

7.01 APREMILAST, Pack containing 4 tablets of 10 mg, 4 tablets of 20 mg and 19 tablets of 30; Tablet 30 mg, Otezla®, Celgene Pty Ltd

1 Purpose of application

- 1.1 Authority required (streamlined) listing for apremilast for treatment of moderate to severe plaque psoriasis in adults. The first submission was March 2015 followed by resubmissions in November 2016 and March 2017 (minor resubmission).
- 1.2 A cost-minimisation analysis of apremilast versus cyclosporin was presented with the cost comparison based on an indirect network meta-analysis, and with the ex-manufacturer price of apremilast incorporating a premium over the price of cyclosporin to account for adverse events and monitoring costs associated with the latter.

Table 1: Key components of the clinical issue addressed by the resubmission

Component	Description
Population	Moderate to severe plaque psoriasis in adults
Intervention	Apremilast 30 mg twice daily. An initial dose titration over a period of 6 days. Treatment is orally administered and ongoing if a response continues to be achieved.
Comparator	Cyclosporin 3 mg/kg twice daily. Cyclosporin dose is corrected to 3 mg/kg orally daily (1.5 mg/kg/ twice daily) up to a maximum of 2 years of continuous treatment.
Outcomes	Proportion of patients achieving at least a 75% reduction in PASI (PASI-75) at 16 weeks. Adverse events associated with treatment.
Clinical claim	In moderate to severe plaque psoriasis, apremilast is as effective as cyclosporin at achieving PASI-75 and results in similar rates of adverse events with a superior safety profile.

Source: Table 1.2.1, p3 of the resubmission

PASI = psoriasis area and severity index; Italics = adjustments due to errors or additional information

2 Requested listing

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

Table 2: Requested restriction for apremilast – Initial titration phase

Name, Restriction, Manner of administration and form	Max. Qty (packs)	No. of Rpts	Dispensed Price for Max. Qty	Proprietary Name and Manufacturer
APREMILAST				
10 mg tablet (4 tablets) (&)				
20 mg tablet (4 tablets) (&)	1	0	\$ [REDACTED]	Otezla®, Celgene Pty Ltd
30 mg tablet (19 tablets)				

Name, Restriction, Manner of administration and form	Max. Qty (packs)	No. of Rpts	Dispensed Price for Max. Qty	Proprietary Name and Manufacturer
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			
Severity:	Moderate to severe			
Condition:	Plaque psoriasis			
PBS Indication:	Moderate to severe plaque psoriasis			
Treatment phase:	Initial treatment for dose titration			
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:	<ul style="list-style-type: none"> • Must be treated by a dermatologist or general physician with expertise in the management of plaque psoriasis. AND <ul style="list-style-type: none"> • Patient must have failed to achieve an adequate response to methotrexate unless contraindicated or not tolerated according to the Therapeutic Goods Administration (TGA) approved Product Information. 			
Administrative Advice:	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.			

Source: Tables 1.5.1, 1.5.2, p6-7 of the resubmission

Table 3: Requested restriction for apremilast – Standard phase

Name, Restriction, Manner of administration and form	Max. Qty	No. of Rpts	Dispersed Price for Max. Qty	Proprietary Name and Manufacturer
APREMILAST 30 mg tablet, 56	1	5	\$ [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			
Severity:	Moderate to severe			
Condition:	Plaque psoriasis			
PBS Indication:	Moderate to severe plaque psoriasis			
Treatment phase:	Continuing treatment			
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:	Patient must have previously received PBS-subsidised treatment with apremilast.			
Administrative Advice	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.			

Source: Tables 1.5.1, 1.5.3, p6-7 of the resubmission

- 2.1 It was noted that details of a special pricing arrangement were not provided in this resubmission. In the November 2016 resubmission, a Special Pricing Arrangement was suggested to be implemented such that the published list price was as per the March 2015 with a proposed effective price representing a [REDACTED] % discount to the March 2015 submission price. The current resubmission offered a proposed price with a ~ [REDACTED] % reduction on the original March 2015 submission.
- 2.2 The current resubmission when contrasted with the previous submissions indicated differences in the requested PBS restrictions as follows:
- The restriction level was changed to a "restricted benefit" compared to the previous submissions' "streamlined authority restriction" in March 2017, November 2016 and March 2015. In the Pre-Sub-Committee Response (PSCR) (p.1) the sponsor agreed that a streamlined restriction would be appropriate.
 - Treatment criteria were changed to include patients who had "not tolerated methotrexate according to the Therapeutics Goods Administration approved Product Information" compared to the previous submissions as follows:

- In March 2017, treatment criteria included "must be treated by a dermatologist,
- OR
- Must be treated by a general physician with expertise in the management of plaque psoriasis".
- AND
- Patient must have failed to achieve an adequate response or be contraindicated to treatment with methotrexate.
- In November 2016, treatment criteria were broad with the only requirement being "must be initiated by a dermatologist";
- In March 2015, the treatment criteria included "must be initiated by a dermatologist or rheumatologist;
 - Patient must have previously received and failed to achieve an adequate response to one or more systemic therapies, including methotrexate;
- OR
- Patient must be clinically inappropriate for treatment with one or more systemic therapies, including methotrexate.

2.3 The Australasian College of Dermatologists released an updated clinical management algorithm for psoriasis (March 2017) which does not include a category of moderate to severe psoriasis as is requested in the proposed restriction. The TGA approved indication is for moderate-severe plaque psoriasis. The PSCR (p.1) argued that the updated clinical management algorithm does not impact upon the proposed restriction or disease classification for apremilast eligible patients; stating that the most significant consideration when treating patients with systemic agents such as apremilast is a patient's disease activity measured by the Psoriasis Area and Severity Index (PASI). The ESC considered that disease severity should be classified according to a validated assessment tool such as a PASI score and suggested that this could be incorporated into the restriction criteria. The pre-PBAC Response (p.1) stated that the sponsor is willing to work with the Department to ensure consistency across the TGA indication for apremilast and other PBS listed treatments for psoriasis.

