7.13 POMALIDOMIDE, Capsule 3 mg, 4 mg, Pomalyst®, Celgene Pty Ltd

1 Purpose of Application

1.1 The minor resubmission sought to address the outstanding clinical, economic and financial areas of concern relating to the previous submission of pomalidomide in combination with bortezomib and dexamethasone (PBd) which was considered at the July 2019 PBAC meeting.

1.2 The minor resubmission requested a Section 100 (Highly Specialised Drugs Program), Authority Required listing for PBd in the treatment of patients with relapsed or refractory multiple myeloma (RRMM) who have undergone or are ineligible for a stem cell transplant (SCT), and who have received one prior treatment regimen including lenalidomide.

2 Background

Registration status

2.1 Pomalidomide, in combination with bortezomib and dexamethasone, was TGA registered on 10 July 2019 for the treatment of patients with RRMM who have received at least one prior treatment regimen including lenalidomide.

2.2 Pomalidomide, in combination with dexamethasone, was registered by the TGA in July 2014 for the treatment of patients with RRMM who have received at least two prior treatment regimens, including both lenalidomide and bortezomib, and have demonstrated disease progression on the last therapy.

Previous PBAC consideration

2.3 Pomalidomide, in combination with bortezomib and dexamethasone, was previously considered by the PBAC for this indication in July 2019. It was not recommended.

2.4 Table 1 provides a summary of the key issues identified by the PBAC at the July 2019 meeting and the manner in which the minor resubmission has addressed them.

Table 1: Key issues identified by the PBAC in July 2019 and how they were addressed in the minor resubmission

Issue identified by PBAC in July 2019 PSD	How issue was addressed in November 2019 resubmission
[paragraph 7.6] Although PBd demonstrated an improvement compared to Bd in terms of PFS (HR = 0.61; 95% CI: 0.49, 0.77) in the OPTIMISMM trial, PBd provided no statistically significant improvement in terms of OS (HR = 0.91; 95% CI: 0.70, 1.18).	No new clinical data from the OPTIMISMM trial were presented.

Issue identified by PBAC in July 2019 PSD	How issue was addressed in November 2019 resubmission
[paragraph 7.8] There was a significant number of transitivity issues between the OPTIMISMM and ENDEAVOR trials including differences in the dosing of the common comparator (Bd), in the eligibility criteria for prior lenalidomide treatment and in pre-treatment, which limited the comparability of the trials and made interpretation of the indirect comparison difficult. No non-inferiority margin was nominated.	The pre-PBAC response considered the differences in the dosing of Bd to be minor. An additional subgroup analysis was presented for OS in patients with prior lenalidomide use. It compared the ITT population from OPTIMISMM with an updated prior lenalidomide use subgroup from ENDEAVOR.
[paragraph 7.9] The point estimates of the indirect comparison between the ITT populations of OPTIMISMM and ENDEAVOR favoured Cd in terms of both PFS (HR = 1.15; 95% CI: 0.85, 1.55) and OS (HR = 1.15, 95% CI: 0.83, 1.60) and the upper limits of the 95% confidence intervals were in the region of 1.6, which may exceed a reasonable non-inferiority margin.	The pre-PBAC response considered the upper 95% CI for the PFS HR of 1.27, and the point estimates for the OS HR of 0.95, for the prior lenalidomide subgroup analyses, supported a claim of non-inferiority.
[paragraph 7.10] The clinical claim was supported by an analysis comparing the ITT population of OPTIMISMM (in which all patients had received prior lenalidomide) with a pre-specified subgroup of patients from ENDEAVOR who had received prior lenalidomide. The PFS results for this indirect comparison were more favourable to PBd (HR = 0.88; 95% CI: 0.61, 1.27) compared with the ITT results (HR = 1.15; 95% CI: 0.85, 1.55). Due to the small patient numbers in the ENDEAVOR subgroup (n = 177 in both the Cd and Bd arms) and differences in the proportions of patients who were refractory to lenalidomide (OPTIMISMM: approximately 70%; ENDEAVOR: approximately 25%), the reliability of the indirect analysis was uncertain.	An additional subgroup analysis was presented for OS in patients with prior lenalidomide use. It compared the ITT population from OPTIMISMM with an updated prior lenalidomide use subgroup from ENDEAVOR.
[paragraph 7.12] The indirect comparison demonstrated that PBd resulted in more statistically significantly ≥ 1 Grade 3+ treatment emergence AEs, ≥ 1 treatment emergent AEs resulting in discontinuation and ≥ 1 treatment emergent AEs resulting in dose reduction compared to Cd. Results for ≥ 1 treatment emergent AE or ≥ 1 serious treatment emergent AE were not significantly different.	No new safety data were presented. The pre-PBAC response noted the additional AEs were accounted for in the cost-minimisation analysis.
[paragraph 7.14] The submission presented a cost-minimisation analysis between PBd and Cd, based on the claims of non-inferiority. The PBAC noted that the analysis had been updated in the pre-PBAC response to accept the changes as suggested by ESC and considered that this was appropriate. The PBAC noted the cost-minimisation should have included: • Increased costs for thromboembolism prophylaxis in the PBd arm as the PBAC considered that many patients would receive novel oral anticoagulants as opposed to aspirin or low molecular weight heparin; and • A more rigorous review of the costs of managing AEs for both PBd and Cd.	The minor submission used equi-effective dosing as proposed by the July 2019 pre-PBAC response. Costs relating to thromboembolism prophylaxis were not updated. Revisions were made to incorporate costs of AEs including diarrhoea, febrile neutropenia and cardiac failure. The pre-PBAC response noted that the CMA included an additional $[redacted] in AE costs per patient in the PBd arm and did not include any AEs which could be higher in the Cd arm (e.g. cardiovascular events).
[paragraph 7.15] Although cost minimised to Cd, the cost of listing PBd on the PBS was estimated in the submission to be approximately $[redacted] in Year 6 due to the assumed substitution of PBd for Bd. The market size of RRMM	The minor resubmission proposed that pomalidomide join the carfilzomib RSA cap, which means the $[redacted] additional cost in Year 6 is no longer applicable.

Issue identified by PBAC in July 2019 PSD	How issue was addressed in November 2019 resubmission
lenalidomide patients was overestimated.	

