

## 6.11 LENALIDOMIDE capsules, 5mg, 10mg, 15mg and 25mg Revlimid®, Celgene Pty Ltd.

### 1 Purpose of Application

- 1.1 To seek a Section 100 (Highly Specialised Drugs) listing for lenalidomide when given in combination with dexamethasone for the treatment of patients with newly diagnosed symptomatic multiple myeloma (NDMM) who are ineligible for stem cell transplant.

### 2 Requested listing

Name, Restriction, Manner of administration and form	Max. Qty	No. of Rpts	Dispensed Price for Max. Qty*	Proprietary Name and Manufacturer
LENALIDOMIDE Capsules 5mg	21	0	\$5,392.38 (Public hospital) \$█ (Effective price) \$5,439.31 (Private hospital)	Revlimid® CJ
Capsules 10mg	21	0	\$█ (Effective price) \$5,643.33 (Public hospital) \$█ (Effective price) \$5,691.07 (Private hospital)	Revlimid® CJ
Capsules 15mg	21	0	\$█ (Effective price) \$6,581.61 (Public hospital) \$█ (Effective price) \$6,628.54 (Private hospital)	Revlimid® CJ
Capsules 25mg	21	0	\$█ (Effective price) \$6,934.20 (Public hospital) \$█ (Effective price) \$6,981.13 (Private hospital) \$█ (Effective price)	Revlimid® CJ

Note: \* the DPMQ for private hospitals was increased by \$0.17 per pack to account for the increase in the dispensing fee from \$6.76 to \$6.93 on 1 July 2015.

Treatment phase: Initial PBS subsidised treatment	
Clinical condition	Symptomatic multiple myeloma
Restriction	Section 100 Private Hospital/Private Clinic Authority Required and Public Hospital Authority Required
Clinical criteria	Patient must be newly diagnosed, AND Patient must be ineligible for stem cell transplant, AND Patient must not be receiving PBS subsidised thalidomide or bortezomib, AND The treatment must be in combination with dexamethasone, AND Patient must be registered in the i-access risk management program.
Treatment phase: Continuing PBS subsidised treatment	
Clinical criteria	Patient must have received an initial authority prescription for lenalidomide for newly diagnosed symptomatic multiple myeloma and be ineligible for stem cell transplant, AND Patient must not have demonstrated progressive disease at the time of application,

	AND Patient must not be receiving PBS subsidised thalidomide or bortezomib, AND The treatment must be in combination with dexamethasone, AND Patient must be registered in the i-access risk management program.
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- 2.1 The submission sought listing for lenalidomide on the basis of a cost-utility analysis comparing lenalidomide plus dexamethasone (Rd) against thalidomide plus melphalan plus prednisone (or prednisolone) (MPT).

### **3 Background**

- 3.1 The submission was made under TGA/PBAC Parallel Process. At the time of PBAC consideration, a first round clinical evaluation report (CER), the TGA Delegate's overview and the ACPM Outcome report were available.
- 3.2 The PBAC noted that a broad TGA indication of 'treatment of multiple myeloma' was sought. The TGA Delegate and the ACPM have approved the proposed indication, however the recommendation has restricted the use of lenalidomide to newly diagnosed multiple myeloma patients who are ineligible for autologous stem cell transplantation.
- 3.3 This was the first application to the PBAC for the requested restriction. Lenalidomide is currently listed on the PBS for the treatment of patients with multiple myeloma (MM) for whom thalidomide therapy has failed or in whom there is severe intolerance or toxicity to thalidomide.

### **4 Clinical place for the proposed therapy**

- 4.1 Multiple myeloma is a B-cell neoplasm that is characterised by the accumulation of clonal plasma cells in the bone marrow. The submission proposed that lenalidomide should be a first-line option for patients with symptomatic MM who are ineligible for stem cell transplant.

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

### **5 Comparator**

- 5.1 The submission nominated thalidomide (as MPT). Bortezomib was nominated as a secondary 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.

## **Consumer hearing**

- 6.2 Representatives of the PBAC met with Leukaemia Foundation prior to the PBAC meeting. The following paragraphs provide a summary of the discussion in relation to the agenda item for multiple myeloma.
- 6.3 A key to achieving the best possible treatment outcomes in myeloma is for the patient to be able to tolerate more lines of therapy. Access to the best possible option early in the treatment pathway is important, as is the reduction in adverse events – neurotoxicity is considered a dose-limiting factor in the case of thalidomide.
- 6.4 The availability of oral agents is highly attractive to patients being treated for myeloma. In the case of bortezomib, the dosing schedule requires regular infusions which present a substantial burden on patients.
- 6.5 The following points relating to the PBS treatment algorithm for myeloma were discussed:
- Bortezomib is available in first line and for rechallenge – this gives access to an effective drug in a certain patient group;
  - While treating a patient, clinicians are mindful of potential options further down the algorithm so as to preserve the patient's eligibility for the maximum number of therapeutic options;
  - Lenalidomide will likely be used until disease progression, were it to be recommended in first-line treatment. The condition is believed to evolve as the patient is exposed to different lines of therapy, and anecdotally it has been reported that patients can respond to lenalidomide rechallenge following a failure to respond to initial exposure to the drug.
- 6.6 The Committee heard that if lenalidomide were to be recommended for first-line treatment, it would likely replace bortezomib and thalidomide.
- 6.7 Of particular note, the current listing for lenalidomide does not permit retreatment after disease progression – this position is not supported by the clinical or patient communities.

