5.13 POMALIDOMIDE, capsules, 3 mg and 4 mg, Pomalyst®, Celgene Pty Ltd.

1 Purpose of Application

1.1 To seek a Section 100 (Highly Specialised Drugs) listing for pomalidomide for treatment of patients with multiple myeloma who have previously received and failed, or are intolerant to, treatment with lenalidomide and bortezomib.

2 Requested listing

2.1

Name, Restriction, Manner of administration and form	Max. Qty	№.of Rpts	Proprietary Name and Manufacturer	
Initial Treatment POMALIDOMIDE Capsules 3 mg	21	5	Pomalyst®	Celgene
Capsules 4 mg	21	5		
Continuing Treatment POMALIDOMIDE Capsules 3 mg	21	5	Pomalyst®	Celgene
Capsules 4 mg	21	5		

Condition:	Multiple myeloma
Treatment phase:	Initial
Restriction:	Section 100 (Highly Specialised Drugs Program) Public Hospital Authority Required Private Hospital Authority Required
Clinical criteria:	The treatment must be in combination with dexamethasone, AND Patient must have undergone or be ineligible for a primary stem cell transplant, AND Patient must have experienced treatment failure with the last lenalidomide-containing regimen or be intolerant to lenalidomide, AND Patient must have experienced treatment failure with the last bortezomib-containing regimen or be intolerant to bortezomib, AND Patient must not be receiving concomitant PBS-subsidised thalidomide, lenalidomide or bortezomib.

Condition:	Multiple myeloma

Treatment phase:	Continuing
Restriction:	Section 100 (Highly Specialised Drugs Program) Public Hospital Authority Required Private Hospital Authority Required
Clinical criteria:	Patient must have previously received an authority prescription for pomalidomide, AND Patient must not have progressive disease, AND The treatment must be in combination with dexamethasone.

2.2 Listing was sought on a cost-utility basis compared to high dose dexamethasone (HDD).

2.3 In the Pre-Sub-Committee Response (PSCR, p1), the sponsor notes the issues raised about the proposed restriction in the Commentary, and indicates a willingness to work with the PBAC and Restrictions Working Group to define a workable version of the restriction.

2.4 The ESC noted that in the key clinical trial (MM-003), the pomalidomide dose reduction regimen allowed for doses of 1 and 2 mg and questioned whether there were any implications if listing did not also include the 1 and 2 mg capsule strengths. The median relative dose intensity in the pivotal study was 0.9 (p59 Clinical Evaluation Report) where the median daily dose was 4 mg.

2.5 In the Pre-PBAC response, the sponsor claims that very few subjects in the study were administered a dose less than 3 mg and it is expected that utilisation of the lower dose tablets in real world practice would be minimal. The sponsor states that they are prepared to consider [redacted] if deemed appropriate by the PBAC and the Restrictions Working Group.

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

3 Background

3.1 Pomalidomide was TGA registered on 1 July 2014: "Pomalidomide, in combination with dexamethasone, is indicated for the treatment of patients with relapsed and refractory multiple myeloma who have received at least two prior treatment regimens, including both lenalidomide and bortezomib, and have demonstrated disease progression on the last therapy".

3.2 The submission was made under TGA/PBAC Parallel Process.

3.3 This submission has not been considered previously by the PBAC.

4 Clinical place for the proposed therapy

4.1 The submission proposes that pomalidomide should be a last line option for the treatment of multiple myeloma, a rapidly progressive disease for which there is no effective cure.

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

5 Comparator

5.1 The submission nominates high dose dexamethasone (HDD) as the main comparator. The arguments provided in support of this are that HDD was used as the comparator for both lenalidomide and bortezomib in their respective PBAC applications. The submission asserts that use of placebo as a comparator would be likely to overestimate the benefit of pomalidomide. The submission states that nominating HDD as the comparator is a conservative choice, and that clinical evidence is available for pomalidomide versus HDD.

5.2 The ESC noted that the Commentary suggests that HDD as the comparator rather than placebo will likely underestimate effectiveness but also overestimate safety, as the toxicity of pomalidomide versus placebo is likely to be greater than the toxicity compared to HDD. The ESC advised that this needed to be considered in the interpretation of the clinical evidence.

