

7.01 CARFILZOMIB, Powder for I.V. infusion 10 mg, 30 mg and 60 mg, Kyprolis[®], Amgen Australia Pty Ltd

1 Purpose of Application

- 1.1 The resubmission requested the Section 100 (Efficient Funding of Chemotherapy – Public and Private Hospital) Authority Required listing of carfilzomib for the treatment of relapsed or refractory multiple myeloma (RRMM).

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

Component	Description
Population	Patients with relapsed or refractory multiple myeloma after ≥ 1 prior therapy.
Intervention	Carfilzomib with dexamethasone (Cd).
Comparator	Bd was proposed as the main comparator.
Outcomes	OS, PFS, QoL adverse events
Clinical claim	Cd is superior in terms of comparative efficacy (based on OS and PFS) with a different safety profile compared with Bd. The PBAC previously accepted this claim against Bd.

Source: Table 1.1-1, p4 of the resubmission

Bd = bortezomib + dexamethasone; Cd = carfilzomib + dexamethasone; IV = intravenous; Ld = lenalidomide + dexamethasone; OS = overall survival; PBAC = Pharmaceutical Benefits Advisory Committee; PFS = progression free survival; QoL = Quality of Life

- 1.2 The only change to the key components of the clinical issue was that the resubmission requested listing of carfilzomib plus dexamethasone (Cd) only. The previous submission had also requested PBS listing of carfilzomib plus lenalidomide plus dexamethasone (CLd). CLd was not requested in the resubmission due to “challenges demonstrating that CLd is cost-effective” which it stated were due to the cost of concomitant lenalidomide.
- 1.3 The previous submission requested separate consideration of the Cd and CLd regimens. However, given both regimens were included in the TGA indication, the PBAC had stated that “the appropriate clinical positioning of each regimen needs to be considered” (Paragraph 7.3, November 2016 Public Summary Document (PSD)). Despite this, the resubmission did not consider the clinical position of Cd if CLd, or other triplet therapies, were available. The availability of CLd may affect the proposed population, the clinical algorithm and the applicability of the key trial. The impact of this was not known - the PBAC previously considered that the role of CLd versus Cd in clinical practice was unclear.

2 Requested listing

Suggestions and additions proposed by the Secretariat to the requested listing are added in italics and suggested deletions are crossed out with strikethrough.

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Initial treatment:

Name, Restriction, Manner of administration and form	Max. Amt	No. of Rpts	Dispensed Max. Amt	Price for	Proprietary Name and Manufacturer
CARFILZOMIB			Published		Kyprolis® AN
Powder for injection, 30 mg	120 mg	17	Public: \$ [REDACTED] Private: \$ [REDACTED]		
Powder for injection, 60 mg			Effective Public: \$ [REDACTED] Private: \$ [REDACTED]		

Category / Program	Section 100 – Efficient funding of Chemotherapy
Prescriber type:	<input type="checkbox"/> Dental <input checked="" type="checkbox"/> Medical Practitioners <input type="checkbox"/> Nurse practitioners <input type="checkbox"/> Optometrists <input type="checkbox"/> Midwives
Condition:	Multiple myeloma
PBS Indication:	Progressive multiple myeloma
Treatment phase:	Initial treatment
Restriction Level / Method:	<input type="checkbox"/> Restricted benefit <input checked="" type="checkbox"/> Authority Required - In Writing <input type="checkbox"/> Authority Required - Telephone <input type="checkbox"/> Authority Required - Emergency <input type="checkbox"/> Authority Required - Electronic <input type="checkbox"/> Streamlined
Clinical criteria:	The condition must be confirmed by a histological diagnosis, AND The treatment must be in combination with dexamethasone, AND Patient must have progressive disease after at least one prior therapy, AND Patient must have undergone or be ineligible for a stem cell transplant, AND Patient must not be receiving concomitant PBS-subsidised thalidomide, lenalidomide, bortezomib, or pomalidomide AND Patient must not receive more than four three cycles of treatment under this restriction AND <i>Patient must not have previously received this drug for this condition</i>
Prescriber Instructions	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

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	<p>(d) at least a 25% relative increase and at least a 10% absolute increase in plasma cells in a bone marrow aspirate or on biopsy; or</p> <p>(e) an increase in the size or number of lytic bone lesions (not including compression fractures); or</p> <p>(f) at least a 25% increase in the size of an existing or the development of a new soft tissue plasmacytoma (determined by clinical examination or diagnostic imaging); or</p> <p>(g) development of hypercalcaemia (corrected serum calcium greater than 2.65 mmol per L not attributable to any other cause).</p> <p>Oligo-secretory and non-secretory patients are defined as having active disease with less than 10 g per L serum M protein.</p> <p>The authority application must be made in writing and must include:</p> <p>(1) a completed authority prescription form; and</p> <p>(2) a completed <name of form> - Supporting Information Form, which includes 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.</p> <p>(3) a signed patient acknowledgment.</p> <p>To enable confirmation of eligibility for treatment, current diagnostic reports of at least one of the following must be provided:</p> <p>(a) the level of serum monoclonal protein; or</p> <p>(b) Bence-Jones proteinuria - the results of 24-hour urinary light chain M protein excretion; or</p> <p>(c) the serum level of free kappa and lambda light chains; or</p> <p>(d) bone marrow aspirate or trephine; or</p> <p>(e) if present, the size and location of lytic bone lesions (not including compression fractures); or</p> <p>(f) if present, the size and location of all soft tissue plasmacytomas by clinical or radiographic examination i.e. MRI or CT-scan; or</p> <p>(g) if present, the level of hypercalcaemia, corrected for albumin concentration.</p> <p>As these parameters will 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) should be provided. Where the prescriber plans to assess response in patients with oligo-secretory or non-secretory multiple myeloma with free light chain assays, evidence of the oligo-secretory or non-secretory nature of the multiple myeloma (current serum M protein less than 10 g per L) must be provided.</p>
<p>Administrative Advice</p>	<p>No increase in the maximum number of repeats may be authorised.</p> <p>No increase in the maximum amount or number of units may be authorised.</p> <p>Special Pricing Arrangements apply.</p>

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Continuing treatment 1:

Name, Restriction, Manner of administration and form	Max. Amt	No. of Rpts	Dispensed Price for Max. Amt	Proprietary Name and Manufacturer
CARFILZOMIB			Published	Kyprolis AN
Powder for injection, 30 mg	120 mg	17	Public: \$ [REDACTED] Private: \$ [REDACTED]	
Powder for injection, 60 mg			Effective Public: \$ [REDACTED] Private: \$ [REDACTED]	

Category / Program	Section 100 – Efficient funding of Chemotherapy
Prescriber type:	<input type="checkbox"/> Dental <input checked="" type="checkbox"/> Medical Practitioners <input type="checkbox"/> Nurse practitioners <input type="checkbox"/> Optometrists <input type="checkbox"/> Midwives
Severity:	Progressive
Condition:	Multiple myeloma
PBS Indication:	Progressive multiple myeloma
Treatment phase:	Continuing treatment
Restriction Level / Method:	<input type="checkbox"/> Restricted benefit <input checked="" type="checkbox"/> Authority Required - In Writing <input type="checkbox"/> Authority Required - Telephone <input type="checkbox"/> Authority Required - Emergency <input type="checkbox"/> Authority Required - Electronic <input type="checkbox"/> Streamlined
Clinical criteria:	Patient must have previously received an authority prescription for this condition with this drug AND The treatment must be in combination with dexamethasone, AND Patient must not have progressive disease while receiving treatment with this drug, AND <i>Patient must not receive more than 3 cycles of treatment per continuing treatment course authorised under this restriction.</i>
Prescriber Instructions	<Progressive disease defined as per initial restriction> <The authority application requirements as per initial restriction>
Administrative Advice	No increase in the maximum number of repeats may be authorised. No increase in the maximum amount or number of units may be authorised. Special Pricing Arrangements apply

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Continuing criteria 2 (cycles 16 +)

Name, Restriction, Manner of administration and form	Max. Amt	No. of Rpts	Dispensed Price for Max. Amt	Proprietary Name and Manufacturer
CARFILZOMIB Powder for injection, 30 mg Powder for injection, 60 mg	120 mg	17	Published Public: \$ [REDACTED] Private: \$ [REDACTED] Effective Public: \$ [REDACTED] Private: \$ [REDACTED]	Kyprolis AN

Category / Program	Section 100 – Efficient funding of Chemotherapy
Prescriber type:	<input type="checkbox"/> Dental <input checked="" type="checkbox"/> Medical Practitioners <input type="checkbox"/> Nurse practitioners <input type="checkbox"/> Optometrists <input type="checkbox"/> Midwives
Severity:	Progressive
Condition:	Multiple myeloma
PBS Indication:	Progressive multiple myeloma
Treatment phase:	Continuing treatment (Cycles 16 and beyond)
Restriction Level / Method:	<input checked="" type="checkbox"/> Authority Required - In Writing
Clinical criteria:	Patient must have previously received an authority prescription for this condition with this drug AND Patients must have previously received 15 cycles of PBS-subsidised carfilzomib AND The treatment must be in combination with dexamethasone, AND Patient must not have progressive disease while receiving treatment with this drug,
Prescriber Instructions	<Progressive disease defined as per initial restriction> <The authority application requirements as per initial restriction>
Administrative Advice	No increase in the maximum number of repeats may be authorised. No increase in the maximum amount or number of units may be authorised. Special Pricing Arrangements apply

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Grandfather treatment:

Name, Restriction, Manner of administration and form	Max. Amt	No. of Rpts	Dispensed Max. Amt	Price for	Proprietary Name and Manufacturer
CARFILZOMIB			Published		Kyprolis AN
Powder for injection, 30 mg	120 mg	17	Public: \$ [REDACTED] Private: \$ [REDACTED]		
Powder for injection, 60 mg			Effective Public: \$ [REDACTED] Private: \$ [REDACTED]		

Category / Program	Section 100 – Efficient funding of Chemotherapy
Prescriber type:	<input type="checkbox"/> Dental <input checked="" type="checkbox"/> Medical Practitioners <input type="checkbox"/> Nurse practitioners <input type="checkbox"/> Optometrists <input type="checkbox"/> Midwives
Condition:	Multiple myeloma
PBS Indication:	Progressive multiple myeloma
Treatment phase:	Grandfathering
Restriction Level / Method:	<input type="checkbox"/> Restricted benefit <input checked="" type="checkbox"/> Authority Required - In Writing <input type="checkbox"/> Authority Required - Telephone <input type="checkbox"/> Authority Required - Emergency <input type="checkbox"/> Authority Required - Electronic <input type="checkbox"/> Streamlined
Clinical criteria:	<i>Patient must have received treatment with carfilzomib for this condition prior to <date of listing> AND Patient must have a documented histological diagnosis, AND The treatment must be in combination with dexamethasone, AND Patient must have had documented progressive disease after at least one prior therapy prior to commencing non-PBS subsidised treatment with carfilzomib for this condition, AND Patient must not have progressive disease while receiving treatment with this drug, AND Patient must have undergone or be ineligible for a stem cell transplant, AND Patient must not be receiving concomitant PBS-subsidised thalidomide, lenalidomide, bortezomib, or pomalidomide AND Patient must not receive more than three cycles of treatment under this restriction.</i>

