

## 7.16 LENALIDOMIDE

### Capsule 5mg, 10 and 15mg, Revlimid<sup>®</sup>, Celgene Pty Ltd.

#### 1 Purpose of Application

- 1.1 The minor resubmission requested a Section 100 (Highly Specialised Drugs) listing for lenalidomide monotherapy as a maintenance treatment in patients with newly diagnosed multiple myeloma (NDMM) who have undergone an autologous stem cell transplant (ASCT). A major resubmission for this indication was deferred at the March 2019 PBAC meeting.

#### 2 Requested listing

- 2.1 The details of the proposed published and effective prices are summarised in Table 1.

Table 1: Proposed published and effective prices

Name, Restriction, Manner of administration and form	Max. Qty (packs)	Max. Qty (units)	No. of Rpts	Dispensed Price for Max. Qty		Proprietary Name and Manufacturer	
Lenalidomide, Capsule, 5 mg	1	28	2	Published:	[REDACTED] (public)	Revlimid <sup>®</sup>	Celgene Pty Ltd
				Effective:	[REDACTED] (private) [REDACTED] (public) [REDACTED] (private)*		
Lenalidomide, Capsule, 10 mg	1	28	2	Published:	[REDACTED] (public)	Revlimid <sup>®</sup>	Celgene Pty Ltd
				Effective:	[REDACTED] (private) [REDACTED] (public) [REDACTED] (private)*		
Lenalidomide, Capsule, 15 mg	1	28	2	Published:	[REDACTED] (public)	Revlimid <sup>®</sup>	Celgene Pty Ltd
				Effective:	[REDACTED] (private) [REDACTED] (public) [REDACTED] (private)*		

\* Calculated by the Secretariat

Source: Table 1-2, p.8 of the minor resubmission

- 2.2 The abbreviated proposed listings for initial and continuing therapy are provided in Table 2 and Table 3.

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**Table 2: Proposed PBS listing – initial treatment**

<b>Category/Program:</b>	Section 100 – HSD
<b>PBS indication:</b>	Multiple Myeloma
<b>Treatment phase:</b>	Initial treatment
<b>Restriction: Section 100 (HSD)</b>	<input type="checkbox"/> Restricted benefit <input checked="" 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 type="checkbox"/> Streamlined
<b>Clinical criteria:</b>	The treatment must be as monotherapy; AND Patient must have undergone an autologous stem cell transplant as part of frontline therapy for newly diagnosed multiple myeloma; AND Patient must not have progressive disease following autologous stem cell transplant

Source: Table 1-3, p.9 of the minor submission

**Table 3: Proposed PBS listing – continuing treatment**

<b>PBS indication:</b>	Multiple Myeloma
<b>Treatment phase:</b>	Continuing treatment
<b>Restriction: Section 100 (HSD)</b>	<input type="checkbox"/> Restricted benefit <input type="checkbox"/> Authority Required - In Writing <input checked="" type="checkbox"/> Authority Required - Telephone <input type="checkbox"/> Authority Required – Emergency <input type="checkbox"/> Authority Required - Electronic <input type="checkbox"/> Streamlined
<b>Clinical criteria:</b>	Patient must have previously been authorised with a PBS prescription with this drug for the condition; AND Patient must not have demonstrated progressive disease; AND The treatment must be as monotherapy.

Source: Table 1-4, p.11 of the minor resubmission

*For more detail on PBAC’s view, see section 6 PBAC outcome.*

### 3 Background

- 3.1 Lenalidomide was approved by the TGA on the 17 January 2018 for the ‘maintenance treatment of patients with newly diagnosed multiple myeloma who have undergone autologous stem cell transplantation’.
- 3.2 Lenalidomide is currently listed as an Authority Required (Initial - Written, Continuing - Telephone) Section 100 Highly Specialised Drug as monotherapy for the treatment of patients with NDMM who are ineligible for ASCT, and as monotherapy or in combination with dexamethasone for the treatment of relapsed or refractory multiple myeloma (RRMM). There are separate risk share arrangements (RSA) in place for each indication.
- 3.3 A multiple myeloma (MM) stakeholder meeting held in May 2018 supported lenalidomide as a maintenance therapy post-ASCT.
- 3.4 Lenalidomide was previously considered for the maintenance treatment of patients with NDMM who have undergone ASCT by the PBAC in March 2018 and March 2019. A summary of the outstanding matters of concern from the March 2019 consideration and how they have been addressed in the current resubmission is provided in Table 4.