AE = adverse event; Bd = bortezomib+dexamethasone; Cd = carfilzomib+dexamethasone; CI = confidence interval; CMA = cost minimisation analysis; ESC = Economics Sub-Committee; HR = hazard ratio; ITT = intention to treat; OS = overall survival; PBAC = Pharmaceutical Benefits Advice Committee; PBd = pomalidomide+bortezomib+dexamethasone; PFS = progression free survival; RRMM = relapsed or refractory multiple myeloma; RSA = Risk Sharing Arrangement; PSD = Public Summary Document

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

3 Requested listing

3.1 The essential elements and proposed PBS restriction for pomalidomide are provided below. Additions are in italics and deletions in strikethrough. The updated restriction accepted the relevant suggestions provided by the Secretariat in July 2019. The major change was that in July 2019 eligible patients must have received prior treatment with a lenalidomide-containing regimen for at least two consecutive cycles; the proposed restriction in the minor resubmission only requires prior treatment with a lenalidomide-containing regimen. The minor resubmission stated that this was changed to align with the TGA approved therapeutic indication of the nominated comparator, carfilzomib [with dexamethasone], as the minor resubmission proposed that pomalidomide join the carfilzomib Risk Sharing Arrangement (RSA) – see paragraph 5.34.

Category/Program	Section 100 (Highly Specialised Drugs Program)
~~Severity:~~	~~Patients must have received prior treatment with a lenalidomide-containing regimen~~
Condition:	Multiple Myeloma
Prescriber type	☐Dental ☒Medical Practitioners ☐Nurse practitioners ☐Optometrists ☐Midwives
PBS Indication:	Multiple myeloma
Treatment phase:	Initial treatment
Restriction:	☒Authority Required – Telephone
Clinical criteria	The condition must be confirmed by a histological diagnosis, AND The treatment must be in combination with bortezomib and dexamethasone, AND Patient must have progressive disease after at least one prior therapy, AND Patient must have received prior treatment with a lenalidomide-containing *regimen*, AND ~~Patient must have undergone or be ineligible for a stem cell transplant,~~ ~~AND~~ Patient must not be receiving concomitant PBS-subsidised carfilzomib, lenalidomide, ~~or~~ thalidomide *or its analogues*

Definitions:	Progressive disease is defined as at least 1 of the following: (a) at least a 25% increase and an absolute increase of at least 5 g per L in serum M protein (monoclonal protein); or (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 (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 (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 (e) an increase in the size or number of lytic bone lesions (not including compression fractures); or (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 (g) development of hypercalcaemia (corrected serum calcium greater than 2.65 mmol per L not attributable to any other cause). Oligo-secretory and non-secretory patients are defined as having active disease with less than 10 g per L serum M protein.
Cautions:	This drug is a category X drug and must not be given to pregnant women. Pregnancy in female patients or in the partners of male patients must be avoided during treatment and for 1 month after cessation of treatment
Notes:	Patients receiving this drug under the PBS listing must be registered in the i-access risk management program Special Pricing Arrangements apply

Category/Program	Section 100 (Highly Specialised Drugs Program)
Condition	Multiple Myeloma
Prescriber type	☐Dental ☒Medical Practitioners ☐Nurse practitioners ☐Optometrists ☐Midwives
PBS Indication	Multiple myeloma
Treatment phase	Continuing treatment
Restriction	☒Authority Required – Telephone
Clinical criteria	Patient must have previously received PBS-subsidised treatment with an authority prescription for this drug for this condition, AND The treatment must be in combination with bortezomib and dexamethasone, AND Patient must not develop disease progression while receiving treatment with this drug for this condition, AND Patient must not be receiving concomitant PBS-subsidised carfilzomib, lenalidomide, ~~or~~ thalidomide *or its analogues.*
Definitions	Progressive disease as defined above for initial treatment
Cautions	This drug is a category X drug and must not be given to pregnant women. Pregnancy in female patients or in the partners of male patients must be avoided during treatment and for 1 month after cessation of treatment.
Notes	Patients receiving this drug under the PBS listing must be registered in the i-access risk management program. Special Pricing Arrangements apply

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

4 Comparator

4.1 The PBAC previously considered that carfilzomib in combination with dexamethasone (Cd) was the appropriate main comparator (paragraph 7.4, Pomalidomide Public Summary Document (PSD), July 2019).

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 (52) and organisations (4) via the Consumer Comments facility on the PBS website. The individuals' comments described a range of benefits of treatment with pomalidomide including positive quality of life benefits of having alternative treatment options and manageable side effects.

5.3 The PBAC noted the advice received from (i) The Leukaemia Foundation, (ii) Myeloma Australia, (iii) Myeloma Australia's Medical and Scientific Advisory Group, and (iv) South East Myeloma Support Group, South Australia clarifying the likely use of pomalidomide in clinical practice. The PBAC specifically noted the advice that the use of pomalidomide in combination with bortezomib and dexamethasone would give patients new treatment options. The PBAC noted that this advice was supportive of the evidence provided in the submission.

Clinical trials

5.4 The minor resubmission presented the same trials as in the July 2019 submission as the basis of the indirect treatment comparison between PBd and Cd: OPTIMISMM (N = 559) and ENDEAVOR (N = 929), respectively. Updated analyses from ENDEAVOR were presented in Orlowski, et al., 2019. Details of the trials presented in the submission are provided in Table 2.

Table 2: Trials and associated reports presented in the minor resubmission

Trial ID	Protocol title/ Publication title	Publication citation
OPTIMISMM (MM-007)	A Randomized, Multicenter, Open-label, Phase 3 Study comparing the efficacy and safety of PBd versus Bd in patients with lenalidomide-pre-treated RRMM	May 2018
	Richardson PG, Rocafiguera AO, Beksac M, et al. Pomalidomide (POM), bortezomib, and lowdose dexamethasone (PVd) vs bortezomib and low-dose dexamethasone (Vd) in lenalidomide (LEN)-exposed patients (pts) with relapsed or refractory multiple myeloma (RRMM): Phase 3 OPTIMISMM trial.	Journal of Clinical Oncology. 2018; 36(15).
	Richardson P, Rocafiguera AO, Beksac M, et al. Optimismm: Phase 3 trial of pomalidomide, bortezomib, and low-dose dexamethasone vs bortezomib and	HemaSphere. 2018; 2: 372-373.