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<p>Prescriber Instructions</p>	<p><Progressive disease defined as per initial restriction> <i>Patient may qualify for PBS-subsidised treatment under this restriction once only. For continuing PBS-subsidised treatment, a Grandfathered patient must qualify under Continuing treatment criteria.</i></p> <p><Authority application requirements as per initial restriction> <i>To enable confirmation of eligibility to continue treatment, current measurements and measurements recorded prior to carfilzomib initiation for at least one of the following must be provided:</i></p> <ul style="list-style-type: none"> <i>(a) the level of serum monoclonal protein; or</i> <i>(b) Bence-Jones proteinuria - the results of 24-hour urinary light chain M protein excretion; or</i> <i>(c) the serum level of free kappa and lambda light chains; or</i> <i>(d) bone marrow aspirate or trephine; or</i> <i>(e) if present, the size and location of lytic bone lesions (not including compression fractures); or</i> <i>(f) if present, the size and location of all soft tissue plasmacytomas by clinical or radiographic examination i.e. MRI or CT-scan; or</i> <i>(g) if present, the level of hypercalcaemia, corrected for albumin concentration.</i> <p><i>As these parameters will 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) should be provided. Where the prescriber plans to assess response in patients with oligo-secretory or non-secretory multiple myeloma with free light chain assays, evidence of the oligo-secretory or non-secretory nature of the multiple myeloma (current serum M protein less than 10 g per L) must be provided.</i></p>
<p>Administrative Advice</p>	<p><i>No increase in the maximum number of repeats may be authorised. No increase in the maximum amount or number of units may be authorised. Special Pricing Arrangements apply.</i></p>

2.1 Compared with the previous submission, the changes to the proposed PBS listing were:

- an increase in the rebate by █% was proposed (█% versus █%);
- a 10 mg vial was proposed for PBS listing, in addition to the TGA-registered strengths (30 mg and 60 mg). The resubmission assumed that the 10 mg strength █. An application to register the 10 mg vials had not been submitted at the time the resubmission was prepared; and
- a Risk Sharing Arrangement (RSA) was proposed to cover the full drug cost of carfilzomib █

2.2 The PBAC noted that in the proposed treatment setting, patients will have already demonstrated that they have multiple myeloma in order to access initial treatment, and that it is not necessary to provide documentation to confirm this again. The PBAC therefore considered that it may be appropriate for carfilzomib to be a telephone authority, rather than a written authority.

2.3 The PBAC also noted that the current listings for bortezomib and lenalidomide require patients to have “...experienced treatment failure after a trial of at least four (4) weeks of thalidomide at a dose of at least 100 mg daily or have failed to achieve at least a minimal response after eight (8) or more weeks of thalidomide-based therapy for progressive disease”. The PBAC noted that it had previously recommended that the requirement for exposure to thalidomide should be removed (Pomalidomide, March 2016 PSD) however, this is still awaiting implementation. The PBAC considered that prior exposure to thalidomide was not required in the restriction for carfilzomib.

2.4 The recommended dose of carfilzomib is 56 mg/m² (except the first two doses, which are 20 mg/m²), given in combination with dexamethasone. Carfilzomib is administered by intravenous infusion on six days of each 28-day cycle. Patients are treated until progression or unacceptable toxicity.

2.5 The resubmission requested listing on a cost-effectiveness basis compared with bortezomib + dexamethasone (Bd), which is unchanged from the previous submission.

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

3 Background

3.1 TGA status: carfilzomib was registered by the TGA in December 2016 as follows –

“Carfilzomib, as part of combination therapy with dexamethasone or lenalidomide and dexamethasone, is indicated for the treatment of patients with relapsed or refractory multiple myeloma who have received at least one prior therapy.”

3.2 This was the second submission for carfilzomib – the first submission was considered by the PBAC in November 2016. The PBAC noted the following key issues:

- while Bd, as nominated by the submission, was an appropriate comparator, Ld was also a relevant comparator;
- the modelled overall survival (OS) gain was uncertain because the data from the clinical trial were immature and the differences were not statistically significant;
- a number of assumptions in the economic model favoured Cd and hence the incremental cost-effectiveness ratio (ICER) was likely to be substantially underestimated. In particular, the PBAC had concerns with the model structure, the persistent treatment effect, the point of extrapolation from the Kaplan-Meier OS curves, the time horizon and the utilities; and
- the financial estimates were underestimated because the number of eligible patients was underestimated and carfilzomib was likely to displace rather than replace other treatment options.

Table 2: Summary of outstanding matters of concern

Matter of concern	November 2016: previous submission	July 2017: resubmission
Clinical Evidence		
The PBAC considered that Bd was an appropriate comparator but that Ld was also a relevant comparator (PSD paragraph 7.4)	Bd as the main comparator. The resubmission considered that a comparison between Cd and Ld was not necessary as Ld was listed on a cost-minimisation basis to Bd. The PBAC considered that Ld was also a relevant comparator.	Bd as the main comparator. The resubmission considered it would not be feasible to conduct an indirect comparison between Ld and Cd. Therefore, there was a lack of evidence of superiority of Cd over Ld.
The different patient populations likely to use CLd versus Cd were not addressed (PSD paragraph 7.3)	Listing of either Cd alone; or both CLd and Cd was sought. Requested the PBAC separately consider the Cd and CLd regimens. The PBAC considered the appropriate clinical positioning of each regimen needed to be considered as both were TGA-registered.	Listing of Cd only was sought. The resubmission did not consider the clinical positioning if triplet therapies such as CLd were available, which would affect the proposed population and trial applicability. There was also a risk of leakage into CLd.
OS based on immature data and the differences were not statistically significant (PSD paragraph 7.9)	Data-cut: 10 November 2014 (CSR) The improvement in OS with Cd was not statistically significant (HR = 0.79; 95% CI: 0.58, 1.08) based on 12.2 months median follow-up for OS.	Data-cut used in the economic model: 3 March 2016: OS HR = 0.81 (0.65, 1.003). A more recent data-cut was available but not used in the model due to its recentness (3 Jan 2017 data-cut). It found a statistically significant improvement in OS with Cd (HR = 0.79; 95% CI: 0.65, 0.96), based on 37.2 months median follow-up for OS. The PSCR (p1) updated model using the 3 Jan 2017 data-cut improved the ICER slightly.

Economic Issues		
It may be appropriate for the model to include multiple lines of therapy and post progression costs (PSD paragraph 7.8)	3-state health model: PFS, progressed disease and dead	Unchanged. While post-progression costs were included in sensitivity analyses, the benefits of subsequent treatments were not (subsequent therapies would have different efficacies, adverse effects and costs).
The ICER was highly sensitive to the point of extrapolation from the KM OS curves (PSD paragraph 7.10)	KM OS curve used for the first █ cycles (18 months) vs. median follow-up of █ cycles (12.2 months).	KM curve used for the first █ cycles (7 months) vs. median follow-up of █ cycles (26.8 months) which meant the ICER was less sensitive to the point of extrapolation.
Persistent treatment effect was not adequately supported; time horizon of 10 years would have been more appropriate (PSD paragraph 7.10)	Registry data were used to extrapolate beyond the trial. OS curves did not converge (4.7% more patients alive in the Cd arm than the Bd arm at 10 years). 15-year time horizon	Registry data continued to be used to extrapolate beyond the trial period. OS curves did not converge (3.1% more patients alive in the Cd arm than the Bd arm at 10 years). This was not adequately justified and may not be appropriate for a relapsing condition. 10-year time horizon
Utilities from van Agthoven 2004 were not applicable to the requested population	Utilities from van Agthoven 2004 used for both the PFS (0.81) and progressed disease (0.64) health states.	Trial-based QoL appropriately used for PFS (0.75) health state. van Agthoven continued to be used for progressed disease (0.64), which did not address PBAC's concerns.
Cd drug costs excluded after █ cycles but no specific RSA was proposed (PSD paragraph 7. 10))	Carfilzomib drug costs were excluded after █ cycles despite listing being requested until progression. No specific RSA was proposed.	Carfilzomib drug costs were excluded after █ cycles. A specific RSA was proposed based on a █ cycles. Carfilzomib administration costs were also excluded which was inappropriate.
Financial Issues		
Eligible patient population was underestimated, particularly those switching from Bd (PSD paragraph 6.58)	Derived from 2013 DUSC report and 10% PBS sample: estimated █ patients would otherwise receive Bd in Year 1 (used to estimate the eligible population).	Derived from 2014-15 PBS sample data: estimated █ patients would receive Bd in Year 1 (used to estimate the eligible population).
Cd drug costs excluded after 18 cycles (PSD paragraph 7.11)	Per economic issues.	Per economic issues.
Cd would likely displace rather than replace other treatment options (PSD paragraph 7.11)	Assumed Cd would replace (not displace) Bd and Ld	Unchanged in the base case. A sensitivity analysis was included in which 10% more Cd cycles were assumed. The basis for this was unclear.
No details of compassionate use programs provided (PSD paragraph 7.12)	No details were provided regarding the number of patients accessing carfilzomib through these programs. A practical approach to grandfathering was not provided.	█ patients were assumed to be grandfathered in Year 1. However, no further details were provided (e.g. whether this was based on actual patient numbers).

Source: Table 1.1-5, p15 of the resubmission and compiled during evaluation

Bd = bortezomib + dexamethasone; Cd = carfilzomib + dexamethasone; CI = confidence interval; CLd = carfilzomib + lenalidomide + dexamethasone; CSR = clinical study report; DUSC = Drug Utilisation Sub Committee; EMA = European Medicines Agency; HR = hazard ratio; ICER = incremental cost-effectiveness ratio; KM = Kaplan Meier; Ld = lenalidomide + dexamethasone; OS = overall survival; PBAC = Pharmaceutical Benefits Advisory Council; PBS = Pharmaceutical Benefits Schedule; PFS = progression free survival; QoL = quality of life; RSA = Risk Sharing Arrangement; TGA = Therapeutic Goods Administration

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

4 Population and disease

- 4.1 Multiple myeloma is considered incurable with approximately one third of patients not responding to first-line therapy, and eventual relapse occurring in virtually all patients who obtain an initial response. In its previous consideration, the PBAC considered there was a clinical need for additional treatment options for patients with relapsed or refractory multiple myeloma.
- 4.2 The resubmission again requested listing of carfilzomib for second and later-line treatment of multiple myeloma. The proposed population was appropriate for the current clinical market.
- 4.3 The ESC noted the treatment algorithm from the European Society for Medical Oncology (ESMO) Guidelines, 2017 (as shown in figure 1 of the PSCR, p5), which shows doublet and triplet combinations of therapy in the same line of treatment; the clinical choice of treatment in the relapsed and refractory setting is largely driven by the choice of and response to induction therapy, and whether patients can tolerate triple therapy.