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Table 4: Summary of the outstanding matters of concern

	Matter of concern by PBAC	How the minor resubmission addresses it
Comparator	Paragraph 7.4: The PBAC considered a more reasonable weighting would be █% BSC and █% thalidomide, which was calculated by excluding █ BSC patients who were considered to be receiving active therapy from the MRDR analysis.	Not addressed.  The resubmission maintains that the proposed relative weights for the mixed comparator of █% BSC and █% thalidomide use is appropriate.
Economic evaluation	Paragraph 7.9: The PBAC considered a lenalidomide price that resulted in a base case ICER in the vicinity of...\$15,000/QALY - \$45,000/QALY would be more reasonable.....	Not addressed.  A price reduction of █ to █% was applied to the prices in the CEA, resulting in an ICER of \$15,000/QALY - \$45,000/QALY (reduced from a base-case of \$15,000/qaly - \$45,000/QALY in the previous submission). Incorporating the effective (rather than published) prices for bortezomib and pomalidomide reduced the ICER.
Financial estimates	Paragraph 7.12: The PBAC noted that the financial implications of listing lenalidomide on the PBS/ RPBS for maintenance treatment following as ASCT were high, uncertain and likely to be underestimated. The PBAC considered that any revised estimations would make only the following changes: <ul style="list-style-type: none"> <li>• Incorporate the revised price of lenalidomide;</li> <li>• Utilise a █% BSC and █% thalidomide split; and</li> <li>• Use the mean time on therapy (█ months from the CALGB trial</li> </ul>	Partially addressed.  A revised lenalidomide price was incorporated.  The weighting between BSC and thalidomide has not been revised and remains █% BSC and █% thalidomide use.  The mean time on therapy has been revised to █ months.  Additional changes not requested by the PBAC were made to the financial estimates. The minor resubmission did not account for cost offsets from reduced use of agents in the RRMM setting that would be expected if lenalidomide was listed in the maintenance setting.
Risk sharing arrangement	Paragraph 7.13: The PBAC considered that in the context of the high and uncertain potential cost, a RSA would be appropriate. The PBAC considered that any RSA should also include the current lenalidomide PBS indications and include hard caps such that any PBS expenditures beyond the cap would result in a █% rebate.	Not addressed.  An RSA with a two-tier cap was proposed with a maximum rebate of █%. The proposed RSA did not include the current lenalidomide PBS indications (i.e., RRMM and NDMM).

Abbreviations: BSC best supportive care; CEA cost effectiveness analysis; ICER incremental cost effectiveness ratio; MRDR Myeloma and Related Diseases Registry; NDMM newly diagnosed multiple myeloma; PBAC Pharmaceutical Benefits Advisory Committee; PBS Pharmaceutical Benefits Scheme; RRMM relapsed refractory multiple myeloma RSA risk share arrangement; QALY quality adjusted life year;

Source: Table 1-1, p.7 of the minor resubmission and the lenalidomide March 2019 PBAC minutes

For more detail on PBAC’s view, see section 6 PBAC outcome.

## 4 Comparator

4.1 Consistent with the resubmission considered in March 2019, the minor resubmission identified a mixed comparator of best supported care (BSC) and thalidomide with a relative weight of █% and █%, respectively. The estimated proportion of use was based on data from the Myeloma and Related Disease Registry (MRDR).

- 4.2 The PBAC previously considered that it would be more reasonable to assume a weighting of ████% BSC and ████% thalidomide, calculated by excluding ████ BSC patients from the MRDR analysis who were considered to be receiving active therapy (paragraph 5.5, March 2019 PBAC minutes).
- 4.3 The minor resubmission did not consider it reasonable to exclude the ████ BSC patients who received active therapy as proposed by the PBAC, stating the relevant issue was what proportion of patients received thalidomide as a post-ASCT maintenance therapy.

*For more detail on PBAC's view, see section 6 PBAC outcome.*

## **5 Consideration of the evidence**

### ***Sponsor hearing***

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

### ***Consumer comments***

- 5.2 The PBAC noted and welcomed the input from individuals (75), health care professionals (1) and organisations (1). The comments described a range of benefits of treatment with lenalidomide including improved overall survival, quality of life and tolerability, and fewer side effects than thalidomide. Many comments raised the issue of affordability should lenalidomide not be included on the PBS.
- 5.3 The PBAC noted that Myeloma Australia considered it important that lenalidomide be available for maintenance treatment after ASCT as it is considered the standard of care for MM patients.

### ***Clinical trials***

- 5.4 The minor resubmission did not present any additional clinical data. The March 2019 resubmission included data from 4 randomised controlled trials (Table 6, lenalidomide March 2019 PBAC minutes).

### ***Clinical claim***

- 5.5 The PBAC previously considered the claim that lenalidomide had non-inferior comparative effectiveness and a different comparative safety profile compared to thalidomide was reasonable (paragraph 6.36 and 6.37, lenalidomide March 2019 PBAC minutes).
- 5.6 The PBAC previously considered the claim that lenalidomide has superior comparative effectiveness and inferior comparative safety to BSC was reasonable (paragraph 6.32 and 6.33, lenalidomide March 2019 PBAC minutes).

**Economic evaluation**

5.7 Consistent with the March 2019 resubmission, the minor resubmission provided a cost-effectiveness analysis (CEA) for the comparison to BSC and a cost-minimisation analysis (CMA) for the comparison to thalidomide.

Cost-effectiveness analysis

5.8 The prices included in the CEA in the minor resubmission were █% to █% lower than in the March 2019 resubmission. The base case incremental cost per quality adjusted life year (QALY) gained incorporating the revised prices was \$15,000/QALY - \$45,000/QALY (Table 5). The base case incremental cost per QALY in the March 2019 resubmission was \$15,000/QALY - \$45,000/QALY. The price of lenalidomide was the only change made to the economic model provided with the minor resubmission.

