4.02 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 The minor submission sought to provide the PBAC with updated utilisation estimates and proposed price and risk share arrangements (RSA) to address the concerns raised by the PBAC when it considered apremilast at its November 2017 meeting.

2 Requested listing

2.1 The submission did not request any changes to the restriction proposed in its application to the November 2017 PBAC meeting.

2.2 At its November 2017 meeting the PBAC considered that if apremilast was to be listed on the PBS, the restriction should be amended to align with current PBS listings for non-biologics for plaque psoriasis and to restrict the treatment population to adults. These changes have been incorporated into the restriction below.

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

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

Category / Program	GENERAL – General Schedule (Code GE)
Prescriber type:	☐Dental ☒Medical Practitioners ☐Nurse practitioners ☐Optometrists ☐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:	☐Restricted benefit ☐Authority Required - In Writing ☐Authority Required - Telephone ☐Authority Required - Emergency ☐Authority Required - Electronic ☒Streamlined
Treatment criteria:	• Must be treated by a dermatologist or general physician with expertise in the management of plaque psoriasis.
Clinical criteria	• 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.
Population criteria	• *Patient must be aged 18 years or older*
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.~~

Name, Restriction, Manner of administration and form	Max. Qty (packs)	№.of Rpts	Dispensed 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:	☐Dental ☒Medical Practitioners ☐Nurse practitioners ☐Optometrists ☐Midwives
Severity:	Moderate to severe
Condition:	Plaque psoriasis
PBS Indication:	~~Moderate to~~ severe plaque psoriasis
Treatment phase:	Continuing treatment
Restriction Level / Method:	☐Restricted benefit ☐Authority Required - In Writing ☐Authority Required - Telephone ☐Authority Required - Emergency ☐Authority Required - Electronic ☒Streamlined
Clinical criteria:	Patient must have previously received PBS-subsidised treatment with *this drug for this condition*.
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.~~

3 Background

3.1 Apremilast was TGA registered on 19 March 2015 for the treatment of signs and symptoms of active psoriatic arthritis in adult patients, and the treatment of adult patients with moderate to severe plaque psoriasis who are candidates for phototherapy or systemic therapy.

3.2 This is the fifth submission to the PBAC seeking a recommendation for PBS listing of apremilast. The most recent submission was to the November 2017 PBAC meeting.

3.3 At its November 2017 meeting, the PBAC deferred making a recommendation on apremilast to allow further work to establish a price that could be considered cost-effective. Key elements of the PBAC consideration included:

- the PBAC noted that the resubmission more appropriately presented a cost-minimisation approach, with offsets for additional monitoring and adverse event costs associated with cyclosporin;

- the PBAC recalled it previously accepted cyclosporin as the appropriate comparator if apremilast was restricted to patients who have failed treatment with methotrexate;
- 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 network meta-analysis. However, on balance, the PBAC considered that the claim of non-inferior comparative efficacy is likely to be reasonable;
- 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;
- 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;
- 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 [redacted]% over cyclosporin, apremilast would likely be acceptably cost-effective for the purposes of the *National Health Act 1953*; and,
- the PBAC considered that there was significant uncertainty in the utilisation estimates presented in the submission, noting that they are likely an underestimate. The PBAC considered that this uncertainty could be addressed through the implementation of a tiered RSA based on patient numbers.

4 Consideration of the evidence

Sponsor hearing

4.1 There was no hearing for this item as it was a minor submission.

Consumer comments

4.2 The PBAC noted and welcomed the input from individuals (2) and organisations (1) via the Consumer Comments facility on the PBS website. The comments described

benefits of treatment with apremilast, including improved psoriasis symptoms and reduced adverse events compared with other treatments for plaque psoriasis.

4.3 The PBAC noted the advice received from Psoriasis Australia clarifying the likely use of apremilast in clinical practice. The PBAC specifically noted the advice that the use of apremilast provides a long-term treatment option for patients with moderate to severe psoriasis, as patients often find current therapies to be toxic and apremilast has a more favourable adverse event profile. Further, the PBAC noted that apremilast may offer improved skin clearance for some patients.

Economic analysis

4.4 At its November 2017 meeting, the PBAC considered a cost-minimisation analysis of apremilast and cyclosporin was appropriate. Taking into account offsets for the reduced toxicity of apremilast compared to cyclosporin and the requirement for reduced monitoring of patients, the PBAC considered that apremilast would likely be acceptably cost-effective, for the purposes of the *National Health Act 1953,* at a price premium of [redacted]% over cyclosporin. This price premium resulted in a decrease in the requested price from $[redacted] (DPMQ per maintenance pack) to $[redacted] - $[redacted] per maintenance pack.