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

6 Consideration of the evidence

Sponsor hearing

6.1 There was no hearing for this item.

Consumer comments

6.2 The PBAC noted and welcomed the input from individuals (175) and organisations (1) via the Consumer Comments facility on the PBS website. The comments described a range of benefits of treatment with pomalidomide including giving patients more time until the next advancement or cure, the convenience of an oral dose form, need for affordability of the drug, and an unmet need in patients with relapsed/refractory myeloma following failure of lenalidomide and bortezomib.

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

Clinical trials

6.3 The submission is based on one head-to-head randomised trial (MM-003) comparing pomalidomide plus low dose dexamethasone (LDD) to HDD. The trial was conducted across Europe, the UK, Canada, Russia and the United States, with 10 sites in Australia. Two supplementary phase I/II randomised trials are also provided. Trial MM-002 compares different doses of pomalidomide and LDD. Trial 2009-02 compares a 21-day treatment cycle versus a 28-day treatment cycle of pomalidomide in combination with LDD. A table summarising the trials and associated reports presented in the submission is shown below.

Trials and associated reports presented in the submission

Trial ID	Protocol title/ Publication title	Publication citation
Direct randomised trial		

Trial ID	Protocol title/ Publication title	Publication citation
MM-003	Internal study report title. CSR MM-003 A phase 3, multicentre, randomised, open-label study to compare the efficacy and safety of pomalidomide in combination with low-dose dexamethasone versus high-dose dexamethasone in patients with refractory or relapsed and refractory multiple myeloma.	-
MM-003/Miguel J.S.	Miguel J.S. Weisel K. Moreau P. Lacy M. et. al. A randomised, open-label, phase 3 trial.	*Lancet Oncology* 2013, 14(11): 1055-1066
MM-003/Weisel K.C.	Weisel K.C. Dimopoulos M.A. Moreau P. Lacy M. et. al. Pomalidomide plus low-dose dexamethasone (POM + LoDEX) versus high-dose dexamethasone (HiDEX) in relapsed/refractory multiple myeloma (RRMM): MM-003 analysis of patients (pts) with moderate renal impairment (RI).	*Journal of Clinical Oncology* 2013, 31(15): Suppl 1
MM-003/Goldschmidt H.	Goldschmidt H. Dimopoulos M.A. Weisel K.C. Moreau P. et. al. Pomalidomide plus low-dose dexamethasone (POM + LoDEX) versus high-dose dexamethasone (HiDEX) in relapsed/refractory multiple myeloma (RRMM): Impact of cytogenetics in MM-003.	*Journal of Clinical Oncology* 2013, 31(15): Suppl 1
MM-003/San-Miguel J.F.	San-Miguel J.F. Weisel K.C. Moreau P. Lacy M. et. al. MM-003: A phase III, multicenter, randomized, open-label study of pomalidomide plus low-dose dexamethasone (LoDEX) versus high-dose dexamethasone (HiDEX) in relapsed/refractory multiple myeloma (RRMM).	*Journal of Clinical Oncology* 2013, 31(15): Suppl 1
MM-003/Song K.W.	Song K.W. Dimopoulos M.A. Weisel K.C. Moreau P. et. al. Quality of life (QOL) improvements for pomalidomide plus low-dose dexamethasone (POM + LoDEX) in relapsed and refractory multiple myeloma (RRMM) patients (pts) enrolled in MM-003.	*Journal of Clinical Oncology* 2013, 31(15): Suppl 1
MM-003/Dimopoulos M.A.	Dimopoulos M.A. Lacy M.Q. Moreau P. Weisel K.C. et. al. Pomalidomide in combination with low-dose dexamethasone: Demonstrates a significant progression free survival and overall survival advantage, in relapsed/refractory MM: A phase 3, multicenter, randomized, open-label study.	*Blood* 2012; 120:21

Source: Table B-3, p32 of the submission

6.4 The table below provides key features of the direct randomised trial comparing pomalidomide plus low dose dexamethasone (LDD) to HDD for the treatment of rrMM.