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

5 Comparator

- 5.1 Consistent with the previous submission, Bd was nominated as the main comparator. The PBAC previously considered that Bd was an appropriate comparator but also considered that Ld was a relevant comparator (Paragraph 7.4, November 2016, PSD). The PSCR (p1-2) argued that bortezomib was the appropriate comparator on the basis that it is a pharmacological analogue of Cd, clinical practice decision making, and the ESMO guidelines¹. However, the ESC noted that the choice of therapy, including in subsequent lines, is clinically based and often dependent on tolerability, and that the ESMO guidelines do not reflect the current PBS subsidy, or Australian clinical practice, as it assumes that triplet therapies are available.
- 5.2 The only new information provided to justify the exclusion of Ld as a comparator was that neither a direct nor indirect comparison of Cd and Ld was possible as there were no trials with common reference arms.
- 5.3 For the requested population, the following PBS-listed medicines are less costly than Cd and are alternative therapies because they could be replaced in practice: Bd and Ld. The resubmission provided evidence that Cd offers a significant improvement in health compared with Bd, but not Ld. In this case, it might not be reasonable to assume non inferior efficacy between Bd and Ld because, at the time of considering the cost-minimisation of Ld to bortezomib, the PBAC noted that OS may possibly favour Ld (Lenalidomide November 2008 Public Summary Document).

¹ Moreau P, San Miguel J, Sonneveld P, et al. Multiple myeloma: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Annals of oncology* : official journal of the European Society for Medical Oncology 2017.

5.4 The PBAC acknowledged the lack of comparative clinical data for Cd compared to Ld, and considered that on balance it was reasonable to use Bd as the comparator. However, the PBAC noted that on the PBS Bd can be used for the first time in the relapsed or refractory setting or as retreatment of progressive disease in patients who received it as part of first-line management. Cd would likely replace Bd in both settings.

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 (75), and organisations (1; Myeloma Australia) via the Consumer Comments facility on the PBS website. The comments described a range of benefits of treatment with carfilzomib, including less peripheral neuropathy, and the availability of an additional treatment option.

Clinical trials

6.3 The re-submission was based on one open-label head-to-head randomised trial comparing Cd with Bd in patients with relapsed and/or refractory multiple myeloma (ENDEAVOR, N = 929). This was the same trial that formed the basis of the previous submission, however two new data-cuts were provided in the resubmission. These were provided to further support the PBAC’s previous conclusion that the claim of superior comparative effectiveness of Cd over Bd was reasonable (if only Cd were available) (Paragraph 7.6, November 2016, PSD).

6.4 Details of the ENDEAVOR trial are provided in the table below.

Table 3: Trials and associated reports presented in the resubmission

Trial ID/First Author	Protocol title/ Publication title	Publication citation
Direct randomised trial		
ENDEAVOR NCT01568866	A Randomised, Open-label, Phase 3 Study of Carfilzomib Plus Dexamethasone vs. Bortezomib Plus Dexamethasone in Patients with Relapsed Multiple Myeloma.	26 May 2015
	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.	<i>Lancet Oncol</i> 2016; 17:27–38.
	Flash Memo of Product AMG 981, Second OS interim analysis.	17 Feb 2017

Source: Table 2.2-4, p43 of the resubmission.
AMG 981 = carfilzomib; OS = overall survival

6.5 The key features of ENDEAVOR are summarised in the Table 4.

Table 4: Key features of the included evidence, Cd versus Bd

Trial	N	Design/ duration of follow-up	Risk of bias	Patient population	Outcomes	Use in modelled evaluation
ENDEAVOR	929	MC, R, OL, Max follow-up available for PFS: 16.6 months Max follow-up available for OS: 37.2 months	Low to unclear ^a	R/R MM, after 1 to 3 lines of prior therapy	PFS, OS, QoL, safety	Yes

Source: Compiled during evaluation

Bd = bortezomib + dexamethasone; Cd = carfilzomib + dexamethasone; MC = multi-centre; MM = multiple myeloma; OL = open label; OS = overall survival; PFS = progression-free survival; QoL = Quality of life; R = randomised; R/R = relapsed/refractory

^a The PBAC 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, November 2016 PSD).

6.6 The three data-cuts provided from the ENDEAVOR trial are summarised in Table 5.

Table 5: ENDEAVOR data-cuts used in the submission and resubmission

Date	Previous submission	Resubmission	
	10 November 2014	3 March 2016	3 January 2017
Background information	First interim analysis of PFS. Based on this analysis, the IDMC recommended un-blinding the trial. Patients continued to be treated and followed for safety and OS	<u>New data-cut</u> Requested by the EMA	<u>New data-cut</u> Second pre-specified interim analysis of OS. Occurred when ~80% of the targeted OS events occurred.
Pre-specified or <i>ad hoc</i>	Pre-specified	<i>Ad hoc</i>	Pre-specified
Median duration of follow-up for OS, months	12.2 months	26.8 months	37.2 months
Results available	PFS, OS, QoL, safety	PFS, OS	OS, safety (no PFS)
Used to support clinical claim?	Yes for previous submission	Yes: PFS and OS	Yes: OS only
Used in model?	Yes for previous submission (PFS, OS) Resubmission used QoL from this data-cut.	Yes (PFS, OS)	No

Source: Compiled during evaluation

CSR = clinical study report; EMA = European Medicines Agency; IDMC = Independent Data Monitoring Committee; OS = overall survival; PFS = progression-free survival; QoL = Quality of life

6.7 The 3 March 2016 data-cut was an *ad hoc* analysis requested by the European Medicines Agency (EMA). The 3 January 2017 data-cut was the second pre-specified interim analysis of OS, which provided an additional 25 months of follow-up compared with the data-cut used in the previous submission.

Comparative effectiveness

6.8 Table 6 summarises the Progression Free Survival (PFS) results presented in the previous submission and the updated results from the 3 March 2016 data-cut, which provided an additional 5.1 months of follow-up. Figure 1 shows the Kaplan-Meier curve for PFS from the 3 March 2016 data-cut. PFS was not reported in the most recent (3 January 2017) data-cut.

Table 6: Results of PFS across the relevant data-cuts of ENDEAVOR

Data-cut (and method of PFS assessment)	Median follow-up for PFS	Cd (N = 464)		Bd (N = 465)		Difference in median, months	P value (log rank test)	HR (95% CI)
		Patients with events (%)	Median PFS (95% CI)	Patients with events (%)	Median PFS (95% CI)			
10 Nov 2014 (IRC-assessed)	11.5 months	171 (36.9%)	18.7 (15.6, NE)	243 (52.3%)	9.4 (8.4, 10.4)	9.3 months	<0.0001	0.53 (0.44, 0.65)
3 Mar 2016 (ORCA computer ^a)	16.6 months ^b	232 (50.0%)	16.8 (14.8, 20.3)	288 (61.9%)	9.3 (8.3, 10.4)	7.5 months	<0.0001	0.55 (0.46, 0.65)

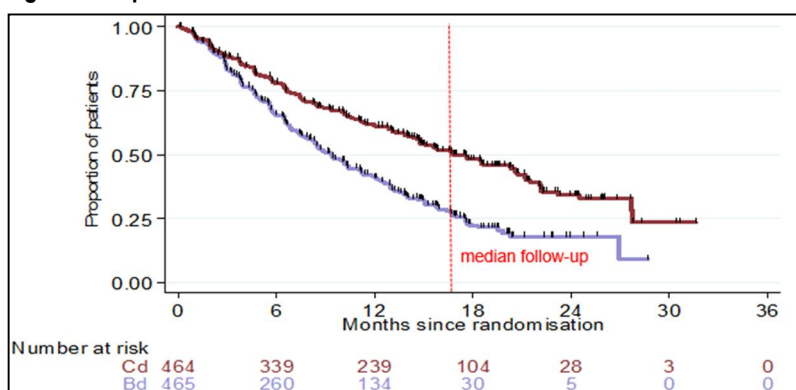
Source: Table 2.5-2, pp67-68 of the resubmission

Bd = bortezomib + dexamethasone; Cd = carfilzomib + dexamethasone; CI = confidence interval; HR = hazard ratio; IRC = Independent Review Committee; Mar = March; NE = not estimable; Nov = November; ORCA = Onyx Response Computational Assessment; PFS = progression free survival; **bold** = statistically significant

^a IRC-assessed PFS (the primary outcome) was not available after the first data-cut. ORCA was a pre-specified computer algorithm. The risk of bias was considered low as determinations of progressive disease were 97.2% consistent between the IRC and ORCA, with ORCA-assessed PFS being slightly more conservative.

^b While this was the 3 March 2016 data-cut, PFS data were only available to the end of April 2015, so the median follow-up for PFS was much shorter than the median follow-up for overall survival.

Figure 1: Kaplan-Meier curve for PFS from the 3 March 2016 data-cut



Source: Figures 2.5-1 to 2.5-2, p69 of the resubmission

Bd = bortezomib + dexamethasone; Cd = carfilzomib + dexamethasone; PFS = progression free survival

6.9 In the updated results, median PFS was reached in both arms and was 16.8 months for Cd versus 9.3 months for Bd, an increase of 7.5 months. The PFS hazard ratio (HR) was consistent between the two data-cuts.

6.10 Table 7 summarises the OS results across the three data-cuts. Figure 2 shows the Kaplan-Meier curves for OS from the most recent data-cut (3 January 2017).