Trial ID	Protocol title/ Publication title	Publication citation
	lowdose dexamethasone in lenalidomide-exposed patients with relapsed/refractory multiple myeloma.	
	Richardson PG, Bensmaine A, Doerr T, et al. MM-007: A phase 3 trial comparing the efficacy and safety of pomalidomide (POM), bortezomib (BTZ), and low-dose dexamethasone (LoDEX [PVD]) versus BTZ and LoDEX (VD) in patients with relapsed or refractory multiple myeloma (RRMM).	Journal of Clinical Oncology. 2015; 33(15).
	Nct. (2012). Safety and Efficacy of Pomalidomide, Bortezomib and Low-dose Dexamethasone in Patients With Relapsed or Refractory Multiple Myeloma. https://clinicaltrials.gov/show/nct01734928.	NCT record
ENDEAVOR	A Randomized, Multicenter, Open-label, Phase 3 Study comparing the efficacy and safety of Cd versus Bd in patients with RRMM.	NA
	Dimopoulos MA, Moreau P, Palumbo A, et al. Carfilzomib and dexamethasone versus bortezomib and dexamethasone for patients with relapsed or refractory multiple myeloma (ENDEAVOR): A randomised, phase 3, open-label, multicentre study.	The Lancet Oncology. 2016; 17(1): 27-38.
	Dimopoulos MA, Moreau P, Palumbo A, et al. Carfilzomib and dexamethasone (Kd) vs bortezomib and dexamethasone (Vd) in patients (pts) with relapsed multiple myeloma (RMM): results from the phase III study ENDEAVOR.	Journal of Clinical Oncology. 2015; 33(15): SUPPL. 1.
	Dimopoulos M, Moreau P, Palumbo A, et al. Carfilzomib and dexamethasone improves progression free survival and response rates vs bortezomib and dexamethasone in patients (PTS) with relapsed multiple myeloma (RMM): The phase 3 study ENDEAVOR.	Haematologica. 2015; 100: 336.
	Dimopoulos MA, Goldschmidt H, Niesvizky R, et al. Carfilzomib or bortezomib in relapsed or refractory multiple myeloma (ENDEAVOR): an interim overall survival analysis of an open-label, randomised, phase 3 trial.	The Lancet Oncology. 2017; 18(10): 1327-1337.
	Correction: Carfilzomib or bortezomib in relapsed or refractory multiple myeloma (ENDEAVOR): an interim overall survival analysis of an open-label, randomised, phase 3 trial.	The Lancet Oncology. 18(10): e562.
	Dimopoulos M, Goldschmidt H, Niesvizky R, et al. Overall survival of patients with relapsed or refractory multiple myeloma treated with carfilzomib and dexamethasone versus bortezomib and dexamethasone in the randomized phase 3 ENDEAVOR trial.	Haematologica. 2017; 102: 168.
	Orlowski RZ, Moreau P, Ludwig H, et al. Carfilzomib and dexamethasone (KD56) vs bortezomib and dexamethasone (VD) in relapsed or refractory multiple myeloma (RRMM): Updated overall survival (os), safety, and subgroup analysis of ENDEAVOR.	HemaSphere. 2018; 2: 230.
	Orlowski RZ, Moreau P, Ludwig H, et al. Carfilzomib and dexamethasone (Kd56) vs bortezomib and dexamethasone (Vd) in relapsed or refractory multiple myeloma (RRMM): Updated overall survival (OS) safety, and subgroup analysis of ENDEAVOR.	Journal of Clinical Oncology. 2018; 36(15).
	Orlowski RZ, Moreau P, Niesvizky R, et al. Carfilzomib-dexamethasone versus bortezomib-dexamethasone in relapsed or refractory multiple myeloma: updated overall survival, safety, and subgroups.	Clinical Lymphoma, Myeloma & Leukemia. 2019; 19(8): 552-530.

Comparative effectiveness

5.5 The July 2019 submission presented indirect comparisons between the intention to treat (ITT) populations of the OPTIMISMM and ENDEAVOR trials for progression free and overall survival. In addition, an analysis between the ITT population of the OPTIMISMM trial (all patients had received prior lenalidomide) and a subgroup of

patients from the ENDEAVOR trial who had received prior lenalidomide was presented for progression free survival (data from the ENDEAVOR trial was not available for overall survival).

5.6 Table 3 re-presents the progression free survival results from the indirect comparison between PBd and Cd from the July 2019 submission.

Table 3: PFS results of the indirect comparison between PBd and Cd

	Data cut	Comparison	Population	HR (95% CI)	Indirect estimate of effect, PBd vs Cd, HR (95% CI), p-value
Base case					
OPTIMISMM	26 Oct 2017	PBd vs Bd	ITT	0.61 (0.49, 0.77)	1.15 (0.85, 1.55), p = 0.3561
ENDEAVOR	10 Nov 2014	Cd vs Bd	ITT	0.53 (0.44, 0.65)	
Additional follow-up					
OPTIMISMM	15 Sep 2018	PBd vs Bd	ITT	[redacted]	[redacted]
ENDEAVOR	10 Nov 2014	Cd vs Bd	ITT	0.53 (0.44, 0.65)	
Prior lenalidomide use population					
OPTIMISMM	26 Oct 2017	PBd vs Bd	ITT	0.61 (0.49, 0.77)	0.88 (0.61, 1.27), p = 0.5069
ENDEAVOR	10 Nov 2014	Cd vs Bd	Subgroup	0.69 (0.52, 0.92)	

Bd = bortezomib+dexamethasone; Cd = carfilzomib+dexamethasone; CI = confidence interval; HR = hazard ratio; ITT= intention to treat; PBd = pomalidomide+bortezomib+dexamethasone; PFS = progression free survival
Source: Table 2.1, p12 of the minor resubmission

5.7 The minor resubmission presented overall survival data for the subgroup of patients from ENDEAVOR who had received prior lenalidomide. Table 4 presents the overall survival results from the indirect comparison between PBd and Cd, with the updated subgroup analysis incorporating the data from the ENDEAVOR trial published in July 2019 (Orlowski, et al.).

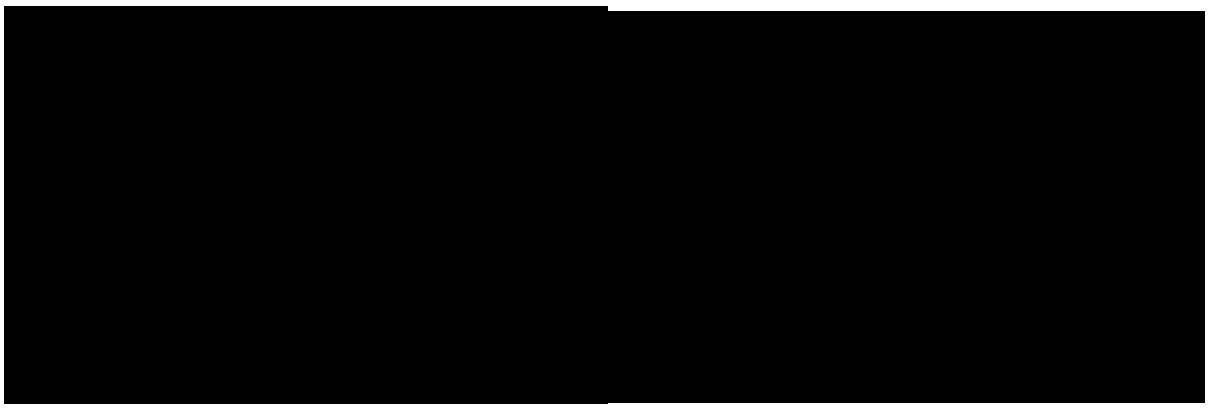
5.8 The Kaplan Meier curves are presented in Figure 1.