Key features of the included evidence

Trial	N	Design/ duration	Risk of bias	Patient population	Outcomes	Use in modelled evaluation
Pomalidomide plus LDD versus HDD						
MM-003	455	R, OL, MC Up to disease progression (max 93 weeks/ 21.5 mths)	Low	Relapsed and/or refractory multiple myeloma in patients who failed prior bortezomib and lenalidomide	PFS, OS	PFS and adjusted OS used

DB=double blind; MC=multi-centre; OL=open label; OS=overall survival; PFS=progression-free survival; R=randomised.
Source: compiled during the evaluation

6.5 The trial population was largely representative of the PBS treatment population. It is likely that a greater proportion of patients in Australia will have received prior treatment with thalidomide than trial patients and Australian patients are less likely to have received vincristine or nitrosureas. On the basis of subgroup analyses stratified by thalidomide treatment exposure, the submission suggests that patients with prior exposure to thalidomide may do better on pomalidomide therapy than those with no prior exposure; possibly underestimating the PFS results of pomalidomide reported in the trial compared to the likely real world setting. No statistical analysis was conducted to support this possibility. Subgroup analysis of outcomes stratified by

vincristine treatment has not been provided. The PSCR (p1) notes that no subgroup analysis of outcomes by prior vincristine treatment was undertaken as part of the study.

6.6 The ESC agreed that there were potential applicability issues given the higher percentage of trial patients receiving vincristine and the lower percentage of trial patients receiving thalidomide at baseline, when compared with the baseline characteristics of the population in the Named Patient Program (NPP). Vincristine does not appear to be used in this disease context in Australia (Multiple Myeloma Clinical Practice Guideline 2012, Medical Scientific Advisory Group to the Myeloma Foundation of Australia), being largely superseded by other regimens. The effect of not receiving vincristine and of prior thalidomide use on response to pomalidomide is not quantified in the submission.

6.7 The submission uses a 'novel two-stage Weibull approach' (Latimer 2014) to adjust for cross-over. As subjects were permitted on progression to cross-over to either the pomalidomide + low-dose dexamethasone (LDD) arm or to a companion pomalidomide monotherapy trial, ESC accepted that the "common treatment effect" assumption required by the less experimental Rank Preserving Structural Failure Time (RPSFT) cross-over correction was not sufficiently satisfied, although there remained uncertainty as to exactly how much of a treatment difference the presence or absence of LDD would ultimately have on OS. The two-stage Weibull approach was considered by the ESC to be the most reliable correction method available to model this data. An Inverse Probability Censoring Weights correction was considered less reliable given the high proportion of patients who crossed-over. Whilst the two-stage correction was considered the most reliable methodologically, reported estimates derived from this method for use in the economic evaluation need to be supplemented with full confidence intervals in order to be able to fully assess the likely range and reliability of the subsequent ICER, particularly given two-stage corrections are yet to be fully validated.

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

Comparative effectiveness

6.8 The use of HDD as comparator rather than placebo may not reflect clinical practice and is likely to be a conservative estimate of the effectiveness associated with pomalidomide.

Results of PFS and OS from Trial MM-003

	Pomalidomide plus LDD (n = 302)	HDD (n=153)	Absolute difference	HR (95% CI)
September 2012 cut-off				
Median PFS (weeks) (95% CI)	15.7 (13.0, 20.1)	8.0 (7.0, 9.0)	7.7	0.45 (0.35, 0.59)
Median OS (weeks) (95% CI)	NE (48.1, NE)	34.0 (23.4, 39.9)	NE	0.53 (0.37, 0.74)
March 2013 cut-off				
Median PFS (weeks) (95% CI)	[redacted]	[redacted]	[redacted]	[redacted]
Median OS (weeks) (95% CI)	[redacted]	[redacted]	[redacted]	[redacted]

PFS = progression free survival; OS = overall survival; NE = not estimable; HR = hazard ratio
Source: Table B-16, and B-18/Figures B-3-6, p 50-53 of the submission

6.9 Trial MM-003 showed that patients treated with pomalidomide plus LDD had statistically significant greater PFS and OS than HDD. There was substantial cross-over at the September 2012 cut-off (29% of HDD-treated patients to pomalidomide monotherapy) and March 2013 cut-off (44% to pomalidomide monotherapy and 6% to pomalidomide plus LDD, for a total of 50%). Results are likely to be confounded by the cross-over.