Table 7: Results of OS across the relevant data-cuts of ENDEAVOR

Data-cut (and whether used in previous submission)	Median follow-up for OS	Cd (N = 464)		Bd (N = 465)		Δ median, months	P value (log rank test)	HR ^a (95% CI)
		Pts with events (%)	Median OS (95% CI)	Pts with events (%)	Median OS (95% CI)			
10 Nov 2014 Seen previously	12.2 months	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 New	26.8 months	153 (33.0%)	NE (NE, NE)	169 (36.3%)	NE (31.0, NE)	NE	0.0263	0.81 (0.65, 1.003)
3 Jan 2017 New	37.2 months	189 (40.7%)	47.6 (42.5, NE)	209 (44.9%)	40.0 (32.6, 42.3)	7.6	0.010^b	0.79 (0.65, 0.96)

Source: Table 2.5-2, pp67-68 of the resubmission

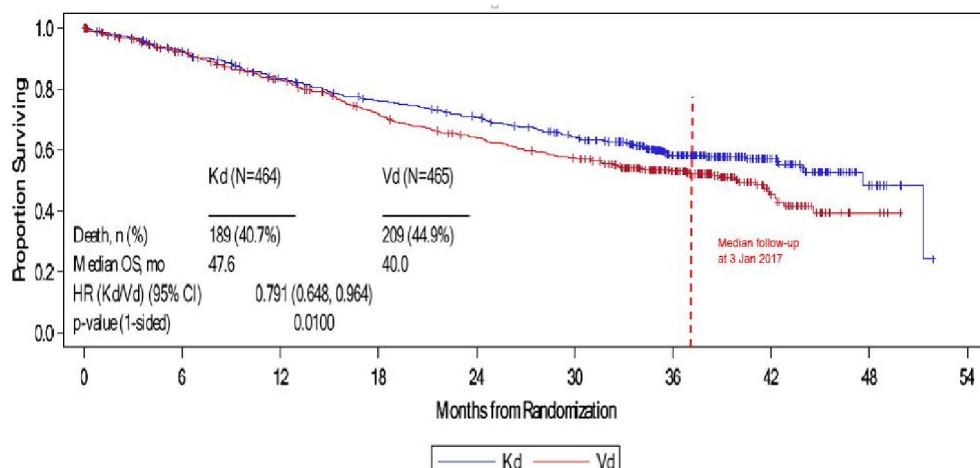
Bd = bortezomib + dexamethasone; Cd = carfilzomib + dexamethasone; CI = confidence interval; HR = hazard ratio; Jan = January;

Mar = March; NE = not estimable; Nov = November; OS = overall survival; Pts = patients; **bold** = statistically significant

^a Stratified for randomisation stratification factors (which was the primary analysis)

^b Significance level of $p < 0.0123$ (one-sided)

Figure 2: Kaplan-Meier curve for OS from the most recent data-cut (3 January 2017)



Number of Subjects at Risk:

Kd	464	423	373	335	308	270	162	66	10	0
Vd	465	402	351	293	256	228	140	39	5	0

Source: Figures 2.5-3 to 2.5-5, pp72-73 of the resubmission

Cd= carfilzomib + dexamethasone, CI = confidence interval; HR = hazard ratio; Jan = January, Kd = carfilzomib + dexamethasone, mo = months; OS = overall survival; Vd = bortezomib + dexamethasone

6.11 The OS results presented in the previous submission were not statistically significant (HR = 0.79; 95% Confidence Interval (CI): 0.58 to 1.08) and were immature, with median follow-up of 12.2 months. In the resubmission, OS results were based on more mature data, with a median follow-up of 37.2 months, at which time 43% of patients had died across both arms (3 January 2017 data-cut). These data showed a statistically significant increase in OS (HR = 0.79; 95% CI: 0.65 to 0.96). Cd was associated with a 7.6 month increase in median OS compared with Bd. The ESC considered that although the improvement in OS was statistically significant, the upper confidence interval was close to the null.

6.12 The PBAC noted that Cd demonstrated a statistically significant improvement in PFS and OS compared to Bd, and that the updated OS, although still immature, provided more robust evidence of benefit.

Comparative harms

6.13 The PBAC previously accepted the claim that Cd has a different safety profile compared with Bd (Paragraph 7.7, November 2016 PSD). Table 8 compares the updated safety results with the previous submission.

Table 8: Summary of treatment-emergent adverse events in the ENDEAVOR trial

	Previous submission 10 November 2014 data-cut ^a			Resubmission 3 January 2017 data-cut		
	Cd (N = 463)	Bd (N = 456)	RR (95% CI)	Cd (N = 463)	Bd (N = 456)	RR (95% CI)
Median treatment duration, months	9.2	6.2		11.0	6.2	-
Treatment-emergent AEs, number of patients with events (%)						
≥ Grade 3	339 (73.2%)	305 (66.9%)	1.09 (1.01, 1.19)	377 (81.4%)	324 (71.1%)	1.15 (1.07, 1.23)
SAE	223 (48.2%)	162 (35.5%)	1.36 (1.16, 1.58)	273 (59.0%)	182 (39.9%)	1.48 (1.29, 1.69)
Treatment-emergent AEs ≥ Grade 3, number of patients with events (%)						
Hypertension	41 (8.9%)	12 (2.6%)	3.37 (1.79, 6.32)	67 (14.5%)	15 (3.3%)	4.40 (2.55, 7.58)
Cardiac failure	10 (2.2%)	3 (0.7%)	3.28 (0.91, 11.85)	13 (2.8%)	3 (0.7%)	4.27 (1.22, 14.88)
Peripheral neuropathy	6 (1.3%)	24 (5.3%)	0.25 (0.01, 0.60)	6 (1.3%)	28 (6.1%)	0.21 (0.09, 0.50)

Source: Table 2.5-7, p78 of the resubmission; Table 14.3.1, p692 of CSR; 3 January 2017 Flash Memo

AEs = adverse events; Bd = bortezomib + dexamethasone; Cd = carfilzomib + dexamethasone; CI = confidence interval; RR = relative risk; SAE = serious adverse event, **Bold**= statistically significance

^a The previous commentary reported treatment-related AEs (rather than treatment-emergent AEs), while treatment-emergent AEs were used in this commentary as these were the only data available for the 3 January 2017 data-cut.

6.14 Although Cd had significantly lower rates of peripheral neuropathy related adverse events, the higher incidence of serious adverse events, in particular for hypertension and cardiac failure, increased with longer follow-up.

6.15 The PBAC noted the higher rate of serious cardiovascular adverse events for Cd in the clinical trial data presented, and also noted the ASCO 2017 systematic review and meta-analysis of carfilzomib-associated cardiovascular adverse events (CVAEs)² which showed all grade and grade ≥3 CVAEs were seen in 18% and 8%, respectively. The most common CVAEs noted were heart failure and hypertension, with undifferentiated dyspnea and edema in 24% and 25% of patients respectively, and higher doses of carfilzomib associated with more high-grade CVAEs. Given CVAEs were more than twice as common in carfilzomib arms of the RCTs reviewed, further monitoring may be needed.

Comparison versus lenalidomide

6.16 PBAC previously considered that Ld may be a relevant comparator. Although Ld was listed on a cost-minimisation basis to Bd, at the time of making the recommendation, the PBAC noted that overall survival may possibly favour lenalidomide with dexamethasone (Lenalidomide November 2008 PSD).

² Waxman AJ et al 'Carfilzomib-associated cardiovascular adverse events: A systematic review and meta-analysis' Poster presented at 2017 ASCO Annual Meeting

- 6.17 The resubmission acknowledged that Cd might also replace Ld, but considered that a comparison between Cd and Ld was not possible as there were no trials with common reference arms. The resubmission also considered there would be significant heterogeneity between the trials.
- 6.18 A literature search conducted during the evaluation identified a systematic review and network meta-analysis of therapies for relapsed/refractory multiple myeloma including Cd and Ld. The network meta-analysis found that the HR for PFS for Cd versus dexamethasone was 0.36 (95% CI: 0.26 to 0.48), which was almost the same as that for Ld versus dexamethasone (HR: 0.35; 95% CI: 0.29 to 0.43). However, the PBAC considered that there were a number of limitations to this study, as noted by the resubmission and it was therefore not informative to decision making.

Benefits and harms

- 6.19 A summary of the comparative benefits and harms for Cd versus Bd is presented in the table below. The most recent data-cuts are used for each outcome.

Table 9: Summary of comparative benefits and harms for Cd versus Bd

Benefits						
	Cd N = 464	Bd N = 465	Absolute Difference	HR (95% CI)		
PFS (data-cut = March 2016). Median follow-up of 16.6 months						
Patients with events	232 (50.0%)	288 (61.9%)	-11.9% ^b	0.55 (0.46, 0.65)		
Median PFS, months (95% CI) ^a	16.8 (14.8, 20.3)	9.3 (8.3, 10.4)	7.5 months			
OS (data-cut = January 2017)^a Median follow-up of 37.2 months						
Patients with events	189 (40.7%)	209 (44.9%)	-4.2% ^b	0.79 (0.65, 0.96)		
Median OS, months (95% CI) ^a	47.6 (42.5, NE)	40.0 (32.6, 42.3)	7.6 months			
Harms - ENDEAVOR (data-cut = 3 January 2017). Median follow-up of 37.2 months						
	Cd ^a N = 463	Bd ^a N = 456	RR (95% CI)	Event rate/100 patients ^a		RD (95% CI)
				Cd	Bd	
Any ≥ Grade 3 treatment emergent AE	377 ^b	324 ^b	1.15 (1.07, 1.23)^b	81.4 ^b	71.1 ^b	10.4% (4.9%, 15.8%)^b
Treatment emergent adverse events ≥ Grade 3, number of patients						
Anaemia	76 ^b	46 ^b	1.63 (1.16, 2.29)^b	16.4 ^b	10.1 ^b	6.3% (2.0%, 10.7%)^b
Hypertension	67 ^b	15 ^b	4.40 (2.55, 7.58)^b	14.5 ^b	3.3 ^b	11.2% (7.6%, 14.8%)^b
Cardiac failure	13 ^b	3 ^b	4.27 (1.22, 14.88)^b	2.8 ^b	0.7 ^b	2.1% (0.5%, 3.8%)^b
Peripheral neuropathy	6 ^b	28 ^b	0.21 (0.09, 0.50)^b	1.3 ^b	6.1 ^b	-4.8% (-7.3%, -2.4%)^b

Source: Compiled during evaluation based on Tables 2.5-1 to 2.5-3, pp66-71 of the resubmission; Table 2.5-3, p78 of the resubmission; "Summary of Safety Results Table" of the flash memo for the 3 January 2017 data-cut

AE = adverse event; Bd = bortezomib + dexamethasone; Cd = carfilzomib + dexamethasone; CI = confidence interval; HR = hazard ratio; NE = not estimable; OS = overall survival; PFS = progression free survival; RD = risk difference; RR = relative risk; **bold** = statistically significant;

^a PFS and OS data were not available with the same duration of follow-up (except for from the first data-cut, which was limited to 12.2 months follow-up).

^b values were calculated during evaluation from Table 2.5.6 of the Commentary

6.20 On the basis of direct evidence presented by the resubmission, for every 100 patients treated with Cd in comparison with Bd there would be:

- Approximately 12 more patients remaining progression free over a median duration of follow-up of 16.6 months;
- Approximately four more patients alive over a median duration of follow-up of 37.2 months;
- Approximately ten additional patients would experience a Grade 3 or higher treatment-related adverse event;
- Approximately two additional patients would experience Grade 3 or higher cardiac failure; and
- Approximately five fewer patients would experience Grade 3 or higher peripheral neuropathy.