Table 4: OS results of the indirect comparison between PBd and Cd, including updated subgroup analysis

	Data cut	Comparison	Population	HR (95% CI)	Indirect estimate of effect, PBd vs Cd, HR (95% CI), p-value
Base case					
OPTIMISMM	15 Sep 2018	PBd vs Bd	ITT	0.91 (0.70, 1.18)	1.15 (0.83, 1.60), p = 0.3950
ENDEAVOR	3 Jan 2017	Cd vs Bd	ITT	0.79 (0.65, 0.96)	
Prior lenalidomide use population					
OPTIMISMM	15 Sep 2018	PBd vs Bd	ITT	0.91 (0.70, 1.18)	1.04 (0.71, 1.52), p = 0.9490
ENDEAVOR	19 Jul 2019	Cd vs Bd	Subgroup	0.88 (0.67, 1.16)	

Bd = bortezomib+dexamethasone; Cd = carfilzomib+dexamethasone; CI = confidence interval; HR = hazard ratio; ITT= intention to treat; OS = overall survival; PBd = pomalidomide+bortezomib+dexamethasone
Source: Table 2.2, p15 of the minor resubmission

Figure 1: Kaplan Meier OS curves from OPTIMISMM and ENDEAVOR: Left panel – ITT populations; Right panel – prior lenalidomide treatment populations



Bd = bortezomib+dexamethasone; Cd = carfilzomib+dexamethasone; ITT = intention to treat; LEN = lenalidomide; OS = overall survival; PBd = pomalidomide+bortezomib+dexamethasone
Source: Figure 2.2, p14 of the minor resubmission

5.9 The minor resubmission stated that the indirect hazard ratio (HR) and associated 95% confidence interval (CI) for the prior lenalidomide populations demonstrated no statistical difference between the treatments for OS with a negligible numerical advantage in favour of Cd over PBd (HR = 1.04; 95% CI: 0.71, 1.52).

Comparative harms

5.10 The minor resubmission did not present any updated data to support the previous claim that PBd was non-inferior to Cd in terms of safety. The PBAC previously considered that the results of the indirect comparison did not demonstrate non-inferiority between PBd and Cd in terms of safety. The pre-PBAC response noted that whilst the clinical claim is one of different but non-inferior safety, the cost-minimisation analysis accounted for additional adverse events with PBd and so effectively assumed inferior safety.

Clinical claim

5.11 The minor resubmission stated that although the additional overall survival indirect comparison was not intended to completely resolve the transitivity issues previously identified, it enabled a comparison with better applicability to the proposed PBS population for PBd and it provided assurance that the clinical claim of non-inferiority between PBd and Cd in terms of comparative effectiveness was appropriate. The pre-PBAC response further considered the transitivity issue relating to the dose regimen for the common comparator (Bd) was relatively minor in nature.

5.12 The pre-PBAC response stated for PFS, the point estimate in the prior lenalidomide subgroup favoured PBd over Cd and the upper 95% confidence limit (1.27) was inside the non-inferiority margin previously noted by the Economics Sub-Committee (ESC) of 1.4, meaning a clinical claim of non-inferiority was warranted. For OS, the pre-PBAC

response stated that there was no clear non-inferiority margin available; however, it was reasonable to expect a small margin for such a clinically meaningful and final health outcome. The pre-PBAC response noted the upper 95% confidence limit for OS was 1.52, meaning PBd would likely fail any formal statistical assessment of non-inferiority. However, the sponsor considered that the clinical claim of non-inferiority could be based on the point estimates of the indirect comparison, especially considering the point estimate was very close to 1 and the p-value was 0.9490 (Cd versus PBd: HR = 1.04; 95% CI: 0.71, 1.52; p=0.9490).

5.13 The minor resubmission did not present any updated data to demonstrate that PBd results in a survival benefit compared to Bd.

5.14 The PBAC considered that the claim of non-inferior comparative effectiveness was uncertain, although reasonable.

5.15 The PBAC considered that the claim of different safety was supported by the evidence, and that the impact of the differences should be accounted for in the cost-minimisation analysis.

Economic analysis

5.16 The minor resubmission presented a cost-minimisation analysis that applied the same equi-effective dosing as presented in the pre-PBAC response for the July 2019 submission:

> Pomalidomide 609 mg (38.3 weeks) + bortezomib 92 mg (33.0 weeks) + dexamethasone 1,239 mg (34.0 weeks) =
> Carfilzomib 6,052 mg (39.9 weeks) + dexamethasone 1,488 mg (39.9 weeks)

5.17 The equi-effective dosing applied in the cost-minimisation analysis is presented in Table 5.

Table 5: Equi-effective doses as proposed in the minor resubmission

	PBd			Cd	
	Pomalidomide	**Bortezomib**	**Dexamethasone**	**Carfilzomib**	**Dexamethasone**
Time on treatment	38.3 weeks; 12.8 cycles	33.0 weeks; 11.0 cycles	34.0 weeks; 11.4 cycles	39.9 weeks; 10.0 cycles	39.9 weeks; 10.0 cycles
Dose, mg	609 mg	92 mg	1,239 mg	6,052 mg	1,488 mg
Packs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Cd = carfilzomib+dexamethasone; PBd = pomalidomide+bortezomib+dexamethasone
Source: Table 3.1, p17 of the minor resubmission

5.18 The Secretariat noted that where the cost per patient calculations are uncertain, the guiding principal is that the Australian Government should not bear the financial risk of this uncertainty because the Australian population already has access to therapy that is at least as effective and safe.

5.19 The PBAC noted the shorter duration of pomalidomide (38.3 weeks) and dexamethasone (34.0 weeks) in PBd compared with carfilzomib (39.9 weeks) and

dexamethasone (39.9 weeks) in Cd resulted in a higher price for PBd. The PBAC considered the differences in treatment duration were not adequately supported and that the same treatment durations should be used in the cost-minimisation analysis.

5.20 The PBAC noted that the relative dose intensities (RDI) used in the minor resubmission, which were based on the OPTIMISMM and ENDEAVOR trials, were 0.85 for pomalidomide, 0.80 for bortezomib and dexamethasone as PBd and 0.93 for carfilzomib and dexamethasone as Cd, and that the lower RDIs for PBd resulted in a higher price for PBd. The PBAC considered the differences in RDI were not adequately supported and that RDIs of 0.85 for pomalidomide and carfilzomib, and 0.80 for dexamethasone (and bortezomib) should be used in the cost-minimisation analysis.

