6.08 POMALIDOMIDE, Capsule 3 mg, 4 mg, Pomalyst®, Celgene Pty Ltd.

1 Purpose of Application

1.1 The submission requested a Section 100 Highly Specialised Drug, Authority Required (Telephone) listing for pomalidomide in combination with bortezomib and dexamethasone (PBd) for 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 at least one prior treatment regimen including lenalidomide for at least two consecutive cycles. This was the first application for PBd to the PBAC.

1.2 The submission presented a cost-minimisation analysis against carfilzomib in combination with dexamethasone (Cd). The key components of the clinical issue presented in the submission are summarised in the table below.

Table 1: Key components of the clinical issue addressed by the submission

Component	Description
Population	Patients with RRMM who have undergone or are ineligible for a stem cell transplant, and who have received at least one prior treatment regimen including lenalidomide for at least two consecutive cycles
Intervention	Pomalidomide in combination with bortezomib and dexamethasone (PBd)
Comparator	Carfilzomib in combination with dexamethasone (Cd)
Outcomes	PFS, OS, ORR, DoR, TEAEs, SAE
Clinical claim	In patients with RRMM who have received at least one prior treatment regimen including lenalidomide for at least two consecutive cycles, PBd is non-inferior to Cd at improving progression-free survival and overall survival, with a different safety profile.

DoR = duration of response; ORR = overall response rate; OS = overall survival; PFS = progression-free survival; RRMM = relapsed or refractory multiple melanoma; SAE = serious adverse event; TEAE = treatment emergent adverse event
Source: Table 1-1, p15 of the submission

2 Requested listing

2.1 The proposed listing is summarised below. Suggested additions are in italics and suggested deletions are in strikethrough.

Table 2: Summary of the proposed PBS listing

Name, Restriction, Manner of administration and form	Max. Qty (packs)	№.of Rpts	DPMQ	Proprietary Name and Manufacturer
POMALIDOMIDE Capsule, 3 mg, 14 Capsule, 4 mg, 14	1	0	Published: $[redacted] (public) $[redacted] (private) Effective: TBD	POMALYST® Celgene Ltd

Category/Program	Section 100 (Highly Specialised Drugs Program)

Severity:	Patients must have received prior treatment with a lenalidomide-containing regimen for at least two consecutive cycles.
Condition:	Multiple Myeloma
Prescriber type	☐Dental ☒Medical Practitioners ☐Nurse practitioners ☐Optometrists ☐Midwives
PBS Indication:	~~Progressive~~ Multiple myeloma
Treatment phase:	Initial treatment
Restriction:	☒Authority Required - Telephone
Clinical criteria	~~Initial:~~ 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 for at least two consecutive cycles, 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
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
~~Administrative Advice~~ Notes:	Patients receiving this drug under the PBS listing must be registered in the i-access risk management program *Special Pricing Arrangements apply*

Source: Table 1-9, p38 of the submission

Category/Program	Section 100 (Highly Specialised Drugs Program)
Condition	Multiple Myeloma
Prescriber type	☐Dental ☒Medical Practitioners ☐Nurse practitioners ☐Optometrists ☐Midwives
PBS Indication	~~Progressive~~ Multiple myeloma
Treatment phase	Continuing treatment
Restriction	☒Authority Required - Telephone
Clinical criteria	~~Continuing:~~ 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
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*

Source: Table 1-10, p39 of the submission

2.2 It was noted that dosing of pomalidomide for patients in the RRMM setting in combination with Bd was 4 mg once daily for days 1 to 14 of each 21 day cycle. Thus, the submission has requested a new pack size of 14 capsules (pomalidomide is currently PBS listed for use in combination with dexamethasone as a 21 capsule pack).

2.3 The proposed published prices for pomalidomide were lower than the prices calculated in the submission based on the cost-minimisation analysis and the published prices of carfilzomib and bortezomib.

2.4 The submission did not propose an effective price for pomalidomide, given a special pricing arrangement (SPA) is in place for both carfilzomib and bortezomib. This was appropriate given the submission presented a cost-minimisation analysis to carfilzomib and related to use in combination with bortezomib; the cost-minimised effective price for pomalidomide would be impacted by the effective prices of carfilzomib and bortezomib.

2.5 It was unclear from the submission if the intent was that prior treatment with lenalidomide be restricted to the RRMM setting or applied also to newly diagnosed transplant ineligible patients treated with lenalidomide first line. The pre-Sub-Committee Response (PSCR) clarified that prior treatment with lenalidomide included lenalidomide received in either the newly diagnosed or RRMM settings. Moreover, it was unclear how the criterion for prior treatment might be affected by the possible advent of the use of daratumumab in combination with bortezomib and dexamethasone (an application to list daratumumab was rejected at the March 2019 meeting of the PBAC).

2.6 The proposed restriction was consistent with the use of pomalidomide in OPTIMISMM, the pivotal PBd trial, and the draft pomalidomide Product Information. The ESC noted that the proposed restriction was narrower than the recommended TGA indication as the proposed PBS restriction required pomalidomide to be used in combination with bortezomib and dexamethasone.

2.7 The PBAC considered that an Authority Required (telephone) listing would be appropriate for pomalidomide as part of the PBd regimen. The PBAC advised that flow-on changes would be required for the bortezomib restrictions.

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

3 Background

Registration status

3.1 An application to the Therapeutic Goods Administration (TGA) for pomalidomide was submitted in July 2018 with the Delegate's decision received after the July 2019 PBAC meeting. At the time of PBAC consideration, the Clinical Evaluation Report (CER) Round 2 was available.

3.2 During the TGA review process the CER recommended the registration of pomalidomide for:

> "the treatment of patients with RRMM who have received at least one prior treatment regimen including lenalidomide."

3.3 The CER to the TGA noted that [redacted] (TGA CER, p120, January 2019).

Previous PBAC considerations

3.4 Pomalidomide in combination with dexamethasone 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 was TGA registered 1 July 2014. The PBAC recommended pomalidomide in combination with dexamethasone in patients with RRMM who have received and failed prior treatment with both lenalidomide and bortezomib at its November 2014 meeting (Pomalidomide PSD, November 2014).

3.5 Carfilzomib in combination with dexamethasone for patients with RRMM who received at least one prior therapy was recommended by the PBAC in July 2017 (Carfilzomib PSD, July 2017). Carfilzomib in combination with lenalidomide and dexamethasone for patients with RRMM who received at least one prior therapy was considered and rejected by the PBAC at its November 2016 meeting (Carfilzomib PSD, November 2016).

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

4 Population and disease

4.1 Multiple myeloma (MM) is a B-cell neoplasm characterised by the multifocal, clonal proliferation of malignant plasma B cells within the bone marrow. Median OS for

patients with newly diagnosed MM ranges from 2 to more than 10 years. Recurrence of myeloma is usually more aggressive with each relapse and is associated with shorter duration of response and shorter survival, indicating the disease becomes increasingly resistant to available treatment options.

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

5 Comparator

5.1 The submission nominated Cd as the main comparator in the second-line setting. The ESC and PBAC considered that the comparator was appropriate.

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 (33), health care professionals (1) and organisations (2) via the Consumer Comments facility on the PBS website. The 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.

6.3 The PBAC noted the advice received from the Leukaemia Foundation and Myeloma Australian 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 options and improved treatment. The PBAC noted that this advice was supportive of the evidence provided in the submission.

Clinical trials

6.4 There were no head-to-head studies comparing PBd with Cd. Accordingly, the submission presented two trials as the basis of an indirect treatment comparison between PBd and Cd: OPTIMISMM (N = 559) and ENDEAVOR (N = 929), respectively. Details of the trials presented in the submission are provided in the table below.

Table 3: Trials and associated reports presented in the submission

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 lowdose dexamethasone in lenalidomide-exposed patients with relapsed/refractory multiple myeloma.	HemaSphere. 2018; 2: 372-373.
	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	Journal of Clinical Oncology. 2018; 36(15).

Trial ID	Protocol title/ Publication title	Publication citation
	multiple myeloma (RRMM): Updated overall survival (OS) safety, and subgroup analysis of ENDEAVOR.	

Cd = carfilzomib+dexamethasone; PBd = pomalidomide+bortezomib+dexamethasone.
Source: Table 2-3, p48 of the submission

6.5 The key features of the randomised trials included in the indirect comparison are summarised in the table below.

6.6 Although both studies were open-label, the assessment of key outcomes was performed in a blinded manner by independent review committees and using objective criteria for determining response. The PBAC has previously noted that although ENDEAVOR was open-label, the assessment of PFS was blinded and was based on objective measures of response (paragraph 7.5, Carfilzomib PSD, November 2016). The ESC considered that both trials had a low risk of bias.