Clinical claim

6.21 As per the previous submission, the resubmission claimed that Cd was superior to Bd in terms of effectiveness with a different comparative safety profile.

- 6.22 The PBAC previously considered that the claim of superior comparative effectiveness of Cd over Bd was reasonable (Paragraph 7.6, November PSD). Further, some of the limitations of the previous clinical data were addressed, namely the data were more mature and a statistically significant improvement in OS was found. The PBAC considered that the claim that Cd is superior in terms of comparative effectiveness versus Bd was reasonable.
- 6.23 The PBAC previously accepted the claim that Cd has a different safety profile compared with Bd. The more recent data, based on longer exposure to Cd, showed an increase in the number of patients experiencing a Grade 3 adverse event and an increase in hypertension, cardiac failure and undifferentiated dyspnoea with Cd. The claim of a different safety profile versus Bd remained reasonable, but the PBAC considered that overall safety was inferior with carfilzomib.

Economic analysis

- 6.24 The resubmission presented a cost-utility analysis based on the updated results from the 3 March 2016 data-cut (i.e. the ad hoc data-cut requested by the EMA). More recent data (3 January 2017) were available but were not used in the economic model due to the recentness of the data and because only summary data were available. The ESC noted that the PSCR (p1) provided an updated economic model that included survival data from the 3 January 2017 data cut. This updated model produced a similar ICER \$45,000/QALY – \$75,000/QALY versus \$45,000/QALY – \$75,000/QALY in the original resubmission base case).
- 6.25 The other key changes to the economic model compared with the previous submission are outlined in the table below.

Table 10: Summary of changes in the economic model

Description	Previous Submission	Resubmission
Data-cut for PFS/OS data in ENDEAVOR	10 November 2014 (CSR) 12 months median follow-up for OS	3 March 2016 (EMA request) 27 months median follow-up for OS
Use of trial OS Kaplan-Meier curve	█ cycles (█ months), which was beyond the median follow-up. The PBAC noted that the ICER was highly sensitive to the point of extrapolation from the Kaplan-Meier curves for OS.	█ cycles (█ months), which was the median follow-up. The more mature trial data meant the ICER was less sensitive to the point of extrapolation.
Utility for <u>progression free</u> health state	0.81 (from van Agthoven, 2004). The PBAC considered these utilities were not applicable to the requested population.	0.75 (from ENDEAVOR trial)
Utility for <u>progressed</u> health state	0.64 (from van Agthoven, 2004) The PBAC considered these utilities were not applicable to the requested population.	Unchanged.
Vial sizes for carfilzomib	60 mg, 30 mg	10 mg vial also included █ █
Rebate for carfilzomib	█% rebate (DPMA of \$█ for 120 mg ^a)	█% rebate (DPMA of \$█ for 120 mg ^b)
Number of cycles of carfilzomib included for drug costs	No carfilzomib drug costs were included beyond █ cycles; Specific RSA not proposed	No carfilzomib drug costs were included beyond █ cycles; A specific RSA was proposed
List price for bortezomib	\$█ (DPMA) for 3.5 mg vial	\$█ (DPMA) for 3 mg vial. This vial size was listed since the previous submission
Time horizon	15 years. The PBAC considered 10 years would have been more appropriate	10 years.

Source: Table 3.1-2, p108 of the resubmission

Bd = bortezomib and dexamethasone; Cd = carfilzomib and dexamethasone; CSR = Clinical Study Report; DPMA = Dispensed price for maximum amount; EMA = European Medicines Agency; OS = overall survival; PFS = progression free survival; RSA = Risk Sharing Arrangement

^a Weighted based on a 32%:68% split of use in public and private hospitals using DPMA proposed in the Pre-Sub Committee Response.

^b Weighted based on a 32%:68% split of use in public and private hospitals based on the DPMA proposed in Section 1.4.

6.26 The structure of the economic model was unchanged from the previous submission. The model included three health states: progression free; progressed disease and dead. The PBAC previously considered that it may be appropriate for the model to include multiple lines of therapy and post-progression treatment costs (Paragraph 7.8, November 2016 PSD). The pre-PBAC response (p2) argued that as this submission only related to Cd, rather than Cd and CLd, a model with multiple lines of therapy would introduce unnecessary complexity and uncertainty. The PBAC accepted this argument.

6.27 A summary of the model structure is presented in Table 11.

Table 11: Summary of model structure and rationale

Component	Summary
Time horizon	10 years in the model base case vs 27 months median OS follow-up in the ENDEAVOR data-cut used (3 March 2016)
Outcomes	LYGs gained and QALYs gained
Methods used to generate results	Decision analytic model that used the area under the curve methods to estimate PFS and OS (Markov model)
Health states	Progression free, progressed disease, dead
Utilities	Progression-free health state: quality of life results from ENDEAVOR trial mapped to EQ-5D using algorithm from Proskorovsky (2014); Progressed health state: van Agthoven (2004)
Cycle length	28-days
Transition probabilities	Partitioned survival method rather than explicit transition probabilities

Source: Compiled during the evaluation

EQ-5D = EuroQol five dimensions questionnaire; LYG = life years gained; OS = overall survival; PD = progressive disease; PFS = progression free survival; QALY = quality-adjusted life year

6.28 The key drivers of the economic model are summarised in Table 12.

Table 12: Key drivers of the model

Description	Method/Value	Impact
Carfilzomib drug costs	A 10 mg vial was included [REDACTED] a TGA application had not been made for the 10 mg vials. No carfilzomib drug costs were included beyond [REDACTED] cycles as an RSA was proposed.	High, favoured Cd
Extrapolation of OS	KM from the ENDEAVOR trial data cut on 3 March 2016 was used until median follow-up. After this, UK registry data were adjusted and fitted with a parametric curve. Thus a persistent treatment effect was assumed, which was not adequately justified and is not a conservative assumption. Further, the use of registry data was not justified and visual inspection of the extrapolated OS curves indicates a poor fit with the ENDEAVOUR trial 3 January 2017 data cut.	High, favoured Cd
Utilities	0.75 for the progression free health state. Based on QoL results from ENDEAVOR (QLQ-C30 and QLQ-MY20) mapped to EQ-5D using algorithm from Proskorovsky (2014). This was appropriate. 0.64 for the progressed health state. Based on van Agthoven 2004. These were not applicable to relapsed multiple myeloma, as previously noted by the PBAC. Utility data on progressed patients are available from the ENDEAVOR trial but were not presented in the submission.	Low to moderate, likely to favour Cd
Pre-progression costs	The base case is sensitive to uncertainty around progression-free health state costs for monitoring, which may be underestimated (at \$ [REDACTED]/cycle).	Moderate, favours Cd

Source: Compiled during the evaluation

EQ-5D = EuroQol five dimensions questionnaire; KM = Kaplan-Meier; OS = overall survival; PBAC = Pharmaceutical Benefits Advisory Committee; PBS = Pharmaceutical Benefits Scheme; PFS = progression free survival; QLQ-C30 = Quality of Life Core Module; QLQ-MY20 = Quality of Life Questionnaire multiple myeloma; QoL = quality of life; RSA = Risk Sharing Arrangement; TGA = Therapeutic Goods Agency; UK = United Kingdom

6.29 Costs in the carfilzomib arm were underestimated:

- a 10 mg vial was included [REDACTED] TGA-registration of the 10 mg vial had not been sought at the time the resubmission was made. The ESC considered that if recommended for listing this would need to be addressed through a risk share arrangement [REDACTED]

██████████ The PBAC considered that this would be appropriate, and noted that the sponsor agreed to this in the pre-PBAC response (p1); and

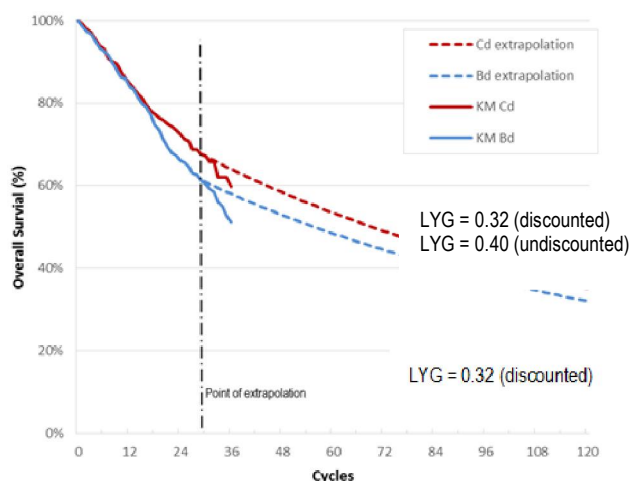
- carfilzomib administration costs were not included beyond █████ cycles because an RSA was proposed. However, the RSA would only cover the carfilzomib drug costs so other costs should have been included in the base case. This was a particular issue as there was substantial likelihood of usage beyond the cap as most patients (████%) used carfilzomib for longer than █████ cycles in the model. The PSCR (p4) accepted this. The PBAC considered that inclusion of administration costs beyond █████ cycles was appropriate and noted that including administration costs beyond █████ cycles increased the ICER to \$45,000/QALY – \$75,000/QALY (Table 15).

6.30 Compared with the previous submission, the more mature trial data meant the ICER was less sensitive to the point of extrapolation from the Kaplan-Meier curves. However, other issues with the extrapolation remained. Per the previous submission, UK registry data were used to extrapolate OS beyond the trial. Thus:

- A persistent treatment effect was assumed (i.e. the survival curves did not converge during the modelled time horizon). Cd is given until progression and patients are likely to cycle through subsequent lines of therapy post-progression. No evidence was presented that the treatment effect of Cd would persist after subsequent treatment; and
- Like the previous submission, the resubmission did not consider fitting a parametric curve directly to the Kaplan-Meier data. The choice of extrapolation method (registry data versus fitting a parametric curve to the Kaplan-Meier data) was not justified or compared with other methods.

6.31 Figure 3 shows the OS curves from the economic model versus the trial data used in the model (Kaplan-Meier curve from the ENDEAVOR trial, 3 March 2016 data-cut).

Figure 3: Extrapolation of OS over the 10 year time horizon, per the model base case (3 March 2016 data-cut)



Source: Constructed during evaluation, Carfilzomib_Section 3_Economic Model.xlsm

Bd = bortezomib + dexamethasone; Cd = carfilzomib + dexamethasone; KM = Kaplan-Meier; LYG = life years gained; OS = overall survival

6.32 During evaluation, the validity of the model was tested using the most recent data-cut (3 January 2017) from ENDEAVOR. Table 13 compares the results at 37 months, which was the median follow-up in the most recent data (the trial results were not

sufficiently mature to meaningfully compare median OS against the model). Figure 4 shows the modelled OS overlaid with the Kaplan-Meier curves from the most recent data-cut.