5.21 The PBAC nominated the following equi-effective doses, which incorporated the revised treatment durations and RDIs:

> Pomalidomide 609 mg (38.3 weeks) + bortezomib 92 mg (33.0 weeks) + dexamethasone 1,239 mg (34.0 weeks) =
>
> Carfilzomib 5,305 mg (38.3 weeks) + dexamethasone 1,091 mg (34.0 weeks)

5.22 In July 2019 the PBAC noted (paragraph 7.14, Pomalidomide PSD, July 2019) the cost-minimisation analysis should have included:

- Increased costs for thromboembolism prophylaxis in the PBd arm as the PBAC considered that many patients would receive novel oral anticoagulants as opposed to aspirin or low molecular weight heparin; and
- A more rigorous review of the costs of managing adverse events for both PBd and Cd.

5.23 Table 6 provides a summary of the additional costs applied in the cost-minimisation analysis.

Table 6: Summary of the additional costs applied in the cost-minimisation analysis – as proposed in minor resubmission

	July 2019		Changes	November 2019	
	PBd	Cd		PBd	Cd
G-CSF use	$[redacted]	$[redacted]	Proportion of patients in Cd arm requiring G-CSF reduced from [redacted]% to [redacted]%	$[redacted]*	$[redacted]*
Thromboembolism prophylaxis	$[redacted]	$[redacted]	Unchanged	$[redacted]	$[redacted]
Administration	$[redacted]	$[redacted]	Removed bortezomib administration costs	$[redacted]	$[redacted]
Grade 3/4 AE hospitalisation costs	$[redacted]	$[redacted]	Added hospitalisation costs for diarrhoea, febrile neutropenia and cardiac failure events	$[redacted]	$[redacted]
Total	$[redacted]	$[redacted]	-	$[redacted]	$[redacted]

* PBd and Cd treatment durations were reduced from 48 weeks to 38.3 weeks for PBd and 39.9 weeks for Cd. This proportionally reduces the total G-CSF use, thromboembolism prophylaxis use and administrations applied

AE = adverse event; AEMP = approved ex-manufacturer price; Cd = carfilzomib+dexamethasone; DPMQ = dispensed price for maximum quantity; G-CSF = granulocyte-colony stimulating factor; PBd = pomalidomide+bortezomib+dexamethasone

Source: Table 3.4, p20 of the minor resubmission

5.24 The minor resubmission applied granulocyte-colony stimulation factor (G-CSF) use to [redacted]% of PBd patients and [redacted]% of Cd patients which was identified as appropriate in the July 2019 submission (paragraph 6.37, Pomalidomide PSD, July 2019). This resulted in a G-CSF cost of $[redacted] per course of PBd and $[redacted] per course of Cd.

5.25 In terms of anticoagulants, the minor resubmission considered that the application of costs related to the administration of novel oral anticoagulants was inappropriate as current PBS restrictions for these agents (e.g. apixaban, rivaroxaban) are restricted to:

- prevention of venous thromboembolism after total hip and knee replacements;
- prevention of stroke or systemic embolism in patients with non-valvular atrial fibrillation; and
- treatment of confirmed symptomatic deep vein thrombosis and pulmonary embolism.

5.26 The PBAC accepted the use of aspirin and low molecular weight heparin as anticoagulants in the cost-minimisation analysis.

5.27 The minor resubmission included hospitalisation costs associated with Grade 3 or 4 diarrhoea ([redacted]% of PBd and [redacted]% of Cd patients), febrile neutropenia ([redacted]% of PBd and [redacted]% of Cd patients) and cardiac failure ([redacted]% of PBd and [redacted]% of Cd patients) based on the OPTIMISMM and ENDEAVOR trials. The costs were derived from the AR-DRG V9, Round 21 (2016-2017) report. Diarrhoea and febrile neutropenia were attributed to code X63B (sequelae of treatment) with an associated cost of $2,812, and cardiac failure events were attributed to a weighted average of codes F62A and F62B (heart failure and shock) with an associated cost of $8,977. The PBAC noted that inclusion of these hospitalisation costs in the cost-minimisation analysis addressed their concern regarding the different safety of PBd and Cd.

5.28 The resulting cost-minimisation analysis using the equi-effective doses proposed in the submission is presented in Table 7. The Secretariat noted that the cost-minimisation analysis was conducted using the dispensed price for maximum quantities (DPMQs) rather than the approved ex-manufacturer prices (AEMPs). Due to differences in fees and mark-ups associated with the different total prescription numbers between treatments, the analysis was recalculated using the AEMPs (Table 7).

5.29 The minor resubmission noted that given Special Pricing Arrangements are in place for carfilzomib and bortezomib, the list prices were used. The sponsor noted that the cost-minimisation price of pomalidomide was expected to be lower than that estimated below.

Table 7: Cost-minimisation analysis of PBd and Cd – based on minor resubmission

	PBd		Cd
CMA analysis as per the minor resubmission – based on DPMQs			
Cost per patient per course	Pomalidomide: $ Bortezomib: $ Dexamethasone: $ Total: $		Carfilzomib: $ Dexamethasone: $ Total: $
Additional costs	$		$
Total cost per course	**$**		**$**
Published DPMQ/DMPA	**Pomalidomide – CMA*** **Public: $** **Private: $**	Pomalidomide – Published* Public: $ Private: $	Carfilzomib Public: $2,622.32 Private: $2,697.07
CMA analysis – based on AEMPs			
Cost per patient per course	Pomalidomide: $ Bortezomib: $ Dexamethasone: $ Total: $		Carfilzomib: $ Dexamethasone: $ Total: $
Additional costs	$		$
Total cost per course	**$**		**$**
Price	**Pomalidomide – CMA*** **AEMP/Public: $** **Private: $**	Pomalidomide – Published* Public: $ Private: $	Carfilzomib Public: $2,622.32 Private: $2,697.07

Cd = carfilzomib+dexamethasone; CMA = cost-minimisation analysis; DPMA = dispensed price for maximum amount; DPMQ = dispensed price for maximum quantity; PBd = pomalidomide+bortezomib+dexamethasone

* The minor resubmission noted that the CMA cost of pomalidomide was higher than the requested published price. The minor resubmission noted that the CMA price was expected to fall below the requested published price when the effective prices for carfilzomib and bortezomib are used.