**Table 5: Base case cost-effectiveness analysis of lenalidomide vs best supportive care**

Discounted outcomes	Lenalidomide	Best supportive care	Incremental
Total costs	\$ █	\$ █	\$ █
Total life years	7.55	5.31	2.24
Total QALYs	5.76	4.02	1.74
Incremental cost per QALY			\$ █

Abbreviations: QALY quality adjusted life year  
Source: Table 3-2, pg 13, minor resubmission

5.9 The redacted table shows ICERs in the range of \$15,000/QALY - \$45,000/QALY. The PBAC previously considered the base case ICER (\$15,000/QALY - \$45,000/QALY) was uncertain and noted that changes to the dataset used and removing the crossover adjustment resulted in considerable increases (revised ICER of \$75,000/QALY - \$105,000/QALY incorporating both changes) (paragraph 6.47 and 7.9, lenalidomide March 2019 PBAC minutes).

5.10 The PBAC previously considered that given the ICER generated by the economic model was uncertain, a base case ICER in the vicinity of \$15,000/QALY - \$45,000/QALY (as provided in the submission considered in March 2018) would be reasonable (paragraph 7.9, lenalidomide March 2019 PBAC minutes).

5.11 Consistent with the March 2019 resubmission, the economic model provided with the minor resubmission assumed post-progression treatment with lenalidomide, bortezomib and pomalidomide, depending on the line of therapy and prior treatment (Table 6). The model assumed for the comparator arm that post-ASCT patients would be treated with BSC and then following relapse with lenalidomide or bortezomib (second line treatment) and then lenalidomide or bortezomib (third line treatment). Patients treated with lenalidomide as maintenance post ASCT who relapsed were assumed to receive bortezomib (second line treatment) and then pomalidomide or lenalidomide (third line treatment). The economic model assumed patients treated

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with lenalidomide received [redacted] cycles as a second line treatment and [redacted] cycles as a third line treatment. Thus the economic model assumed treatment with lenalidomide as maintenance treatment resulted in a substantial reduction in use of lenalidomide in the RRMM setting. The PBAC noted that carfilzomib plus dexamethasone (Cd) may be an alternative second or third line treatment. The PBAC considered that because Cd would be used in both treatment arms (lenalidomide and BSC) and would primarily replace bortezomib, the impact on the ICER would be minimal. The PBAC also considered the inclusion of Cd in the treatment algorithm would not alter the conclusion that with the availability of lenalidomide in the maintenance setting there would be a substantial reduction in the use of lenalidomide in the RRMM setting.

**Table 6: Post-progression treatment assumptions in the economic model**

Maintenance treatment	Second line treatment	Third line treatment
Best supportive care	Assumed treatments: <ul style="list-style-type: none"> <li>lenalidomide ([redacted]%)</li> <li>bortezomib ([redacted]%)</li> </ul> Modelled proportion of patients receiving 2nd line treatment: [redacted]%	Assumed treatments: <ul style="list-style-type: none"> <li>lenalidomide ([redacted]%)</li> <li>bortezomib ([redacted]%)</li> </ul> Modelled proportion of patients receiving 3rd line treatment (of those receiving 2nd line treatment): [redacted]%
Lenalidomide	Assumed treatments: <ul style="list-style-type: none"> <li>bortezomib ([redacted]%)</li> </ul> Modelled proportion of patients receiving 2nd line treatment: [redacted]%	Assumed treatments: <ul style="list-style-type: none"> <li>lenalidomide ([redacted]%)</li> <li>pomalidomide ([redacted]%)</li> </ul> Modelled proportion of patients receiving 3rd line treatment (of those receiving 2nd line treatment): [redacted]%

Source: Results worksheet, Tx following prog worksheet, Celgene-Lenalidomide-Section 3 CEA Model-April 2019.xls

5.12 The PBAC noted the base case ICER presented in Table 5 used the published prices for bortezomib and pomalidomide and incorporating the effective prices resulted in a lower base case ICER (see paragraph 5.14).

5.13 The minor resubmission provided a number of sensitivity analyses as summarised in Table 7. These analyses used the published prices for bortezomib and pomalidomide.

**Table 7: Results of the sensitivity analysis of lenalidomide versus BSC**

	Incremental cost	Incremental QALY	ICER
Base case (March 2019)	\$ [redacted]	1.74	\$ [redacted]
Base case (minor resubmission)	\$ [redacted]	1.74	\$ [redacted]
Efficacy source (base-case CALGB trial)			
- No cross over adjustment	\$ [redacted]	1.34	\$ [redacted]
- Derived from pooled trial dataset	\$ [redacted]	0.77	\$ [redacted]
Lenalidomide acquisition costs:			
- Incorporating a [redacted]% SPR to the weighted price from 1 April 2020	\$ [redacted]	1.74	\$ [redacted]

Abbreviations: ICER incremental cost effectiveness ratio; QALY quality adjusted life year; SPR statutory price reduction;

Source: Table 3-3, pg 14, minor resubmission

The redacted table shows ICERs in the range of \$15,000/QALY to \$45,000/QALY.