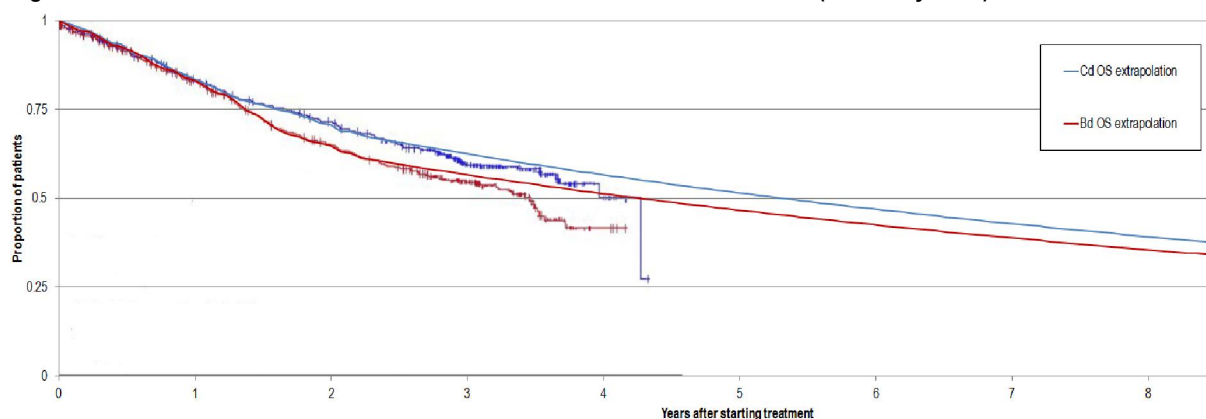
Table 13: Economic model versus most recent data-cut of ENDEAVOR: per cent of patients alive at 37 months

	ENDEAVOR trial 3 January 2017 data-cut	Economic model (undiscounted)	% difference
Per cent of patients still alive at 37 months			
Cd	59.3% alive	62.1% alive	5% higher in the economic model
Bd	55.1% alive	56.3% alive	2% higher in the economic model

Source: Compiled during evaluation

Bd = bortezomib + dexamethasone; Cd = carfilzomib + dexamethasone; OS = overall survival

Figure 4: Modelled OS overlaid with KM curves from the most recent data-cut (3 January 2017)



Source: Constructed during evaluation based on Carfilzomib_Section 3_Economic Model.xlsm

Notes: Modelled OS was based on undiscounted OS converted from cycles to years to enable the comparison.

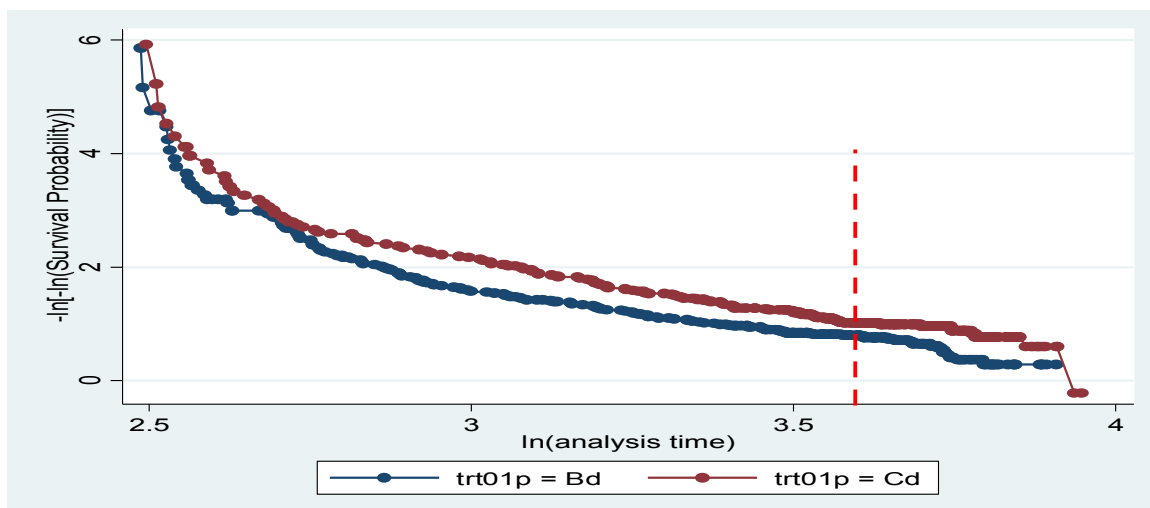
Bd = bortezomib + dexamethasone; Cd = carfilzomib + dexamethasone; KM = Kaplan-Meier curve; OS = overall survival

At 37 months (3.1 years), the economic model estimated there would be 5% more Cd patients alive than observed in the most recent trial data. The most recent trial results suggest that the economic model overestimated survival.

6.33 The ESC noted the PSCR (p3) provided an analysis of parametric curves fitted to the Bd OS trial data at the latest data cut (after 12 months). The ESC also noted that the analyses in the PSCR continued to apply a persistent treatment effect. This was justified in the PSCR based on the proportional-hazards plot for OS from the ENDEAVOR trial (attachment 1, reproduced in Figure 5 below) which the PSCR stated was consistent with a constant difference between the two treatment groups, with the treatment effect persisting past median follow-up (indicated by the dashed red line in Figure 5). ESC noted, based on visual inspection, that the assumption of proportional hazards may not be met, with the plots suggesting convergence around the median follow-up timepoint. The PBAC noted the ESC’s concerns, however, considered that the updated data and additional analyses presented in the PSCR and the pre-PBAC response indicated that the extrapolated survival may be reasonable.

Figure 5: Proportional hazards plot for overall survival after one year in the ENDEAVOR trial.

Dotted line indicates median follow up. Source: PSCR Attachment 1, figure 2, p6.



6.34 To address the PBAC’s previous concerns that the utilities (from van Agthoven 2004) were not applicable to the relapsed / refractory multiple myeloma population, the resubmission appropriately used trial-based quality of life results from ENDEAVOR for the progression free health state (mapped to the EQ-5D). However, the resubmission inappropriately continued to use the utilities from van Agthoven (2004) for the progressed health state. The ESC also noted that utility data for the progressed state from the ENDEAVOUR trial was available, and that these should have at least been presented for comparison purposes. The pre-PBAC response (p3) advised that the protocol for ENDEAVOUR did not include collecting post-progression utility data, but noted that for the subset of patients where this may have occurred due to a delay in progression and confirmatory testing, the utility values were consistent with the base case used in the economic model. The PBAC therefore considered that the utility values used were appropriate.

6.35 The results of the economic evaluation including results from the model updated with the 3 January 2017 data cut are presented below.

Table 14: Results of the economic evaluation

	Cd	Bd	Incremental outcome
Cost in resubmission (unchanged)	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]
Updated in PSCR (3 January 2017 data-cut)			
LYG (discounted)	4.518	4.189	0.329
Incremental cost/extra LYG			\$ [REDACTED]
QALYs (discounted)	3.064	2.800	0.264
Incremental cost/extra QALY gained			\$ [REDACTED]
Original resubmission (3 March 2016 data-cut)			
LYG (discounted)	4.684	4.360	0.324
Incremental cost/extra LYG			\$ [REDACTED]
QALYs (discounted)	3.170	2.909	0.260
Incremental cost/extra QALY gained			\$ [REDACTED]
November 2016 submission (corrected base case)			
Cost	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]
LYG (discounted)	5.83	5.21	0.61
Incremental cost/extra LYG			\$ [REDACTED]
QALYs (discounted)	4.01	3.51	0.49
Incremental cost/extra QALY gained			\$ [REDACTED]

Source: Carfilzomib_Economic Model.xlsm; Carfilzomib Economic Model OS update in PSCR

Bd = bortezomib + dexamethasone; Cd = carfilzomib + dexamethasone; CLd = carfilzomib + lenalidomide + dexamethasone; Ld = lenalidomide + dexamethasone; LYG = life years gained; QALY = quality-adjusted life year; vs = versus

The redacted table shows ICERs in the range of \$45,000/QALY – \$75,000/QALY.

6.36 The economic evaluation using the most recent data cut (3 January 2017) resulted in an ICER of \$45,000/QALY – \$75,000/QALY. The ICER was likely to be underestimated due to the underestimated carfilzomib costs and favourable extrapolation assumptions (e.g. the persistent treatment effect).

6.37 The ICER was lower than in the previous submission due to lower carfilzomib drug costs which outweighed the lower QALY gains (which arose due to the shorter time horizon and lower utilities in the progression free health state). The PBAC noted that the impact of the updated survival data on the model was minimal, because although OS had been overestimated in the previous model, the reduction in OS was approximately proportionate in both the treatment and comparator arms.

6.38 Table 15 presents the results of sensitivity analyses presented in the resubmission and performed during the evaluation. The additional sensitivity analyses conducted during evaluation included:

- the cost of carfilzomib administration was included beyond [REDACTED] cycles;
- the time horizon was shortened to five years. As almost all patients (98% in the Cd arm) had progressed at this point, this was used as a proxy for converging the OS curves at five years. As patients are likely to cycle through further treatment options, it is possible that the treatment effect may start to wane upon progression; and
- for the progressed health state, the utility value from the pomalidomide re-submission (0.47, per the November 2014 Public Summary Document) was used. This was a later-line population than requested for Cd, so this would underestimate quality of life in the population proposed for Cd.

Table 15: Results of sensitivity analyses based on the original resubmission model

	Incremental costs	Incremental effectiveness	ICER
Base case	\$████	0.26	\$████
Univariate analyses (base case values are presented in brackets)			
Utilities (PFS 0.75; PD 0.64) • PFS 0.75; PD: 0.47	\$████	0.29 ^b	\$████ ^b
Vial sizes available (10 mg, 30 mg, 60 mg vials) • No 10 mg vials (only 30 mg and 60 mg vials)	\$████	0.26	\$████
Cd administration costs (drug costs capped at █ cycles) • included until progression ^a	\$████ ^b	0.26	\$████ ^b
Carfilzomib drug and administration costs (capped at █ cycles i.e. █% rebate after █ cycles) • capped at █ cycles	\$████	0.26 ^b	\$████
• ██████████	\$████ ^b	0.26 ^b	\$████ ^b
Time horizon (10 years) • 5 years	\$████ ^b	0.17 ^b	\$████ ^b
• 15 years	\$████	0.31	\$████
Multivariate sensitivity analyses			
No 10 mg vials and Cd administration costs included ██████████ ^a	\$████ ^b	0.26 ^b	\$████ ^b
No 10 mg vials and 5 year time horizon	\$████ ^b	0.17	\$████ ^b

Source: Tables 3.9.9, p156 of the resubmission; Carfilzomib_Section 3_Economic Model.xlsm

Carf = carfilzomib; Cd = carfilzomib + dexamethasone; ICER = incremental cost-effectiveness ratio; PD = progressed disease; PFS = progression free survival

^a Also includes dexamethasone drug costs until progression

^b values were calculated during evaluation

6.39 The ICER was most sensitive to the carfilzomib drug costs (including the availability of the 10 mg vial) and the time horizon (conducted as a proxy for the persistent treatment effect). In particular, the model was sensitive to carfilzomib drug costs being rebated after █ cycles (if no cap were in place the ICER would increase from \$45,000/QALY – \$75,000/QALY to more than \$200,000/QALY).