Source: Table 3.5, p20 of the minor resubmission and using PBd-CMA and BIM Excel workbook

5.30 The cost-minimisation analysis using the PBAC determined equi-effective doses is presented in Table 8.

Table 8: Cost-minimisation analysis using PBAC determined equi-effective doses and AEMPs

	PBd	Cd
Cost per patient per course	Pomalidomide: $ Bortezomib: $ Dexamethasone: $ Total: $	Carfilzomib: $ Dexamethasone: $ Total: $
Additional costs	$	$ #
Total cost per course	$	$
Price	**Pomalidomide – CMA*** **AEMP/Public: $** **Private: $**	-

AEMP = approved ex-manufacturer price; C = carfilzomib; Cd = carfilzomib+dexamethasone; CMA = cost-minimisation analysis; d = dexamethasone; DPMA = dispensed price for maximum amount; DPMQ = dispensed price for maximum quantity; P = pomalidomide; PBd = pomalidomide+bortezomib+dexamethasone; Pd = pomalidomide and dexamethasone; RDI = relative dosing intensity

Additional costs were reduced in Cd arm due to reduction in carfilzomib and dexamethasone treatment durations and RDIs. This proportionally reduces the total G-CSF use, thromboembolism prophylaxis use and administrations applied

48 weeks to 38.3 weeks for PBd and 39.9 weeks for Cd. This proportionally reduces the total G-CSF use, thromboembolism prophylaxis use and administrations applied.

* The minor resubmission noted that the CMA cost of pomalidomide was higher than the requested published price. The minor resubmission noted that the CMA price was expected to fall below the requested published price when the effective prices for carfilzomib and bortezomib are used.

Source: Calculated using PBd-CMA and BIM Excel workbook

Drug cost/patient/course:

5.31 The estimated pomalidomide cost/patient/course, as per the minor resubmission, was $92,199, based on a course duration of 38.3 weeks or [redacted] packs and a dispensed price for maximum quantity (DPMQ) of $[redacted] ([redacted]% public, [redacted]% private).

5.32 The estimated pomalidomide cost/patient/course, based on the AEMP cost-minimisation analysis and the PBAC nominated equi-effective doses and RDIs, would be $[redacted], based on a course duration of 38.3 weeks or [redacted] packs and a DPMQ of $[redacted] ([redacted]% public, [redacted]% private).

Estimated PBS usage & financial implications

5.33 In July 2019, the PBAC noted that although cost-minimised to Cd, the cost of listing PBd on the PBS was estimated in the submission to be approximately $30 - $60 million in Year 6 due to the assumed substitution of PBd for Bd (paragraph 7.15, Pomalidomide PSD, July 2019).

5.34 The minor resubmission proposed that pomalidomide join the current carfilzomib RSA to ensure that PBd does not have an incremental financial impact to the PBS over or above that which has already been agreed for carfilzomib. The budget impact model from July 2019 was updated to reflect [redacted]% substitution of PBd for Cd – see Table 9. The minor resubmission stated that the net incremental cost to the PBS/RPBS was due to the costs of G-CSF and anticoagulation associated with PBd which sit outside the proposed RSA. These costs are partially offset by the cost savings to the MBS.

5.35 The PBAC noted that in 2018, based on PBS utilisation data, 839 patients were treated with Cd.

Table 9: Estimated use and financial implications of PBd on the PBS/RPBS (as estimated in minor resubmission)

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
Estimated extent of use						
Number of patients treated	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
1st line RR	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
2nd line RR	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Number of scripts dispensed[a]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Pomalidomide	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Bortezomib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Dexamethasone	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Estimated financial implications of PBd						
Cost of pomalidomide	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]
Cost of bortezomib	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]
Cost of dexamethasone	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]
Cost to PBd to the PBS/RPBS	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]
Copayments	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]
Total cost to PBS/RPBS	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]
Estimated financial implications for other medicines (substitution of Cd)						
Cost to PBS/RPBS	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]
Copayments	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]
Total cost to PBS/RPBS	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]
Estimated financial implications for other medicines (AE and concomitant medications)						
Cost to PBS/RPBS	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]
Copayments	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]
Total cost to PBS/RPBS	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]
Estimated financial implications for IV administrations						
Cost to MBS	-$[redacted]	-$[redacted]	-$[redacted]	-$[redacted]	-$[redacted]	-$[redacted]
Copayments	-$[redacted]	-$[redacted]	-$[redacted]	-$[redacted]	-$[redacted]	-$[redacted]
Total cost to MBS	-$[redacted]	-$[redacted]	-$[redacted]	-$[redacted]	-$[redacted]	-$[redacted]
Net financial implications						
Net cost to PBS/RPBS	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]
Net cost to MBS	-$[redacted]	-$[redacted]	-$[redacted]	-$[redacted]	-$[redacted]	-$[redacted]
Net cost to patients	-$[redacted]	-$[redacted]	-$[redacted]	-$[redacted]	-$[redacted]	-$[redacted]
Net cost to hospitals	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]
Net cost to health care system	$0	$0	$0	$0	$0	$0

[a] Assuming [redacted] per year as estimated by the submission.

AE = adverse event; Cd = carfilzomib+dexamethasone; IV = intra-venous; MBS = Medicare Benefits Schedule; PBd = pomalidomide+bortezomib+dexamethasone; PBS = Pharmaceutical Benefits Scheme; RPBS = Repatriation Pharmaceutical Benefits Scheme; RR = relapsed and/or refractory

Source: Table 4.1, p22 of the minor resubmission

The redacted table shows that at Year 6, the estimated number of patients was less than 10,000.

Risk-Sharing Arrangement

5.36 As outlined above (paragraph 5.34), if pomalidomide is recommended, the Sponsor has stated that it would join the current RSA for carfilzomib.

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

6 PBAC Outcome

6.1 The PBAC recommended the listing of pomalidomide in combination with bortezomib and dexamethasone (PBd) for the treatment of patients with RRMM who have been previously treated with lenalidomide. The PBAC recommended the listing of pomalidomide on the basis that it should be available only under special arrangements under Section 100, Highly Specialised Drug Program. The PBAC recommended the special arrangements and circumstances described in the tables in Section 7 below.

6.2 The PBAC was satisfied that PBd will deliver similar clinical outcomes to carfilzomib and dexamethasone (Cd). The PBAC's recommendation for listing was based on, among other matters, its assessment that the cost-effectiveness of PBd would be acceptable if it were cost-minimised against Cd, with the analysis accounting for the differences in adverse events across the treatments.

6.3 The PBAC noted that there was strong consumer support for the use of PBd in RRMM from both individuals and organisations. The individuals' comments described a range of benefits of treatment with pomalidomide including positive quality of life benefits associated with having alternative treatment options and manageable side effects. The PBAC further noted that the advice from the organisations was supportive of PBd, noting that it would give patients increased treatment options.

6.4 The PBAC noted that the requested restriction was consistent with the clinical trial evidence. Although the Sponsor requested no repeats, the PBAC indicated that two repeats would be appropriate. The PBAC noted that the proposed restriction does not prevent sequential use of PBd following Cd, or of Cd following PBd, and indicated that this was appropriate. The PBAC noted that flow-on restriction changes would be required for bortezomib (PBS item codes 4706Q and 7268M) to enable treatment in combination with pomalidomide and dexamethasone.

