a treatment option for plaque psoriasis. Celgene will continue to work with the Department to exhaust all feasible options with the PBAC and Department to make apremilast available to Australian patients.