6.40 The ICER was less sensitive to the utility value used in the progressed disease health state. The value used in the resubmission’s base case was based on newly diagnosed patients after their first progression (from van Agthoven 2004), and thus likely overestimated quality of life in the population proposed for Cd. However, the use of a lower value (e.g. the value for a later-line population) decreased the ICER. Thus, the progressed disease health state utilities, though inappropriately derived, were likely conservative.

6.41 The PBAC considered that, as accepted in the PSCR (p4), it would be appropriate to include administration costs beyond █ cycles, and noted that the model was somewhat sensitive to this. The PBAC also noted that the model was sensitive to the effective price of the comparator bortezomib. The PBAC considered that Cd would replace Bd when Bd is first used in the RRMM treatment setting and when Bd is re-used in the progressive disease setting (ie re-treatment) and recalled that it had previously recommended different prices for Bd in these two treatment settings.

6.42 The PBAC considered that the ICER presented in the re-submission of \$45,000/QALY – \$75,000/QALY could be considered cost-effective, in the context of adjustments to the model to account for:

- The cost of administration beyond [REDACTED] cycles of treatment; and,
- The current proportion of bortezomib use between the RRMM treatment and retreatment settings, and the differing effective prices at which the PBAC recommended these listings.

The PBAC noted that this would require a price reduction to carfilzomib in order to maintain an ICER of no more than \$45,000/QALY – \$75,000/QALY.

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

6.43 The total cost of carfilzomib was \$ [REDACTED] per patient per course. This was based on a mean treatment of [REDACTED] doses ([REDACTED] cycles with six infusions a cycle and 79% compliance, assuming [REDACTED] cycles) and an average cost of \$ [REDACTED] per dose (based on the distribution of vials per infusion for ENDEAVOR including a 10 mg vial size). This was lower than estimated in the previous submission (\$ [REDACTED]) because a higher rebate was proposed, a 10 mg vial was included and an RSA was proposed to cover carfilzomib costs beyond [REDACTED] cycles.

6.44 If the 10 mg vial [REDACTED], the carfilzomib drug cost/patient/course would be \$ [REDACTED] (using corresponding methods to those outlined above, with an average cost of \$ [REDACTED] per dose).

6.45 The total cost of bortezomib was \$ [REDACTED] per patient per course of treatment (using published prices). This was based on a mean treatment of [REDACTED] doses ([REDACTED] cycles with around [REDACTED] doses a cycle and 73% compliance) and an average cost of \$ [REDACTED] per dose.

6.46 The PBAC noted that in order to maintain the ICER proposed in the submission, the proposed price of carfilzomib would need to be reduced and that this would reduce the total cost per patient.

Estimated PBS usage & financial implications

6.47 This resubmission was not considered by DUSC.

6.48 The resubmission, as per the previous submission, used a mixed epidemiological and market share approach to estimate the utilisation and financial impact of listing carfilzomib.

6.49 The resubmission updated the financial estimates. In particular, the estimates of the eligible patient population were updated to be based on more recent PBS sample data (2014-15 rather than a 2013 DUSC analysis). This was to address the PBAC's previous concerns that the number of eligible patients was underestimated, particularly the number of patients initiating bortezomib. The previous submission assumed that half of all bortezomib patients were continuing from the previous year. This assumption was not required in the resubmission as the underpinning data were more complete.

6.50 Other changes were that: grandfathered patients were included (█ in year 1); a 10 mg vial was included; and all carfilzomib drug costs beyond █ cycles were assumed to be rebated. The PSCR (p5) indicated that although █ will be eligible for PBS subsidy through a grandfather arrangement because of discontinuations due to toxicity, disease progression and death, prior to PBS listing.

Table 16: 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	█	█	█	█	█	█
Doses dispensed ^a	█	█	█	█	█	█
Estimated financial implications of carfilzomib						
Cost to PBS/RPBS	\$█	\$█	\$█	\$█	\$█	\$█
Co-payments ^b	-\$█	-\$█	-\$█	-\$█	-\$█	-\$█
Cost to PBS/RPBS less co-payments	\$█	\$█	\$█	\$█	\$█	\$█
Estimated financial implications for bortezomib and lenalidomide						
Cost to PBS/RPBS	\$█	\$█	\$█	\$█	\$█	\$█
Co-payments ^b	-\$█	-\$█	-\$█	-\$█	-\$█	-\$█
Cost to PBS/RPBS less co-payments	\$█	\$█	\$█	\$█	█	█
Net financial implications						
Net cost to PBS/RPBS	█	█	█	█	\$█	\$█
Net cost to MBS ^c	\$█	\$█	\$█	\$█	\$█	\$█
Net cost to PBS/RPBS/MBS	\$█	\$█	\$█	\$█	\$█	\$█
Previous submission	\$█	\$█	\$█	\$█	\$█	-

Source: Calculated during evaluation based on 'Carfilzomib Section 4.xlsx' spreadsheet
MBS = Medicare Benefits Schedule; PBS = Pharmaceutical Benefits Scheme; RPBS = Repatriation Pharmaceutical Benefits Scheme; values were corrected during the evaluation to apply a co-payment per initial prescription for Efficient Funding of Chemotherapy drugs
^a Assuming █ doses per year, as estimated by the submission.
^b Co-payments were included during evaluation. For carfilzomib these were based on the average number of doses (█) divided by the number of scripts per original dispensing (█) to give █ original scripts per patient.
^c Only MBS offsets were included (the resubmission also included public hospital costs)

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

6.51 The resubmission estimated that the net cost to the PBS/RPBS would be \$60 – \$100 million over six years. The estimated cost to the PBS/RPBS/MBS was \$10 – \$20 million in Year 5. This was less than the estimated in the previous submission (\$10 – \$20 million) due to lower carfilzomib drug costs. However, the financial impact was higher in Year 1 due to the higher patient numbers.

6.52 The net cost to government may be higher than estimated because:

- there might be leakage into use as CLd, thus cost-offsets for lenalidomide might not be realised;
- costs for carfilzomib administration were not included beyond █ cycles because an RSA was proposed. However, the RSA would only reimburse the carfilzomib

drug costs so other costs should have been included in the base case. The PSCR (p4) agreed that administration costs should be included; these additional costs were included in a sensitivity analysis (refer to table 17, below);

- the 10 mg vial may not be TGA registered at the time of PBS listing, which would substantially increase the financial costs;
- cost offsets might not be realised because Cd may add another line of therapy;
- there might be higher uptake in the eligible population currently treated with Ld; and
- the number of prevalent patients with relapsed multiple myeloma might have increased at a higher rate than estimated, due to the survival benefits of newer treatment.

6.53 The PBAC considered that the risks associated with use outside the restriction, higher than expected use, and costs associated with the absence of the 10 mg vial could be adequately addressed through risk sharing arrangements.

6.54 The ESC also noted that grandfathered patients were assumed to receive all doses under the PBS (an average of █ doses per patient), despite already having commenced Cd, which would overestimate the cost to the PBS of these patients. The PBAC considered that it would more appropriate to assume that all grandfathered patients had already received an average of █ cycles prior to receiving PBS subsidisation.

6.55 Two sensitivity analyses were conducted during the evaluation to assess the impact of: the 10 mg vial not being available; and the carfilzomib administration costs being included until progression.

Table 17: Results of sensitivity analyses conducted during the evaluation on the net cost to the PBS/RPBS/MBS ^a

Net cost to PBS/RPBS/MBS	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
Base case	\$█	\$█	\$█	\$█	\$█	\$█
Vial available in base case: 10 mg, 30 mg and 60 mg vials						
No 10 mg vials	\$█	\$█	\$█	\$█	\$█	\$█
Carfilzomib administration costs in base case capped at 15 cycles						
Carfilzomib administration costs until progression	\$█	\$█	\$█	\$█	\$█	\$█

Source: Calculated during evaluation based on 'Carfilzomib Section 4.xlsx' spreadsheet

Avg = average; Cd = carfilzomib + dexamethasone; PBS = Pharmaceutical Benefits Scheme; RPBS = Repatriation Pharmaceutical Benefits Scheme

^a Based on patient co-payments being appropriately applied, as calculated during the evaluation.

“The redacted table shows that at year 6, the net cost to the PBS would be \$10 - \$20 million.

6.56 The PBAC considered that because the price of carfilzomib would need to be reduced as outlined in paragraph 6.42, the actual financial impact to the PBS would likely be lower than calculated.

Quality Use of Medicines

6.57 The resubmission did not provide specific information on the quality use of medicines.

Financial Management – Risk Sharing Arrangements

- 6.58 The resubmission proposed a [REDACTED] % rebate on carfilzomib costs beyond [REDACTED] cycles. To facilitate this, a [REDACTED]
- 6.59 If the 10 mg strength is not registered at the time of PBS-listing, [REDACTED] The resubmission proposed that increased wastage could be identified by a review of PBS/Authorities data. It was not clear whether this could be implemented as it would require data at the individual patient level, which may not be feasible given the estimated patient numbers.
- 6.60 The ESC considered that rather than a resource-intensive review of the authorities data, it may be appropriate to address this through an arrangement where the sponsor [REDACTED]
- 6.61 The PBAC considered that there remained a risk of use outside the restriction, and that although this was likely to be clinically appropriate use; the cost-effectiveness of such use was unknown. The PBAC therefore considered that the RSA should take into account the following:
- a [REDACTED] rebate on all use beyond [REDACTED] cycles of treatment as proposed by the sponsor;
 - a [REDACTED] rebate on the [REDACTED] [REDACTED] if the 10 mg vial was available;
 - a patient number cap, based on the financial estimates, with a moderate rebate above the thresholds; and,
 - assumed average use of [REDACTED] carfilzomib cycles prior to receiving PBS subsidised treatment for grandfather patients for the purposed of the treatment cycle caps.