## **Consumer comments**

- 6.8 The PBAC noted and welcomed the input from a health care professional via the Consumer Comments facility on the PBS website. The comments expressed concern regarding the current PBS restriction for lenalidomide, which permits use only as second-line treatment, as long as there is no disease progression, with no break in treatment allowed. The comments described the clinical complications that may arise from indefinite treatment with lenalidomide (e.g. bone marrow toxicity, secondary malignancy, neuropathy etc.). The comments noted that where a patient has shown good response to lenalidomide and then discontinued treatment, they are not permitted to be re-treated under the PBS restrictions as agreed with the sponsor, but must instead try 'more expensive, inconvenient, treatment with no guarantee of response', which was viewed as clinically and economically inappropriate.

## Clinical trials

- 6.9 The submission was based on one head-to-head trial comparing lenalidomide plus dexamethasone (Rd) to thalidomide (as MPT) (MM-020; N=1,623).
- 6.10 Details of the trial presented in the submission are provided in the table below.

**Table 1: Trial presented in the submission**

Trial ID/First Author	Protocol title/ Publication title	Publication citation
<b>Direct randomised trial</b>		
MM-020	A phase 3, randomised open-label, 3-arm study to determine the efficacy and safety of lenalidomide (Revlimid®) plus low-dose dexamethasone when given until progressive disease or for 18 four-week cycles versus the combination of melphalan, prednisone, and thalidomide given for 12 six-week cycles in patients with previously untreated multiple myeloma who are either 65 years of age or older or not candidates for stem cell transplantation (IFM 07-01)	23/12/2013
	Bemboubker et al. Lenalidomide and dexamethasone in transplant ineligible patients with myeloma	<i>N Engl J Med</i> 2014; 371(10):906-17

Source: Table B.3, p32 of the submission

- 6.11 The key features of the direct randomised trial are summarised in Table 2.

**Table 2: Key features of the included evidence**

Trial	N	Design/duration*	Risk of bias	Patient population	Outcomes	Use in modelled evaluation
MM-020	1,623	R, OL, MC, AB 37.0 months	Low	NDMM	PFS, OS, utility values	Extrapolated OS and PFS

AB=assessor blinded; MC=multi-centre; OL=open label; OS=overall survival; PFS=progression-free survival; R=randomised; NDMM=newly diagnosed multiple myeloma.

\*Median duration of follow-up for 24 May 2013 data cut-off; For OS median duration of follow-up was 45.5 months at 3 March 2014 data cut-off

Source: compiled during the evaluation

- 6.12 The submission also provided a supplementary multi-step indirect comparison of Rd to bortezomib, which was based on a comparison of Rd to MPT, MPT to MP, and MP to bortezomib in combination with melphalan and prednisone (VMP). The results of this comparison were not used in the economic model and were considered uninformative for the current evaluation. The ESC concurred with the Commentary.

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

## Comparative effectiveness

- 6.13 Progression-free survival (primary outcome): Rd treated patients had statistically significantly longer median progression-free survival compared to MPT with a gain of 4.3 months at the first data cut-off of 24 May 2013. As stated in the CSR (p102), this gain in progression-free survival is lower than the percentage improvement considered to be clinically relevant (25%). The ESC noted and agreed with Pre-Sub-Committee Response (PSCR, p2) that the improvement in median PFS was not in reference to the minimal important clinical difference but rather the determination of

the sample size of the clinical trial. The ESC acknowledged the issues and considered that the statistically significant results in OS supported the claim for a clinical benefit.

- 6.14 Overall survival (secondary outcome): Rd treated patients had statistically significantly longer overall survival compared to MPT with a gain of 10.4 months at the later data cut-off of 3 March 2014.

**Table 3: Results of progression free and overall survival across Trial MM-020**

	Rd (n=535)	MPT (n=547)	Absolute difference	HR (95% CI)
<b>24 May 2013 cut-off</b>				
Median PFS (months) (95% CI)	25.5	21.2	4.3	0.72 (0.61, 0.85)
<b>3 March 2014 cut-off</b>				
Median OS (months) (95% CI)	58.9	48.5	10.4	0.75 (0.62, 0.90)

Rd=lenalidomide plus dexamethasone; MPT=melphalan plus prednisone plus thalidomide; PFS=progression-free survival; OS=overall survival

Source: Table B.16, p48 and of the submission, and Table 39, p129 of the clinical study report (CSR)

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

## Comparative harms

- 6.15 During the trial most patients in both treatment groups experienced a treatment related adverse event and a similar proportion of patients experienced a serious treatment related adverse event. More patients in the Rd treatment arm experienced grade 3 cataract and more patients in the MPT treatment arm experienced grade 3 or neutropenia and/or peripheral sensory neuropathy at the first cut-off date. The differences for neutropenia and peripheral sensory neuropathy were statistically significant. While deaths during active treatment were lower on Rd compared to MPT, the ESC noted there was a statistically significant difference for cardiac related death, with more patients in the Rd treatment arm experiencing this event during the active treatment phase of Trial MM-020.

**Table 4: Summary of key adverse events in MM-020 at 24 May 2013 data cut-off**

	Rd (N=532)	MPT (N=541)	RD % (95% CI)
At least one TEAE	529 (99.4%)	539 (99.6%)	-0.2 (-5.4, 2.7)
At least one serious AE	359 (67.5%)	270 (49.9%)	17.6 (4.4, 31.0)
Neutropenia (grade 3 or 4)	148 (27.8%)	243 (44.9%)	-17.1 (-29.8, -3.6)
Peripheral sensory neuropathy (grade 3 or 4)	6 (1.1%)	51 (9.4%)	-8.3 (-15.3, -2.4)
Cataract (grade 3)	31 (5.8%)	3 (0.6%)	5.2 (-0.14, 11.6)

AE=adverse event; Rd=lenalidomide plus dexamethasone; MPT=melphalan plus prednisone plus thalidomide; RD=risk difference; TEAE=treatment emergent adverse event

Source: Tables B.27-B.34, p63-70 of the submission

## Benefits/harms

- 6.16 A summary of the comparative benefits and harms for Rd versus MPT is presented in Table 5.