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

3 Background

Registration status

3.1 TGA status: Apremilast was TGA registered on 19 March 2015 for the following indications:

- The treatment of signs and symptoms of active psoriatic arthritis in adult patients
- The treatment of adult patients with moderate to severe plaque psoriasis who are candidates for phototherapy or systemic therapy

Previous PBAC consideration

3.2 This is the fourth submission to the PBAC seeking a recommendation for PBS listing of apremilast.

Table 4: Summary of outstanding matters of concern (November 2016 and March 2017)

Matters of concern Nov 2016	Matters of concern March 2017 (minor resubmission)	Current resubmission
"...the submission did not demonstrate that apremilast was associated with improvements in health outcomes relevant to psoriasis (compared with cyclosporin)." (paragraph 7.7)	Not addressed. (paragraph 7.6)	Non-inferior efficacy and safety between apremilast and cyclosporin was not adequately supported by the indirect network meta-analysis due to the uneven distribution of effect modifiers between the trials resulting in failure of the transitivity assumption.
"...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 [to cyclosporin]" (paragraph 7.7)	Not addressed. (paragraph 7.6)	All included studies in the indirect network meta-analysis were randomised controlled trials but structure had no closed loops, and showed a high risk of bias in the trials containing the common references.
Issues with economic model (paragraph 7.8)	Issues with the economic model not addressed. The requested effective price of apremilast was reduced but a revised ICER was not presented. (paragraph 6.11)	Economic model changed to a cost minimisation model but results are uncertain due to method of estimating cyclosporin costs, overestimation of monitoring costs for cyclosporin and the inclusion of an adverse events rate when the indirect network analysis did not show a difference in adverse event rate between apremilast and cyclosporin.
"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." (paragraph 7.9)	Reduction in requested effective price and proposed risk sharing arrangement with two-tiered financial cap. (paragraphs 6.20, 7.10)	Lowered DPMQ for titration and standard packs and suggested a financial based risk sharing arrangement (RSA). The sponsor proposed that under the RSA █% of any expenditure over estimated annual net cost to the PBS/RPBS would be reimbursed.
"...the utilisation estimates were likely to be underestimated due to limitations with the METIS ^a survey, and the assumptions used to estimate the population eligible to receive apremilast." (paragraph 7.9)	Revised utilisation estimates using a market share approach was not evaluated. A risk sharing arrangement with two-tiered financial cap was proposed. (paragraph 6.16)	Revised utilisation estimates using a mixed method with epidemiological and market share approaches resulting in conflicting estimates. Data from a dermatologists' survey with a low response rate was used to estimate the eligible population.

Source: Compiled during the evaluation; Paragraph references refer to the November 2016 and March 2017 apremilast Public Summary Documents

DPMQ = dispensed price for maximum quantity; ICER = incremental cost-effective ratio; PFP = Product Familiarisation Program; RCT = randomised controlled trial

^a METIS refers to METIS Healthcare Research, an Australian pharmaceutical market research company

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

4 Population and disease

4.1 Psoriasis is a chronic, systemic, immune-mediated, inflammatory skin condition with significant co-morbidities and a reduction in quality of life in sufferers. The plaque-

type of psoriasis represents the most common presentation of the disease, occurring in 80-90% of cases. Treatment of the condition is considered to be long-term.

- 4.2 Apremilast is proposed to be used in the same line of therapy as an alternative to cyclosporin, after treatment with methotrexate has failed to achieve an adequate response or is contraindicated or not tolerated. The previous and current resubmissions have indicated the target population as patients with moderate to severe psoriasis.
- 4.3 A new psoriasis treatment guideline that only includes two psoriasis severity classifications (mild to moderate or severe) was released in March 2017 by the Australasian College of Dermatologists. The moderate to severe classification of psoriasis that was proposed as the target population in the indication for the PBS listing will now overlap both of the new classifications. The ESC noted that the mild to moderate classification in the new guideline has a treatment recommendation for topical therapies only with the systemic treatments reserved for the severe classification of psoriasis. The ESC considered that this issue could be addressed by the use of a validated score to identify a population with moderate-severe psoriasis, such as a PASI >12, which could be included in the restriction criteria.
- 4.4 It was noted that the proposed treatment criteria and PBS indication in the current resubmission was broader than the TGA approved indication where the intended population for treatment is adult patients with moderate to severe plaque psoriasis. The proposed omission of adults in the PBS indication has broadened the target population to possibly include paediatric patients. The sponsor confirmed in its PSCR (p.1) that the target population is adults and agreed that the proposed restriction should be updated to reflect this.

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

5 Comparator

- 5.1 The resubmission nominated cyclosporin as the main comparator for moderate to severe psoriasis patients who have failed or are contraindicated or intolerant to methotrexate. The PBAC had previously accepted in the November 2016 resubmission (paragraph 7.5) that cyclosporin was the appropriate main comparator if apremilast was restricted to patients who have failed treatment with methotrexate. Further, for the minor resubmission in March 2017, "the proposed place in therapy for apremilast was as an additional treatment option in the same line as cyclosporin in patients who have failed to achieve an adequate response or are contraindicated to treatment with methotrexate".

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

6 Consideration of the evidence

Sponsor hearing

- 6.1 There was no hearing for this item.

Consumer comments

- 6.2 The PBAC noted and welcomed the input from individuals (72) and health care professionals (22) via the Consumer Comments facility on the PBS website. The comments described a range of benefits of treatment with apremilast including sustained efficacy and ability to continue treatment long term; limited side effects; and the availability of another treatment option for patients which may eliminate the need for, or extend the time until, treatment with biologic agents. In particular the comments highlighted the better safety profile of apremilast compared to alternative treatments, such as cyclosporin and the large impact apremilast treatment has had on quality of life for a number of patients.

Clinical trials

- 6.3 No direct RCTs comparing apremilast to cyclosporin were identified in the search strategy. This finding is consistent with all previous submissions. The resubmission provided an updated Section 2, different to previous submissions (Section B), by presenting indirect comparative evidence of the efficacy and safety of apremilast compared to cyclosporin. This was in line with previous feedback from the PBAC. The submission is based on five RCTs comparing apremilast to placebo, one RCT comparing methotrexate to placebo and one RCT comparing cyclosporin to methotrexate. The two later RCTs were not presented in previous submissions.
- 6.4 Details of the trials presented in the submission are provided in the table below.