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- 5.14 The PBAC noted the ICER incorporating both the change to the dataset used and removing the crossover adjustment was \$ [REDACTED] (using published prices for bortezomib and pomalidomide).
- 5.15 The PBAC noted the sensitivity analysis incorporating a [REDACTED]% statutory price reduction (SPR) inappropriately applied the price reduction to the weighted price rather than the CEA price. Additionally, the price reduction was not applied to the lenalidomide price in the RRMM setting. Applying the SPR to the CEA price and to the lenalidomide price in the RRMM setting resulted in a revised ICER of \$ [REDACTED] (using published prices for bortezomib and pomalidomide).

**\*\*Committee in Confidence \*\***

- 5.16 The revised ICER incorporating the effective prices of bortezomib and pomalidomide is presented in Table 8.

**Table 8: Impact on ICER of using effective prices for subsequent therapies**

Analyses	Incremental cost	Incremental QALY	ICER
Base case	\$ [REDACTED]	1.74	\$ [REDACTED]
Second and third line therapy – effective prices (bortezomib 3 mg at [REDACTED]; pomalidomide 4 mg at [REDACTED])	[REDACTED]	1.74	[REDACTED]
Incorporating a [REDACTED]% SPR to the CEA price and the lenalidomide price in the RRMM setting	[REDACTED]	1.74	[REDACTED]

Abbreviations: ICER incremental cost effectiveness ratio; QALY quality adjusted life years; RRMM relapsed refractory multiple myeloma  
SPR statutory price reduction

Source: Calculated during evaluation using Celgene-Lenalidomide-Section 3 CEA model – April 2019.xls,

- 5.17 The revised ICER changing the dataset used, removing the crossover adjustment and using the effective prices for bortezomib and pomalidomide was [REDACTED].

**\*\*End Committee in Confidence \*\***

- 5.18 The minor resubmission provided a summary of ICER thresholds for MM medicines that have previously been recommended by the PBAC to support the cost-effectiveness of lenalidomide in the maintenance setting. The ICERs were sourced from Public Summary Documents and ranged from an incremental cost of \$45,000 to \$75,000 per QALY.

Cost-minimisation analysis

- 5.19 The price determined by the CMA in the minor resubmission remains unchanged from the March 2019 resubmission. The PBAC previously considered the proposed equi-effective doses and the CMA methodology were reasonable (paragraph 6.50 and 6.54 lenalidomide March 2019 PBAC minutes).

**Drug cost per patient per course: \$ [REDACTED]**

5.20 The minor resubmission proposed prices for lenalidomide 5 mg, 10 mg and 15 mg based on a weighted analysis of the prices used in the CEA (lenalidomide versus BSC) and the prices determined from the CMA (lenalidomide versus thalidomide). The weighted price in the resubmission assumed [REDACTED]% of patients would be treated with BSC and [REDACTED]% of patients would be treated with thalidomide (Table 9).

**Table 9: Weighted price for lenalidomide**

AEMP	Lenalidomide 5 mg x 28	Lenalidomide 10 mg x 28	Lenalidomide 25 mg x 28	Weight
CEA price vs BSC	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	[REDACTED]%
CMA price vs thalidomide	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	[REDACTED]%
Weighted price	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	-

Abbreviations: AEMP approved ex-manufacturer price; BSC best supportive care; CEA cost utility analysis; CMA cost minimisation analysis; Source: Table 3-6, page 16, minor resubmission

5.21 The PBAC previously considered the weighting between BSC (i.e., the CEA price) and thalidomide (i.e., the CMA price) should be [REDACTED]% and [REDACTED]% which would result in a weighted price of \$ [REDACTED] for the 5 mg capsules, \$ [REDACTED] for the 10 mg capsules and \$ [REDACTED] for the 15 mg capsules ([REDACTED] to [REDACTED]% lower than proposed in the minor resubmission).

5.22 The average cost of lenalidomide per patient per 28 day cycle in the March 2019 resubmission was estimated to be \$ [REDACTED] (Table 29, lenalidomide March 2019 PBAC minutes) based on the proposed weighted effective price. The average cost of lenalidomide per patient per year and per treatment course was \$ [REDACTED] and \$ [REDACTED] (based on a treatment duration of [REDACTED] months), respectively.

5.23 The average cost of lenalidomide per patient per 28 day cycle in the minor resubmission was \$ [REDACTED] based on the proposed weighted effective price. The average cost of lenalidomide per patient per year and per treatment course was \$ [REDACTED] and \$ [REDACTED] (based on a treatment duration of [REDACTED] months), respectively. This was based on the dose distribution used in the March 2019 resubmission (22.2% x 5 mg, 33.5% x 10 mg and 44.3% x 15 mg). Applying the dose distribution used in the minor resubmission (16% x 5 mg, 33.5% x 10 mg and 44.3% x 15 mg) the average cost per patient per year and per treatment course was \$ [REDACTED] and \$ [REDACTED], respectively. The dose distribution applied in the minor resubmission did not add to 100% to account for patients not receiving a prescription due to dose interruptions.

*For more detail on PBAC's view, see section 6 PBAC outcome.*

**Estimated PBS usage & financial implications**

5.24 During review of the March 2019 resubmission, the DUSC were unable to directly evaluate the financial estimates because they were developed in a specialised software which could not be readily accessed. The estimates provided with the minor

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resubmission used a standard patient estimation model following the financial estimates template; however, comparison of the assumptions between the March 2019 resubmission and the minor resubmission was difficult given the different formats.