6.10 The submission does not apply any adjustments for cross-over to the evidence used for the clinical claim, but does adjust OS for use in the modelled evaluation.

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

Comparative harms

6.11 The use of HDD as comparator rather than placebo may not reflect clinical practice and is likely to underestimate the safety concerns associated with pomalidomide.

6.12 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 pomalidomide treatment arm experienced grade 3 or 4 neutropenia, leukopenia and/or febrile neutropenia at both cut-off dates, with statistically significant differences at the September 2012 and March 2013 cut-off.

6.13 The ESC noted that the majority of patients in the treatment arm of the trial received antiplatelet (aspirin) therapy prophylactically. The use of other anticoagulants, e.g. enoxaparin, was not discussed in the submission. This may be relevant given the known increased risk of deep vein thrombosis (DVT) and pulmonary embolism (PE) with pomalidomide and that the primary trial (MM-003) evaluated pomalidomide against HDD rather than placebo and thus the side effect profile may be attenuated.

Summary of key adverse events in MM-003

Adverse events	September 2012 data cut-off			March 2013 data cut-off		
	POM + LDD (N=300)	HDD (N=149)	RD % (95% CI)	POM + LDD (N=300)	HDD (N=150)	RD % (95% CI)
At least one TEAE	291 (97.0%)	139 (93.3%)	3.7 (-0.2, 9.1)	[redacted]	[redacted]	[redacted]
At least one serious AE	153 (51.0%)	75 (50.3%)	0.7 (-9.1, 10.4)	[redacted]	[redacted]	[redacted]
AEs leading to permanent discontinuation	24 (8.0%)	8 (5.4%)	2.6 (-2.8, 7.2)	[redacted]	[redacted]	[redacted]
AEs leading to dose reduction	71 (23.7%)	35 (23.5%)	0.2 (-8.5, 8.1)	[redacted]	[redacted]	[redacted]
AEs leading to dose interruption/delay	184 (61.3%)	65 (43.6%)	17.7 (7.9, 27.2)	[redacted]	[redacted]	[redacted]
SAEs related to study treatment	63 (21.0%)	34 (22.8%)	-1.8 (-10.4, 6.0)	[redacted]	[redacted]	[redacted]
Adverse events of special interest						
DVT	-	-	-	[redacted]	[redacted]	[redacted]
Pulmonary embolism	-	-	-	[redacted]	[redacted]	[redacted]
Any teratogenic events	-	-	-	[redacted]	[redacted]	[redacted]
Neutropenia (grade 3 or 4)	125 (41.7%)	22 (14.8%)	26.9 (18.5, 34.5)	[redacted]	[redacted]	[redacted]

Leukopenia (grade 3 or 4)	26 (8.7%)	5 (3.4%)	5.3 (0.4, 9.6)	[redacted]	[redacted]	[redacted]
Febrile neutropenia (grade 3/4)	20 (6.7%)	0 (0.0%)	6.7 (4.1, 10.1)	[redacted]	[redacted]	[redacted]
Febrile neutropenia (grade 3)	16 (5.3%)	0 (0.0%)	5.3 (2.8, 8.4)	[redacted]	[redacted]	[redacted]
Febrile neutropenia (grade 4)	4 (1.3%)	0 (0.0%)	1.3 (-1.2, 3.4)	[redacted]	[redacted]	[redacted]

AE=adverse event; HDD=high dose dexamethasone; LDD=low dose dexamethasone; POM=pomalidomide; RD=risk difference; TEAE=treatment emergent adverse event
Source: Tables B.26 to B.30, p 63-68 of the submission, Table 57, p 215 of the CSR for MM-003

6.14 A summary of the comparative benefits and harms for pomalidomide plus LDD versus HDD is presented in the table below.