Table 4: Key features of the included evidence

Trial	N	Design/ median follow-up	Risk of bias	Patient population	Outcomes	Use in modelled evaluation
PBd vs. Bd						
OPTIMISMM	559	Phase III, R, OL, MC 15.9 months (cut-off 26 Oct 2017); 26.2 months (cut-off 15 Sep 2018)	Low	RRMM patients who have undergone or are ineligible for an SCT, and who have received at least one prior treatment regimen including lenalidomide for at least two consecutive cycles.	PFS, OS, ORR, DoR, TEAEs, SAE	Not used
Cd vs. Bd						
ENDEAVOR	929	Phase III, R, OL, MC PFS: 11.5 months OS: 12.2 months (cut-off 10 Nov 2014); PFS: 16.6 months OS: 26.8 months (cut-off 3 Mar 2016); OS: 37.2 months (cut-off 3 Jan 2017)	Low	RRMM patients who had received one to three prior lines of therapy and achieved at least a partial response to at least one previous treatment.	PFS, OS, ORR, DoR, TEAEs, SAE	Not used

Bd = bortezomib+dexamethasone; Cd = carfilzomib+dexamethasone; DB = double blind; DoR = duration of response; MC = multi-centre; OL = open label; PBd = pomalidomide+bortezomib+dexamethasone; ORR = overall response rate; OS = overall survival; PFS = progression-free survival; R = randomised; RRMM = relapsed or refractory multiple myeloma; SAE = serious adverse event; SCT = stem cell transplant; TEAE = treatment emergent adverse event
Source: compiled during the evaluation

Comparative effectiveness

6.7 A summary of survival outcomes from OPTIMISMM is presented below, with the corresponding Kaplan-Meier plots presented in Figure 1.

6.8 Patients in the PBd arm of OPTIMISMM had statistically significantly longer PFS compared to Bd. There was no statistically significant improvement in OS. Median OS

had not been reached for PBd and was 31.24 months (95% CI: 27.01, NE) for Bd. The ESC considered the OS data to be immature.

Table 5: Results of PFS and OS in OPTIMISMM

	PBd		Bd		Difference in median, months	P value (log rank test)	HR (95% CI)
	Patients with event, n (%)	Median, months (95% CI)	Patients with event, n (%)	Median, months (95% CI)			
PFS							
26 Oct 2017 – IRAC	154 (54.8%)	11.2 (9.66, 13.73)	162 (58.3%)	7.1 (5.88, 8.48)	4.1	**< 0.0001**	**0.61 (0.49, 0.77)**
15 Sep 2018 - INV	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
OS							
26 Oct 2017	87 (31.0%)	NE (28.48, NE)	89 (32.0%)	31.2 (27.01, NE)	NE	0.894	0.98 (0.73, 1.32)
15 Sep 2018	116 (41.3%)	40.5 (29.83, NE)	126 (45.3%)	30.5 (24.61, 35.94)	10.1	0.476	0.91 (0.70, 1.18)

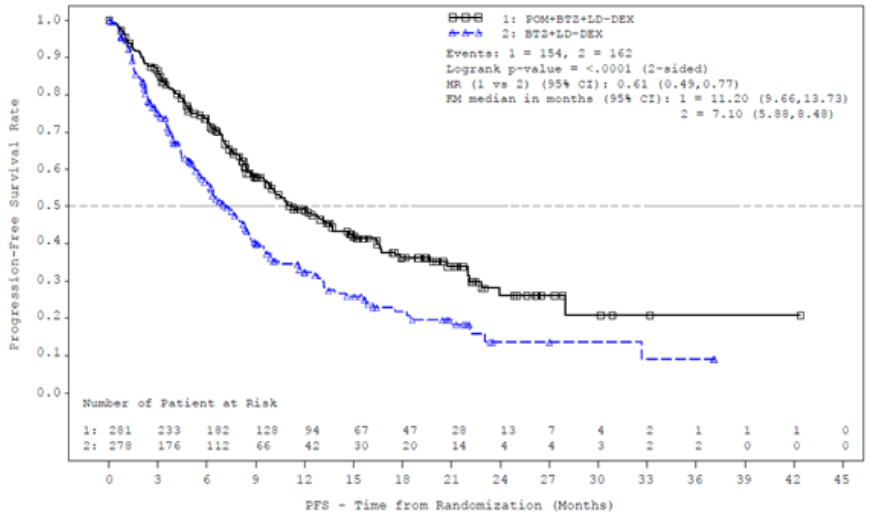
Bd = bortezomib+dexamethasone; CI = confidence interval; HR = hazard ratio; INV = investigator assessment; IRAC = Independent Response Adjudication Committee; NE = not estimable; OS = overall survival; PFS = progression free survival; PBd = pomalidomide+bortezomib+dexamethasone

Bold = statistically significant

Source: Table 2-15, p98; Table 2-16, p102 of the submission

Figure 1: Kaplan-Meier curve of PFS and OS, OPTIMISMM (26 October 2017 data-cut)

PFS



OS

[redacted]

BTZ = bortezomib; CI = confidence interval; DEX = dexamethasone; HR = hazard ratio; NE = not estimable; KM = Kaplan-Meier; LD = low dose; OS = overall survival; PFS = progression free survival; POM = pomalidomide
Source: Figure 2-7, p 91; Figure 2-13, p99 of the submission

6.9 Results for the overall response rate (ORR) and duration of response (DoR) favoured PBd, but were only statistically significantly different for the ORR.

Table 6: Summary of efficacy results: ORR, DoR, OPTIMISMM (26 Oct 2017 data-cut)

	PBd		Bd		Difference in median, months	P value (log rank test)	HR (95% CI)
	Patients with events, n (%)	Median, months (95% CI)	Patients with events, n (%)	Median, months (95% CI)			
DoR	NR	13.70 (10.94, 18.10)	NR	10.94 (8.11, 14.78)	NR	NR	0.76 (0.56, 1.02)
ORR	231/281 (82.2%)	NR	139/278 (50.0%)	NR	NR	**< 0.001**	**5.02 (3.35, 7.52)**

Bd = bortezomib+dexamethasone; CI = confidence interval; DoR = duration of response; HR = hazard ratio; NR = not reported; PBd = pomalidomide+bortezomib+dexamethasone; ORR = overall response rate
Bold = statistically significant.
Source: Table 2-17, p103; Table 2-18, p104 of the submission

6.10 The summary of survival outcomes and the corresponding Kaplan-Meier plots from ENDEAVOR are presented below.

6.11 The patients in the Cd arm of ENDEAVOR had statistically significantly longer PFS and OS (at the final data cut) compared to patients in the Bd arm. The ESC previously considered that although the improvement in OS was statistically significant, the upper confidence interval (of the HR) was close to the null (paragraph 6.11, Carfilzomib PSD, July 2017). The PBAC previously noted that Cd demonstrated a statistically significant improvement in PFS and OS compared to Bd, and the updated OS, although still immature, provided more robust evidence of benefit (paragraph 6.12, Carfilzomib PSD, July 2017).

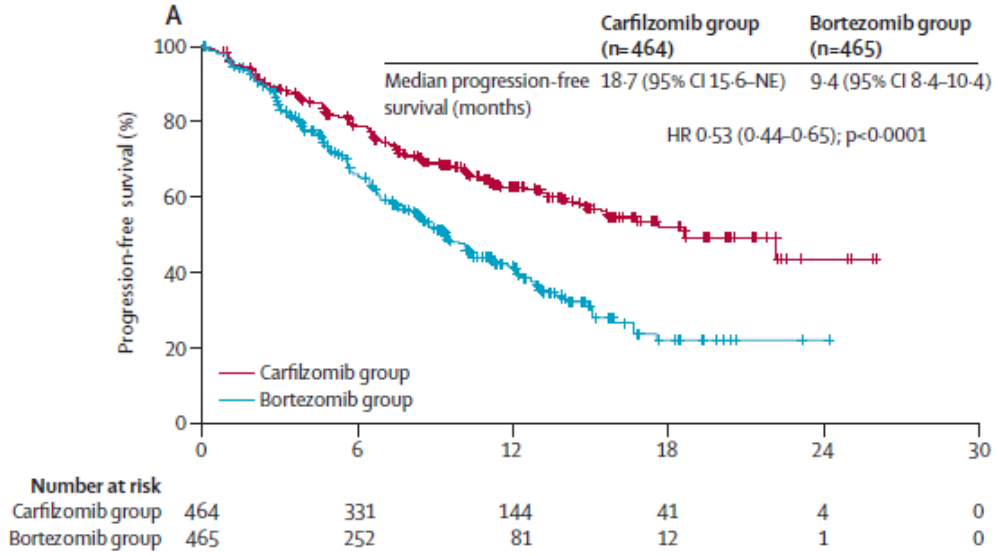
Table 7: Results of PFS and OS in ENDEAVOR*