4.5 The minor resubmission did not present an updated economic analysis. An RSA was proposed, which the sponsor claimed would achieve an effective price premium within this range over the lifetime of the agreement. Further information is presented in paragraph 4.9 and onwards.

Drug cost/patient year: $[redacted] (submission)

4.6 The requested DPMQ of the titration pack ($[redacted], 1 pack per year) and standard pack ($[redacted], 12.5 packs per year) has not changed from the November 2017 submission. The sponsor noted that a proposed effective price of $[redacted] for the titration pack and $[redacted] for the standard pack would be achieved through the tiered RSA; however, this effective price could only be achieved if all the caps in the RSA were met in all years. In its pre-PBAC response the sponsor proposed a reduced DPMQ of $[redacted] for the titration pack (1 pack per year) and $[redacted] for the standard pack (12.5 packs per year). The proposed average effective prices, achieved through the tiered RSA, were $[redacted] for the titration pack and $[redacted] (AEMP) for the standard pack.

Estimated PBS usage & financial implications

4.7 In its pre-PBAC response, the sponsor provided updated financial estimates, and estimated a net cost to the PBS/RPBS of approximately $20 - $30 million in Year 5 of listing, with a total net cost to the PBS/RPBS of approximately $60 - $100 million over the first 6 years of listing. This, as well as the expected patient/prescription numbers based on the figures provided in the pre-PBAC response, is summarised in the table below.

Table 1: Estimated use and financial implications of apremilast listing on the PBS/RPBS (Pre-PBAC response)

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

Source: Apremilast Pre-PBAC response

The redacted table shows that at year 6, the estimated number of patients was 10,000 – 50,000 per year, the estimated number of scripts was 100,000 – 200,000 per year, and the net cost to the PBS $30 - $60 million per year.

4.8 The financial estimates above rely entirely on the utilisation of apremilast meeting the caps defined in the proposed RSA (based on the DUSC estimates provided for the November meeting). If these caps are not reached, an overall price per patient for apremilast within the range the PBAC considered cost-effective at its November 2017 meeting would not be achieved.

4.9 The number of scripts per patient per year may be overestimated. The resubmission appropriately accounts for patients receiving 11.08 packs of apremilast per year (assuming compliance of 85% as advised by DUSC). However, the resubmission also includes one titration pack for every prevalent treated patient every year.

Financial management – risk sharing arrangements

4.10 In its consideration of apremilast at the November 2017 meeting the PBAC recommended that a tiered RSA based on patient numbers estimated by the submission be implemented if apremilast were to be listed on the PBS, with the aim of reducing uncertainty regarding the utilisation estimates. The PBAC considered 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. The PBAC considered that apremilast would likely be acceptably cost-effective at a price premium of [redacted]% over cyclosporin.
- 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 [redacted]% 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.

4.11 In the current submission, the sponsor proposed a multi-tiered RSA which was different to that recommended by the PBAC. The RSA proposed by the sponsor was based on patient numbers presented in the November 2017 submission and the upper limit of the DUSC estimates provided for the November meeting. The proposed patient cap levels in the PBAC-recommended RSA and sponsor-proposed RSA are presented below:

Figure 1: Comparison of PBAC recommended and sponsor requested RSAs

[redacted]

Source: Apremilast minor submission Figure 1, p. 14

4.12 The sponsor identified key aspects of its RSA as follows:

- Tier 1 - Has been established at a [redacted]% lower threshold than proposed by the PBAC – a total of [redacted] patients over the entire period vs. total [redacted] patients in the PBAC model. A DPMQ of $[redacted] applies to Tier 1.
- Tier 2 - Once patient numbers exceed Tier 1, an average [redacted]% discount (see Table 2) to the cyclosporin price is applied over the six-year period within Tier 2. This is reflected as an annual rebate within Tier 2. Tier 2 is an additional [redacted] patients above the tier 1 cap over the six-year term of the proposed agreement.
- Tier 3 - Once patient numbers exceed Tier 2 an average [redacted]% discount (see Table 2) to the cyclosporin price is applied over the six-year period. Tier 3 is an additional [redacted] patients over Tier 2.
- Above Tier 3 – The Tier 3 cap is set based on the DUSC's previous estimate. If this cap is breached a variable rebate is applied starting at [redacted]% in year 1 and increasing to [redacted]% in year 6 for all expenditure over the tier 3 cap.

4.13 The sponsor did not propose a reduction in the list price of apremilast in the current submission. The sponsor claimed that across the life of the RSA proposal (6 years), the average annual weighted premium of apremilast over cyclosporin would be [redacted]% - equating to an effective price of approximately $[redacted] (AEMP) per maintenance pack. The sponsor summary of the tier expenditure and rebates is presented in Table 2.

