

**7.09 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 patients with moderate-to-severe plaque psoriasis who have failed to achieve an adequate response or are contraindicated to treatment with methotrexate.

2 Requested listing

2.1 The submission requested the following new listing (with additions to the requested listing compared with the previous submission in italics):

Name, Restriction, Manner of administration and form	Max. Qty	No. of Rpts	Dispensed Price for Max. Qty	Proprietary Manufacturer	Name and
APREMILAST Tablets, titration pack (10 mg x 4, 20 mg x 4, 30 mg x 19)	1	0	\$ [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:	-
Severity:	Moderate to severe
Condition:	plaque psoriasis
PBS Indication:	Moderate to severe plaque psoriasis
Treatment phase:	Initial 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:	Must be treated by a dermatologist, OR Must be treated by a general physician with expertise in the management of plaque psoriasis.
Clinical criteria:	<i>Patient must have failed to achieve an adequate response or be contraindicated to treatment with methotrexate</i>

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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.
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Name, Restriction, Manner of administration and form	Max. Qty	No. of Rpts	Dispensed Price for Max. Qty	Proprietary Name and Manufacturer
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APREMILAST Tablets, 30mg	56	5	\$ [REDACTED] \$ [REDACTED]	Otezla® Celgene Pty Ltd
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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:	-
Severity:	Moderate to severe
Condition:	plaque psoriasis
PBS Indication:	Moderate to severe plaque psoriasis
Treatment phase:	<i>Continuing treatment</i>
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 Must be treated by a general physician with expertise in the management of plaque psoriasis.
Clinical criteria:	<i>Patient must have previously received PBS-subsidised treatment with apremilast</i>
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.

- 2.2 The change to the requested restriction in the minor resubmission is an additional requirement that patients must have failed to achieve an adequate response or be contraindicated to treatment with methotrexate. In its pre-PBAC response (p3), the sponsor requested the inclusion of a grandfathering restriction to allow Patient Familiarisation Program patients PBS subsidised access to the continuing treatment pack.

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

3 Background

- 3.1 Apremilast was TGA registered on 19 March 2015 for the 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 and November 2016 meetings. A summary of the comparison of the March 2015 submission, November 2016 resubmission and the current resubmission is outlined in Table 1.

Table 1: Summary of the previous submissions and current resubmission

	March 2015 submission	November 2016 resubmission	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. PBAC Comment: (paragraph 7.2) 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.	Moderate-to-severe plaque psoriasis in patients who have failed to achieve an adequate response or are contraindicated to treatment with methotrexate.
Requested effective DPMQs	<ul style="list-style-type: none"> • Apremilast 10mg x 4, 20mg x 4, 30mg x 19: \$ [REDACTED] • Apremilast 30 mg x 56: \$ [REDACTED] 	<ul style="list-style-type: none"> • Apremilast 10mg x 4, 20mg x 4, 30mg x 19: \$ [REDACTED] • Apremilast 30 mg x 56: \$ [REDACTED] 	<ul style="list-style-type: none"> • Apremilast (10mg x 4, 20mg x 4, 30mg x 19): \$ [REDACTED] • Apremilast 30 mg x 56: \$ [REDACTED]
Comparator	<ul style="list-style-type: none"> • Cyclosporin PBAC Comment: (paragraph 7.3) The PBAC accepted this, but noted that acitretin would also be a relevant comparator.	<ul style="list-style-type: none"> • Cyclosporin PBAC Comment: (paragraph 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 PBAC accepted cyclosporin as the main comparator if apremilast was restricted to patients who have failed treatment with methotrexate.	<ul style="list-style-type: none"> • Not stated, but assumed to be unchanged.
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 dose of cyclosporin 2.5mg/kg/day for 10 weeks in the Meffert (1997) trial was not the recommended dose regimen.	<ul style="list-style-type: none"> • Randomised evidence: Apremilast versus placebo: 3 trials, plus 1 inappropriately excluded trial. • Non-randomised evidence: Apremilast versus cyclosporin: 1 pivotal study. • Apremilast single arm: 3 supportive studies 	No additional clinical evidence presented.