**Table 5: Summary of comparative benefits and harms for Rd and MPT**

<b>Benefits</b>						
<b>PFS/OS: Trial MM-020</b>						
	<b>Rd</b>	<b>MPT</b>	<b>Absolute difference</b>	<b>HR (95% CI)</b>		
<b>PFS May 2013 cut-off</b>						
Progressed	222/535	278/547		0.72		
Median PFS (months)	25.5	21.2	4.3	(0.61, 0.85)		
<b>OS May 2013 cut-off</b>						
Died	173/535	209/547		0.78		
Median OS (months)	55.1	48.2	6.9	(0.64, 0.96)		
<b>OS March 2014 cut-off</b>						
Died	208/535	261/547		0.75		
Median OS (months)	58.9	48.5	10.4	(0.62, 0.90)		
<b>Harms</b>						
<b>Trial</b>	<b>Rd</b>	<b>MPT</b>	<b>RR (95% CI)</b>	<b>Event rate/100 patients*</b>		<b>RD % (95% CI)</b>
				<b>Rd</b>	<b>MPT</b>	
<b>Grade 3 or 4 neutropenia</b>						
MM-020	148/532	243/541	0.84 (0.57, 1.22)	27.8	44.9	-17.1 (-29.8, -3.6)
<b>Grade 3 or 4 cataract</b>						
MM-020	31/532	3/541	9.67 (1.11, 86.1)	5.8	0.6	5.2 (-0.14, 11.6)
<b>Grade 3 or 4 peripheral sensory neuropathy</b>						
MM-020	6/532	51/541	0.18 (0.02, 0.65)	1.1	9.4	-8.3 (-15.3, -2.4)

\* Median/duration of follow-up: 37.0 months for 24 May 2013 data cut-off and 45.5 months for 3 March 2014 data cut-off; Rd=lenalidomide plus dexamethasone; MPT=melphalan plus prednisone plus thalidomide; HR=hazard ratio; RD = risk difference; RR = risk ratio; PFS=progression-free survival; OS=overall survival  
Source: Compiled during the evaluation/Table B.27-B.34, p63-70 of the submission

- 6.17 On the basis of direct evidence presented by the submission, for every 100 patients treated with Rd in comparison to MPT:
- Approximately 10 fewer patients would have progressed over a median duration of follow-up of 37.0 months and 9 fewer patients died over a median duration of follow-up of 45.5 months;
  - Approximately 18 more patients would experience at least one serious adverse event over a median duration of follow-up of 37.0 months
  - Approximately 17 fewer patients would have grade 3 or 4 neutropenia over a median duration of follow-up of 37.0 months.
  - Approximately 8 fewer patients would have grade 3 or 4 peripheral sensory neuropathy over a median duration of follow-up of 37.0 months.

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

### **Clinical claim**

- 6.18 The submission described Rd as superior in terms of comparative effectiveness with a different safety profile compared to MPT, and better treatment tolerance compared to MPT. In relation to comparative effectiveness and safety, the ESC considered this claim was adequately supported.

- 6.19 The claim that treatment tolerance was better with Rd compared to MPT on the basis of less adverse events leading to discontinuation or a dose reduction was not considered adequately supported. The differences were not statistically significant.
- 6.20 While deaths during active treatment were lower on Rd compared to MPT, the ESC noted there was a statistically significant difference for cardiac related death, with more patients in the Rd treatment arm experiencing this event during the active treatment phase of Trial MM-020.

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

**Economic analysis**

- 6.21 The submission presented a modelled cost-utility analysis of Rd compared to MPT. The ESC noted that there was no trial-based evaluation included within the submission. The ESC considered that an evaluation of shorter duration (perhaps up until the March 2014 OS) cut-off using the observed data to demonstrate the extent to which the model is driven by the extrapolation and other model assumptions.

**Table 6: Summary of model structure and rationale**

<b>Component</b>	<b>Summary</b>
Time horizon	15 years in the model base case versus 45.5 months in Trial MM-020
Outcomes	LYG and QALYs
Methods used to generate results	Markov-like partitioned survival model
Health states	Three mutually exclusive states of pre-progression, post-progression and death (absorbing)
Cycle length	7 days
Transition probabilities	Economic model based on an extrapolation of PFS and OS