Summary of comparative benefits and harms for pomalidomide plus LDD and HDD

Benefits				
PFS/OS: Trial MM-003				
	Pomalidomide plus LDD	HDD	Absolute Difference	HR (95% CI)
PFS September 2012 cut-off				
Progressed	164/302	103/153		0.45
Median PFS (weeks)	15.7	8.1	7.6	(0.35, 0.59)
PFS March 2013 cut-off				
Progressed	[redacted]	[redacted]	[redacted]	[redacted]
Median PFS (weeks)	[redacted]	[redacted]	[redacted]	[redacted]
OS September 2012 cut-off				
Died	76/302	58/153		0.53
Median OS (weeks)	NE	34.0	NE	(0.37, 0.74)
OS March 2013 cut-off				
Died	[redacted]	[redacted]	[redacted]	[redacted]
Median OS (weeks)	[redacted]	[redacted]	[redacted]	[redacted]

Harms						
Trial	Pomalidomide plus LDD	HDD	RR (95% CI)	Event rate/100 patients*		RD (95% CI)
				Pomalidomide plus LDD	HDD	
Grade 3 or 4 neutropenia						
MM-003	145/300	23/150	3.2 (2.2, 4.7)	48.3	15.3	33.0 (24.5, 40.7)
Grade 3 or 4 leukopenia						
MM-003	27/300	5/150	2.7 (1.1, 6.7)	9.0	3.3	5.7 (0.7, 10.0)
Grade 3 or 4 febrile neutropenia						
MM-003	28/300	0/150	NE	9.3	0	9.3% (6.5, 13.2)

* Duration of exposure: average treatment duration of 5.5 months
HDD = high dose dexamethasone; LDD = low dose dexamethasone; NE = not estimable; RD = risk difference; RR = risk ratio;
Source: Compiled during the evaluation; Table B-16, B-18, p50-52 of the submission

6.15 On the basis of the direct ITT comparison evidence presented by the submission, the comparison of pomalidomide plus LDD and HDD resulted in:

- A median [redacted] improvement in PFS and [redacted] improvement in OS (March 2013 data cut-off).
- Approximately 33 additional episodes of grade 3 or 4 neutropenia, 5.7 episodes of grade 3 or 4 leukopenia and an additional 9.3 episodes of grade 3 or 4 febrile neutropenia over an average treatment duration of 5.5 months.

6.16 The Periodic Safety Update Report (PSUR) was provided with the PSCR response. Causal relationships between pomalidomide and TLS or pancytopenia could not be excluded. Although the Company Core Data Sheet (CCDS) is being updated to include this risk, no additional labelling or risk mitigation measures were considered warranted.

6.17 The PSCR (p1) argues that the significant cross-over in trial MM-003 likely underestimates the benefit of pomalidomide plus LDD, and the ESC noted the cross-over may also potentially overestimate the safety of pomalidomide plus LDD.

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

Clinical claim

6.18 The submission claims that pomalidomide plus LDD is superior in terms of comparative effectiveness and slightly inferior in terms of comparative safety compared to HDD

6.19 The PBAC considered that the claim of superior comparative effectiveness was reasonable.

6.20 The PBAC considered that the claim of inferior comparative safety was reasonable.

Economic analysis

6.21 A summary of the model structure and key drivers of the model are shown below.

Summary of model structure and rationale

Component	Summary
Time horizon	10 years in the model base case versus [redacted] in trial
Outcomes	LYG and QALYs
Methods used to generate results and health states	Markov-like partitioned survival model with three mutually exclusive states of stable disease, progressive disease and death (absorbing). An adjustment is made to OS for cross-over (see Section C.1 of the Commentary) and both PFS and OS are extrapolated using parametric functions.
Cycle length	7 days
Transition probabilities	Economic model based on an extrapolation of OS and PFS.