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	March 2015 submission	November 2016 resubmission	Current resubmission								
Key effectiveness data	<p>PASI 75 response at 16 weeks for apremilast</p> <p>PASI 75 response at 10 weeks for cyclosporin (Meffert 1997)</p> <p>Indirect comparison of apremilast versus cyclosporin: RR=0.94 (95% CI: 0.22, 4.12)</p> <p>PBAC comment: (paragraph 7.4) PASI 50 response at 16 weeks favoured cyclosporin and the cyclosporin dosing in the Meffert 1997 trial may have been suboptimal.</p>	<p>PASI 75 response at 16 weeks for apremilast</p> <p>Pooled RR of apremilast versus placebo = 5.16 (95% CI: 3.74, 7.12)</p> <p><u>Non-randomised studies</u></p> <p>Persistence rates at 1 month; 4 months:</p> <table border="1"> <tbody> <tr> <td>US</td> <td> <p>Apremilast: █%; █%,</p> <p>Cyclosporin: █%; █%</p> </td> </tr> <tr> <td>Australian</td> <td> <p>Apremilast: █%; █% (C1 cohort)</p> <p>█%; █% (C2 cohort)</p> <p>█%; █% (C3 cohort)</p> </td> </tr> <tr> <td>German</td> <td> <p>Apremilast: █%; █%</p> </td> </tr> <tr> <td>Canadian</td> <td> <p>Apremilast: █%; █%</p> </td> </tr> </tbody> </table>	US	<p>Apremilast: █%; █%,</p> <p>Cyclosporin: █%; █%</p>	Australian	<p>Apremilast: █%; █% (C1 cohort)</p> <p>█%; █% (C2 cohort)</p> <p>█%; █% (C3 cohort)</p>	German	<p>Apremilast: █%; █%</p>	Canadian	<p>Apremilast: █%; █%</p>	<p>No additional clinical evidence presented.</p>
US	<p>Apremilast: █%; █%,</p> <p>Cyclosporin: █%; █%</p>										
Australian	<p>Apremilast: █%; █% (C1 cohort)</p> <p>█%; █% (C2 cohort)</p> <p>█%; █% (C3 cohort)</p>										
German	<p>Apremilast: █%; █%</p>										
Canadian	<p>Apremilast: █%; █%</p>										

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	March 2015 submission	November 2016 resubmission	Current resubmission
Clinical claim	<p>Apremilast is non-inferior in terms of comparative effectiveness and superior in terms of safety over cyclosporin.</p> <p>PBAC Comment: (paragraphs 7.4, 7.5) In the absence of a formal indirect comparison between apremilast and cyclosporin in terms of comparative harms and the absence of long-term comparative safety data for apremilast, the PBAC did not consider the submission's claim of superior safety to have been adequately supported. Non-inferiority in terms of comparative effectiveness was not established.</p>	<p>Apremilast is superior in terms of comparative effectiveness and superior in terms of comparative safety over cyclosporin, based on the real-world comparative claims data from the US.</p> <p>PBAC Comment: (paragraph 7.7) non-randomised persistence data was relevant supportive information, but it was an insufficient basis to support the claim of superiority in comparative effectiveness or safety.</p>	Not addressed.
Economic evaluation	<p>Assumption that apremilast will <u>extend the period of time patients would be treated with systemic therapies</u> for psoriasis, but this was deemed to be uninformative.</p>	<p>Cost-utility model of apremilast versus cyclosporin with cost/QALY \$15,000 - \$45,000. Based on persistence rates from the <u>non-randomised</u> US comparative data.</p> <p>PBAC Comment: (paragraph 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 was uncertain and unacceptably high when the effective prices of the biologics were used in the model.</p>	Not addressed.
Number of patients	<p>Expansion of the treatment sequence for plaque psoriasis: less than 10,000 in Year 1, increasing to less than 10,000 in Year 5.</p>	<p>Combined epidemiological and market share approach: less than 10,000 in Year 1, decreasing to less than 10,000 in Year 5.</p>	<p>Market share approach: less than 10,000 in Year 1, increasing to 10,000 – 50,000 in Year 5.</p>