	Cd		Bd		Difference in median, months	P value (log rank test)	HR (95% CI)
	Patients with events, n (%)	Median, months (95% CI)	Patients with events, n (%)	Median, months (95% CI)			
PFS							
10 Nov 2014 - IRC	171 (36.9%)	18.7 (15.6, NE)	243 (52.3%)	9.4 (8.4, 10.4)	9.3	**< 0.0001**	**0.53 (0.44, 0.65)**
3 Mar 2016 - ORCA	232 (50.0%)	16.8 (14.8, 20.3)	288 (61.9%)	9.3 (8.3, 10.4)	7.5	**< 0.0001**	**0.55 (0.46, 0.65)**
OS							
10 Nov 2014 - IRC	75 (16.2%)	NE (NE, NE)	88 (18.9%)	24.3 (24.3, NE)	NE	0.0650	0.79 (0.58, 1.08)
3 Mar 2016 - ORCA	153 (33.0%)	NE (NE, NE)	169 (36.3%)	NE (31.0, NE)	NE	0.0263	0.81 (0.65, 1.00)
3 Jan 2017 - ORCA	189 (40.7%)	47.6 (42.5, NE)	209 (44.9%)	40.0 (32.6, 42.3)	7.6	**0.010**	**0.79 (0.65, 0.96)**

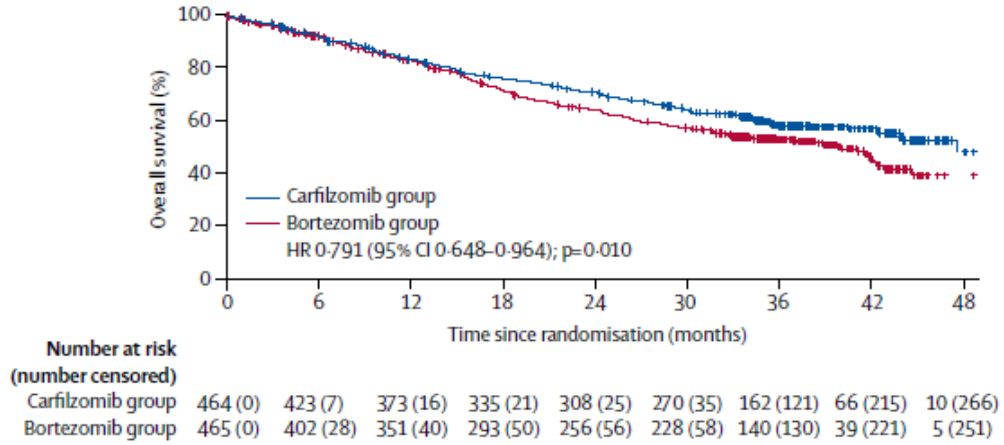
Bd = bortezomib+dexamethasone; Cd = carfilzomib+dexamethasone; CI = confidence interval; HR = hazard ratio; IRC = Independent Review Committee; NE = not estimable; ORCA = Onyx Response Computational Assessment; OS = overall survival; PFS = progression free survival
Bold = statistically significant
* No PFS data were available for the ENDEAVOR trial from the more recent OS analysis (3 Jan 2017 data cut)
Source: Table 2-15, p98; Table 2-16, p102 of the submission

Figure 2: Kaplan-Meier curve of PFS (10 Nov 2014 data-cut) and OS (3 January 2017 data-cut), ENDEAVOR

PFS



OS



CI = confidence intervals; HR = hazard ratio; NE = non evaluable; POS = overall survival; FS = progression free survival
Source: Figure 2-10, p95; Figure 2-15, p101 of the submission

6.12 The ORR and DoR favoured patients receiving Cd compared with Bd.

Table 8: Summary of efficacy results: ORR, DoR, ENDEAVOR (10 Nov 2014 data-cut)

	Cd		Bd		Difference in median, months	P value (log rank test)	HR (95% CI)
	Patients with events, n (%)	Median, months (95% CI)	Patients with events, n (%)	Median, months (95% CI)			
DoR	NR	21.3 (21.3, NE)	NR	10.4 (9.3, 13.8)	NR	NR	NR
ORR	357/464 (76.9%)	NR	293/465 (63.0%)	NR	NR	**<0.0001**	**2.03 (1.52, 2.72)**

Bd = bortezomib+dexamethasone; Cd = carfilzomib+dexamethasone; CI = confidence interval; DoR = duration of response; HR = hazard ratio; NR = not reported; ORR = overall response rate

Bold = statistically significant
Source: Table 2-17, p103; Table 2-18, p104 of the submission

Subgroup analyses

6.13 The results of the pre-specified subgroup analyses are presented below. Since all patients in OPTIMISMM had been pre-treated with lenalidomide, the ITT population from OPTIMISMM corresponds to the lenalidomide pre-treated subgroup from ENDEAVOR, and all subgroups from OPTIMISMM represent patients who received prior-treatment with lenalidomide. Subgroup populations from ENDEAVOR may have included patients who had not received prior lenalidomide treatment.

6.14 The submission claimed that results of the subgroup analyses for PFS in patients with more than one prior line of therapy, and prior lenalidomide use are more applicable to the population proposed for listing of PBd.

Table 9: Results of subgroup analysis for PFS based on number of prior treatments and refractoriness to lenalidomide

Population	Trial ID	PBd or Cd n with event/N (%)	Bd n with event/N (%)	HR (95% CI)
Whole trial population	OPTIMISMM (PBd vs Bd)	154/281 (54%)	162/278 (58%)	**0.61 (0.49, 0.77)**
	ENDEAVOR (Cd vs. Bd)	171/464 (36%)	243/465 (52%)	**0.53 (0.44, 0.65)**
Prior lines of therapy	OPTIMISMM (PBd vs Bd)			
	One prior line	45/111 (40%)	52/115 (45%)	**0.54 (0.36, 0.82)**
	> 1 prior line	109/170 (64%)	110/163 (67%)	**0.63 (0.48, 0.83)**
	Test for subgroup differences*	Chi^2 = 0.38, df = 1 (p = 0.54)		
	I^2 with 95% uncertainty interval	I^2 = 0%		
	ENDEAVOR (Cd vs Bd)			
	One prior line	70/232 (30%)	109/232 (47%)	**0.45 (0.33, 0.61)**
	≥ 2 prior lines	101/232 (44%)	134/233 (58%)	**0.60 (0.47, 0.78)**
	Test for subgroup differences*	Chi^2 = 2.04, df = 1 (p = 0.15)		
	I^2 with 95% uncertainty interval	I^2 = 51%		
Prior use of lenalidomide	ENDEAVOR (Cd vs Bd)			
	Yes	85/177 (48%)	103/177 (58%)	**0.69 (0.52, 0.92)**
	No	86/287 (30%)	140/288 (49%)	**0.43 (0.32, 0.56)**
	Test for subgroup differences*	**Chi^2 = 5.14, df = 1 (p = 0.02**)		
	I^2 with 95% uncertainty interval	I^2 = 81%		
Refractory to lenalidomide in last lenalidomide regimen	OPTIMISMM (PBd vs Bd)			
	Yes	120/200 (60%)	118/191 (61%)	**0.65 (0.50, 0.84)**
	No	34/81 (41%)	44/87 (50%)	**0.48 (0.30, 0.75)**
	Test for subgroup differences*	Chi^2 = 1.22, df = 1 (p = 0.27)		
	I^2 with 95% uncertainty interval	I^2 = 18%		
	ENDEAVOR (Cd vs Bd)			
	Yes	66/113 (58%)	76/122 (62%)	0.80 (0.57, 1.11)
	No	105/351 (30%)	167/343 (49%)	**0.44 (0.34, 0.56)**
	Test for subgroup differences*	**Chi^2 = 7.58, df = 1 (p = 0.006)**		
	I^2 with 95% uncertainty interval	I^2 = 87%		
Prior proteasome inhibitor (bortezomib)	OPTIMISMM (PBd vs Bd)			
	Yes	118 (212) (56%)	132 (213) (61%)	**0.57 (0.44, 0.73)**
	Test for subgroup differences*	NA**		
	I^2 with 95% uncertainty interval	NA**		
	ENDEAVOR (Cd vs Bd)			
	Yes	105/250 (42%)	141/252 (56%)	**0.56 (0.44, 0.73)**
	No	66/214 (31%)	102/213 (48%)	**0.48 (0.36, 0.66)**
	Test for subgroup differences*	Chi^2 = 0.65, df = 1 (p = 0.42)		
	I^2 with 95% uncertainty interval	I^2 = 0%		

Bd = bortezomib+dexamethasone; Cd = carfilzomib+dexamethasone; CI = confidence interval; HR = hazard ratio; NA = not applicable; PBd = pomalidomide+bortezomib+dexamethasone; PFS = progression free survival

* Calculated by the submission using Review Manager 5.3

** Complementary subgroup results not reported in source data

Source: Table 2-26, p125; Table 2-27, p125 of the submission

Indirect treatment comparison

6.15 The results for the indirect treatment comparison for the outcomes of PFS and OS are presented below.

6.16 There were no statistically significant differences between PBd and Cd in terms of PFS

and OS. A non-inferiority margin was not nominated by the submission. This was noted by the ESC and considered to complicate the interpretation of the results.