Table 5: Trials and associated reports presented in the resubmission

Trial ID/Author	Protocol title/ Publication title	Publication citation
Randomised trials – Apremilast versus placebo		
Core	Celgene Clinical study report: CC-10004/ APREMILAST STUDY CC-10004-PSOR-005-E-LTE. A phase 2b, multicenter, randomized, 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-OOSE & PSOR-OOSLTE).	2012
Papp, K.	Papp, K., Cather, J. C., Rosoph, L., Sofen, H., Langley, R. G., Matheson, R. T., & Day, R. M. Efficacy of apremilast in the treatment of moderate to severe psoriasis: a randomised controlled trial.	2012 The Lancet, 380(9843), 738-746.
ESTEEM-1.	Celgene Clinical study report: APREMILAST (CC-10004) CC-10004-PSOR-008. 2013. A phase 3, multicenter, randomized, double-blind, placebo-controlled, efficacy and safety study of apremilast (CC-10004) in subjects with moderate to severe plaque psoriasis.	2015
Papp, K	Papp, K., Reich, K., Leonardi, C. L., Kircik, L., Chimenti, S., Langley, R. G. & Korman, N. J. Apremilast, an oral phosphodiesterase 4 (PDE4) 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	2015 Journal of the American Academy of Dermatology, 73(1), 37-49
ESTEEM-2.	Celgene Clinical study report: APREMILAST (CC-10004) CC-10004-PSOR-009. 2013. A phase 3, multicenter, randomized, double-blind, placebo-controlled, efficacy and safety study of apremilast (CC-10004) in subjects with moderate to severe plaque psoriasis.	2015
Paul, C.	Paul, C., Cather, J., Gooderham, M., Poulin, Y., Mrowietz, U., Ferrandiz, C. & Day, R. M. 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)	2015 British Journal of Dermatology, 173(6), 1387-1399.
PSOR-11.	Celgene Clinical study report: APREMILAST (CC-10004) CC-10004-PSOR-011A phase 2b, multicenter, randomized, double blind, placebo-controlled, efficacy and safety study of two doses of apremilast (CC-10004) in Japanese subjects with moderate-to-severe plaque-type psoriasis	2017
Ohtsuki, M	Ohtsuki, M., Okubo, Y., Komine, M., Imafuku, S., Day, R. M., Chen, P., & Nemoto, O. Apremilast, an oral phosphodiesterase 4 inhibitor, in the treatment of Japanese patients with moderate to severe plaque psoriasis: Efficacy, safety and tolerability results from a phase 2b randomized controlled trial.	2017 The Journal of Dermatology, 1-12.
Randomised trial – Cyclosporin versus methotrexate		
Heydendael, V.	Heydendael, V. M., Spuls, P. I., Opmeer, B. C., de Borgie, C. A., Reitsma, J. B., Goldschmidt, W. F., & de Rie, M. A. Methotrexate versus cyclosporine in moderate-to-severe chronic plaque psoriasis.	2003 New England Journal of Medicine, 349(7), 658-65.
Randomised trial – Methotrexate versus placebo		
Saurat, J.	Saurat, J. H., Stingl, G., Dubertret, L., Papp, K., Langley, R. G., Ortonne, J. P., & Camez, A. Efficacy and safety results from the randomized controlled comparative study of adalimumab vs. methotrexate vs. placebo in patients with psoriasis (CHAMPION).	2008 British Journal of Dermatology, 158(3), 558-566.
Randomised trial – Apremilast versus etanercept versus placebo		
LIBERATE. Gooderham, M.	Celgene Clinical study report: 10004-PSOR-010. A phase 3b, multicenter, randomized, 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.	2014

Source: Tables 2.4.1, 2.5.3, 2.5.5, 2.5.6, 2.5.7, pp11, 13, 14, 15 of the resubmission

Table 6: Additional trials and associated reports presented in the resubmission for the supplementary analysis

Trial ID/Author	Protocol title/ Publication title	Publication citation
Cyclosporin versus placebo		
Meffert, H.	Low-dose (1.25 mg/kg) cyclosporin A: treatment of psoriasis and investigation of the influence on lipid profile.	1997 Acta Dermatovenereologica-Stockholm, 77, 137-141.
Cyclosporin versus methotrexate		
Flystrom, I.	Flytström, I., Stenberg, B., Svensson, Å., & Bergbrant, I. M. Methotrexate vs. ciclosporin in psoriasis: effectiveness, quality of life and safety. A randomized controlled trial.	2008 British Journal of Dermatology, 158(1), 116-121.
Etanercept versus placebo		
Gottlieb, A.	Gottlieb, A. B., Matheson, R. T., Lowe, N., Krueger, G. G., Kang, S., Goffe, B. S., & Gordon, K. B. A randomized trial of etanercept as monotherapy for psoriasis.	2003 Archives of Dermatology, 139(12), 1627-1632.
Leonardi, C.	Leonardi, C. L., Powers, J. L., Matheson, R. T., Goffe, B. S., Zitnik, R., Wang, A. & Gottlieb, A. B. Etanercept as monotherapy in patients with psoriasis.	2003 New England Journal of Medicine, 349(21), 2014-2022.
Papp, K.	Papp, K. A., Tying, S., Lahfa, M., Prinz, J., Griffiths, C. E. M., Nakanishi, A. M. & Van De Kerkhof, P. C. M. A global phase III randomized controlled trial of etanercept in psoriasis: safety, efficacy, and effect of dose reduction.	2005 British Journal of Dermatology, 152(6), 1304-1312.
Van de Kerkhof, P.	Van de Kerkhof, P. C. M., Segaert, S., Lahfa, M., Luger, T. A., Karolyi, Z., Kaszuba, A. & Boussuge, M. P. Once weekly administration of etanercept 50 mg is efficacious and well tolerated in patients with moderate-to-severe plaque psoriasis: a randomized controlled trial with open-label extension.	2008 British Journal of Dermatology, 159(5), 1177-1185.

Source: Tables 2.4.1, 2.5.3, 2.5.5 to 2.5.7, pp11, 13-15 of the resubmission

6.5 The key features of the indirect randomised trials are summarised in the table below. These trials were included in an indirect network meta-analysis with placebo and methotrexate as the common references or linkage drugs. One key eligibility criterion for the RCTs was the PASI measurement which is a measure of the severity of psoriasis. The apremilast versus placebo trials had a baseline measurement of PASI ≥ 12 . However, the key common reference trials in the indirect network had lower eligibility criteria. In particular, the Heydendael (2003) trial RCT had an eligibility criterion of PASI ≥ 8 which was not consistent with the other included studies and indicated that patients with a less severe form of psoriasis were eligible for entry. Further, the Heydendael (2003) trial was an open label RCT and therefore the risk of bias is greater than with the other included trials.