Table 2: Gross financial cost and rebate values (sponsor)

Year	2018	2019	2020	2021	2022	2023	Cumulative
T1	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]
T2	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]
T2 Rebate	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]
Premium vs CsA T2	[redacted]%	[redacted]%	[redacted]%	[redacted]%	[redacted]%	[redacted]%	
T3	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]
T3 Rebate	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]
Premium vs CsA T3	[redacted]%	[redacted]%	[redacted]%	[redacted]%	[redacted]%	[redacted]%	
Overall Premium vs CSA	[redacted]%	[redacted]%	[redacted]%	[redacted]%	[redacted]%	[redacted]%	

Source: Apremilast minor submission, Table 9 p. 16

4.14 The proposed RSA achieves the weighted premium by means of higher rebates in the highest tier/later years of the proposal, while retaining a higher price of apremilast in the lower tiers/earlier years of the RSA.

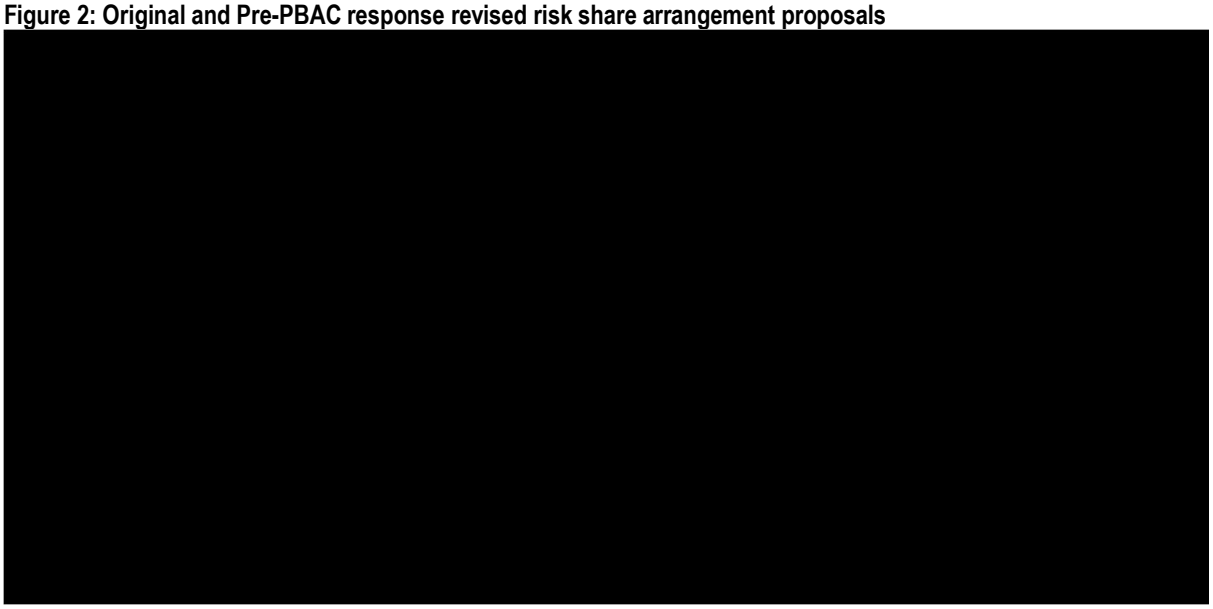
4.15 The proposed RSA represents a high degree of risk to the Commonwealth as the cost-effective price of apremilast would not be achieved if usage is lower than estimated. This is because the claimed premium over cyclosporin of [redacted]% is averaged over the three tiers of the RSA across all years of the arrangement and will not be realised if usage does not exceed all caps in each year. This impact of not reaching all three caps would have a particularly large effect in the early years of the RSA as the percentage rebate paid by the sponsor is lower in earlier years (see Table 2).

4.16 In tier 1, the requested dispensed price for the titration pack ($[redacted]) and standard pack ($[redacted]) has not changed from the November 2017 submission. Under this model, if the use of apremilast does not exceed the T1 patient cap, the average cost of apremilast will be substantially more per patient than estimated.

4.17 The number of patient/pack numbers captured in Tiers 1 and 2 are higher than the patient estimates from the November 2017 submission. If actual usage is in line with the November 2017 estimates, Tier 3 will not be reached in any year of the agreement. If this were to occur, the Commonwealth will pay substantially more for apremilast over the life of the agreement (approximately $[redacted] over 6 years). The overall premium will further increase if usage is lower.

4.18 In its pre-PBAC response, noting the issues raised in paragraphs 4.15 – 4.17, the sponsor proposed a revised RSA, which reduced the number of tiers to two, and reduced the prices in the two tiers relative to tiers one and two of the original risk share proposal presented in the submission. The sponsor stated that it was "…confident that the higher rebates and lower price will deliver the cost-effective price to the PBAC earlier than the previous proposal presented within the minor submission (Pre-PBAC response)". A summary of the RSA proposal in the pre-PBAC response is presented in the figure below.