6.17 The submission stated that the results of the indirect comparison, using the subgroup of patients from ENDEAVOR who had received prior treatment with lenalidomide, demonstrated a numerical advantage in terms of PFS in favour of PBd relative to Cd (HR = 0.88; 95% CI: 0.61, 1.27). The submission further stated the comparisons using the ITT populations demonstrated a numerical advantage in favour of Cd over PBd (HR = 1.15; 95% CI: 0.85, 1.55), suggesting that the comparison using the ITT results was biased in favour of Cd. The analysis for patients with prior use of lenalidomide (and by extension, at least one prior line of therapy) utilised the ITT population for OPTIMISMM and a subgroup of relevant patients from ENDEAVOR.

Table 10: Summary of results of the indirect comparison for PFS and OS, between OPTIMISMM and ENDEAVOR

	Median duration of follow-up	PBd or Cd n/N (%)	Bd n/N (%)	Absolute difference*	HR (95% CI)
PFS – ITT populations					
OPTIMISMM (26 Oct 2017) PBd vs Bd	15.9 months	154/281 (54.8%)	162/278 (58.3%)	3.5%	**0.61 (0.49, 0.77)**
ENDEAVOR (10 Nov 2014) Cd vs Bd	11.5 months	171/464 (36.9%)	243/465 (52.3%)	15.4%	**0.53 (0.44, 0.65)**
Indirect comparison PBd vs. Cd*					1.15 (0.85, 1.55)
PFS – prior treatment with lenalidomide					
OPTIMISMM (26 Oct 2017) PBd vs Bd	15.9 months	154/281 (54.8%)	162/278 (58.3%)	3.5%	**0.61 (0.49, 0.77)**
ENDEAVOR (10 Nov 2014) Cd vs Bd	11.5 months	85/177 (48.0%)	103/177 (58.1%)	10.1%	**0.69 (0.52, 0.92)**
Indirect comparison PBd vs. Cd*					0.88 (0.61, 1.27)
OS – ITT populations					
OPTIMISMM (15 Sep 2018) PBd vs Bd	26.2 months	116/281 (41.3%)	126/278 (45.3%)	4.0%	0.91 (0.70, 1.18)
ENDEAVOR (3 Jan 2017) Cd vs Bd	37.2 months	189/464 (40.7%)	209/465 (44.9%)	4.2%	**0.79 (0.65, 0.96)**
Indirect comparison PBd vs. Cd*					1.15 (0.83, 1.60)

Bd = bortezomib+dexamethasone; Cd = carfilzomib+dexamethasone; CI = confidence interval; HR = hazard ratio; ITT = intention-to-treat; LEN = lenalidomide; OS = overall survival; PBd = pomalidomide+bortezomib+dexamethasone; PFS = progression-free survival
Bold = statistically significant
* Performed using the Bucher ITC method (Source: "BucherITC_PBdversusCd indirect analysis.xls")
Source: Table 2-29, p132; Table 2-30, p134 of the submission

6.18 The ESC noted the potential transitivity issues between the trials, including:

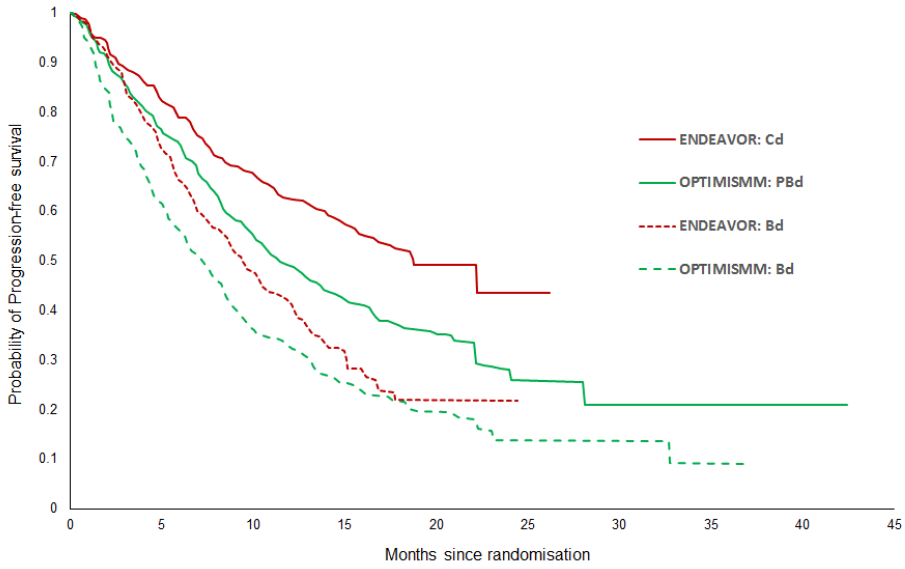
- A greater proportion of patients in OPTIMISMM had disease classified as International Staging System (ISS) Stage I (53% vs 49.6% in PBd and Bd arms, respectively) compared to ENDEAVOR (44.2% vs. 43.9% in Cd and Bd respectively). Based on ISS staging, fewer patients in OPTIMISMM had less advanced disease than in ENDEAVOR.

- The common comparator (Bd) was dosed differently in the two trials, being lower for ENDEAVOR compared with OPTIMISMM and potentially biasing in favour of Cd. The median relative dose intensity (RDI) in the Bd arm of OPTIMISMM (RDI = 0.9; Inter-quartile range (IQR): 0.4, 1.8; October-2017 cut-off) was higher than that in the Bd arm of ENDEAVOR (RDI = 0.86; IQR: 0.71, 0.96; Nov-2014 cut-off).
- The trials had different eligibility criteria for previous lines of treatment with lenalidomide. All patients in OPTIMISMM were required to have received prior treatment with lenalidomide, whereas this was not a requirement in ENDEAVOR with 38.1% of patients in each of the Cd and Bd arms previously treated with lenalidomide. Accordingly, the majority of patients in OPTIMISMM were refractory to lenalidomide (71.2% and 68.7% in the PBd and Bd arms, respectively), with the vast majority of these patients (89.0% and 87.4%) receiving lenalidomide in their last anti-myeloma regimen prior to study entry. This contrasted with ENDEAVOR where fewer patients were refractory to lenalidomide (24.4% and 26.2% in the Cd and Bd arms, respectively). Results of the subgroup analysis demonstrated that prior lenalidomide exposure resulted in a smaller reduction in the hazard for remaining progression free or alive for Cd relative to Bd.
- Patients in OPTIMISMM were more heavily pre-treated than patients in ENDEAVOR. Approximately 40% of patients in OPTIMISMM had one prior line of therapy, whilst 60% had two or more; the distribution in ENDEAVOR was evenly split between one (50%) and two or more (50%) prior lines of therapy. The impact of the number of prior lines of therapy on PFS was not statistically significant (see Table 9).
- Most patients (75.4% and 76.6% in the PBd and Bd arms, respectively) in OPTIMISMM had received a proteasome inhibitor (almost exclusively bortezomib) prior to study entry, compared with ENDEAVOR where fewer patients received a proteasome inhibitor (54.2% and 53.9% in the Cd and Bd arms respectively). The PBAC noted that patients in ENDEAVOR were excluded from the trial unless they had at least a partial response to bortezomib in previous lines of therapy and had at least a six month proteasome inhibitor treatment-free interval before enrolment; this was not a requirement for OPTIMISMM, which included all patients who had received prior bortezomib, including bortezomib-refractory patients, provided they did not have progressive disease during prior bortezomib therapy or within 60 days of the last dose of bortezomib-containing therapy. The impact of prior bortezomib exposure on PFS was not statistically significant (see Table 9).

6.19 The ESC agreed that, combined, these differences indicated that overall patients in OPTIMISMM were more heavily pre-treated and had more progressed disease at study entry, than patients in ENDEAVOR. This was despite a slightly higher proportion of patients in ENDEAVOR having more advanced ISS stage disease at study entry

compared with those in OPTIMISMM. This was supported by the overlay of Kaplan-Meier PFS-curves (see Figure 3), which suggested that patients in ENDEAVOR who received Bd had a lower rate of progression than those in OPTIMISMM.