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	March 2015 submission	November 2016 resubmission	Current resubmission
Estimated net cost to PBS	Less than \$10 million in Year 1 increasing to \$30 - \$60 million in Year 5 for a total of more than \$100 million over the first 5 years of listing.	\$30 - \$60 million in Year 1 increasing to more than \$100 million in Year 5 for a total of more than \$100 million over the first 5 years of listing. PBAC Comment: (paragraph 7.9) 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.	\$10 - \$20 million in Year 1 increasing to \$60 - \$100 million in Year 5 for a total of more than \$100 million over the first 5 years of listing.
Risk sharing arrangement	Not proposed.	The resubmission did not propose an 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.	 Estimated net cost to PBS with caps over the first 5 years of listing: more than \$100 million.

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	March 2015 submission	November 2016 resubmission	Current resubmission
PBAC decision	Reject. PBAC Comment: (paragraph 7.1) The PBAC rejected the submission on the basis that cost-effectiveness compared to cyclosporin treatment had not been adequately established at the price proposed in the submission.	Reject PBAC Comment: (paragraph 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.	-

Source: Compiled during the evaluation. Paragraph references for March 2015 refer to the apremilast (plaque psoriasis) public summary document. Paragraph references for November 2016 refer to the apremilast public summary document.

Table 2: PBAC matters of concern in previous consideration (November 2016)

Matters of concern	How the resubmission addresses it
"...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
"...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
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 for apremilast was uncertain due to the following issues: <ul style="list-style-type: none"> • 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 at the requested price for apremilast was unacceptably high." (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.
"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.
"...the utilisation estimates were likely to be underestimated due to	Revised utilisation estimates using a

limitations with the METIS survey, and the assumptions used to estimate the population eligible to receive apremilast.” (paragraph 7.9)	market share approach and proposed risk sharing arrangement with two tiered financial cap.
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Source: Compiled during the evaluation. Paragraph references refer to the November 2016 apremilast public summary document.

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

4 Clinical place for the proposed therapy

- 4.1 The resubmission proposed that apremilast be an alternative to cyclosporin for patients who failed to achieve an adequate response or are contraindicated to treatment with methotrexate. This differed to the previous resubmission which proposed that apremilast be an additional treatment option in the same line of therapy as cyclosporin, methotrexate and acitretin.
- 4.2 The previous 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. The minor resubmission did not indicate a change to this proposal.

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

5 Comparator

- 5.1 The previous resubmission nominated cyclosporin as the main comparator. The PBAC accepted cyclosporin as the main comparator if apremilast was restricted to patients who have failed treatment with methotrexate. The minor resubmission did not change the main comparator.

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 as it was a minor submission.

Consumer comments

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

Clinical trials

- 6.3 No new clinical trials were presented in the minor resubmission. The November 2016 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). The November 2016 resubmission also presented three head-to-head trials comparing apremilast to placebo (ESTEEM-1, ESTEEM-2, LIBERATE; n=1,424).
- 6.4 The minor resubmission sought to address the PBAC's previous concerns with a change to the requested restriction, a reduction in the published and effective prices of apremilast and a two-tiered financial risk sharing arrangement (RSA).

Clinical claim

- 6.5 The March 2015 major submission described apremilast as having non-inferior effectiveness and superior safety compared with cyclosporin. The PBAC previously considered that neither of these claims had been adequately supported (paragraph 7.4-7.5, March 2015 Public Summary Document).
- 6.6 The November 2016 major resubmission revised the clinical claim to describe apremilast as superior to cyclosporin in terms of comparative effectiveness and safety. 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. 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 (paragraph 7.7, November 2016 Public Summary Document).
- 6.7 The minor resubmission did not address the PBAC's previous concerns with the clinical claim of superiority in effectiveness and safety compared with cyclosporin. The sponsor argued in its pre-PBAC response that the non-randomised persistence data for apremilast and cyclosporin should be considered as primary evidence in the absence of more robust clinical trials comparing apremilast and cyclosporin.
- 6.8 The sponsor further stated in its pre-PBAC response that the intent of this minor resubmission was not to directly address clinical concerns raised by the PBAC in its consideration of the November 2016 major resubmission, but to reduce the uncertainty to a level of cost-effectiveness that will enable the PBAC to make a positive recommendation.
- 6.9 The PBAC considered that the claim of superior comparative effectiveness and safety remained inadequately supported by the data.