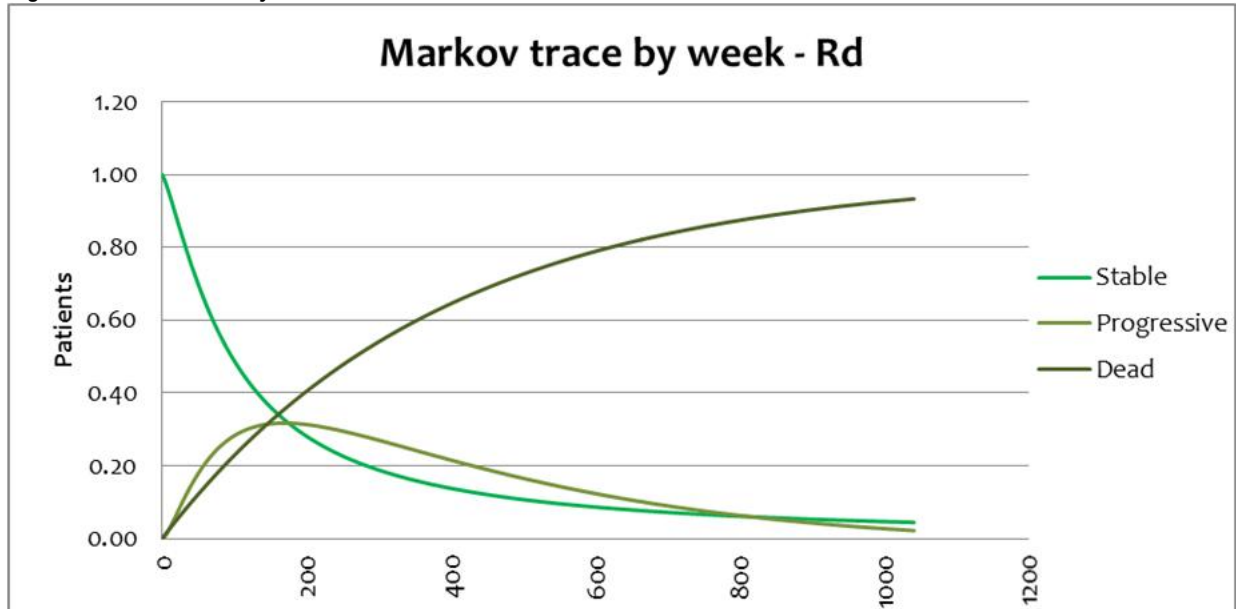
LYG=life years gained; QALYs=quality adjusted life years saved; PFS=progression-free survival; OS=overall survival  
 Source: compiled during the evaluation

**Table 7: Key drivers of the model**

Description	Method/Value	Impact
Cost of subsequent AMT pre-progression for MPT	Trial MM-020: Determination of number of patients who have only a partial response to MPT. Analysis of subsequent AMT from Trial MM-020 and an assumption of pre-progression therapy with either lenalidomide or bortezomib	High, favours Rd. Use of pre-progression AMT with lenalidomide or bortezomib for MPT treated patients who only have a partial response is extremely unlikely since these therapies are not able to be prescribed on the PBS for use in conjunction with thalidomide pre-progression. <i>PSCR refutes the commentary's claim and states that in practice it appears that the therapies are used in people who do not progress but have a poorer response.</i>
Cost of subsequent AMT post-progression for MPT and Rd	Analysis of subsequent AMT from Trial MM-020	Moderate, favours Rd. The cost of post-progression AMT is too high as use of therapies less costly than lenalidomide, thalidomide or bortezomib were not considered. Use of post-progression AMT was also assumed to continue until death or the end of the model, which will not occur.
Treatment effect	Parametric modelling: log-logistic for Rd and exponential for MPT for PFS, exponential for both Rd and MPT for OS	High, favours Rd. Use of other parametric curves to extrapolate OS has a large impact on the ICER. <i>Furthermore the long duration of model appears to be very favourable to RD. Given the age of the population modelled (73 years) by the end of 15 years a continued survival advantage (as present in the Figure 1 Markov traces) is optimistic.</i>
Utilities	van Agthoven 2004; 0.81 for stable disease; 0.64 for progressive disease; 0.77 at baseline	Moderate, favours Rd. The utilities from van Agthoven 2004 do not inform HrQoL for patients with NDMM due to differences in interventions <i>and populations</i> when compared to MM-020; and the inability ( <i>and the incorrectness</i> ) of the correction factor (0.19) to adequately inform utilities associated with the progressive disease health state. The use of trial based utilities for the health states is hampered by the use of best on study score for utility during treatment and reporting of utilities to only one decimal place. <i>Trial base utilities to 2-decimal places are included in the PSCR although it is not clear if they are still best on study scores.</i>

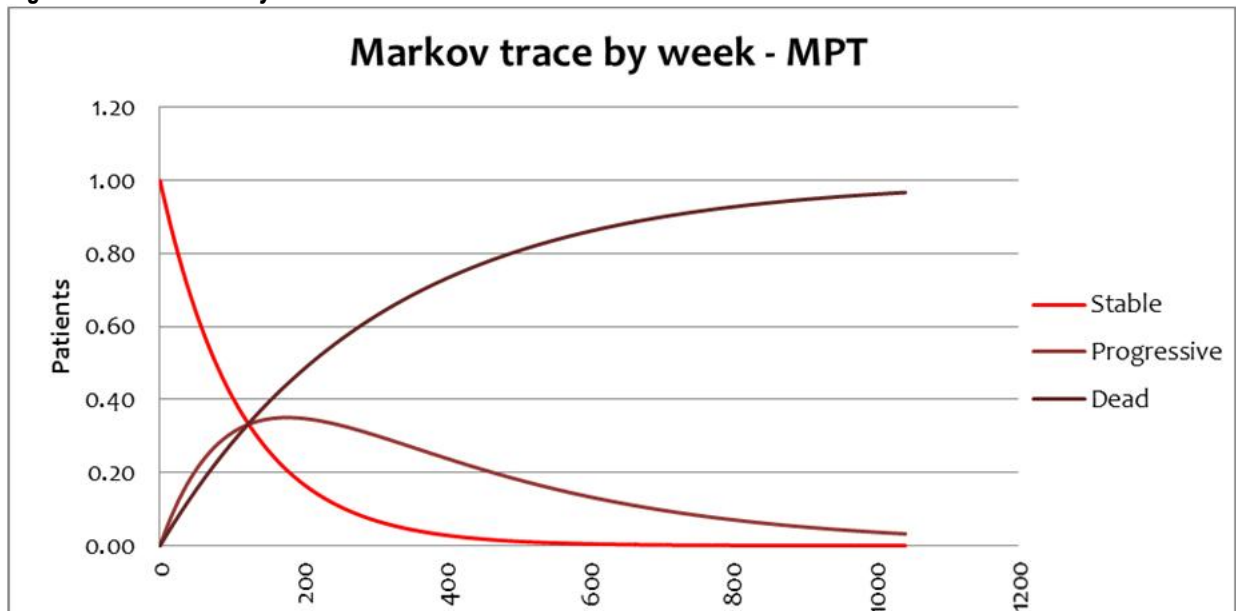
AMT=anti-myeloma therapy; PFS=progression-free survival; OS=overall survival; Rd=lenalidomide plus dexamethasone; MPT=melphalan plus prednisone plus thalidomide; HrQoL=health-related quality of life  
 Source: compiled during the evaluation