Figure 3: Overlay of PFS curves from OPTIMISMM and ENDEAVOR (ITT population)



Bd = bortezomib+dexamethasone; Cd = carfilzomib+dexamethasone; ITT = intention to treat; PBd = pomalidomide+bortezomib+dexamethasone; PFS = progression free survival
Source: Figure 2-17, p131 of the submission

Comparative harms

6.20 The summary of treatment emergent adverse events (TEAEs) reported in OPTIMISMM is presented below. Treatment with PBd was associated with more TEAEs than Bd.

Table 11: Summary of TEAE, OPTIMISMM (Safety Population)

	PBd, n/N (%)	Bd, n/N (%)	RR (95% CI)*
Median duration of treatment, weeks	38.3 weeks	21.4 weeks	-
Patients with at least 1 TEAE	277/278 (99.6%)	264/270 (97.8%)	1.02 (1.00, 1.04)
Patients with at least 1 Grade 3/4 TEAE	251/278 (90.3%)	190/270 (70.4%)	**1.28 (1.18, 1.40)**
Patients with Grade 5 TEAE	27/278 (9.7%)	12/270 (4.4%)	**2.19 (1.13, 4.22)**
Patients with at least 1 serious TEAE	159/278 (57.2%)	114/270 (42.2%)	**1.35 (1.14, 1.61)**
Patients with at least 1 TEAE leading to discontinuation	80/278 (28.8%)	51/270 (18.9%)	**1.52 (1.12, 2.07)**
Patients with at least 1 TEAE leading to dose reduction	200/278 (71.9%)	139/270 (51.5%)	**1.40 (1.22, 1.60)**

Bd = bortezomib+dexamethasone; CI = confidence interval; PBd = pomalidomide+bortezomib+dexamethasone; RR = risk ratio; TEAE = treatment emergent adverse event
* Calculated by the submission using Review Manager 5.3
Source: Table 2-19, p108 of the submission

6.21 The summary of TEAEs reported in ENDEAVOR is presented below. Treatment with Cd was associated with more TEAEs than Bd.

Table 12: Summary of TEAEs in ENDEAVOR (Safety Population)

	Cd, n/N (%)	Bd, n/N (%)	RR (95% CI)*
10 Nov 2014 data-cut			
Median duration of treatment, weeks	39.9 weeks	26.8 weeks	
Patients with at least 1 TEAE	455/463 (98.3%)	447/456 (98.0%)	1.00 (0.98, 1.02)
Patients with at least 1 Grade 3+ TEAE	339/463 (73.2%)	305/456 (66.9%)	**1.09 (1.01, 1.19)**
Patients with at least 1 serious TEAE	224/463 (48.4%)	162/456 (35.5%)	**1.36 (1.17, 1.59)**
Patients with at least 1 TEAE leading to discontinuation	57/463 (12.3%)	59/456 (12.9%)	0.95 (0.68, 1.34)
Patients with at least 1 TEAE leading to dose reduction	106/463 (22.9%)	218/456 (47.8%)	**0.48 (0.39, 0.58)**

Bd = bortezomib+dexamethasone; Cd = carfilzomib+dexamethasone; CI = confidence interval; RR = risk ratio; TEAE = treatment emergent adverse event

* Calculated by the submission using Review Manager 5.3

Source: Table 2-19, p108 of the submission

6.22 The submission identified neutropenia and thrombocytopenia as events associated with pomalidomide. Costs of using growth-colony stimulating factors (G-CSF) associated with neutropenia were included in the cost-minimisation analysis (CMA).

6.23 At its July 2017 meeting, the PBAC noted the higher rate of serious cardiovascular adverse events (CVAEs) for Cd compared to Bd in the clinical trial data, and stated that given CVAEs were more than twice as common in the carfilzomib arms of the reviewed trials (all grade and grade ≥ 3 CVAEs were seen in 18% and 8% of patients, respectively), further monitoring may be needed (paragraph 6.15, Carfilzomib PSD, July 2017). The PBAC considered the overall safety of Cd was inferior compared with Bd (paragraph 6.23, Carfilzomib PSD, July 2017). CVAEs were reported less than 5% of patients in the PBd arm of the OPTIMISMM trial.

6.24 The proportions of patients with events in the Bd arms of OPTIMISMM and ENDEAVOR (10 November 2014 data cut) were different for thrombocytopenia (29.3% vs 9.4%) and anaemia (14.1% vs 9.9%). This may indicate differences in transitivity that would affect the comparability of the studies, and hence the robustness of the claims for safety based on the indirect comparison. The ESC considered that the differences in rates of thrombocytopenia and anaemia may reflect the more highly pre-treated population in OPTIMISMM compared to ENDEAVOR.

<u>Indirect comparison of safety</u>

6.25 The results of the indirect treatment comparison of TEAEs between OPTIMISMM and ENDEAVOR are presented below (Table 13). The risk of a Grade 3/4 TEAE, TEAE leading to discontinuation of study treatment or TEAE leading to dose reduction was found to be statistically greater for PBd relative to Cd. In addition, treatment with PBd was less favourable in terms of Grade 3/4 neutropenia and peripheral neuropathy related events, while treatment with Cd was less favourable in terms of anaemia and hypertension.

Table 13: The key results of the indirect comparison for adverse events

	Outcome	PBd or Cd, n/N (%)	Bd, n/N (%)	Absolute difference*	RR (95% CI)
OPTIMISMM - PBd vs Bd	≥ 1 TEAE	277/278 (99.6%)	264/270 (97.8%)	1.8	1.02 (1.00, 1.04)
ENDEAVOR - Cd vs Bd		455/463 (98.3%)	447/456 (98.0%)	0.3	1.00 (0.98, 1.02)
Indirect comparison PBd vs. Cd					1.02 (0.99, 1.05)
OPTIMISMM - PBd vs Bd	≥ 1 Grade 3+ TEAE**	251/278 (90.3%)	190/270 (70.4%)	19.9	**1.28 (1.18, 1.40)**
ENDEAVOR - Cd vs Bd		339/463 (73.2%)	305/456 (66.9%)	6.3	**1.09 (1.01, 1.19)**
Indirect comparison PBd vs. Cd					**1.17 (1.04, 1.32)**
OPTIMISMM - PBd vs Bd	≥ 1 serious TEAE	159/278 (57.2%)	114/270 (42.2%)	15	**1.35 (1.14, 1.61)**
ENDEAVOR - Cd vs Bd		224/463 (48.4%)	162/456 (35.5%)	12.9	**1.36 (1.17, 1.59)**
Indirect comparison PBd vs. Cd					0.99 (0.79, 1.25)
OPTIMISMM - PBd vs Bd	≥ 1 TEAE leading to discontinuation	80/278 (28.8%)	51/270 (18.9%)	9.9	**1.52 (1.12, 2.07)**
ENDEAVOR - Cd vs Bd		57/463 (12.3%)	59/456 (12.9%)	0.6	0.95 (0.68, 1.34)
Indirect comparison PBd vs. Cd					**1.6 (1.01, 2.53)**
OPTIMISMM - PBd vs Bd	≥ 1 TEAE leading to dose reduction	200/278 (71.9%)	139/270 (51.5%)	20.4	**1.40 (1.22, 1.60)**
ENDEAVOR - Cd vs Bd		106/463 (22.9%)	218/456 (47.8%)	24.9	**0.48 (0.39, 0.58)**
Indirect comparison PBd vs. Cd					**2.92 (2.29, 3.71)**

Bd = bortezomib+dexamathasone; Cd = carfilzomib+dexamethasone; CI = confidence interval; PBd = pomalidomide+bortezomib+dexamethasone; RR = risk ratio; TEAE = treatment emergent adverse events.
* Performed using the Bucher ITC method (Source: "BucherITC_PBdversusCd indirect analysis.xls");
** Rate of Grade 3 or 4 TEAEs from OPTIMISMM used (as all patients who had grade 5 TEAEs also had at least one grade 3 or 4 TEAE)
Source: Table 2-32, p136 of the submission

Benefits/harms

6.26 A summary of the benefits and harms was not presented given the non-inferiority nature of the claim.

Clinical claim

6.27 On the basis of the indirect treatment comparison, the submission claimed that PBd was non-inferior in terms of effectiveness compared with Cd. The submission stated that the results of subgroup analyses indicated that potential differences in baseline disease characteristics were not anticipated to materially impact on the comparison.