6.5 The PBAC recalled that in July 2019 it had accepted the nominated comparator, carfilzomib in combination with dexamethasone (Cd).

6.6 The PBAC recalled that the previous submission was based on an indirect comparison between PBd and Cd, with Bd as the common reference. This was based on the OPTIMISMM (PBd versus Bd) and ENDEAVOR (Cd versus Bd) trials. The PBAC recalled it previously did not accept the claim of non-inferior efficacy to Cd due to transitivity issues across the trials and lack of a nominated non-inferiority margin.

6.7 The PBAC noted that the minor resubmission provided an additional indirect comparison of overall survival between PBd patients from the OPTIMISMM trial, all of whom had received prior lenalidomide, and a subgroup of Cd patients from the ENDEAVOR trial who had received prior lenalidomide. The indirect HR for overall

survival in the "prior lenalidomide use" analysis demonstrated no statistical difference between PBd and Cd (HR = 1.04; 95% CI: 0.71, 1.52).

6.8 The PBAC considered, based on the results for the indirect comparisons using the ITT trial populations, together with those for the prior lenalidomide treated populations, that the claim of non-inferior comparative effectiveness was uncertain, although reasonable.

6.9 The PBAC considered the safety profile of PBd and Cd to be different and considered that the differences should be accounted for in the cost-minimisation analysis.

6.10 The PBAC noted that the minor resubmission was based on a cost-minimisation analysis between PBd and Cd. The PBAC noted that the equi-effective doses of PBd and Cd nominated in the minor resubmission were based on differing treatment durations and relative dosing intensities. The PBAC considered the differences were not adequately supported and nominated the following the equi-effective doses:

> Pomalidomide 609 mg (38.3 weeks) + bortezomib 92 mg (33.0 weeks) + dexamethasone 1,239 mg (34.0 weeks) =
>
> Carfilzomib 5,305 mg (38.3 weeks) + dexamethasone 1,091 mg (34.0 weeks)

6.11 The PBAC recalled that in July 2019 it advised that any future cost-minimisation analysis should include a more rigorous review of the costs of managing adverse events for both PBd and Cd. The PBAC noted that the minor submission included Grade 3/4 hospitalisation costs associated with diarrhoea, febrile neutropenia and cardiac failure. The PBAC considered that the inclusions were appropriate. The PBAC accepted that aspirin and low molecular weight heparin should be used as anticoagulants in the cost-minimisation analysis.

6.12 In July 2019 the PBAC noted that although cost minimised to Cd, the cost of listing PBd on the PBS was estimated to be approximately $30 - $60 million in Year 6 due to the assumed substitution of PBd for the lower cost Bd. The PBAC noted that the budget impact in the minor resubmission was updated to reflect [redacted]% substitution of PBd for Cd. The PBAC noted that the minor resubmission estimated that there would be a net incremental cost to the PBS/RPBS of less than $10 million in Year 6 due to the costs of G-CSF and anticoagulation associated with PBd; however, this would be partially offset by cost savings to the MBS.

6.13 The PBAC noted that the Sponsor had proposed that pomalidomide would join the current RSA for carfilzomib. The PBAC considered that an increase in the expenditure caps would not be appropriate as the sponsor presented the listing as cost-neutral. A further major submission would be required to justify any additional costs to the Commonwealth due to sequential or increased use as the submission did not assess the effectiveness and cost-effectiveness of sequential use or of use beyond the current Cd population. The PBAC considered that this would ensure that

pomalidomide does not have an incremental financial impact to the PBS over or above that which has already been agreed for carfilzomib.

6.14 The PBAC noted that its recommendation was on a cost-minimisation basis and advised that because pomalidomide, as PBd, is not expected to provide a substantial and clinically relevant improvement in efficacy or reduction in toxicity over Cd and not expected to address a high and urgent unmet clinical need, the criteria prescribed by the National Health (Pharmaceuticals and Vaccines – Cost Recovery) Regulations 2009 for Pricing Pathway A were not met.

6.15 Pomalidomide is not suitable for prescribing by nurse practitioners as antineoplastic agents are currently considered to be out of scope for prescribing by nurse practitioners.

6.16 The PBAC recommended that the Early Supply Rule should not apply to pomalidomide.

6.17 The PBAC recommended that pomalidomide should not be treated as interchangeable on an individual patient basis with any other drugs.

6.18 The PBAC noted that this submission was not eligible for an Independent Review as it was a positive recommendation.

Outcome:
Recommended

7 Recommended listing

7.1 Add to existing item:

Name, Restriction, Manner of administration and form	Max. Qty (packs)	№.of Rpts	Proprietary Name and Manufacturer
POMALIDOMIDE 3 mg capsule, 14 4 mg capsule, 14	1	2	POMALYST® Celgene Ltd

Category/Program	Section 100 (Highly Specialised Drugs Program)
Condition:	Multiple Myeloma
Prescriber type	☐Dental ☒Medical Practitioners ☐Nurse practitioners ☐Optometrists ☐Midwives
PBS Indication:	Multiple myeloma
Treatment phase:	Initial treatment
Restriction:	☒Authority Required - Telephone
Clinical criteria	The condition must be confirmed by a histological diagnosis, AND The treatment must be in combination with bortezomib and dexamethasone, AND Patient must have progressive disease after at least one prior therapy, AND Patient must have received prior treatment with a lenalidomide-containing regimen, AND Patient must not be receiving concomitant PBS-subsidised carfilzomib, lenalidomide, thalidomide or its analogues

Definitions:	Progressive disease is defined as at least 1 of the following: (a) at least a 25% increase and an absolute increase of at least 5 g per L in serum M protein (monoclonal protein); or (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 (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 (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 (e) an increase in the size or number of lytic bone lesions (not including compression fractures); or (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 (g) development of hypercalcaemia (corrected serum calcium greater than 2.65 mmol per L not attributable to any other cause). Oligo-secretory and non-secretory patients are defined as having active disease with less than 10 g per L serum M protein.
Cautions:	This drug is a category X drug and must not be given to pregnant women. Pregnancy in female patients or in the partners of male patients must be avoided during treatment and for 1 month after cessation of treatment
Notes:	Patients receiving this drug under the PBS listing must be registered in the i-access risk management program Special Pricing Arrangements apply