- 5.25 The resubmission considered in March 2019 calculated the number of patients that would initiate treatment with lenalidomide based on the incidence of MM. The minor resubmission calculated the number of patients that would initiate treatment with lenalidomide based on the number of ACSTs performed for MM per year. A comparison of the estimated number of patients treated with lenalidomide per year is summarised in Table 10.

**Table 10: Number of incident patients treated with lenalidomide per year**

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
<b>March 2019</b>						
Number of MM incident patients	■	■	■	■	■	■
Symptomatic and eligible for ASCT (■% x ■%)	■	■	■	■	■	■
Number of patients in remission following ASCT (■%)	■	■	■	■	■	■
Number of patients initiating treatment with lenalidomide (■%)	■	■	■	■	■	■
<b>July 2019</b>						
Number of patients with MM receiving an ASCT	■	■	■	■	■	■
Number of patients in remission following ASCT (■%)	■	■	■	■	■	■
Patients electing treatment	■	■	■	■	■	■
Number of patients initiating treatment with lenalidomide	■	■	■	■	■	■

Abbreviations: ASCT autologous stem cell transplant; MM multiple myeloma

Estimates previously considered by the PBAC are shaded

\*Assumes ■% of patients receiving an ASCT in 2019 treated in 2020 (■ patients)

Source: March 2019 – 7.07 lenalidomide COM 03-2019 Attachment Section 4 DUSC Table.xls; July 2019: Celgene – Lenalidomide – Utilisation and Cost Model – April 2019.xls.

- 5.26 The number of patients undergoing an ASCT was determined using data from the Australian Bone Marrow Transplant Recipient Registry with a linear extrapolation applied. The number of patients receiving an ASCT for MM in 2013 was ■, ■ in 2015 and ■ in 2017. The extrapolation resulted in growth in the number of ASCTs of around ■% in 2020 (Year 1) to ■% in 2025 (Year 6).
- 5.27 The PBAC considered the approach to determining the number of patients initiating treatment with lenalidomide in the minor resubmission was reasonable.
- 5.28 The estimated use and financial implications of listing lenalidomide for the maintenance treatment of patients with NDMM who have undergone an ASCT are summarised in Table 11. The patient numbers reflect the prevalent treated

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population, incorporating a duration of treatment of [redacted] months and [redacted] months for the March 2019 resubmission and minor resubmission, respectively.

Table 11: Estimated use and financial implications

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
<b>Estimated extent of use</b>						
<b>March 2019</b>						
Number of patients treated*	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Number of packs dispensed	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
<b>July 2019</b>						
Number of patients treated	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Number of packs dispensed	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
<b>Estimated financial implications of lenalidomide</b>						
<b>March 2019</b>						
Cost to PBS/RPBS less co-payments	\$ [redacted]	\$ [redacted]	\$ [redacted]	\$ [redacted]	\$ [redacted]	\$ [redacted]
<b>July 2019</b>						
Cost to PBS/RPBS less co-payments	\$ [redacted]	\$ [redacted]	\$ [redacted]	\$ [redacted]	\$ [redacted]	\$ [redacted]
<b>Estimated financial implications for replacement of thalidomide and other RRRM medicines</b>						
<b>March 2019</b>						
Net cost offset from substituted thalidomide	\$ [redacted]	\$ [redacted]	\$ [redacted]	\$ [redacted]	\$ [redacted]	\$ [redacted]
Net cost offset attributed to displaced use of medicines in the RRMM setting**	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total Net PBS/RPBS savings	\$ [redacted]	\$ [redacted]	\$ [redacted]	\$ [redacted]	\$ [redacted]	\$ [redacted]
<b>July 2019</b>						
Net cost offset from substituted thalidomide	\$ [redacted]	\$ [redacted]	\$ [redacted]	\$ [redacted]	\$ [redacted]	\$ [redacted]
Net cost offset attributed to displaced use of medicines in the RRMM setting	-	-	-	-	-	-
Total Net PBS/RPBS savings	\$ [redacted]	\$ [redacted]	\$ [redacted]	\$ [redacted]	\$ [redacted]	\$ [redacted]
<b>Net financial implications</b>						
<b>March 2019</b>						
Net cost to PBS/RPBS	\$ [redacted]	\$ [redacted]	\$ [redacted]	\$ [redacted]	\$ [redacted]	\$ [redacted]
<b>July 2019</b>						
Net cost to PBS/RPBS	\$ [redacted]	\$ [redacted]	\$ [redacted]	\$ [redacted]	\$ [redacted]	\$ [redacted]

\* This was calculated during evaluation of the March 2019 resubmission based on the total patient-months treated

\*\* Cost offset due to reduced use of lenalidomide in the RRMM setting was \$ [redacted]m to \$ [redacted]m per year

Abbreviations: PBS Pharmaceutical Benefits Scheme; RPBS Repatriation Pharmaceutical Benefits Scheme; RRMM relapsed and refractory multiple myeloma

Estimates previously considered by the PBAC are shaded

Source: March 2019: Table 30, pg 36, Agenda Item 7.07 March 2019 PBAC minutes; July 2019: Celgene – Lenalidomide – Utilisation and Cost Model – April 2019.xls

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- 5.29 The estimated net cost to the PBS/RPBS over the first 6 years was estimated to be \$30-\$60 million.
- 5.30 The changes to the assumptions in the financial model between the March 2019 resubmission and the minor resubmission are summarised in Table 12.