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

7 PBAC Outcome

- 7.1 The PBAC recommended the listing of carfilzomib for use in combination with dexamethasone (Cd) in patients with relapsed or refractory multiple myeloma (RRMM), on the basis that the claim of superior comparative effectiveness of Cd over Bd was supported by updated clinical trial data, with a clinically meaningful overall survival advantage, and many of the economic concerns from the previous submission were addressed. Carfilzomib should be available only under special arrangements under Section 100 – Efficient Funding of Chemotherapy Public and Private Hospital.
- 7.2 The PBAC is satisfied that carfilzomib provides, for some patients, a significant improvement in efficacy over bortezomib in combination with dexamethasone (Bd). The PBAC considered that the incremental cost-effectiveness ratio (ICER) of \$45,000/QALY – \$75,000/QALY presented in the submission was acceptable.

- 7.3 The PBAC accepted that Bd was the appropriate comparator. Although lenalidomide with dexamethasone (Ld) could also be a reasonable comparator, the PBAC noted the paucity of evidence comparing Cd with Ld, and that bortezomib is a pharmacological analogue of carfilzomib, which informs treatment choices in this setting. The PBAC noted that Cd was likely to replace Bd in both first-use treatment and retreatment in the relapsed or refractory multiple myeloma (RRMM) setting.
- 7.4 The PBAC noted the updated clinical data from the ENDEAVOR trial (data-cut 3 January 2017) showed a statistically significant overall survival benefit for Cd over Bd, which was supported by the progression free survival benefit at the 3 March 2016 data-cut. The PBAC also noted that the clinical data indicated a reduction in the rates of peripheral neuropathy, but an increase in serious cardiovascular adverse events for Cd compared to Bd. The PBAC noted that consumer comments indicated that the reduction in peripheral neuropathy was important to patients.
- 7.5 The PBAC considered that the claim of superior efficacy and a different safety profile for Cd compared to Bd was not adequately supported in that the PBAC considered the overall safety profile of carfilzomib was inferior to bortezomib.
- 7.6 The PBAC considered that the resubmission addressed many of the issues with the economic model raised in the previous submission. The PBAC noted that although the updated survival data confirmed that OS was overestimated, the overestimate was proportional across the treatment arms, and therefore the modelled incremental survival gain was similar to that based on the earlier data cut. The PBAC noted the request to include multiple lines of therapy in the model would create additional uncertainty and accepted the pre-PBAC response (p2) suggestion to consider a simpler model, despite it not fully reflecting how RRMM will be treated in clinical practice.
- 7.7 The PBAC considered that the effective prices of bortezomib first-use treatment and retreatment in RRMM would need to be accounted for in the cost of the bortezomib comparator arm. The PBAC also considered administration costs beyond [REDACTED] cycles should be included in the model. The PBAC noted that the economic model assumed that the 10 mg vial would be listed, and that the amount paid for carfilzomib in the absence of the 10 mg should [REDACTED]. This agreement would need to be included in the RSA.
- 7.8 The PBAC considered that the ICER presented in the re-submission of \$45,000/QALY – \$75,000/QALY could be considered cost-effective, in the context of adjustments to the model as noted in paragraph 6.42.
- 7.9 The PBAC considered that there remained a risk of greater than expected utilisation due to greater than expected patient numbers, and of use outside the restriction. Although this use would potentially be clinically appropriate, the cost-effectiveness was unknown. Therefore, the PBAC considered that this would need to be addressed through risk sharing arrangements. See paragraph 6.61 for recommendations for the RSA.
- 7.10 For the PBS restriction, the PBAC considered that there is no need for patients to provide additional documentary evidence that they have multiple myeloma as this will have been established with their first-line treatment, and therefore that it would be

appropriate for the carfilzomib listing to be a telephone authority. The PBAC also advised that a single continuing restriction would be adequate.

- 7.11 The PBAC also noted that the listings for carfilzomib would not require patients to have “experienced treatment failure after a trial of at least four (4) weeks of thalidomide at a dose of at least 100 mg daily or have failed to achieve at least a minimal response after eight (8) or more weeks of thalidomide-based therapy for progressive disease” as this requirement has been recommended for removal from the current lenalidomide and bortezomib restrictions.
- 7.12 The PBAC recommended that carfilzomib should not be treated as interchangeable on an individual patient basis with any other drug.
- 7.13 The PBAC advised that carfilzomib is not suitable for prescribing by nurse practitioners.
- 7.14 The PBAC noted that the Early Supply Rule should not apply, as it doesn’t currently apply to section 100 – Efficient Funding of Chemotherapy items.
- 7.15 The PBAC noted that flow-on restriction changes to all PBS listings for bortezomib, lenalidomide, thalidomide, and pomalidomide will be required to indicate that “Patient must not be receiving PBS-subsidised thalidomide, lenalidomide, pomalidomide, *or carfilzomib*” will also be required.
- 7.16 The PBAC noted that this submission is not eligible for an Independent Review because it was recommended.

Outcome:

Recommended

8 Recommended listing

8.1 Add new item:

Restriction to be finalised, draft restriction included below for review amendments to the proposed restriction in the overview (to take into account recommendation for phone authority) indicated as per usual practice.

- 8.2 Flow-on restriction changes to all PBS listings for bortezomib, lenalidomide, thalidomide, and pomalidomide will be required to indicate that “Patient must not be receiving PBS-subsidised thalidomide, lenalidomide, pomalidomide, *or carfilzomib*” will also be required.

Initial treatment:

Name, Restriction, Manner of administration and form	Max. Amt	No. of Rpts	Proprietary Name and Manufacturer
CARFILZOMIB Powder for injection, 30 mg	120 mg	17	Kyprolis AN

Powder for injection, 60 mg

Category / Program	Section 100 – Efficient funding of Chemotherapy
Prescriber type:	<input type="checkbox"/> Dental <input checked="" type="checkbox"/> Medical Practitioners <input type="checkbox"/> Nurse practitioners <input type="checkbox"/> Optometrists <input type="checkbox"/> Midwives
Condition:	Multiple myeloma
PBS Indication:	Multiple myeloma
Treatment phase:	Initial treatment
Restriction Level / Method:	<input type="checkbox"/> Restricted benefit <input type="checkbox"/> Authority Required - In Writing <input checked="" type="checkbox"/> Authority Required - Telephone <input checked="" type="checkbox"/> Authority Required - Emergency <input checked="" type="checkbox"/> Authority Required - Electronic <input type="checkbox"/> Streamlined
Clinical criteria:	The condition must be confirmed by a histological diagnosis, AND The treatment must be in combination with dexamethasone, AND Patient must have progressive disease after at least one prior therapy, AND Patient must have undergone or be ineligible for a stem cell transplant, AND Patient must not be receiving concomitant PBS-subsidised thalidomide, lenalidomide, bortezomib, or pomalidomide AND Patient must not receive more than three cycles of treatment under this restriction AND Patient must not have previously received this drug for this condition
Prescriber Instructions	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

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	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.
Administrative Advice	No increase in the maximum number of repeats may be authorised. No increase in the maximum amount or number of units may be authorised. Special Pricing Arrangements apply.

Continuing treatment:

Name, Restriction, Manner of administration and form	Max. Amt	No. of Rpts	Proprietary Name and Manufacturer	
CARFILZOMIB Powder for injection, 30 mg	120 mg	17	Kyprolis	AN
Powder for injection, 60 mg				

Category / Program	Section 100 – Efficient funding of Chemotherapy
Prescriber type:	<input type="checkbox"/> Dental <input checked="" type="checkbox"/> Medical Practitioners <input type="checkbox"/> Nurse practitioners <input type="checkbox"/> Optometrists <input type="checkbox"/> Midwives
Severity:	Progressive
Condition:	Multiple myeloma
PBS Indication:	Multiple myeloma
Treatment phase:	Continuing treatment
Restriction Level / Method:	<input type="checkbox"/> Restricted benefit <input type="checkbox"/> Authority Required - In Writing <input checked="" type="checkbox"/> Authority Required - Telephone <input checked="" type="checkbox"/> Authority Required - Emergency <input checked="" type="checkbox"/> Authority Required - Electronic <input type="checkbox"/> Streamlined
Clinical criteria:	Patient must have previously received PBS-subsidised treatment with this drug for this condition AND The treatment must be in combination with 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 thalidomide, lenalidomide, bortezomib, or pomalidomide AND Patient must not receive more than 3 cycles of treatment per continuing treatment course authorised under this restriction.
Prescriber Instructions	<Progressive disease defined as per initial restriction>
Administrative Advice	No increase in the maximum number of repeats may be authorised. No increase in the maximum amount or number of units may be authorised. Special Pricing Arrangements apply

Grandfather treatment:

Name, Restriction, Manner of administration and form	Max. Amt	No. of Rpts	Proprietary Name and Manufacturer	
CARFILZOMIB Powder for injection, 30 mg Powder for injection, 60 mg	120 mg	17	Kyprolis	AN

Category / Program	Section 100 – Efficient funding of Chemotherapy
Prescriber type:	<input type="checkbox"/> Dental <input checked="" type="checkbox"/> Medical Practitioners <input type="checkbox"/> Nurse practitioners <input type="checkbox"/> Optometrists <input type="checkbox"/> Midwives
Condition:	Multiple myeloma
PBS Indication:	Multiple myeloma
Treatment phase:	Grandfathering
Restriction Level / Method:	<input type="checkbox"/> Restricted benefit <input type="checkbox"/> Authority Required - In Writing <input checked="" type="checkbox"/> Authority Required - Telephone <input checked="" type="checkbox"/> Authority Required - Emergency <input checked="" type="checkbox"/> Authority Required - Electronic <input type="checkbox"/> Streamlined
Clinical criteria:	Patient must have received treatment with this drug for this condition prior to <date of listing> AND Patient must have a documented histological diagnosis, AND The treatment must be in combination with dexamethasone, AND Patient must have had documented progressive disease after at least one prior therapy prior to commencing non-PBS subsidised treatment with this drug for this condition, AND Patient must not have developed disease progression while receiving treatment with this drug for this condition AND Patient must have undergone or be ineligible for a stem cell transplant, AND Patient must not be receiving concomitant PBS-subsidised thalidomide, lenalidomide, bortezomib, or pomalidomide AND Patient must not receive more than three cycles of treatment under this restriction.
Prescriber Instructions	<Progressive disease defined as per initial restriction> Patient may qualify for PBS-subsidised treatment under this restriction once only. For continuing PBS-subsidised treatment, a Grandfathered patient must qualify under the Continuing treatment criteria.
Administrative Advice	No increase in the maximum number of repeats may be authorised. No increase in the maximum amount or number of units may be authorised. Special Pricing Arrangements apply.

9 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.

10 Sponsor's Comment

Amgen is pleased with the PBAC's recommendation and recognition of the clinical benefits of carfilzomib. We are committed to working with the PBAC to achieve a PBS listing for carfilzomib at the earliest opportunity.