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

Key drivers of the model

Description	Method/Value	Impact
Adjustment for cross-over	Experimental two-stage Weibull approach	High, favours pomalidomide. The two-stage approach is an experimental approach that has not been tested or validated. The submission does not provide any adjusted treatment effect values or confidence intervals; consequently there is no ability to assess the potential uncertainty of the results.
Treatment effect	Parametric modeling: Extreme value for PFS, log-normal for OS	High, favours pomalidomide. The model assumes that the pomalidomide plus LDD treatment effect is maintained for the duration of the model. As the submission has not provided any sensitivity analyses of the extrapolation method used; and there is no data available for such analyses to be conducted during the evaluation, it is not possible to judge the reliability of the treatment effect modelled in the economic evaluation. Variations of the extrapolation curves used as presented in the PSCR demonstrates that the results are highly sensitive to the

Description	Method/Value	Impact
		functional format chosen. The preferred approach would be to weight each extrapolation method according to its goodness-of-fit and estimate a weighted average base case ICER.
Utilities	van Agthoven 2004; 0.81 for stable disease; 0.645 for progressive disease	High, favours pomalidomide. The utilities from van Agthoven 2004 do not adequately inform HrQoL for patients with rrMM due to differences in patient characteristics and interventions when compared to MM-003; and the incorrect use of a Burden of Disease Disability Weight as the correction factor for an EQ 5D weight to adequately inform utilities associated with the progressive disease health state. Burden of Disease Disability Weights as used in Australia are based on the Dutch Disability weights which are derived in a very different manner to EQ 5D weights (person-trade-off is used as the weighting procedure and the health states were defined differently to the EQ5D).

Source: Compiled during the evaluation

Results of the economic evaluation

Component	Pomalidomide plus LDD	HDD	Increment
Costs	$	$	$
QALY			
		Incremental cost/QALY gained	$

Note: Figures in italics were updated during the evaluation to appropriately account for costs associated with febrile neutropenia (Grade 4)

Source: Table D-9, p119 of the submission

6.22 Overall, the values chosen by the submission for use in the model are likely to favour pomalidomide and the lack of ability to assess alternate cross-over and extrapolation methods (given lack of required data) indicate the model results are not reliable. ESC noted from Table 3 of the PSCR the chosen extrapolation method has a considerable impact on the ICER. At the ESC's request, the sponsor provided a measure of goodness of fit for each extrapolation method, which could inform a weighted average ICER across the relevant extrapolations.

Corrected ICER values for pomalidomide pre-PBAC response

Time horizon	ICER based on best fitting model		ICER based on weighted goodness of fit (correct)
	Incorrect values pre-PBAC response	*Corrected values*	
10 years	$	$	$
7 years	$	$	$
5 years	$	$	$
3 years	$	$	$

Source: Table 3, p3 pre-PBAC response; corrections made by evaluator

6.23 The ESC agreed with the Commentary that it is highly unlikely that utilities informed by van Agthoven 2004 adequately inform health states used in the economic evaluation due to the lack of applicability in the relapsed/refractory MM population and the appropriateness of methods used to derive the progressive disease health state utilities. Given the availability of trial based utilities, this alternative approach would have been more appropriate for use in the economic model.

6.24 The ESC noted that the PSCR presented trial-based utility values of and for stable disease and for progressive disease. The ESC commented that both the trial based utilities provided for stable disease are not the best options, and that as the trial collected data at every cycle, an average across the cycles during stable disease may be a better reflection of the utility during this state.

6.25 The ESC noted that the sponsor proposed a new base case ICER of $[redacted] in the PSCR (p5) based on different extrapolation models and utilities.

Additional sensitivity analysis using trial based EQ-5D utility scores

Analysis	Discounted ICER
Revised base case (utilities from van Agthoven)*	$[redacted]
Common trial based utility weights	$[redacted]
Group specific trial based utility weights	$[redacted]

*Revised base case as described Table 3, Appendix 1 of the PSCR
Source: Table 5, Appendix 2 of the PSCR

6.26 The ESC considered that a more conservative model duration would be preferable as pomalidomide is a last-line therapy, and requested a revised analysis based on a model duration of 3, 5 and 7 years and the trial-based utility values provided in the PSCR.