Table 7: Key features of the included evidence – indirect comparison

Trial	N	Design/ duration of follow-up	Risk of bias	Patient population	Outcome
RCTs - Apremilast vs. placebo (common reference)					
CORE	Apremilast - 88	R, DB 16 weeks followed by 4 weeks follow-up	Low	Adults with PASI ≥ 12	Proportion of patients who achieved at least a PASI-75 at week 16 relative to the baseline measurement.
	Placebo - 88				
ESTEEM-1	Apremilast - 562	R, DB 16 week treatment followed by extension phases to 260 weeks	Low	Adults with PASI ≥ 12	
	Placebo - 282				
ESTEEM-2	Apremilast - 275	R, DB 16 week treatment followed by extension phases to 260 weeks	Low	Adults with PASI ≥ 12	
	Placebo - 138				
LIBERATE	Apremilast - 83	R, DB 16 week treatment followed by extension phases to 104 weeks	Low	Adults with PASI ≥ 12	
	Placebo - 84				
	Etanercept - 83				
PSOR-11. Ohtsuki 2017	Apremilast - 85	R, DB 16 weeks treatment followed by 4 week follow-up	Low	Japanese adults with PASI ≥ 12	
	Placebo - 84				
RCT - linking trials - Methotrexate vs placebo (common reference)					
Saurat 2008 ^a	Methotrexate – 110	R, DB 16 weeks of treatment with no further follow-up indicated	Low	Adults with PASI of ≥ 10.	
	Placebo - 53				
RCT - linking trials - Cyclosporin vs methotrexate (common reference)					
Heydendael 2003	Cyclosporin - 44	R, OL 16 weeks treatment with another 36 weeks follow-up	High	Adults with at least 8 on the PASI	Main outcome: difference in PASI score at week 16. Secondary outcome: proportion of patients who achieved a PASI-75.
	Methotrexate – 44				

Source: compiled during the evaluation

DB = double blind; OL = open label; PASI = psoriasis area and severity index; PASI-75 = 75% reduction in psoriasis area and severity index; R = randomised controlled trial

^a included an adalimumab arm

Comparative effectiveness

6.6 In the March 2015 submission, the result from the indirect comparison of apremilast versus cyclosporin was a relative risk ratio of 0.94 (95% CI: 0.22, 4.12) for the key outcome of PASI-75. The pooled result from the November 2016 resubmission for the meta-analysis of apremilast versus cyclosporin was a relative risk ratio of 0.81 (95% CI: 0.19, 3.52). The current results for the PASI-75 outcome measures at 16 weeks post induction for the whole trial population across the included studies are presented in the table below.

Table 8: Results of PASI-75 across the studies at 16 weeks

Trial ID	Proposed drug n/N (%)	Main comparator n/N (%)	Relative risk (95% CI) (apremilast/placebo)	Risk difference (95% CI) (apremilast - placebo)
Apremilast versus placebo				
	Apremilast	Placebo		
CORE	36/88 (40.1%)	5/88 (5.7%)	7.20 (2.96, 17.49)	0.35 (0.24, 0.47)
ESTEEM -1	186/562 (33.1%)	15/282 (5.3%)	6.22 (3.75, 10.32)	0.28 (0.23, 0.32)
ESTEEM-2	79/274 (28.8%)	8/137 (5.8%)	4.94 (2.46, 9.92)	0.23 (0.16, 0.30)
LIBERATE	33/83 (39.8%)	10/84 (11.9%)	3.34 (1.76, 6.33)	0.28 (0.15, 0.40)
PSOR-11 (Ohtsuki 2017)	24/85 (28.2%)	6/84 (7.1%)	3.95 (1.7, 9.18)	0.21 (0.1, 0.32)
Meta-analysis	Response rate 33%		4.99 (3.69, 6.73)	0.27 (0.23, 0.30)
Methotrexate versus Placebo				
	Methotrexate	Placebo		
Saurat 2008 ^a	39/110 (35.5%)	10/53 (18.9%)	1.88 (1.02, 3.47)	0.17 (0.03, 0.3)
Cyclosporin versus methotrexate				
	Cyclosporin	Methotrexate		
Heydendael 2003	30/42 (71.4%)	26/43 (67.4%)	1.18 (0.87, 1.61)	0.11 (-0.09, 0.31)

Source: Table 2.8.1 p36 of the resubmission and calculated during evaluation

CI = confidence interval; n = number of participants with event; N = total participants in group; PASI = psoriasis area and severity index;

Bold = statistically significant

^a Included an adalimumab arm

6.7 The response rate for PASI-75 across the trials for the common reference drugs was dissimilar for both placebo and methotrexate. Methotrexate response was considerably different in the two trials that included methotrexate: 35.5% of patients responded to methotrexate in Saurat (2008); whereas, 67.4% responded to methotrexate in Heydendael (2003). The differences between the trials included the eligibility criteria (Saurat [2008] enrolled adults with PASI ≥ 10 and Heydendael [2003] enrolled adults with PASI ≥ 8), study design (Saurat [2008] was double blind, Heydendael [2003] was open label) and in Saurat (2008), methotrexate treated patients were not titrated upwards after reaching PASI-50 (at 8 weeks) which may have had an impact on the numbers reaching PASI-75 (at week 16); this protocol was different to the other trials including Heydendael (2003). This varied treatment response provided evidence that the transitivity assumption may not hold for the indirect network meta-analysis.

6.8 The results from the indirect comparison for apremilast and cyclosporin arising from the network meta-analysis are presented in the table below.

Table 9: Summary of results of the indirect treatment comparison from the resubmission

	Outcome	Estimate	95% Confidence Interval	P-value	Test of Heterogeneity	I ²
Risk difference (%) (apremilast – cyclosporin)	PASI-75	-1.0%	-26.0%, 24.0%	0.939	Q(df=4) = 4.6, P = 0.333	12.8%
Risk ratio (%)	PASI-75	2.25	1.06, 4.75	0.034	Q(df=4) = 3.2, P = 0.526	0%

Source: Table 2.9.2, p40 of the resubmission

df = degrees of freedom; I² = measure of heterogeneity derived from Q; PASI-75 = 75% reduction in the psoriasis area and severity index;

Q = chi-square statistic from Cochran's Q test

- 6.9 For the PASI-75 outcome, the estimate for the risk difference is quite small and therefore this suggests that apremilast may be non-inferior to cyclosporin. However, the ESC noted that the lower and upper boundaries of the 95% confidence interval for the risk difference exceeded the non-inferiority margin of 20% for the PASI-75 outcome and considered that there is uncertainty whether non-inferiority has been met as the true value of the difference could lie beyond the 20% non-inferiority margin.
- 6.10 There is uncertainty in the clinical efficacy results as the indirect network meta-analysis was not reliable due to a number of issues:
- There was considerable clinical heterogeneity across the included trials (it was not possible to test consistency);
 - Heydendael (2003) was substantially different to the rest of the included trials and should have not have been included in the analysis (although the ESC noted that this would have meant that the network meta-analysis could not have been conducted); and
 - In Saurat (2008) the proportion of patients in the placebo arm who achieved an outcome of PASI-75 is higher compared to the remaining placebo trials suggesting a possible irregularity in the conduct of the trial; and
 - using a naïve indirect comparison suggests that apremilast (response rate; 33%) is inferior to cyclosporin (71%) (cyclosporin single arm from Heydendael (2003) and meta-analysis of the four apremilast trials (conducted during evaluation)). This comparison should be interpreted with caution
- 6.11 The PSCR (p.2) agreed that the inclusion of the Saurat (2008) and Heydendael (2003) trials may be sources of heterogeneity, but stated that this was not necessarily reflected in formal tests. The PSCR (p.2) also noted that the extent of heterogeneity/inconsistency depends on the comparative measure used and that using the odds ratio as the principal statistical measure demonstrates that apremilast “is not only non-inferior to cyclosporin but notably the ratio estimates are positive”. The sponsor maintained that despite potential exchangeability issues, the evidence presented in the submission demonstrates that apremilast is at least non-inferior to cyclosporin in terms of comparative efficacy.
- 6.12 The evaluation and ESC considered that there appears to be a fundamental flaw in the indirect network analysis caused by the inclusion of the Saurat (2008) and Heydendael (2003) trials. This resulted in the uneven distribution of effect modifiers between the trials indicating that the transitivity assumption may not hold. The evaluation and ESC considered this may make the network meta-analysis unsuitable for use for decision making.