6.28 The ESC considered the claim of non-inferior effectiveness was uncertain for the following reasons:

- A statistically significant improvement in OS was demonstrated for Cd over Bd (HR = 0.79; 95% CI: 0.65, 0.96) in the ENDEAVOR trial; however, an improvement in OS was not demonstrated for PBd over Bd (HR = 0.91; 95% CI: 0.70, 1.18) in the OPTIMISMM trial. The ESC noted the TGA CER's comment that [redacted].
- The hazard ratio point estimates from the indirect treatment comparisons based on the trial ITT populations for both PFS and OS favoured Cd and the upper margins of the 95% CIs were approximately 1.6 (PFS: HR = 1.15, 95% CI: 0.85, 1.55; OS: HR =

1.15, 95% CI: 0.83, 1.6). As the submission did not nominate a non-inferiority margin it was unclear if these results supported a claim of non-inferiority. The ESC recalled, although for solid tumours, that a non-inferiority margin of 1.4 has previously been used to establish non-inferiority with respect to PFS (for example, for palbociclib for breast cancer (paragraph 5.11, Palbociclib PSD, March 2018)). However, the ESC noted the potential differences between the trials were likely to have biased against PBd, and the point estimate for the PFS indirect treatment comparison using the ITT population from OPTIMISMM and the 'prior treatment with lenalidomide' subgroup from ENDEAVOR favoured PBd (HR = 0.88; 95% CI: 0.61, 1.27).

6.29 The submission claimed that the indirect comparison demonstrated that PBd and Cd have different safety profiles. PBd was potentially inferior to Cd in terms of a higher incidence of Grade 3/4 TEAEs, TEAEs leading to discontinuation and TEAEs leading to dose reduction. The submission noted that clinically significant events such as neutropenia and peripheral neuropathy were more common with PBd, and that treatment with PBd seemingly avoided the more common CVAEs such as hypertension associated with carfilzomib, which might be of particular relevance for patients with existing risk factors for cardiovascular disease. The ESC considered that the evidence presented supported the claim of differing safety profiles for PBd and Cd.

6.30 The PBAC considered that the claim of non-inferior comparative effectiveness was not adequately supported by the data.

6.31 The PBAC considered that the claim of non-inferior comparative safety was not adequately supported by the data.

Economic analysis

6.32 The submission presented a cost minimisation analysis (CMA) comparing PBd to Cd.

6.33 The submission reported that for a 48 week treatment duration the equi-effective doses were:

764 mg of pomalidomide, 92 mg of bortezomib and 1,216 mg of dexamethasone = 7,150 mg of carfilzomib and 1,752 mg of dexamethasone

6.34 The evaluation considered that the use of a 48 week median treatment duration was inappropriate as only the ENDEAVOUR trial incorporated a 48-week median treatment duration (data cut 3 January 2017). Moreover, the use of a 48 week median treatment duration to calculate the equi-effective doses did not align with the median treatment durations from which the efficacy endpoints in the indirect comparison were claimed to be non-inferior (i.e. efficacy of PBd at 38.3 weeks versus Cd at 39.9 weeks). The PSCR claimed that the use of 48 weeks median duration utilised the best available evidence to calculate the cost-minimised price for PBd. The ESC considered that the use of 48 week median treatment duration data did not reflect the trial efficacy data

cut-offs for PBd (median treatment duration of 38.3 weeks) or Cd (median treatment duration of 39.9 weeks) and noted that there was no evidence presented that demonstrated that the PBd outcomes at 48 weeks treatment duration were non-inferior to Cd. The ESC noted that increasing the period over which the equi-effective doses were estimated to 48 weeks resulted in a higher price for pomalidomide as the duration of the concomitant bortezomib was assumed to remain at 11 cycles (33 weeks) of treatment. In addition, the ESC considered it may not be appropriate for the duration of PBd and Cd to be different (i.e. 38.3 vs 39.9 weeks). Overall, where the cost per patient calculations are uncertain, the guiding principle 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. In the pre-PBAC response the sponsor disagreed with ESC, reiterating that the 48 week treatment duration was based on the latest data-cut of the ENDEAVOR trial; however, stated that they were willing to accept the use of treatment duration data that reflected the trial efficacy data (i.e. 38.3 weeks for PBd and 39.9 weeks for Cd).

6.35 When the Cd and PBd treatment durations were aligned with those applied in the indirect comparison (38.3 weeks for PBd (26 October 2017 cut) and 39.9 weeks for Cd (10 November 2014 cut) the equi-effective dose regimens were:

609 mg of pomalidomide, 92 mg of bortezomib and 1,237 mg of dexamethasone = 6,052 mg of carfilzomib and 1,488 mg of dexamethasone.

6.36 The CMA applied RDIs directly from OPTIMISMM (October 2017 cut) and ENDEAVOR (January 2017 cut). Thus, RDIs of 0.85 (pomalidomide), 0.80 (bortezomib) and 0.80 (dexamethasone) were applied to the PBd regimen, and 0.91 (carfilzomib and dexamethasone) was applied to the Cd regimen. The RDI applied for Cd was from the January 2017 cut (48 weeks median treatment duration). This was inappropriate given that the indirect comparison for PFS used the November-2014 cut-off (39.9 weeks median treatment duration). The RDI for Cd at the earlier data-cut was higher at 0.93. The ESC considered that using the RDIs that corresponded to the indirect treatment comparison data cuts may be appropriate, although it was noted that the higher RDI for Cd increased the price for PBd relative to that for Cd.

6.37 The submission included additional costs and/or cost offsets associated with differences in the use of prophylactic medications, the modes of administration and management of adverse events for PBd compared with Cd. The following points are noted with the estimation of those costs:

- PBd patients in OPTIMISMM received concomitant treatment with an anticoagulant for thromboembolism prophylaxis. The submission included a cost for that therapy, where approximately [redacted]% of PBd patients in OPTIMISMM used aspirin and [redacted]% used enoxaparin (OPTIMISMM CSR). The OPTIMISMM CSR stated that [redacted] patients ([redacted]%) took low-dose aspirin, [redacted] patients ([redacted]%) took low molecular weight heparin and [redacted] patients ([redacted]%) took other antithrombotic

agents implying that some patients took more than one antithrombotic, likely sequentially. The PSCR noted that a plausible clinical scenario was that patients on aspirin or low molecular weight heparin were switched to novel oral anticoagulants which became available in some countries during the course of the trial. The ESC considered this explanation to be reasonable. The PSCR maintained that the CMA was conservative in assuming that all patients treated with PBd would receive prophylaxis with an antithrombotic or anticoagulant. The PBAC considered that patients could receive novel oral anticoagulants rather than aspirin or heparin.

- The submission applied MBS item 13915 ($65.05) to the intravenous (IV) administration of bortezomib and carfilzomib. This was appropriate for carfilzomib as it is administered as an IV infusion over 10 or 30 minutes (Kyprolis PI, 2019). The PSCR acknowledged that the application of MBS item 13915 to bortezomib was inappropriate given that it is administered via subcutaneous (SC) injection. The PBAC advised that no MBS item was available for SC administrations.

- The submission stated that only the difference in neutropenia was clinically meaningful and therefore this was the only adverse event costed in the CMA. The indirect comparison of Grade 3/4 adverse events demonstrated the incidence of neutropenia, peripheral sensory neuropathy, fatigue and diarrhoea as being statistically significantly higher for PBd in OPTIMISMM than for Cd in ENDEAVOR. Given these differences, the submission's claim of neutropenia being the only clinically meaningful adverse event may be unreasonable. Moreover, the approach assumed that only the cost implications of any differences in adverse events were of relevance. There may be relevant quality of life effects associated with some events, albeit of a transitory nature where those events resolve. The PSCR noted that it would be inappropriate to apply the adverse event costs of neutropenia, peripheral sensory neuropathy, fatigue or diarrhoea to PBd treatment without accounting for adverse events costs relating to Cd, such as CVAEs. The PSCR calculated that the difference in adverse event management costs were minimal between the arms (PBd = $[redacted]; Cd = $[redacted]). The ESC considered that it would be appropriate to include hospitalisation costs associated with Grade 3/4 diarrhoea and febrile neutropenia. The pre-PBAC response accepted the inclusions recommended by ESC, but noted that the inclusion of differential costing methodology was not appropriate and stated that hospitalisation costs for CVAEs related to Cd treatment should also be included in the CMA.

- The CMA attributed a cost relating to neutropenia in the CMA to the use of the G-CSF therapy, pegfilgrastim for [redacted]% of PBd patients and [redacted]% of Cd patients. The PSCR noted that the evaluation correctly identified that only [redacted]% of Cd patients would receive G-CSF. The CMA appropriately excluded costs for SC administration of pegfilgrastim.