**Table 12: Changes to estimated use and financial implications: March 2019 resubmission vs minor resubmission**

Assumption	March 2019 resubmission	Minor resubmission	Comment
Treatment duration	■ months (paragraph 6.66, lenalidomide March 2019 PBAC minutes)	■ months	As requested by PBAC
Uptake of lenalidomide	Unclear – submission stated ■%, model applied ■% in Yr 1 and ■% in Yr 6 (paragraph 6.65, lenalidomide March 2019 PBAC minutes)	■% in Yr 1 and ■% in Yr 6  Also includes ■% uptake in patients diagnosed the year prior to listing.	While there was some uncertainty in the uptake rates in the March 2019 resubmission, the DUSC considered that all new patients were likely to commence lenalidomide and patients on thalidomide would transition fairly rapidly (paragraph 6.71, lenalidomide March 2019 PBAC minutes).  The inclusion of a proportion of patients diagnosed in the previous year is consistent with DUSC advice (7.07.DUSC ADV.5).
Cost offsets	Included cost-offsets due to reduced use of thalidomide, lenalidomide, bortezomib and pomalidomide in the RRMM setting	No cost offsets for reduced use in the RRMM setting.	While the DUSC previously considered it is likely the proposed listing of lenalidomide will displace rather than replace therapies used to treat RRMM (7.07.DUSC ADV.7) there is likely to be reduced use of lenalidomide in the RRMM setting and this has not been accounted for in the estimates.

Abbreviations: RRMM relapsed refractory multiple myeloma  
Estimates previously considered by the PBAC are shaded

- 5.31 The PBAC noted the March 2019 resubmission included cost-offsets in the financial estimates to reflect a reduction in the use of medicines (including lenalidomide) in the RRMM setting after receiving maintenance treatment with lenalidomide in the NDMM setting, consistent with the assumptions included in the economic model (paragraph 5.11). The minor resubmission did not include any cost-offsets for a reduction in lenalidomide use in the RRMM setting.
- 5.32 The Secretariat noted the AEMP was used rather than a weighted dispensed price accounting for public and private hospital use when estimating the financial implications in the minor resubmission. The pre-PBAC response stated that as the majority of use (■%) is in the public hospital setting this will have negligible impact

on the financial estimates and the sponsor is willing to incorporate private hospital use should a positive recommendation be made.

### **Risk sharing arrangement**

5.33 The minor resubmission indicated the sponsor is willing to enter into a RSA to mitigate any outstanding uncertainties regarding the budget impact, or concerns regarding the use of lenalidomide outside of the restriction. An RSA incorporating a two tier expenditure cap and rebate was proposed as outlined in Table 13.

**Table 13: Estimated use and financial implications**

Cap	Expenditure cap	Rebate when exceeded
First tier	Base case financial estimates presented in Table 8	█%
Second tier	Financial estimates assuming 100% of patients treated with an ASCT will receive treatment with lenalidomide maintenance.	█%

Abbreviations: ASCT autologous stem cell transplant

5.34 The minor resubmission proposed that the first tier expenditure cap would be consistent with the financial estimates in the submission from \$10-\$60 million over the first six years, Table 11), but did not provide any details regarding the second tier expenditure cap.

5.35 The minor resubmission stated that the first tier rebate (█%) will limit the financial impact to the PBS if utilisation is greater than what has been estimated, and the second tier rebate (█%) will limit the financial impact of use outside of the intended PBS population.

5.36 The PBAC previously considered that in the context of the high and uncertain cost of including lenalidomide on the PBS for this indication, an RSA would be required. The PBAC further considered that any RSA should include the current lenalidomide PBS indications (NDMM and RRMM), and should include a █% rebate above any expected PBS expenditure (paragraph 7.13, lenalidomide March 2019 PBAC minutes). The minor resubmission did not propose a combined RSA or a █% rebate above any expected PBS expenditure. The pre-PBAC response stated that the sponsor is unable to consider a █% rebate and the proposed RSA incorporating a █% rebate was a significant compromise.

*For more detail on PBAC’s view, see section 6 PBAC outcome.*

## **6 PBAC outcome**

6.1 The PBAC recommended the listing of lenalidomide for the maintenance treatment of patients with NDMM following an ASCT on the basis that it should be available only under special arrangements under Section 100. The PBAC considered the cost-effectiveness of lenalidomide was acceptable at the price proposed in the resubmission, however, the proposed RSA for lenalidomide as maintenance treatment

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and the existing RSA for lenalidomide as a treatment for RRMM should be revised as outlined below.