Comparative harms

- 6.13 The resubmission presented additional safety evidence to previous submissions to include the indirect network meta-analysis above.
- 6.14 The adverse event results of the network meta-analysis of apremilast and cyclosporin at 16 weeks from the resubmission are presented in the table below.

Table 10: Network meta-analysis of apremilast and cyclosporin on adverse events at 16 weeks

	Outcome	Estimate	95% confidence interval	P-value	Test of heterogeneity	I ²
Risk difference (%) (apremilast – cyclosporin)	Adverse events	-6.4%	-29.1%, 16.3%	0.582	Q(df=4) = 1.6, P = 0.804	0%
	SAEs	1.1%	-5.1%, 7.3%	0.726	Q(df=4) = 3.5, P = 0.482	0%
Risk ratio (apremilast / cyclosporin)	Adverse events	0.95	0.70, 1.29	0.741	Q(df=4) = 1.3, P = 0.866	0%
	SAEs	2.05	0.02, 252.75	0.771	Q(df=4) = 2.8, P = 0.591	0%
Odds ratio (apremilast / cyclosporin)	Adverse events	0.59	0.16, 2.25	0.443	Q(df=4) = 2.2, P = 0.703	0%
	SAEs	2.07	0.02, 272.06	0.770	Q(df=4) = 2.8, P = 0.586	0%

Source: Table 2.9.2, p41 of the resubmission

df = degrees of freedom; I² = measure of heterogeneity derived from Q; Q = chi-square statistic from Cochran's Q test; SAE = serious adverse events

- 6.15 The risk of adverse events appears to be approximately equal between apremilast and cyclosporin. However, the risk of serious adverse events (SAE) appeared greater with apremilast treatment compared to cyclosporin. Further, the 95% confidence intervals are very large for the risk ratio and there is likely wide variability due to the low number of events occurring.
- 6.16 An updated PSUR (Periodic Safety Update Report – March 2017) was provided on potential safety concerns and confirmed that the benefit-risk balance of apremilast remains favourable for the approved conditions including psoriasis. The Pharmacovigilance Risk Assessment Committee (PRAC) had recommended the addition of suicidal ideation and behaviour as adverse drug reactions. Subsequently, these recommendations were implemented in the current Australian product information for apremilast in November 2016.
- 6.17 Cyclosporin has a well-established safety profile with very common adverse events including hypertension, hirsutism, impaired renal function, gingival hypertrophy, gastrointestinal disturbances, tremor and fatigue and hyperlipidaemia. Further, the Australian Medicines Handbook (2017) reports that long term continuous treatment with cyclosporin is not recommended beyond a period of two years in the treatment of psoriasis due to the risk of nephrotoxicity. In comparison, the product information for apremilast reported the most frequently reported adverse events as gastrointestinal related. However, assessment of renal function is recommended prior to initiation of apremilast.

Benefits and harms

- 6.18 In the resubmission, a claim of non-inferiority was made on the outcome of efficacy and the rate of adverse events. Therefore, a benefits/harms table has not been presented.

Interpretation of clinical evidence

- 6.19 The clinical claim presented in the current resubmission was that apremilast was non-inferior in terms of comparative effectiveness and non-inferior in terms of

comparative rates of adverse events but with a superior safety profile. This claim differed from all previous submissions as follows:

- non-inferiority in effectiveness and superiority in safety compared to cyclosporin in the March 2015 submission;
- superiority in both effectiveness and safety compared to cyclosporin in the November 2016 resubmission.

6.20 The PBAC agreed that there was remaining uncertainty regarding the claim of non-inferior effectiveness versus cyclosporin based on the clinical evidence provided and that the network meta-analysis. However, on balance, the PBAC considered that the claim of non-inferior comparative effectiveness was reasonable.

6.21 The PBAC considered that the claim of non-inferior comparative safety in terms of adverse events and a superior safety profile was reasonable, noting the well documented cumulative toxicity of cyclosporin and the limitation on its use in psoriasis to no more than two years.

Economic analysis

6.22 Previous submissions in March 2015, November 2016 and March 2017 were based on cost-utility models involving apremilast versus cyclosporin. The current resubmission presented a cost-minimisation analysis of apremilast versus cyclosporin.

6.23 The equi-effective doses were based on clinical data from the indirect network meta-analysis from the clinical evidence and the sources of the estimates were as follows:

- Apremilast dose was based on the dosing regimen (one week titration period followed by 60 mg/day for a total of 16 weeks) used in the clinical trials (apremilast versus placebo) included in the network analysis; and
- Cyclosporin dose was 3.2 mg/kg/day and based on the average dose/kg/day used in the Heydendael (2003) trial.

6.24 Based on the results of the analysis, the equi-effective doses for apremilast and cyclosporin were as follows:

- Apremilast 30 mg BID after an initial titration period over 6 days and cyclosporin 3.29 mg/kg/day are equi-effective over 16 weeks.

6.25 The submission appropriately estimated the cost of cyclosporin at the Approved Ex-Manufacturer Price (AEMP) per mg; however, as cyclosporin is available in four strengths (10mg, 25 mg, 50 mg and 100 mg) with different AEMP/mg prices, the submission calculated an unweighted average price per mg across the four strengths. The PBAC noted the Department's advice that the usual pricing methodology used in these situations is the "closest pack method", where the price of the PBS pack of cyclosporin that contains the number of mg closest to the amount needed to provide one month's treatment at the equi-effective dose is used. This is the 100 mg cyclosporin pack, with an AEMP of \$136.60 for 30 capsules or \$0.0455 per mg, as opposed to the \$0.049 used by the submission.

6.26 The resubmission presented cost offsets associated with different rates of hospitalisation and monitoring arising from increased management of potential toxicities with cyclosporin compared to apremilast.