6.38 A course of Cd was estimated to cost $[redacted] per patient and the non-pomalidomide components of a course of PBd were expected to be $[redacted]. Via cost-minimisation, the submission calculated pomalidomide drug costs of $[redacted] per course of PBd. This translated to a proposed approved ex-manufacturer price (AEMP) of [redacted] per 14 x 4 mg pack of pomalidomide. This was higher than the proposed published price (see Table 2).

6.39 When the Cd and PBd treatment duration was reduced from 48 to 38.3 weeks (PBd) and to 39.9 weeks (Cd) to reflect the indirect comparison, the pomalidomide drug cost reduced to $[redacted] per course of PBd and the pomalidomide AEMP reduced to $[redacted] per 14 x 4 mg pack of pomalidomide.

6.40 A revised base case in which effective prices were used for carfilzomib and bortezomib, equi-effective doses and RDIs were determined using the median treatment durations from the indirect treatment comparison, the cost of IV administration of carfilzomib was included, no cost was associated with the SC administration of bortezomib or G-CSF, [redacted]% of Cd patients received G-CSF and hospitalisation costs for Grade 3/4 diarrhoea and febrile neutropenia were included for PBd and Cd patients was suggested by ESC.

6.41 Although the pre-PBAC response accepted the revised base case, the Sponsor disagreed with the revised median treatment durations for PBd and Cd, stating that a 48-week treatment duration was based on the latest data-cut of the ENDEAVOR trial and therefore represented the best available evidence. Additionally, the pre-PBAC response stated that costs for adverse events that are more frequent with Cd treatment, for example CVAEs, should be included in the analysis.

Drug cost/patient/course

6.42 Using median treatment durations from OPTIMISMM (38.3 weeks) and ENDEAVOR (39.9 weeks) resulted in a drug cost per patient of $[redacted] for PBd and of $[redacted] for Cd (see Table 14). The corresponding price per pack of pomalidomide is the alternative noted above; $[redacted]. Both the drug cost per patient and price are lower than those estimated by the submission which assumed a 48-week treatment cycle, resulting in a drug cost of $[redacted] per patient.

Table 14: Drug cost per patient for proposed and comparator drugs

	PBd			Cd		
	Trial dose and duration	**CMA**	**Financial estimates**	**Trial dose and duration**	**CMA**	**Financial estimates**
Equi-effective dose (as per submission)	POM: 4 mg BTZ: 1.3 mg/m^2 DEX: 20 mg/day (≤ 75 years) or 10 mg/day (> 75 years)	POM 764 mg BTZ: 92 mg DEX: 1,216 mg	POM 764 mg BTZ: 92 mg DEX: 1,216 mg	CFZ: 20 mg/m² IV on Days 1 and 2 of Cycle 1, 56 mg/m² thereafter. DEX: 20 mg	CFZ: 7,150 mg DEX: 1,752 mg	CFZ: 7,150 mg DEX: 1,752 mg
Frequency/cycle	POM: 14 BTZ: Cycles 1-8 (x 4) Cycles 9+ (x 2) DEX: Cycles 1-8 (x 8) Cycles 9+ (x 4) 21-day cycle	POM: 14 BTZ: Cycles 1-8 (x 4) Cycles 9+ (x 2) DEX: Cycles 1-8 (x 8) Cycles 9+ (x 4) 21-day cycle	POM: 14 BTZ: Cycles 1-8 (x 4) Cycles 9+ (x 2) DEX: Cycles 1-8 (x 8) Cycles 9+ (x 4) 21-day cycle	CFZ: Cycle 1: 20 mg/m^2 (x 2) Cycles 1+: 56 mg/m^2 (x 4) DEX: 8 28-day cycle	CFZ: Cycle 1: 20 mg/m^2 (x 2) Cycles 2+: 56 mg/m^2 (x 4) DEX: 8 28-day cycle	CFZ: Cycle 1: 20 mg/m^2 (x 2) Cycles 2+: 56 mg/m^2 (x 4) DEX: 8 28-day cycle
Median duration	POM: 38.3 weeks (BTZ: 33 weeks, DEX: 34 weeks)	POM: 48 weeks (BTZ: 33 weeks, DEX: 33 weeks)	POM: 48 weeks (BTZ: 33 weeks, DEX: 33 weeks)	CFZ: 39.9 weeks (DEX: 39.9 weeks)	CFZ: 48 weeks (DEX: 48 weeks)	CFZ: 48 weeks (DEX: 48 weeks)
Cost/patient/cycle	POM $[redacted] (private) [a] $[redacted] (public)[a]	POM $[redacted] (private) $[redacted] (public)	POM $[redacted] (private) $[redacted] (public)	CFZ $[redacted] (private) $[redacted] (public)	CFZ $[redacted] (private) $[redacted]32 (public)	CFZ $[redacted] (private) $[redacted] (public)
Cost/patient/course	PBd: $[redacted] (POM: $[redacted] BTZ: $[redacted] DEX: $[redacted])	PBd: $[redacted] (POM: $[redacted] BTZ: $[redacted] DEX: $[redacted])	PBd: $[redacted] (POM: $[redacted] BTZ: $[redacted] DEX: $[redacted])	Cd: $[redacted] (CFZ: $[redacted] DEX: $[redacted])	Cd: $[redacted] (CFZ: $[redacted] DEX: $[redacted])	Cd: $[redacted] (CFZ: $[redacted] DEX: $[redacted])

BTZ = bortezomib; Cd = carfilzomib+dexamethasone; CFZ = carfilzomib; CMA = cost minimisation analysis; DEX = dexamethasone; DPMQ = dispensed price for maximum quantity; PBd = pomalidomide+bortezomib+dexamethasone; POM = pomalidomide

a Proposed DPMQ public and private hospital price of pomalidomide from Section 1 of the submission (different to effective price in Section 3 of the submission)

Source: Table 1-8 p.37 and Table 3-2 p. 156 of the submission, workbook PBd_CMA_BIM.xls and calculated during evaluation.

Estimated PBS usage & financial implications

6.43 This submission was not considered by DUSC.

6.44 The submission adopted a mixed model approach combining epidemiology and market share data to estimate the potential utilisation of PBd on the PBS/RPBS. This was reasonable given that utilisation details of carfilzomib for a strict market share approach would not have stabilised. The financial workbook estimated the PBd eligible population based on historical PBS utilisation of lenalidomide, estimated treatment durations and RDIs, and the expected progressions between lines of treatment in an Australian MM population, as follows:

- The submission estimated that [redacted] newly diagnosed and [redacted] relapsed or refractory lenalidomide scripts will be accessed in 2019, increasing to [redacted] and [redacted] respectively in 2025. The PBAC considered that the submission, in using a linear extrapolation, had overestimated the market size of RRMM patients as market growth shows signs of slowing. Patient volumes grew by [redacted]% from 2014 to 2015, [redacted]% from 2016 to 2017 but slowed to [redacted]% growth between 2017 and 2018. There was uncertainty surrounding the future utilisation of lenalidomide due to the recent listing of carfilzomib (carfilzomib market uptake is yet to mature) and potential near future listing of additional treatment options, e.g. daratumumab in RRMM and lenalidomide as maintenance therapy in post-ASCT newly diagnosed MM.

- Data from a DUSC (2017) report on utilisation of PBS medicines between 2014 and 2016 in MM showed 38.5% of patients received a second-line treatment, of which 41% went on to receive third-line treatment. The submission acknowledged there have been changes to the MM treatment market since the DUSC report (2017), i.e. carfilzomib is now available in the relapsed or refractory treatment setting and lenalidomide is now available in the induction treatment setting. It is uncertain how the proportions of patients progressing through the treatment lines has changed since 2016.

- In order to derive an estimate of the market size for PBd, the submission converted lenalidomide scripts into patient equivalents by adjusting lenalidomide scripts by exposure per patient based on an assumed RDI of 0.90 (sourced from an ad-hoc literature review). This resulted in an estimated 9.2 lenalidomide scripts per patient. This seemed reasonable.

6.45 A total lenalidomide treated population was subsequently estimated by dividing the total projected lenalidomide utilisation on the PBS by the estimated number of scripts per patient. The submission estimated the number of lenalidomide patients eligible for PBd each year by applying the proportions of patients' progressing through each line of MM treatment (DUSC 2017) to the lenalidomide patient estimates. The

submission assumed that patients progress to the next line of treatment the following year. This was considered reasonable based on median treatment durations of PBd, Cd, Bd and Ld which are all estimated to be below one year (OPTIMISMM; ENDEAVOR; DUSC 2017). Uptake of PBd within the incident population was assumed to increase from [redacted]% in Year 1 to [redacted]% in Year 2, [redacted]% in Year 3 and [redacted]% in Year 4, remaining stable thereafter from Year 4 to Year 6. The submission acknowledged uncertainty in these uptake rates and explored different uptake rates in its sensitivity analyses. The ESC expected that, if listed on the PBS, that uptake of PBd would be high as it would be the first PBS-available triplet therapy. In addition, the ESC noted that the availability of PBd on the PBS may result in an increased use of lenalidomide in the newly diagnosed MM setting.