Pomalidomide model sensitivities

Analyses		Incremental costs	Incremental QALY	Cost/QALY
Amended base case[a]		$[redacted]	[redacted]	$[redacted]
Utilities of [redacted] for stable disease and [redacted] for progressive disease		$[redacted]	[redacted]	$[redacted]
Utilities of [redacted] for stable disease and [redacted] for progressive disease		$[redacted]	[redacted]	$[redacted]
Utilities of [redacted] for stable disease and [redacted] for progressive disease	Time horizon 7 years	$[redacted]	[redacted]	$[redacted]
	Time horizon 5 years	$[redacted]	[redacted]	$[redacted]
	Time horizon 3 years	$[redacted]	[redacted]	$[redacted]
Utilities of [redacted] for stable disease and [redacted] for progressive disease	Time horizon 7 years	$[redacted]	[redacted]	$[redacted]
	Time horizon 5 years	$[redacted]	[redacted]	$[redacted]
	Time horizon 3 years	$[redacted]	[redacted]	$[redacted]

[a] Presented in the PSCR – an exponential extrapolation of PFS was used instead of the extreme value used in the submission's base case; utilities remained as per base case of 0.810 for stable disease and 0.645 for progressive disease. The PSCR also corrected adverse events costs as done in the commentary. Other base case components remained the same as used in the submission – the two-stage Weibull method for cross-over; log-normal extrapolation for OS and use of the September 2012 data cut-off.

6.27 ESC considered the most relevant new base case to be between $[redacted]/QALY and $[redacted]/QALY based on the trial-based utilities. If a shorter time horizon was considered appropriate the ICER would increase.

6.28 The PBAC noted the ESC respecified base case, but considered it to be uncertain due to concerns with numerous model inputs. Use of a time horizon of 5 years, trial utilities and weighted OS extrapolation, but without extra costs associated with adverse events, resulted in an estimated ICER of over $[redacted] per QALY. The PBAC considered that a price reduction would be required to give an ICER in a range of $45,000 – $75,000 per QALY in the respecified base case.

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

Drug cost/patient/year:

6.29 $[redacted] for pomalidomide plus compared with a cost/patient/year of $493 for HDD.

Estimated PBS usage & financial implications

6.30 This submission was not considered by DUSC. Given that the submission has assumed that pomalidomide plus LDD and all other rrMM treatments have a treatment duration of [redacted]cycles[redacted]; and guideline and trial based treatment

durations are less than half of this assumption, the reliability of the financial estimates is highly questionable.

Estimated use and financial implications

	Year 1	Year 2	Year 3	Year 4	Year 5
Estimated extent of use					
Number treated					
Scripts[a]					
Estimated net cost to PBS/RPBS					
Net cost to PBS					
Net cost to RPBS					
Estimated total net cost					
Net cost to PBS/RPBS					
Net impact on other healthcare budgets					
Total net cost to Government					

Source: Table E-6, p 132; Table E-9, p 135 of the submission; Section Excel Workbook Sheets E1, E2, E4

6.31 The PSCR (p4) argues that the submission uses a simple "prevalence based" approach to model the financial estimates, and that it does not assume that the treatment duration is [redacted] cycles per patient. Rather the model assumes that at any given point in time there are a certain number of eligible patients on treatment. The ESC disagreed with this response as the submission calculates the prevalent number of people multiplied by [redacted] cycles of treatment.

6.32 The ESC also noted the Periodic Safety Update Report (PSUR) regarding tumour lysis syndrome and pancytopenia. The costs associated with pancytopenia as an adverse event is potentially accounted for within the costs assigned for neutropenia, febrile neutropenia grade 3/4 and leukopenia adverse events within the submission, however treatment of tumour lysis syndrome may incur additional costs if preventive treatment is deemed necessary and/or treatment is required.

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

7 PBAC Outcome

7.1 The PBAC rejected the submission requesting PBS listing of pomalidomide for multiple myeloma on the basis that cost-effectiveness had not been demonstrated. The true ICER had not been adequately estimated by the sponsor and the most plausible ICERs calculated after the final input from the sponsor were unacceptably high and highly uncertain.

7.2 The PBAC considered that multiple myeloma remains incurable while becoming an increasingly more common disease. Noting the consumer comments in support of pomalidomide, the PBAC recognised that there may be a clinical place for the drug in patients who have failed bortezomib and lenalidomide.

7.3 The PBAC accepted that HDD was the appropriate comparator, while noting that other salvage therapies would also be replaced in practice.