Figure 1: Markov trace by week for Rd



Rd=lenalidomide plus dexamethasone  
Source: Section D Microsoft Excel workbook

Figure 2: Markov trace by week for MPT



MPT=melphalan plus prednisone plus thalidomide  
Source: Section D Microsoft Excel workbook

6.22 The model presented by the submission used the published price for lenalidomide when it was used in subsequent AMT. The ESC noted that correction of this during the evaluation changed the ICER considerably, from a base case value of \$45,000/QALY – \$75,000/QALY to \$105,000/QALY – \$200,000/QALY (the \$45,000–\$75,000 ICER was calculated using updated 1 July 2015 PBS prices; the submission presented an ICER of \$45,000 – \$75,000).

**Table 8: Results of the economic evaluation**

	Rd	MPT	Increment
Costs	\$ [REDACTED]	\$282,451	\$ [REDACTED]
QALY	3.82	3.18	0.64
<b>Incremental cost/QALY saved</b>			<b>\$ [REDACTED]*</b>

Rd=lenalidomide plus dexamethasone; MPT=melphalan plus prednisolone plus thalidomide; QALY=quality adjusted life year

\*The ICER was corrected during the evaluation. The ICER presented in the submission (updated using 1 July 2015 PBS prices) of \$ [REDACTED] incorrectly used the published price of lenalidomide rather than the effective price in its calculations for the cost of subsequent AMT.

Source: Table D.9, p125 of the submission

6.23 While the use of the lenalidomide effective price for subsequent AMT therapy considerably altered the submission’s base case ICER, there remain further concerns with the modelled evaluation:

- The cost of MPT was largely driven by the cost of subsequent anti-myeloma therapy (AMT), prior to progressive disease for patients who have only a partial response to MPT. This is an artificial cost that is unlikely to be realised, given that neither lenalidomide nor bortezomib, which the submission assumed are the only therapies used, cannot be prescribed for patients taking thalidomide on the PBS.
- In addition, when these therapies are for second-line use the patient must have progressive disease prior to commencing treatment. Inclusion of the cost of pre-progression treatment for MPT treated patients resulted in a substantial underestimation of the ICER. With no AMT pre-progression, the ICER increases to \$105,000/QALY – \$200,000/QALY.
- The ESC noted that the PSCR maintained that the values and assumptions used in the submission’s base case were appropriate and reflected “real life” clinical practice. The ESC considered that if that is true, then it would indicate that these therapies are being used “off label”.
- In response to the commentary’s request of trial-based utility values to two decimal places and mean utility values on treatment, the PSCR provided additional analyses including the trial based utilities, a revised base case and sensitivity analysis reflecting new drug costs, based on the 3 march 2014 data cut-off, see tables 9,10 and 11 below. It should be noted that these revised ICERs are calculated using published prices, and will therefore underestimate the actual ICER.

**Table 9: Revised utility values**

Visit	Overall (N=960)	Mean
Baseline	865	0.51
Best score prior to PD	854	0.73
Score at PD	523	0.59
	<b>Rd</b>	<b>MPT</b>
Mean utility score on treatment	0.66	0.63
Score at PD	0.59	0.59

Source: Pre-Sub-Committee Response, p5

Table 10: Revised summary results and ICERs (See attached 'Revised Section D Workbook')

Note: treatment costs have been updated to reflect 1 July 2015 PBS published prices

Submission results	Discounted	Undiscounted
<b>Costs</b>	\$ [REDACTED]	\$ [REDACTED]
Lys	0.74	1.04
QALYs	0.65	0.90
<b>ICER (</b>		
Cost/LY	\$ [REDACTED]	\$ [REDACTED]
Cost/QALY	\$ [REDACTED]	\$ [REDACTED]
<b>Revised results (treatment costs have been updated to reflect 1 July 2015 PBS published price)</b>		
<b>Costs</b>	\$ [REDACTED]	\$ [REDACTED]
Lys	0.74	1.04
QALYs	0.65	0.90
<b>ICER</b>		
Cost/LY	\$ [REDACTED]	\$ [REDACTED]
Cost/QALY	\$ [REDACTED]	\$ [REDACTED]

Source: Pre-Sub-Committee Response, p5

Table 11: Based on the above revised base case, revised one way sensitivity analysis results (discounted) are presented below.