- The submission stated the monitoring services estimates were based on assumptions taken from the PIs of apremilast and cyclosporin, these estimates are presented in Table 11;
- The adverse event rates were based on the naïve indirect comparison of Heydendael, (2003) compared to a meta-analysis of the apremilast trials rather than the network meta-analysis; and
- The service utilisation due to adverse events was based on a survey of dermatologists in the Otezla® Product Familiarisation Program.

Table 11: Submission’s estimates of differences monitoring costs associated with apremilast and cyclosporin

Item description	Cost per item	MBS item number	Cyclosporin		Apremilast	
			Pre-treatment	Week 1-16	Pre-treatment	Week 1-16
Specialist consultation (subsequent)	\$43.00	105	■	■	■	■
Full blood examination (FBE)	\$16.95	65070	■	■	■	■
Liver function tests, Lipid studies, Urea, Electrolytes, Creatinine (LFT, FATS, U&E)	\$17.70	66512	■	■	■	■
Urinalysis (microscopy)	\$12.50	69300	■	■	■	■
Serology – HIV	\$15.65	69384	■	■	■	■
Serology – hepatitis	\$15.65	69384	■	■	■	■
HCG (pregnancy)	\$39.75	66750	■	■	■	■
Tuberculosis	\$34.90	69471	■	■	■	■
Chest x-ray	\$35.35	58500	■	■	■	■
Total			■	■	■	■

Source: Table 3.4.1, p53 of the submission

HCG = human chorionic gonadotropin; HIV = human immunodeficiency virus; MBS = Medicare benefits schedule

6.27 The impact of these cost offsets as estimated by the submission is presented in Table 12 below.

Table 12: Submission’s estimate of comparative cost of treatment over 16 weeks

	Total cost of treatment	Adverse event costs	Monitoring costs	PBS costs (AEMP)
Cyclosporin	■	■	■	\$1,621*
Apremilast	■	■	■	■

Source: Table 3.5.2, p 56 of the resubmission and correction of error in the text; AEMP = approved ex-manufacturer price; PBS = Pharmaceutical Benefits Scheme; * uses price per mg of cyclosporin of \$0.049

6.28 The PBAC noted that if the treatment duration was extended to two years using the same inputs the impact of the cost offsets would be:

Table 13: Submission’s estimate of comparative cost of treatment extended over 2 year period

	Total cost of treatment	Adverse event costs	Monitoring costs	PBS costs (AEMP)
Cyclosporin	██████	██████	██████	\$10,537
Apremilast	██████	██	████	██████
	██	██████	██████	██████

6.29 The PBAC considered that the submission overestimated the cost minimised price for apremilast for the following reasons.

- The cost of cyclosporin treatment was overestimated by the submission, both through the use of the incorrect per mg price and through the assumption of an average weight of 92.2 kg for cyclosporin treated patients;
- The costs associated with monitoring were overestimated by the submission for cyclosporin and underestimated for apremilast. In particular medical consultations and the number of tests of renal function and LFTs were overestimated for cyclosporin; while apremilast costs should include one HCG test and one renal function test.
- The inclusion of differences in adverse event rate based on the outcomes of a naïve indirect comparison of heterogeneous trials in the network meta-analysis provided by the resubmission, which showed no difference, favoured apremilast;
- The survey of clinicians used to determine the severity and resource utilisation associated with adverse events in apremilast and cyclosporin was likely to have considerable selection bias given the source (apremilast experience program) and the response rate (29 of 129 dermatologists (22%));
- The submission calculated the cost-minimised price for apremilast over the initial treatment period of 16 weeks, whereas treatment will continue for longer. This over-estimates the costs of monitoring and treating adverse events for cyclosporine; and
- Adjusting the cost of managing adverse events to account for a longer treatment horizon is difficult. One of the issues is that the cost of adverse events is based on the proportion of patients with an event rather than the number of events. The sources for the data in terms of adverse events and how they will be treated are also not reliable.

6.30 The PBAC noted that in the PSCR (p.2) and the pre-PBAC response (p.2), the sponsor maintained that the monitoring costs included were appropriate and in line with the approved PI and clinical guidelines of the 2017 Australian Medical Handbook (AMH). However the PBAC noted that the AMH 2017 recommendations for monitoring of patients receiving cyclosporin for psoriasis are to “measure creatinine concentration every 2 weeks for the first 3 months, then every 2 months (or each month if the dose > 2.5 mg/kg/day” (AMH2017, pp 378). The more extensive and frequent monitoring included in the sponsor’s analysis is recommended for cyclosporin when it is used at

higher doses for conditions including prevention of transplant rejection (AMH 2017, pp 664).

- 6.31 In the PSCR (p.3) and pre-PBAC response (p.2) the sponsor argued that the calculation of the cost minimisation over 2 years as proposed by the commentary and the ESC is redundant as the comparative efficacy and safety of apremilast and cyclosporin has not been established over this period. The sponsor further noted that data previously presented to the PBAC, supporting a 1 and 2 year comparison of treatment costs (persistence date based on real world evidence), was rejected by the PBAC. However, the PBAC noted that the submission’s approach to cost-minimising the two treatments over a period of 16 weeks had a large impact on the cost-minimisation outcome, as this approach implausibly assumes all additional costs associated with cyclosporin compared to apremilast over the first 16 week period, will continue to accrue at the same rate over longer treatment periods.
- 6.32 On the request of the Minister (delegate) under section 101(3) of the *National Health Act 1953* (Act), the PBAC considered the price or range of prices at which it considered treatment with apremilast would be acceptably cost-effective for the purposes of the Act.
- 6.33 The PBAC noted that it will be difficult to address all the areas of uncertainty with the cost-minimised calculation. However, the Committee considered the following approach to be appropriate.

Step 1: correct price per mg of cyclosporin to \$0.0455 mg (NB weight assumption unchanged)

Table 14: Submission’s estimate of comparative costs of treatment over 16 weeks with corrected price of cyclosporin

	Total cost of treatment	Adverse event costs	Monitoring costs	PBS costs (AEMP)
Cyclosporin	████	████	████	\$1,547
Apremilast	████	█	█	████

Step 2: Monitoring and adverse event costs adjusted to assume:

- █████ extra specialist visits over 2 years are assumed for cyclosporin treated patients compared with apremilast treated patients;
- █████ extra creatinine tests are conducted over 2 years for cyclosporin treated patients (█ pre-treatment, then █████ every █ weeks for █████ months, then █████ every █████ months for █ months; apremilast patients receive █████ creatinine test pre-treatment and █████ per █████ for 2 years; and █████ renal function test pre-treatment);
- the same proportions of apremilast and cyclosporin patients are assumed to require pregnancy testing;
- no differences in other routine monitoring costs; and
- the submission’s estimate of adverse event costs over a 16 week period applies over a 2 year period without adjustment, or these costs are doubled.