Economic analysis

6.10 The November 2016 major resubmission presented a cost-effectiveness analysis against cyclosporin. The PBAC considered that the economic model was uninformative for decision making given that it used non-randomised persistence data as an unsubstantiated proxy for the comparative effectiveness and safety of apremilast and cyclosporin. In addition, the PBAC considered the incremental cost effectiveness ratio (ICER) 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 (██████) 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, the PBAC considered that the ICER at the requested price for apremilast was unacceptably high (November 2016 Public Summary Document, paragraph 7.8).

6.11 The minor resubmission did not address the issues raised by the PBAC with regards to the economic model and did not present a revised ICER using the reduced effective price.

6.12 In its pre-PBAC response (p3), the sponsor provided a revised indicative ICER of \$15,000 - \$45,000 per QALY which assumed a 40% rebate for all biological DMARDs listed for plaque psoriasis and the net price of apremilast under the proposed RSA. This ICER was not verified prior to PBAC consideration.

Drug cost/patient/year: \$██████

6.13 The drug cost per patient per year was calculated at \$██████ assuming one titration script (lasting for 2 weeks) at an effective DPMQ of \$██████ and 12.5 maintenance scripts per year (lasting for 50 weeks) at an effective DPMQ of \$██████.

6.14 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 November 2016 major resubmission (and revised in the evaluation) was \$██████ per patient per year assuming the varying dosage (mg per day) from the US MarketScan® databases and \$4,993.49 assuming a cyclosporin fixed daily dose of 250 mg per day.

Estimated PBS usage & financial implications

6.15 The minor resubmission revised the previous utilisation estimates using a market based approach to reflect the proposed post-methotrexate PBS listing. By

comparison, the November 2016 major resubmission used a combined epidemiological and market share approach. The revised approach was not evaluated as this was a minor submission.

- 6.16 The minor resubmission estimated the number of patients eligible for apremilast by estimating the number of patients initiating and prevalent to methotrexate using NostraData. The Secretariat checked this estimate by counting patients initiating and prevalent to methotrexate in the full PBS prescription dataset. This showed that the submission had overestimated methotrexate initiators by approximately 35% and underestimated prevalent patients by approximately 34%. If the PBS dataset methotrexate patient counts were used in the submission's utilisation spreadsheet (i.e. keeping all other submission assumptions) then the number of patients in Year 1 increased by 16% (due to the higher number of prevalent patients) and decreased by 22% in Year 5 (due to the lower number of initiating patients). Over the 5 year period the total number of patients treated is approximately the same (i.e. a 4% decrease when using the PBS dataset methotrexate patient counts). However, the cost to the PBS of apremilast in Year 5 would be reduced to around \$30 - 60 million which is below Cap 1 of the proposed RSA (see Table 4).
- 6.17 In its pre-PBAC response (p3), the sponsor stated it is willing to establish appropriate inputs for methotrexate initiation and prevalence, and recalculate the proposed RSA caps to result in the same net price for apremilast as proposed in this submission.
- 6.18 The minor resubmission estimated 10,000 – 50,000 patients and a net cost to the PBS/RPBS of \$60 - \$100 million in Year 5 of listing, with a total net cost to the PBS/RPBS of more than \$100 million over the first five years. This is summarised in Table 3.



6.20 The proposed RSA reduced the estimated net cost to the PBS/RPBS over the first five years of listing from more than \$100 million to more than \$100 million.