- 6.2 The PBAC recalled it had previously considered that lenalidomide provides, for some patients, a significant improvement in efficacy over placebo, and a different toxicity profile, with notably lower rates of peripheral neuropathy, compared to thalidomide.
- 6.3 The PBAC again acknowledged the clinical need for an effective and tolerable treatment in the maintenance setting following an ASCT. This was supported at the MM stakeholder meeting held in May 2018 and by the consumer comments received.
- 6.4 The PBAC considered that the relative weights for the mixed comparator of █% BSC and █% thalidomide proposed in the minor resubmission may not be reasonable. The PBAC considered including the █ patients from the MRDR who were receiving active therapy in the calculation likely overestimated the proportion of BSC patients. The PBAC noted that applying a weighting of █% BSC and █% thalidomide as requested previously, resulted in a weighted price approximately █% lower than proposed in the minor resubmission, however in the overall context of the economic analyses presented, considered that the weighted price proposed in the minor resubmission was acceptable.
- 6.5 The PBAC reaffirmed that the proposed equi-effective doses of lenalidomide and thalidomide and the cost minimisation analysis methodology were reasonable.
- 6.6 The PBAC noted the base case ICER in the minor resubmission (\$█) was higher than the ICER previously considered reasonable given the uncertainties in the economic model (\$█). However, the PBAC noted incorporating the effective prices for post-progression therapies reduced the ICER (refer to 5.16) to an acceptable level, and this was further supported by the scenario including the █% statutory price reduction for lenalidomide which will be implemented as of 1 April 2020. The PBAC noted the financial estimates need to be revised to include a weighted dispensed price accounting for public and private hospital use rather than the ex-manufacturer price.
- 6.7 The PBAC considered the first tier expenditure cap proposed by the minor resubmission for the RSA was appropriate. However, the PBAC considered the second tier expenditure cap should be reduced to account for no more than █% of patients achieving remission after an ASCT and hence being eligible for treatment, and the uptake being less than █% in all forward years, with lower uptake at listing, as it is unlikely that all eligible patients would be treated with maintenance. The PBAC considered the assumption that █% of patients that received an ASCT in the year prior to listing would receive maintenance treatment with lenalidomide was appropriate for the second tier expenditure cap. The PBAC considered the rebates proposed in the minor resubmission (█% for between the first tier and the second tier, and █% for above the second tier) to be reasonable.
- 6.8 The PBAC noted cost-offsets from reduced use of medicines in the RRMM setting were not included in the financial estimates for the minor resubmission. The PBAC further

noted the cost-effectiveness of lenalidomide as maintenance treatment post ASCT relied on reduced use of lenalidomide as a treatment for RRMM. The PBAC therefore considered it would be appropriate to reduce the lenalidomide expenditure caps in the RRMM setting to ensure the cost-offsets were realised. The PBAC considered the assumptions and outputs from the economic model for post-progression treatments (paragraph 5.11 and Table 6) were appropriate to determine the reduction in the RRMM expenditure caps required. The PBAC recalled that at the March 2019 meeting it was recommended that any RSA should also include the current lenalidomide PBS indications (RRMM and NDMM). The PBAC considered that while a combined RSA would still be the preferred approach, a separate RSA for maintenance treatment may be reasonable provided the RRMM expenditure caps are reduced by the amount calculated by multiplying the number of patients avoiding 2nd and 3rd line treatment with lenalidomide by the number of cycles in each line of treatment by the cost of a cycle in the RRMM setting.

- 6.9 The PBAC found that the criteria prescribed by the National Health (Pharmaceuticals and Vaccines – Cost Recovery) Regulations 2009 for Pricing Pathway A were not met. Specifically the PBAC found that in the circumstances of its recommendation for lenalidomide:
- (a) The treatment is not expected to provide a substantial and clinically relevant improvement in efficacy over alternative therapies, noting the PBAC considered lenalidomide to be non-inferior in terms of efficacy with a different safety profile compared to thalidomide;
  - (b) The treatment is not expected to address a high and urgent unmet clinical need because there are alternative therapies (thalidomide) available;
  - (c) It was not necessary to make a finding in relation to whether it would be in the public interest for the subsequent pricing application to be progressed under Pricing Pathway A because one or more of the preceding tests had failed.
- 6.10 Lenalidomide is not suitable for prescribing by nurse practitioners as antineoplastic agents are currently considered to be out of scope for prescribing by nurse practitioners.
- 6.11 The PBAC considered the Early Supply Rule should not apply to lenalidomide.
- 6.12 The PBAC recommended that lenalidomide should not be treated as interchangeable on an individual patient basis with any other drugs.