Analysis	Base Case	Worst case		Best case	
	Value	Value	Cost/QALY	Value	Cost/QALY
Time horizon (years)	15	10	\$ [REDACTED]	20	\$ [REDACTED]
Survival parameters - PFS					
Rd	Log-logistic	Weibull	\$ [REDACTED]	Exponential	\$ [REDACTED]
MPT	Exponential	Gompertz	\$ [REDACTED]	Weibull	\$ [REDACTED]
Survival parameters - OS					
Rd	Exponential	Log-logistic	\$ [REDACTED]	Weibull	\$ [REDACTED]
MPT	Exponential	Weibull	\$ [REDACTED]	Log-logistic	Dominant
Extrapolation method	Full	Partial	\$ [REDACTED]	NA	NA
Utilities	0.77; 0.81; 0.64	0.51; 0.73; 0.59	\$ [REDACTED]	NA	NA
		0.66 (Rd); 0.63 (MPT); 0.59	\$ [REDACTED]	NA	NA
Lenalidomide weighted price	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]
Dose intensity (mg/week)	90.4	99.4	\$ [REDACTED]	81.4	\$ [REDACTED]
Probability of subsequent pre-progression AMT (MPT)	34.2%	30.8%	\$ [REDACTED]	37.6%	\$ [REDACTED]
Cost of second-line treatment	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	NA	NA

Source: Pre-Sub-Committee Response, p5

- 6.24 Overall, the values chosen by the submission for use in the model favour Rd, and the submission’s approach to costing of subsequent AMT both pre- and post-progression indicates the model results were considered highly uncertain.

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

**Drug cost/patient/course: \$ [REDACTED].**

- 6.25 The cost of Rd per patient per course of \$ [REDACTED] assumed treatment at the same dose intensity in Trial MM-020 of 90.4mg/week until disease progression or death. The overall cost was based on modelled PFS and OS. While a similar dose intensity to the trial is likely in the PBS population, the overall duration of PFS and OS is uncertain. As such, the cost of Rd per patient per course may be different in clinical practice.

**Estimated PBS usage & financial implications**

- 6.26 This submission was not considered by DUSC. The submission used an epidemiological approach to estimate the number of patients with NDMM who are ineligible for a stem cell transplant, and a market share approach to estimate the proportion of patients likely to be displaced from MPT or bortezomib. The submission assumed 13.04 scripts of lenalidomide in Year 1 and 8.36 scripts in Year 2 per patient. The financial analysis was limited to the costs associated with first-line use only, and subsequent AMT was not costed.

**Table 12: Estimated use and financial implications**

	Year 1	Year 2	Year 3	Year 4	Year 5
<b>Estimated extent of use</b>					
Number treated <sup>a</sup>	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
Scripts <sup>b</sup>	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
<b>Estimated net cost to PBS/RPBS/MBS</b>					
Net cost to PBS/RPBS	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]
<b>Net cost to Government</b>	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]

<sup>a</sup> Updated numbers calculated during the evaluation. The number of patients ineligible for a stem cell transplant was corrected from 67% to 66%

<sup>b</sup> Assuming 13.04 scripts of lenalidomide in Year 1 and 8.36 scripts in Year 2 per patient, as estimated by the submission.

Source: Section E workbook, sheet E5

*The redacted table above shows that the number of patients treated with lenalidomide is estimated to be less than 10,000 per year at a net cost of \$20 – \$30 million in Year 1 to \$60 – 100 million in Year 5.*

- 6.27 While there is some potential that lenalidomide may be used outside of the requested restriction in patients eligible for stem cell transplant, but prior to stem cell transplant, thereby increasing the market size, the overall estimated number of patients is reasonable.
- 6.28 The financial estimates are most sensitive to increasing the duration of treatment for Rd. Increasing the duration of treatment from 21.4 to 26.07 cycles of 28-days (2 years of treatment) increases the financial estimate of the overall cost to the Government for the first 5 years of listing [REDACTED] to more than \$100 million. The ESC noted that the PSCR provided financial estimates to reflect the

updated and increased duration of treatment (3<sup>rd</sup> March 2014 23.3 treatment cycles), representing an overall cost to Government of more than \$100 million for the first 5 years of listing, based on revised base case and revised one way sensitivity analysis results as below.

Table 13: Revised net changes to Government health budgets (See attached 'Revised Section E Workbook')

Total net cost to Government health budgets	Year 1	Year 2	Year 3	Year 4	Year 5
Net cost to PBS/RPBS	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]
Net impact on other budgets	-\$ [REDACTED]	-\$ [REDACTED]	-\$ [REDACTED]	-\$ [REDACTED]	-\$ [REDACTED]
Total net cost to Government	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]

Note: treatment costs have been updated to reflect 1 July 2015 PBS published prices

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

### Quality Use of Medicines

6.29 The submission presented a description of the special distribution *i-access* program which is currently in place for lenalidomide.

### Financial Management – Risk Sharing Arrangements

6.30 There is an effective price for lenalidomide for relapsed/refractory MM. The submission requests the same effective price and the same published price for NDMM. A cap or a risk sharing arrangement was not specifically discussed in the submission.

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

## 7 PBAC Outcome

7.1 The PBAC deferred making a recommendation for the submission seeking to list lenalidomide in combination with dexamethasone (Rd) as first line therapy for patients who are newly diagnosed with multiple myeloma (NDMM) due to the appropriate comparators, the inclusion of many favourable assumptions to Rd in the presented the model and a highly uncertain and high ICER for the requested treatment setting.

7.2 The PBAC acknowledged there is a high clinical need for oral therapies in the treatment of multiple myeloma (MM). The PBAC welcomed the input received from the Consumer Hearing, which indicated a strong preference for oral therapies for the treatment of MM. The PBAC also noted and welcomed the input received from an individual healthcare professional in support of the submission.

7.3 The PBAC considered that mixed comparators of thalidomide and bortezomib would have been an appropriate basis for cost-effectiveness decision-making as PBS-subsidised bortezomib-based treatment is commonly used as first-line therapy in the

treatment of multiple myeloma (MM). The PBAC noted the submission's justification for its nomination of thalidomide as the only main comparator was based on the NCCN 2015 guidelines which recommend thalidomide-based regimens and lenalidomide-based regimen as primary first-line treatments for patients NDMM, and the guidelines recommend bortezomib-based regimens as optional only. The PBAC considered that the NCCN guidelines are tailored for the US health system, and noted that recently-published Australian guidelines recommend either thalidomide-based or bortezomib-based treatment as first-line therapy.