7.4 The PBAC noted that the primary clinical trial, MM-003, was an open label trial with Australian centres involved and well balanced for prognostic features. The primary endpoint was investigator assigned PFS, with OS as a secondary endpoint. There was cross-over at progression. The PBAC noted ESC advice about potential

applicability issues given the higher percentage of trial patients receiving vincristine and the lower percentage of trial patients receiving thalidomide at baseline, when compared with the baseline characteristics of the population in the Named Patient Program (NPP). However the PBAC considered that these differences were unlikely to significantly affect either the clinical place or the cost-effectiveness of pomalidomide.

7.5 The PBAC considered that pomalidomide has superior effectiveness compared with HDD, showing an improvement of [redacted]s in PFS and [redacted] in OS. The PBAC also noted that the EQ-5D instrument showed a trend towards improved quality of life with pomalidomide plus LDD compared with HDD, noting however that the differences in the EQ-5D utility index score between treatment arms were generally not statistically significant.

7.6 The PBAC considered that pomalidomide has inferior, but manageable, safety compared with HDD.

7.7 The PBAC noted the ESC advice that the two-stage Weibull approach to adjust for cross-over in the MM-003 trial was favoured. The PBAC considered that a sensitivity analysis using the RPSFT method may be informative given that the effect of LDD on median OS between the treatment arm (pomalidomide plus LDD) and the cross-over treatment (pomalidomide plus LDD or pomalidomide alone) may be small, noting the difference in median OS between pomalidomide plus LDD (16.5 months) and pomalidomide alone (13.6 months) demonstrated in the trial MM-002 (Richardson et al, *Blood* 2014). The PBAC was also concerned about assumptions that the treatment effect would be maintained beyond the trial duration.

7.8 The PBAC considered that the model structure was reasonable. However several model inputs were not reasonable, including the extrapolation, utilities, time horizon, and cost offsets:

- Time horizon: the time horizon of 10 years was not considered appropriate, and the PBAC considered that a more conservative model duration of 5 years would be more reasonable given that this is a last-line therapy, and the median OS of 54 weeks only in the pomalidomide plus LDD arm of the MM-003 trial.
- Extrapolation method: the extrapolation method has considerable impact on the estimated ICER. The PBAC agreed with the ESC, that using goodness of fit measures for each of the extrapolation methods to inform a weighted average, would be a more reasonable approach.
- Utilities: the PBAC considered that using the trial based utilities would be more appropriate.
- Cost offsets: the PBAC noted that costs for anti-thrombotic prophylaxis should be included in the economic analysis.

Modifying several of these inputs resulted in an estimated ICER between $75,000 – $105,000/QALY. The PBAC considered that these estimates indicated that pomalidomide was not cost effective at the price proposed in the submission.

7.9 The PBAC agreed with the ESC view that the reliability of the financial estimates was questionable. The sponsor used a duration of therapy that is inflated beyond that in the trial to calculate estimated PBS usage. The PBAC agreed with ESC that this was unreasonable.

7.10 The PBAC identified that a major resubmission would be required to address the Committee's concerns regarding the high and uncertain ICER. The base case would need to be respecified as per the PBAC's recommendations, and a price reduction would be required to achieve an ICER in the range of $45,000 – $75,000/QALY. Further, appropriate multivariate sensitivity analyses would be required to enable some of the residual uncertainty to be understood.

7.11 The PBAC considered the following with regard to the requested restriction:

- that it would be appropriate for it to be a written Authority application, providing evidence of progression and information about prior therapy with bortezomib and lenalidomide.
- that the words "or are intolerant to" be removed from the proposed restriction, so that the restriction reads "for treatment of patients with multiple myeloma who have previously received and failed treatment with lenalidomide and bortezomib."
- that a definition of failure of treatment, in line with that of the entry criteria of the MM-003 trial, is included in the restriction. i.e. "Treatment failure is defined as confirmed progressive disease during treatment or within 6 months of discontinuing treatment".
- that no repeats are included in line with the current listing of lenalidomide.

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

Outcome:
Rejected.

8 Context for Decision

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

9 Sponsor's Comment

The sponsor is disappointed with the decision but remains committed to working with PBAC to facilitate PBS listing of pomalidomide at the earliest possible opportunity.