The adjusted monitoring costs are detailed in Table 15.

Table 15: PBAC estimated differences in monitoring costs associated with apremilast and cyclosporin

Item description	Cost per item	MBS item number	Cyclosporin		Apremilast	
			Pre-treatment	Week 1-104	Pre-treatment	Week 1-104
Specialist consultation (subsequent)	\$43.00	105	■	■	■	■
Full blood examination (FBE)	\$16.95	65070	■	■	■	■
Liver function tests, Lipid studies, Urea, Electrolytes, Creatinine (LFT, FATS, U&E)	\$17.70	66512	■	■	■	■
Urinalysis (microscopy)	\$12.50	69300	■	■	■	■
Serology – HIV	\$15.65	69384	■	■	■	■
Serology – hepatitis	\$15.65	69384	■	■	■	■
HCG (pregnancy)	\$39.75	66750	■	■	■	■
Tuberculosis	\$34.90	69471	■	■	■	■
Chest x-ray	\$35.35	58500	■	■	■	■
Total			■	■	■	■

HCG = human chorionic gonadotropin; HIV = human immunodeficiency virus; MBS = Medicare benefits schedule

6.34 The PBAC noted the minimum and maximum apremilast prices that result from these adjustments, as recorded in Tables 16 and 17.

Table 16: Cost minimised price of apremilast over 2 years (minimum)

	Total cost of treatment per 104 weeks	Adverse event costs	Monitoring costs	PBS costs (AEMP)	Premium
Cyclosporin	■	■	■	\$9,834.50	
Apremilast	■	■	■	■	■%
Difference	■	■	■	■	

Table 17: Cost minimised price of apremilast over 2 years (maximum)

	Total cost of treatment per 104 weeks	Adverse event costs	Monitoring costs	PBS costs (AEMP)	Premium
Cyclosporin	■	■	■	\$9,834.50	
Apremilast	■	■	■	■	■%
Difference	■	■	■	■	

6.35 On balance the PBAC considered that, with a premium in this range, apremilast would be likely be acceptably cost-effective for the purposes of the *National Health Act 1953*.

Drug cost/patient/year: \$ ■ (submission)

6.36 Psoriasis is considered a chronic condition and either apremilast or cyclosporin would be given as ongoing treatment if the patient is responsive. However,

cyclosporin should only be given for a maximum of two years continuous treatment of psoriasis due to the risk of nephrotoxicity. Apremilast has no restriction on duration of use.

- 6.37 The drug cost of apremilast was calculated by the submission to be \$ [REDACTED] per patient per year, based on a DPMQ of \$ [REDACTED] for the titration pack and \$ [REDACTED] for the standard pack, assuming 12.5 prescriptions per year for the standard pack and one titration pack (lasting 2 weeks) at the commencement of drug treatment. The total cost of cyclosporin treatment was estimated to be \$4,975 based on an average DPMQ of \$551.38 (used in the resubmission) for the 100 mg strength formulations, assuming continuous treatment for one year with an estimated daily dose of [REDACTED] mg/day (based on a weighted average of a 92.29 kg patient in the apremilast trials) and nine prescriptions per year.

Estimated PBS usage & financial implications

- 6.38 This resubmission was considered by DUSC.
- 6.39 The resubmission used an mixed epidemiological and market share approach for estimating the utilisation and financial implications associated with the requested PBS listing of apremilast for the treatment of moderate to severe psoriasis. The main difference to the previous submission was the use of a dermatologists' survey to estimate the eligible population, displacement and uptake of apremilast.

Table 18: Estimated use and financial implications of apremilast listing on the PBS/RPBS

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
Estimated extent of use						
Number of patients Treated	████	████	████	████	████	████
Number of scripts dispensed ^a	████	████	████	████	████	████
Estimated financial implications of apremilast						
Cost to PBS/RPBS ^a	\$████	\$████	\$████	\$████	\$████	\$████
Co-payments ^a	-\$████	-\$████	-\$████	-\$████	-\$████	-\$████
Cost to PBS/RPBS less co-payments ^a (rounded)	\$████	\$████	\$████	\$████	\$████	\$████
Estimated financial implications for other medicines						
Cost to PBS/RPBS ^b	\$████	\$████	\$████	\$████	\$████	\$████
Co-payments ^b	-\$████	-\$████	-\$████	-\$████	-\$████	-\$████
Cost to PBS/RPBS ^b less co-payments (rounded)	\$████	\$████	\$████	\$████	\$████	\$████
Net financial implications						
Net cost to PBS/RPBS (rounded) for listing of apremilast on PBS	\$████	\$████	\$████	\$████	\$████	\$████
Net cost to MBS	-\$████	-\$████	-\$████	-\$████	-\$████	-\$████
Net cost (rounded) to health budget	\$████	\$████	\$████	\$████	\$████	\$████

Source: Table 4.3.1 of the resubmission/Excel workbook and *calculated during the evaluation*

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

^a = includes titration and standard packs of apremilast; ^b = for cyclosporin, acitretin, ustekinumab and secukinumab

The redacted table shows that at year 5, the estimated number of patients was less than 10,000 per year and the net cost to the PBS would be \$30 – \$60 million per year.

6.40 The cost of listing apremilast on the PBS/RPBS was estimated by the submission to be approximately less than \$10 million per year in Year 1, \$30 – \$60 million per year in Year 6 and to total more than \$100 million over the first six years.

6.41 The DUSC considered that the actual cost of apremilast to the PBS/RPBS could potentially vary from the estimates provided in the resubmission as:

- the proposed restriction does not clearly define the eligible patient population and is open to clinical interpretation.
- the size of the eligible population is uncertain and likely to be underestimated. Derivation of the eligible treated population relies heavily on a survey of dermatologists which may have a high risk of bias and not be representative of all dermatologists. The pre-PBAC response contends that as the results were derived from 37 clinicians whom together see ~18,500 patients per month that these are accurate averages for a diverse range of clinicians.
- the proportion of eligible prevalent patients treated by a dermatologist is underestimated. Further, a possible increase in the proportion of moderate

to severe plaque psoriasis patients seeing a dermatologist once apremilast is available has not been accounted for.

- the uptake rate of apremilast is underestimated. The submission estimated an uptake of █% in Year 1 increasing to █% in Year 6. The pre-PBAC response reiterates that the estimated numbers of patients treated with apremilast is comparable to overseas markets where apremilast has been available for several years.
- the methods and calculations used to quantify the cost of medicines displaced by apremilast were unclear and cannot be relied on to determine the net financial impact to the PBS arising from the listing of apremilast.