**Outcome:**

Recommended

## 7 Recommended listing

### 7.1 Add new item:

Name, Restriction, Manner of administration and form	Max. Qty (packs)	Max. Qty (units)	No. of Rpts	Proprietary Name and Manufacturer
Lenalidomide, Capsule, 5 mg	1	28	2	Revlimid® Celgene Pty Ltd
Lenalidomide, Capsule, 10 mg	1	28	2	Revlimid® Celgene Pty Ltd
Lenalidomide Capsule, 15 mg	1	28	2	Revlimid® Celgene Pty Ltd

#### Initial treatment

Category/Program:	Section 100 – HSD
Condition:	Multiple Myeloma
PBS indication:	Multiple Myeloma
Treatment phase:	Initial treatment
Restriction:	<input type="checkbox"/> Restricted benefit <input checked="" 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 type="checkbox"/> Streamlined
Clinical criteria:	The treatment must be as monotherapy; AND Patient must have undergone an autologous stem cell transplant as part of frontline therapy for newly diagnosed multiple myeloma; AND Patient must not have progressive disease following autologous stem cell transplant
Prescriber criteria:	The authority application must be made in writing and must include: (1) a completed authority prescription form; and (2) a completed Multiple Myeloma lenalidomide Authority Application - Supporting Information Form, which includes details of the histological diagnosis of multiple myeloma; details of autologous stem cell transplant; and nomination of which disease activity parameters will be used to assess progression; and (3) a signed patient acknowledgement. To enable confirmation of eligibility for treatment, diagnostic reports from initial diagnosis of myeloma and current reports of at least one of the following must be provided: (a) the level of serum monoclonal protein; or (b) Bence-Jones proteinuria - the results of 24-hour urinary light chain M protein excretion; or (c) the serum level of free kappa and lambda light chains; or (d) bone marrow aspirate or trephine; or (e) if present, the size and location of lytic bone lesions (not including compression fractures); or (f) if present, the size and location of all soft tissue plasmacytomas by clinical or radiographic examination i.e. MRI or CT-scan; or

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	<p>(g) if present, the level of hypercalcaemia, corrected for albumin concentration.</p> <p>As these parameters will be used to determine progression, results for either (a) or (b) or (c) should be provided for all patients. Where the patient has oligo-secretory or non-secretory multiple myeloma, either (c) or (d) or if relevant (e), (f) or (g) should be provided. Where the prescriber plans to assess response in patients with oligo-secretory or non-secretory multiple myeloma with free light chain assays, evidence of the oligo-secretory or non-secretory nature of the multiple myeloma (current serum M protein less than 10 g per L) must be provided.</p> <p>Patient must be registered in the i-access risk management program.</p>
Administrative Advice	<p>Written applications for authority to prescribe should be forwarded to:</p> <p>Department of Human Services Complex Drugs Reply Paid 9826 HOBART TAS 7001</p>
Cautions	<p>This drug is a category X drug and must not be given to pregnant women. If lenalidomide is taken during pregnancy, a teratogenic effect of lenalidomide in humans cannot be ruled out.</p>

**Continuing treatment restriction**

Category/Program:	Section 100 – HSD
Condition:	Multiple Myeloma
PBS indication:	Multiple Myeloma
Treatment phase:	Continuing treatment
Restriction:	<p><input type="checkbox"/> Restricted benefit</p> <p><input type="checkbox"/> Authority Required - In Writing</p> <p><input checked="" type="checkbox"/> Authority Required - Telephone</p> <p><input type="checkbox"/> Authority Required – Emergency</p> <p><input type="checkbox"/> Authority Required - Electronic</p> <p><input type="checkbox"/> Streamlined</p>
Clinical criteria:	<p>Patient must have previously been authorised with a PBS prescription with this drug for the condition; AND</p> <p>Patient must not have demonstrated progressive disease; AND</p> <p>The treatment must be as monotherapy.</p>
Prescriber criteria:	<p>Progressive disease is defined as at least 1 of the following:</p> <p>(a) at least a 25% increase and an absolute increase of at least 5 g per L in serum M protein (monoclonal protein); or</p> <p>(b) at least a 25% increase in 24-hour urinary light chain M protein excretion, and an absolute increase of at least 200 mg per 24 hours; or</p> <p>(c) in oligo-secretory and non-secretory myeloma patients only, at least a 50% increase of the difference between involved free light chain and uninvolved free light chain; or</p> <p>(d) at least a 25% relative increase and at least a 10% absolute increase in plasma cells in a bone marrow aspirate or on biopsy; or</p> <p>(e) an increase in the size or number of lytic bone lesions (not including compression fractures); or</p> <p>(f) at least a 25% increase in the size of an existing or the development of a new soft tissue plasmacytoma (determined by clinical examination or diagnostic imaging); or</p> <p>(g) development of hypercalcaemia (corrected serum calcium greater than 2.65 mmol per L not attributable to any other cause).</p>

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	<p>Oligo-secretory and non-secretory patients are defined as having active disease with less than 10 g per L serum M protein.</p> <p>Patients receiving this drug under the PBS listing must be registered in the i-access risk management program.</p> <p>Note</p> <p>Authority applications for continuing treatment may be made by telephone to the Department of Human Services on 1800 700 270 (hours of operation 8 a.m. to 5 p.m. EST Monday to Friday).</p>
<b>Cautions</b>	<p>This drug is a category X drug and must not be given to pregnant women. If lenalidomide is taken during pregnancy, a teratogenic effect of lenalidomide in humans cannot be ruled out.</p>

## **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 welcomes the positive recommendation for the listing of lenalidomide monotherapy as a maintenance treatment in patients with newly diagnosed multiple myeloma (NDMM) who have undergone an autologous stem cell transplant (ASCT) and would like to acknowledge the contribution of clinicians, patients and advocacy groups in helping the PBAC recognise the importance of this medicine for patients living with MM in Australia.