- 7.4 The PBAC noted that the submission's estimate that 5-10% of MM patients would use lenalidomide-based therapy to replace bortezomib-based therapy. The PBAC considered this was an underestimate, and noted it was inconsistent with the submission's claim of lenalidomide-based treatment is superior to bortezomib-based treatment in the presented supplementary indirect comparison (pg 74). Moreover, as mentioned above, at the Consumer Hearing there was a strong preference for oral therapies, so it may reasonably be expected that the lenalidomide-based therapy substitution for bortezomib-based therapy is likely much higher than estimated, should lenalidomide be listed for first-line therapy. Therefore, the PBAC considered that bortezomib should have also been considered a relevant main comparator.
- 7.5 The PBAC also noted that the primary data that directly inform the current split between thalidomide-based and bortezomib-based first line therapy in transplant-ineligible patients were not provided. The submission's estimates of 64% and 36% for the currently receiving thalidomide or bortezomib, respectively, as first line therapy were therefore based on untested assumptions. The methodology used in the submission most likely underestimated the proportion of patients currently receiving bortezomib-based as first-line therapy. The PBAC therefore considered that data obtained from Australian registry could have been informative.
- 7.6 The submission presented a head to head comparison between lenalidomide plus dexamethasone (Rd) and thalidomide (as MPT) (MM-020). The submission also presented a supplementary multi-step comparison of lenalidomide to bortezomib, which was based on a comparison of Rd to MPT, MPT to MP, and MP to bortezomib in combination with melphalan and prednisone (VMP). The PBAC noted that the results of this indirect comparison were not used in the economic model the subsequent effect on the cost effectiveness of lenalidomide could not be evaluated. The PBAC considered that the mature follow-up of the VISTA trial has confirmed the survival advantage of VMP over MP, while more recent comparisons between MP and MPT than considered by PBAC previously have created uncertainty about the magnitude of the survival benefit of thalidomide over MP when modern salvage therapies are available. The PBAC considered that the informal comparison of survival data for Rd (March 2014 cut-off) and mature data for bortezomib-based therapy (San Miguel 2013) do not suggest greater survival for patients treated with lenalidomide-based therapy. The PBAC therefore considered that a more detailed evaluation of the indirect comparison is necessary.
- 7.7 With respect to trial MM-020, the PBAC agreed with the ESC that the claim of treatment tolerance was better with lenalidomide-based therapy compared to thalidomide-based therapy on the basis of less adverse events leading to discontinuation or a dose reduction was not adequately supported and that the differences were not statistically significant.

- 7.8 The PBAC noted the ESC's concerns regarding that statistically significantly more patients had cardiac related death in the lenalidomide-based treatment arm during the active treatment phase of Trial MM-020 has been addressed by the sponsor's Pre-PBAC response (pg1). The sponsor had clarified that the higher percentage of deaths during active treatment on lenalidomide-based therapy compared with thalidomide-based therapy was due to the longer duration of treatment associated with lenalidomide compared with thalidomide (9.6% vs.7.0%), but was lower over the duration of the study (32.1% vs.38.4%). It was noted that the majority of events occurred in patients with pre-existing cardiac disease, and that many of the events occurred within the first 6 months of therapy.
- 7.9 The PBAC noted an improvement of 4.3 months in median progression free survival (PFS) was observed at the pre-specified analysis point, after a median duration of follow-up of 37 months. An estimated median overall survival (OS) of 58.9 months after a median duration of follow-up of 45.5 months, representing an estimated improvement of 10.4 months in OS compared with thalidomide, was observed for patients receiving lenalidomide. The PBAC agreed with the ESC that the statistically significant results in OS supported the submission's claim of superior comparative effectiveness and a different safety profile compared to thalidomide.
- 7.10 The submission presented a modelled cost-utility analysis of lenalidomide-based therapy compared to thalidomide-based therapy. The ESC noted that there was no trial-based evaluation included within the submission. The ESC considered that an evaluation of shorter duration (perhaps up until the March 2014 OS) cut-off using the observed data to demonstrate the extent to which the model is driven by the extrapolation and other model assumptions. The PBAC agreed with the ESC that a trial-based evaluation would have been informative.
- 7.11 The reliability of the ICER given that the submission's approach towards subsequent anti-myeloma therapies (AMT) in the model did not reflect treatment in the clinical setting and overestimated future costs, particularly for thalidomide treated patients. The ESC noted that changing costs to only patients with designated PD substantially increased the ICER. The PSCR maintained the submission's approach to partially responsive patients. This was considered an important issue as it substantially impacts the ICER, increasing it to over \$105,000/QALY – \$200,000/QALY. The PSCR argued that the approach was appropriate, and correctly identify that patient not achieving a PR on thalidomide-based therapy may commence second-line therapy if not in PR after at least two months of therapy. However, the sponsor incorrectly stated that most of these patients will have features of progressive disease. The PBAC considered that using such an approach in the economic model diverges the model from the trial design which did not allow pre-progression change of therapy except for toxicity. The effect of moving to a second line therapy pre-progression on PFS and OS is not known, but could delay progression and disease-related mortality, thereby diminishing the clinical benefits observed in the trial. Therefore the base case ICER favours Lenalidomide, and is highly uncertain.
- 7.12 The use of utilities from van Agthoven 2004 was considered inappropriate. These utilities were not representative of the target population for this submission and have been incorrectly adjusted. The main pivotal trial collected EQ 5D data, however the trial based utilities were not used to inform the economic model. The reasons given