6.46 The submission made the following assumptions in estimating substitution within the financial estimates:

- There will be zero market growth. This was reasonable.
- Pending available alternatives, a patient will not receive sequential lines of the same treatment. This was reasonable.
- PBd will not substitute for Pd use. This was reasonable as Pd is used in a subsequent treatment line to PBd.
- The market share of PBd will come from equal substitution of Cd ([redacted]%) and Bd ([redacted]%), acknowledging that these substitution rates are uncertain. The submission's estimates regarding substitution were based on an arbitrary assumption. It is possible that substitution may differ from this estimate. The PSCR noted that given the recent PBS listing of Cd, the market share of Cd was expected to surpass that of Bd. The ESC agreed.

6.47 A summary of the estimated use and financial implications for listing PBd for the treatment of RRMM on the PBS is presented in Table 15 below.

Table 15: Estimated use and financial implications

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
Estimated extent of use						
Number of patients treated 1st line RR 2nd line RR						
Number of scripts dispensed[a] Pomalidomide Bortezomib Dexamethasone						
Estimated financial implications of PBd						
Cost to PBS/RPBS						
Copayments						
Cost to PBS/RPBS less copayments						
Estimated financial implications for other medicines (substitution of Cd and Bd)						
Cost to PBS/RPBS						
Copayments						
Cost to PBS/RPBS less copayments						
Estimated financial implications for other medicines (AE and concomitant medications)						
Cost to PBS/RPBS						
Copayments						
Cost to PBS/RPBS less copayments						
Net financial implications						
Net cost to PBS/RPBS						
Net cost to MBS						
Net cost to Govt.						

AE = adverse events; Cd = carfilzomib+dexamethasone; DHS = Department of Human Services; MBS = Medicare Benefits Schedule; PBS = Pharmaceutical Benefits Scheme; PBd = pomalidomide+bortezomib+dexamethasone; RPBS = Repatriation Pharmaceutical Benefits Scheme; RR = relapsed or refractory

[a] Assuming {number of scripts} per year as estimated by the submission.

Source: Table 4-12 p.187, Table 4-13 p.188, Table 4-22 p.198 and Table 4-28 p.205 of the submission.

6.48 The submission assumed that the PBd median treatment duration was 48 weeks. This was not the duration associated with efficacy included in the indirect comparison (38.3 weeks). Once median treatment duration was adjusted to [redacted] weeks, the net cost to government decreased to less than $10 million in Year 1 and to $30-$60 million in Year 6.

6.49 The substantial net costs to the PBS/RPBS can be explained by the substitution of Bd which is less costly and less effective based on previous PBAC recommendations (i.e. PBd=Cd>Ld=Bd). The submission has not presented a CUA of PBd against Bd alone.

6.50 The net cost to the government was most sensitive to the proportional substitution of Cd and Bd (when PBd substituted for 100% Cd, i.e. 0% subsidisation of Bd, the net cost was $0). The submission stated that this was expected since PBd and Cd regimens were cost-minimised and carfilzomib has a price premium over bortezomib.

6.51 The PSCR also highlighted that by [redacted] generic agents for both pomalidomide and bortezomib were expected to be available. As a result, the prices of these drugs in the later years of the estimates could be overestimated, and the substitution of carfilzomib by pomalidomide could represent cost-savings for the PBS.

Risk sharing arrangements

6.52 The PSCR stated that in order to address any residual uncertainty, the Sponsor would be willing to develop an indication specific Deed of Agreement and Risk Sharing Arrangement (RSA) for the use of pomalidomide in combination with bortezomib and dexamethasone.

6.53 The ESC noted that as carfilzomib is subject to a RSA, should pomalidomide be recommended it would be appropriate for pomalidomide to join the carfilzomib RSA caps. The Sponsor advised in the pre-PBAC response that it would be willing for pomalidomide to join the carfilzomib RSA caps, but that the expenditure limits would need to be increased to permit the sequential use of PBd and Cd in a proportion of patients and to account for substitution of Bd. Any possible increase in subsidisation caps to allow for sequential use of Cd and PBd would require PBAC consideration that sequential use was appropriate in this setting.

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

7 PBAC Outcome

7.1 The PBAC did not recommended the listing of pomalidomide, for use in combination with bortezomib and dexamethasone (PBd), for 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 been previously treated with lenalidomide. The PBAC considered, due to differences between the key trials, that the indirect comparison with carfilzomib plus dexamethasone (Cd) was difficult to interpret and did not adequately demonstrate non-inferiority between the treatments. The PBAC were also concerned that, in contrast to Cd, PBd did not demonstrate an improvement in overall survival compared to bortezomib plus dexamethasone (Bd) treatment.

7.2 The PBAC noted the consumer comments received in support of a PBS listing and considered that these reflected the ongoing clinical need for additional treatment options for patients with RRMM.

7.3 The PBAC considered that the clinical place in therapy of PBd, as proposed by the requested PBS restriction, was appropriate based on the available evidence. The PBAC noted that a PBS listing for PBd could result in a higher proportion of patients receiving lenalidomide plus dexamethasone (Ld) as first-line treatment so that they would be eligible to receive PBd in the relapsed or refractory state.

7.4 The PBAC considered that Cd was the appropriate main comparator.

7.5 The PBAC noted that the submission presented 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.

7.6 The PBAC noted that although PBd demonstrated an improvement compared to Bd in terms of progression free survival (HR = 0.61; 95% CI: 0.49, 0.77) in the OPTIMISMM trial, PBd provided no statistically significant improvement in terms of overall survival (HR = 0.91; 95% CI: 0.70, 1.18).

7.7 The PBAC noted that in the ENDEAVOR trial, patients treated with Cd had significantly longer progression free survival (HR = 0.55; 95% CI: 0.46, 0.65) and overall survival (HR = 0.79; 95% CI: 0.65, 0.96) compared to those who received Bd.

7.8 The PBAC noted that there was a significant number of transitivity issues between the OPTIMISMM and ENDEAVOR trials (as outlined in paragraph 6.18) 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. The PBAC also noted that no non-inferiority margin was nominated.

7.9 The PBAC noted that the point estimates of the indirect comparison between the ITT populations of OPTIMISMM and ENDEAVOR favoured Cd in terms of both progression free survival (HR = 1.15; 95% CI: 0.85, 1.55) and overall survival (HR = 1.15, 95% CI: 0.83, 1.60) and that the upper limits of the 95% confidence intervals were in the region of 1.6, which may exceed a reasonable non-inferiority margin.

7.10 The PBAC noted that 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 progression free survival 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). However, the PBAC, noting 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%), considered that the reliability of the indirect analysis was uncertain.

7.11 Overall, the PBAC considered that the significant differences between the OPTIMISMM and ENDEAVOR trials meant that the reliability of the indirect comparisons was highly uncertain. This, combined with the lack of a nominated non-inferiority margin, and the fact that PBd did not demonstrate a benefit compared to Bd in terms of overall survival, meant the PBAC considered that the results did not

adequately demonstrate non-inferiority between PBd and Cd in terms of efficacy.

7.12 The PBAC noted that the indirect comparison demonstrated that PBd resulted in more statistically significantly ≥ 1 Grade 3+ treatment emergence adverse events, ≥ 1 treatment emergent adverse events resulting in discontinuation and ≥ 1 treatment emergent adverse events resulting in dose reduction compared to Cd. Results for ≥ 1 treatment emergent adverse event or ≥ 1 serious treatment emergent adverse event were not significantly different.

7.13 The PBAC considered that the results of the indirect comparisons did not demonstrate non-inferiority between PBd and Cd in terms of safety.

7.14 The PBAC noted that 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 adverse events for both PBd and Cd.

7.15 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 $60-$100 million in Year 6 due to the assumed substitution of PBd for Bd. The PBAC noted that the market size of RRMM lenalidomide patients was overestimated.

7.16 The PBAC considered that any future submission should be a major submission and address the uncertainties surrounding the non-inferiority claim and update the economic evaluation and the financial impact of listing PBd on the PBS. Alternatively, the PBAC noted that if there was a defined patient population unable to be treated with Cd, that a submission comparing PBd to Bd may be appropriate.

7.17 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

Celgene is disappointed with the outcome and are committed to working with the PBAC in order to achieve a PBS listing for Pomalyst as a triplet regimen in rrMM, so patients with multiple myeloma have more options in the future.