Figure 2: Original and Pre-PBAC response revised risk share arrangement proposals



Source: Apremilast Pre-PBAC response (p.3)

4.19 Key aspects of the revised RSA proposal are as follows:

- Tier 1 - Maintained at a [redacted]% lower threshold than proposed by the PBAC ([redacted] patients). The requested DPMQ of apremilast in Tier 1 was reduced by about [redacted]% to an effective price of $[redacted] for the standard pack. This represents a price premium of approximately [redacted]% over the price of cyclosporin.
- Tier 2 - Once patient numbers exceed Tier 1, the price of apremilast will be rebated to an average effective price of $[redacted] for the titration pack, and $[redacted] for the standard pack for all patients above the Tier 1 limit of [redacted] patients. The revised price represents an approximate [redacted]% reduction over the submission tier 2 price for both packs, and an approximate [redacted]% discount over the price of cyclosporin.
- Above Tier 2: No further tiers or hard caps on expenditure are proposed beyond the second tier.

4.20 The sponsor summary of the revised tier rebates and expenditure are provided in the table below.

Table 3: Gross financial cost and rebate values (sponsor, Pre-PBAC response)

Year	2018	2019	2020	2021	2022	2023	Cumulative
T1	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]
T2	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]
T2 Rebate	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]
Premium vs CsA T2	-[redacted]%	-[redacted]%	-[redacted]%	-[redacted]%	-[redacted]%	-[redacted]%	

Source: Apremilast Pre-PBAC response (p.4)

4.21 The revised RSA continues to attempt to achieve a price premium by means of higher rebates in the second tier, while retaining a price for apremilast in the first tier substantially higher than the price premium the PBAC considered acceptable for apremilast over cyclosporin at its November 2017 meeting.

4.22 The sponsor utilisation estimates did not change in the pre-PBAC response. Under the revised prices and RSA proposal, if the DUSC estimates are reached the sponsor claimed the weighted price of apremilast will result in a modest price decrease over cyclosporin. However, the sponsor did not propose any additional rebates over the DUSC estimates as recommended by the PBAC.

4.23 A special pricing arrangement (SPA) in which the effective price is set at a level considered by the PBAC to be cost-effective would be an alternative method for achieving a listing with the higher published price sought by the sponsor. In its pre-PBAC response, the sponsor indicated that it cannot enter into a SPA.

For more detail on PBAC's view, see section 5 PBAC Outcome.

5 PBAC Outcome

5.1 The PBAC did not recommend apremilast for the treatment of moderate to severe plaque psoriasis on the basis that the risk share arrangement (RSA) proposed by the sponsor was unlikely to achieve an overall price per patient for apremilast within the range the PBAC considered cost-effective at its November 2017 meeting.

5.2 In rejecting this application, the PBAC considered that there was a clinical need for apremilast, but recalling its discussion from the November 2017 reiterated the parameters of its original deferral of apremilast - that apremilast should be priced on a cost-minimisation basis with cyclosporin, with a [redacted]% price premium to account for safety offsets - remained appropriate.

5.3 The PBAC noted that the RSA proposed by the sponsor was considerably different to that put forward by the PBAC at the November 2017 meeting as being a potentially acceptable approach, and relied heavily on the uptake and utilisation of apremilast to achieve a weighted overall price within the range the PBAC considered to be cost-effective. The PBAC considered that this method was a highly uncertain mechanism to achieve a cost-effective price for apremilast as there was substantial uncertainty regarding the utilisation estimates. Further, the PBAC noted that the proposed RSA did not include a hard cap with a [redacted]% rebate for use beyond the DUSC estimates, as requested in the November 2017 deferral. The PBAC advised that any future RSA proposal should be structured to ensure the cost of apremilast is within the price range considered by the Committee to be cost-effective for every patient, regardless of utilisation.

5.4 The PBAC considered that other mechanisms may help to provide certainty with regards to achieving a cost-effective listing for apremilast. Such methods could include (among other options):

- a special pricing arrangement where the effective price of apremilast is within the price range the PBAC considered cost-effective from the first patient, as recommended by the committee at the November 2017 meeting; or,
- an annual reconciliation component of the RSA, whereby the sponsor agrees to rebate the Commonwealth to the cost-effective price for every patient if utilisation is lower than expected.

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

Outcome:
Rejected

6 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.

7 Sponsor's Comment

Celgene is committed to development of innovative medicines for patients with immune inflammatory diseases such as Psoriasis.

Our commitment to patients is to monitor changes that would allow apremilast to be reconsidered for PBS listing. Apremilast is currently reimbursed for psoriasis in 28 countries around the world, excluding Australia.