6.42 The pre-PBAC response (p.3) presented a sensitivity analyses to address the DUSC concerns outlined above. The results are presented in the table below.

Table 19: Estimated use and financial implications of apremilast listing on the PBS/RPBS

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
	(2018)	(2019)	(2020)	(2021)	(2022)	(2023)
Base case (November 2017 submission)						
Apremilast uptake	█	█	█	█	█	█
Cost to PBS (\$)	█	█	█	█	█	█
Cost to RPBS (\$)	█	█	█	█	█	█
Net cost to PBS/RPBS (\$)	█	█	█	█	█	█
Sensitivity analysis 3: DUSC assumptions						
Apremilast uptake	█	█	█	█	█	█
Cost to PBS (\$)	█	█	█	█	█	█
Cost to RPBS (\$)	█	█	█	█	█	█
Net cost to PBS/RPBS (\$)	█	█	█	█	█	█

The redacted table shows that at year 6, the estimated net cost to the PBS for the base case (July 2017 submission) would be \$30 – \$60 million per year. The estimated net cost to the PBS for the sensitivity analysis (DUSC assumptions) would be \$60 – \$100 million per year.

Quality use of medicines

6.43 No issues regarding the quality use of medicines were identified in the resubmission. A post-marketing surveillance study had not been proposed.

Financial management – risk sharing arrangements

6.44 In the resubmission, a financial-based risk sharing arrangement (RSA) was proposed to address the uncertainty surrounding the expected usage and overall financial impact of the proposed PBS listing of apremilast. The submission proposed that █% of any expenditure over the estimated annual net cost to the PBS/RPBS would be reimbursed.

6.45 Based on the uncertainty regarding the utilisation estimates, the PBAC recommended that a tiered RSA based on the patient numbers estimated by the submission be put in place if apremilast is listed on the PBS. The PBAC considered that this RSA should have three tiers as outlined below:

- Tier 1 – for expenditure relating to patient numbers up to those estimated in the submission, the appropriate cost-effective price for apremilast should apply.
- Tier 2 – for expenditure relating to patient numbers above those estimated by the submission and up to those estimated using the DUSC assumptions and the sponsor’s projected uptake rate, the cyclosporin price should apply.
- Tier 3 – a hard cap should apply, with ■■■% of Commonwealth expenditure above the annual caps reimbursed, for expenditure resulting from patient numbers in excess of those in sensitivity analysis 3 presented in the pre-PBAC Response based on DUSC assumptions and the sponsor’s projected uptake rate.

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

7 PBAC Outcome

- 7.1 The PBAC deferred making a recommendation on whether apremilast should be listed on the PBS for the treatment of moderate to severe plaque psoriasis in adults to allow further work to establish a price that could be considered cost effective.
- 7.2 In making this decision, the PBAC considered that the monitoring and adverse event cost offsets presented in the submission, which gave apremilast a significant price advantage over cyclosporin, were considerably overestimated. Further, the committee considered there was significant uncertainty in the utilisation estimates presented. Overall, the PBAC considered that apremilast was not cost-effective at the proposed price.
- 7.3 The PBAC recalled that that it had rejected apremilast for moderate to severe plaque psoriasis in its previous considerations in March 2017 and November 2016 on the basis that the evidence presented was insufficient to support a claim of superior comparative efficacy or safety versus cyclosporin. The PBAC noted that the current resubmission more appropriately presented a cost-minimisation approach, with offsets for additional monitoring and adverse event costs associated with cyclosporin.
- 7.4 The PBAC noted the input received from individuals and health professionals and acknowledged that there was a consumer need for an alternative therapy for psoriasis. In particular, the committee noted that apremilast would likely provide patients with a safer, longer term treatment option compared to cyclosporin, which has limitations of its therapeutic use in psoriasis to no more than two years.
- 7.5 The PBAC noted the comparator and clinical place of therapy were unchanged from the previous submission. The PBAC recalled it previously accepted cyclosporin as the appropriate comparator if apremilast was restricted to patients who have failed treatment with methotrexate. The committee also noted it previously accepted the proposed place in therapy as an additional treatment option in the same line as cyclosporin in patients who have failed to achieve an adequate response or are contraindicated to treatment with methotrexate.
- 7.6 The PBAC agreed with its ESC that the claim of non-inferior efficacy was not well

supported by the evidence presented in the submission, in particular noting the clinical heterogeneity of the trials included in the NMA. However, on balance, the PBAC considered that the claim of non-inferior comparative effectiveness is likely to be reasonable.

- 7.7 The PBAC considered that the claim of non-inferior comparative safety in terms of adverse events was reasonable. The PBAC considered that the superiority claim for safety profile was not well supported by the clinical evidence provided. However, noting the well documented cumulative toxicity of cyclosporin and the limitations of its therapeutic use in psoriasis to no more than two years, the PBAC considered that the safety profile of apremilast was likely to be superior to cyclosporin.
- 7.8 The PBAC agreed with ESC that the cost-offsets associated with monitoring and adverse events in the resubmission were overestimated, noting that while the resubmission presented a cost-minimisation analysis, the application of the cost offsets provided apremilast with a substantial price premium over cyclosporin. The committee also noted the sponsor's argument in both the PSCR and pre-PBAC Response that the offsets applied in the submission align with recommended clinical practice. The PBAC considered that the cost offsets for monitoring and adverse events likely lie between the figures provided in the resubmission and those presented in the sensitivity analysis conducted during the evaluation, but are overall closer to those provided in the sensitivity analysis.
- 7.9 Based on the uncertainty in the clinical data provided regarding non-inferior efficacy, but taking into account the reduced toxicity of apremilast compared to cyclosporin and the requirement for less monitoring, the PBAC considered that with a price premium of ■-■% over cyclosporin, apremilast would be likely to be acceptably cost-effective for the purposes of the *National Health Act 1953*.
- 7.10 The PBAC considered that there was significant uncertainty in the utilisation estimates presented in the submission, noting that they are likely to be underestimated. The PBAC considered that this uncertainty could be addressed through the implementation of a tiered RSA based on patient numbers (see Section 6).
- 7.11 The PBAC considered that if apremilast were to be listed on the PBS, the indication should be changed from 'moderate to severe plaque psoriasis' to 'severe plaque psoriasis' so that it is aligned with current restrictions for existing plaque psoriasis treatments on the PBS. In addition the PBAC considered that the restriction should specify the treatment population as adults.
- 7.12 The PBAC noted that this submission is not eligible for an Independent Review as it has been deferred.

Outcome:

Deferred

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 will continue to work with the Department and the PBAC to make apremilast available to Australian patients.