Category/Program	Section 100 (Highly Specialised Drugs Program)
Condition	Multiple Myeloma
Prescriber type	☐Dental ☒Medical Practitioners ☐Nurse practitioners ☐Optometrists ☐Midwives
PBS Indication	Multiple myeloma
Treatment phase	Continuing treatment
Restriction	☒Authority Required - Telephone
Clinical criteria	Patient must have previously received PBS-subsidised treatment with an authority prescription for this drug for this condition, AND The treatment must be in combination with bortezomib and dexamethasone, AND Patient must not develop disease progression while receiving treatment with this drug for this condition, AND Patient must not be receiving concomitant PBS-subsidised carfilzomib, lenalidomide, thalidomide or its analogues.
Definitions	Progressive disease as defined above for initial treatment
Cautions	This drug is a category X drug and must not be given to pregnant women. Pregnancy in female patients or in the partners of male patients must be avoided during treatment and for 1 month after cessation of treatment.
Notes	Patients receiving this drug under the PBS listing must be registered in the i-access risk management program. Special Pricing Arrangements apply

Flow on changes for bortezomib PBS item codes 4706Q and 7268M:

Category/Program	Section 100 (Efficient Funding of Chemotherapy)
Condition:	Multiple Myeloma
Prescriber type	☐Dental ☒Medical Practitioners ☐Nurse practitioners ☐Optometrists ☐Midwives
PBS Indication:	Multiple myeloma

Treatment phase:	Treatment of progressive disease - Initial PBS-subsidised treatment
Restriction:	☒Authority Required (STREAMLINED)
Clinical criteria	The condition must be confirmed by a histological diagnosis; AND The treatment must be as monotherapy; OR The treatment must be in combination with a corticosteroid and/or cyclophosphamide; OR *The treatment must be in combination with pomalidomide and dexamethasone*; AND Patient must have progressive disease after at least one prior therapy; ~~AND~~ ~~Patient must have undergone or be ineligible for a primary stem cell transplant;~~ AND Patient must not be receiving concomitant PBS-subsidised carfilzomib, thalidomide or its analogues; AND Patient must not receive more than 4 cycles of treatment with bortezomib under this restriction
Definitions:	Progressive disease is defined as at least 1 of the following: (a) at least a 25% increase and an absolute increase of at least 5 g per L in serum M protein (monoclonal protein); or (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 (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 (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 (e) an increase in the size or number of lytic bone lesions (not including compression fractures); or (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 (g) development of hypercalcaemia (corrected serum calcium greater than 2.65 mmol per L not attributable to any other cause). Oligo-secretory and non-secretory patients are defined as having active disease with less than 10 g per L serum M protein. Details of the histological diagnosis of multiple myeloma, prior treatments including name(s) of drug(s) and date of most recent treatment cycle and record of prior stem cell transplant or ineligibility for prior stem cell transplant; details of the basis of the diagnosis of progressive disease or failure to respond; and nomination of which disease activity parameters will be used to assess response must be documented in the patient's medical records. Confirmation of eligibility for treatment with current diagnostic reports of at least one of the following must be documented in the patient's medical records: (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 (g) if present, the level of hypercalcaemia, corrected for albumin concentration. As these parameters must be used to determine response, 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) must be documented in the patient's medical records. 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 documented in the patient's medical records.
Notes:	Special Pricing Arrangements apply

Category/Program	Section 100 (Efficient Funding of Chemotherapy)
Condition:	Multiple Myeloma
Prescriber type	☐Dental ☒Medical Practitioners ☐Nurse practitioners ☐Optometrists ☐Midwives
PBS Indication:	Multiple myeloma
Treatment phase:	Treatment of progressive disease – Continuing PBS-subsidised treatment
Restriction:	☒Authority Required (STREAMLINED)
Clinical criteria	The condition must be confirmed by a histological diagnosis; AND The treatment must be as monotherapy; OR The treatment must be in combination with a corticosteroid and/or cyclophosphamide; OR *The treatment must be in combination with pomalidomide and dexamethasone*; AND Patient must have previously received 4 treatment cycles of bortezomib for progressive disease; AND Patient must have demonstrated at the completion of cycle 4 at least a partial response to bortezomib; AND Patient must not have received 2 treatment cycles after first achieving a confirmed complete response *if treatment is being given as monotherapy or in combination with a corticosteroid and/or cyclophosphamide*; AND Patient must not have a gap of more than 6 months between the initial PBS-subsidised treatment with this drug for this condition and continuing PBS-subsidised treatment with this drug for this condition; AND Patient must not receive more than 4 cycles of treatment with bortezomib under this restriction
Definitions:	Diagnostic reports demonstrating the patient has achieved at least a partial response must be documented in the patient's medical records. If serum M protein is measurable, partial response (PR) compared with baseline (prior to treatment with bortezomib) is defined as at least a 50% reduction in the level of serum M protein (monoclonal protein). If urine Bence-Jones protein levels are being used to monitor disease activity, partial response (PR) compared with baseline (prior to treatment with bortezomib) is defined as at least a 90% reduction in 24-hour urinary light chain M protein excretion or to less than 200 mg per 24 hours. If serum M protein is unmeasurable as in non-secretory/oligo-secretory multiple myeloma, partial response compared with baseline is defined as at least a 50% reduction in the difference between involved and uninvolved serum free light chain (FLC) levels. If serum M protein and urine Bence-Jones protein and serum FLC are unmeasurable/unavailable, partial response compared with baseline is defined as: (a) at least a 50% reduction in bone marrow plasma cells; or (b) no increase in size or number of lytic bone lesions (development of compression fracture does not exclude response); or (c) at least a 50% reduction in the size of soft tissue plasmacytoma (by clinical or applicable radiographic examination, i.e. MRI or CT-Scan); or (d) normalisation of corrected serum calcium to less than or equal to 2.65 mmol per L. Diagnostic reports must be no more than one month old at the time of prescribing.

	A response assessment prior to cycle 5 must be documented in the patient's medical records. Confirmation of complete response requires 2 determinations a minimum of 6 weeks apart. **Note** Patients who fail to demonstrate at least a partial response after 8 cycles will not be eligible to receive further PBS-subsidised treatment with bortezomib. *Patients who receive bortezomib in combination with pomalidomide and dexamethasone may receive treatment until disease progression.*
Notes:	Special Pricing Arrangements apply

These restrictions may be subject to further review. Should there be any changes made to the restrictions the Sponsor will be informed.

8 Context for Decision

The PBAC helps decide whether and, if so, how medicines should be subsidised through the Pharmaceutical Benefits Scheme (PBS) in Australia. It considers applications regarding the listing of medicines on the PBS and provides advice about other matters relating to the operation of the PBS in this context. A PBAC decision in relation to PBS listings does not necessarily represent a final PBAC view about the merits of the medicine or the circumstances in which it should be made available through the PBS. The PBAC welcomes applications containing new information at any time.

9 Sponsor's Comment

Celgene welcomes the positive recommendation for the listing of pomalidomide in combination with bortezomib and dexamethasone (PBd) for the treatment of patients with RRMM who have been previously treated with lenalidomide on the PBS. Celgene would like to thank clinicians, patients and advocacy groups for their contribution in this submission.