- by the submission for not using these utilities was unsatisfactory. The PSCR provided revised utility values using 0.51 at baseline, 0.73 best score prior to progressive disease and 0.59 at progressive disease. The PBAC noted that the Sponsor adjusted the base case ICER to manage this issue.
- 7.13 The PBAC overall noted that several of the issues in the economic analysis such as the inappropriate use of utilities from van Agthoven 2004 instead of the trial-based utilities, inconsistent prices for lenalidomide in calculation of the cost of first line therapy and subsequent anti multiple myeloma therapy (AMT); and the inadequate justification for the use of a log-logistic curve in the base case analysis for progression free survival in Rd arm were addressed in the Pre-PBAC response. However, the PBAC considered that the two key issues of pre-progression second line therapy and an extrapolation of clinical benefits to 15 years remained.
- 7.14 Regarding the issue of pre-progression second line therapy, the PBAC noted that pre-progression therapy is allowed on the PBS for patients initiating with thalidomide if they fail to achieve at least a minimal response after at least eight weeks of therapy. However, the PBAC noted the trial did not allow pre-progression changes to other therapies except for toxicity and the impact of second therapy pre-progression on PFS and OS was not informed by the trial. The PBAC therefore considered that the trial-based hazard ratios were likely to overestimate the treatment benefit of Rd if applied to a model that includes pre-progression AMT; and that the impact may be high, favour Rd and generate significant uncertainty. The PBAC therefore considered the presented base case ICER favours Rd and is highly uncertain.
- 7.15 Regarding the issue of extrapolation of clinical benefits to 15 years, the PBAC considered that time horizon of 15 years may be appropriate duration in the model for first-line myeloma therapy in this population. However, the PBAC considered that the assumption of a survival advantage throughout the model is optimistic and favours Rd. The PBAC also noted that most QALYG are accrued in the extrapolations 10+ years post trial, and there was no trial-based evaluation to support these findings. The PBAC recommended that convergence be modelled earlier, by year 12 for PFS, year 15 for OS and adjustments from year 10 would be required.
- 7.16 The PBAC noted the cost of post-progression AMT is too high as use of therapies less costly than lenalidomide, thalidomide or bortezomib were not considered and that treatment was assumed to continue until death or the end of the model, which will not happen. The PBAC considered that the proposed treatment algorithms should Rd be PBS-subsidised and the assumption that patients will receive thalidomide-based therapy after a failure of Rd are questionable. The PBAC considered that whilst it would be true if this was the only change to the existing lenalidomide (and Bortezomib) restrictions, it would be clinically inappropriate to use thalidomide immediately after the failure of lenalidomide, and additional changes to the restriction will be required. The PBAC considered it would be informative that this was considered as part of the submission and this would reduce uncertainties.
- 7.17 The submission used an epidemiological approach to estimate the number of patients with NDMM who are ineligible for a stem cell transplant, and a market share approach to estimate the proportion of patients likely to be displaced from MPT or bortezomib. As mentioned previously, PBAC considered these estimates are uncertain, because of significant uncertainty about the current split between bortezomib-based therapy and thalidomide-based first line therapy.

- 7.18 The PBAC noted that there is potential for use outside restriction in patients who are eligible for stem cell transplant. Rd could be used prior to stem cell transplant, thereby increasing the market size. The PBAC considered that the estimated market size is highly uncertain.
- 7.19 The PBAC also noted that the financial estimates were most sensitive to increasing the duration of treatment for Rd. The submission's assumption of a mean duration of therapy of 21.4 cycles for Rd substantially underestimates costs. Increasing the duration of treatment from 21.4 to 26.07 cycles of 28-days (2 years of treatment) increases the financial estimate of the overall cost to the Government for the first 5 years of listing [REDACTED] to more than \$100 million. The PBAC noted that the PSCR provided revised financial estimates, based on a revised base case and revised one way sensitivity analysis results, to reflect the updated and increased duration of treatment (3<sup>rd</sup> March 2014 23.3 treatment cycles), representing an overall cost to Government of more than \$100 million for the first 5 years of listing. The PBAC considered that this is likely to underestimate average use, as the trial is ongoing, and contributes significant uncertainties in the financial estimates. The PBAC therefore considered the way to mitigate the uncertainties is by having a cap in place, with rebate to price of thalidomide when exceeded.
- 7.20 Overall, the PBAC considered the economic analysis and the financial estimates provided by the sponsor are highly uncertain, with most of the issues identified likely to favour Rd in the model. The economic modelling proposed by the sponsor did not provide a basis for the PBAC to be satisfied that the cost-effectiveness of Rd could be established. The PBAC recommended that the financial estimate should account for more realistic estimation of market shares compared with bortezomib.
- 7.21 Based on the adjustments made by the sponsors in the Pre-PBAC response, adjustments required following PBAC deliberations, and with knowledge of committee-in-confidence information not available to the sponsor, a re-specified base case was constructed. This estimated a robust ICER of \$75,000/QALY-\$105,000/QALY. The PBAC considered that this approach did reliably inform decision-making about cost-effectiveness. The PBAC considered that to be cost-effective, the price should be reduced to bring the ICER to less than \$45,000/QALY – \$75,000/QALY. Further, it recommended that a financial cap be implemented to mitigate the significant financial risk created by uncertainties surrounding use outside the restriction, with a rebate to the price of thalidomide to be required if when the cap is exceeded.

**Outcome:**

Deferred

**8 Context for Decision**

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

**9 Sponsor's Comment**

The sponsor had no comment.