Table 4: Proposed risk sharing arrangement

	Year 1	Year 2	Year 3	Year 4	Year 5	Total
	\$ [redacted]	\$ [redacted]	\$ [redacted]	\$ [redacted]	\$ [redacted]	\$ [redacted]
Estimated expenditure [redacted]	\$ [redacted]	\$ [redacted]	\$ [redacted]	\$ [redacted]	\$ [redacted]	\$ [redacted]
	\$ [redacted]	\$ [redacted]	\$ [redacted]	\$ [redacted]	\$ [redacted]	\$ [redacted]
Estimated expenditure [redacted]	\$ [redacted]	\$ [redacted]	\$ [redacted]	\$ [redacted]	\$ [redacted]	\$ [redacted]
Estimated reimbursement [redacted]	\$ [redacted]	\$ [redacted]	\$ [redacted]	\$ [redacted]	\$ [redacted]	\$ [redacted]
Estimated cost to PBS/RPBS of apremilast	\$ [redacted]	\$ [redacted]	\$ [redacted]	\$ [redacted]	\$ [redacted]	\$ [redacted]
Estimated net cost to PBS/RPBS	\$ [redacted]	\$ [redacted]	\$ [redacted]	\$ [redacted]	\$ [redacted]	\$ [redacted]
Estimated net cost to government	\$ [redacted]	\$ [redacted]	\$ [redacted]	\$ [redacted]	\$ [redacted]	\$ [redacted]

Source: Table 12 of the minor resubmission and calculated during the preparation of the minor overview.

The redacted table shows that at year 5, the estimated net cost to the PBS would be \$30 - \$60 million.

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

7 PBAC Outcome

- 7.1 The PBAC did not recommend the listing of apremilast for the treatment of patients with moderate-to-severe plaque psoriasis who have failed to achieve an adequate response or are contraindicated to treatment with methotrexate.
- 7.2 The PBAC recalled that it rejected apremilast for moderate to severe plaque psoriasis in its previous consideration in November 2016 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. The PBAC noted that the resubmission did not address the issues it previously identified in its consideration of the November 2016 major resubmission (see Tables 1 and 2).
- 7.3 The PBAC noted the input received prior to the November 2016 PBAC meeting from individuals, health care professionals and organisations, including advice received from the Australian College of Dermatologists clarifying the likely use of apremilast in clinical practice.
- 7.4 The PBAC noted 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.
- 7.5 The PBAC recalled it previously accepted cyclosporin as the main comparator if apremilast was restricted to patients who have failed treatment with methotrexate. The PBAC noted that the minor resubmission did not change the comparator.
- 7.6 The PBAC recalled that the November 2016 resubmission revised the clinical claim to superiority versus cyclosporin on the basis of real-world persistence data, from non-inferiority in the March 2015 submission (see paragraphs 6.5 and 6.6). In November 2016, the PBAC considered that the non-randomised persistence data was relevant supportive information but was an insufficient basis to support the claim of superiority in comparative effectiveness or safety. The PBAC considered that these issues had not been addressed by the minor resubmission.
- 7.7 The PBAC noted that the pre-PBAC response (p1) stated that “the intent of this minor submission is not to directly address these concerns [with the clinical evidence and claim] but rather to reduce the uncertainty to a level of cost-effectiveness that will enable the PBAC to make a positive recommendation”. The PBAC considered that as its concerns with the claim of superior effectiveness and safety had not been addressed, the minor resubmission did not present a basis on which to recommend apremilast on a cost-effectiveness basis, compared with cyclosporin.
- 7.8 The PBAC noted that the minor resubmission requested a reduced effective price of apremilast but did not address the PBAC’s previous concerns with the economic model presented in the November 2016 submission (see paragraph 6.10). However, the PBAC reiterated that the economic model was uninformative for decision making as there was not a sufficient justification to recommend apremilast on a cost-effectiveness basis compared with cyclosporin.
- 7.9 The PBAC noted the minor resubmission presented revised utilisation estimates using a market based approach to reflect the proposed post-methotrexate PBS listing, and that these estimates had not been evaluated.

7.10 The PBAC noted that the minor resubmission reduced the net cost of apremilast to the PBS over the first five years of listing from more than \$100 million to \$more than \$100 million through a proposed reduction in the effective price and additional financial caps through an RSA. In the context of the uncertain treatment benefit over other systemic therapies the PBAC considered the opportunity cost of listing apremilast for moderate to severe plaque psoriasis was substantial.

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

Outcome:

Rejected

8 Context for Decision

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

9 Sponsor's Comment

The sponsor had no comment.