7.03 CARFILZOMIB, Powder for injection 10 mg, Powder for injection 30 mg, Powder for injection 60 mg, Kyprolis®, Amgen Australia Pty Limited.

1 Purpose of submission

1.1 The Standard Re-Entry resubmission requested a Section 100 (Efficient Funding of Chemotherapy), Authority Required (Streamlined) listing for carfilzomib in combination with lenalidomide and dexamethasone (CLd) for the treatment of relapsed or refractory multiple myeloma (RRMM).

1.2 Listing was requested on the basis of a cost-minimisation approach (CMA) versus carfilzomib in combination with dexamethasone (Cd). The key components of the clinical issues addressed by the submission are provided in Table 1.

Table 1: **Key components of the clinical issue addressed by the submission (as stated in the resubmission)**

Component	Description
Population	Treatment of RRMM after at least one prior therapy.
Intervention	**Carfilzomib in combination with lenalidomide and dexamethasone (CLd)** 28-day cycles: *Carfilzomib:* Cycle 1: 20 mg/m^2 IV on Days 1 and 2, 27 mg/m^2 on Day 8 of 28-day cycles. Cycle 2-12: 27 mg/m^2 IV on Days 1, 2, 8, 9, 15 and 16. Cycle 13+: 27 mg/m^2 IV on Days 1, 2, 15 and 16. Carfilzomib is omitted on Days 8 and 9. *Lenalidomide:* 25 mg orally on Days 1-21 *Dexamethasone:* 40 mg orally or IV on Days 1, 8, 15 and 22
Comparators	**Main:** **Carfilzomib in combination with dexamethasone (Cd)** 28-day cycles: Cd twice weekly (Cd56 BIW) *Carfilzomib:* Cycle 1: 20 mg/m^2 on Days 1 and 2, 56 mg/m^2 on Days 8, 9, 15 and 16 Cycle 2+: 56 mg/m^2 IV on Days 1, 2, 8, 9, 15 and 16 *Dexamethasone:* 20 mg orally or IV on Days 1, 2, 8, 9, 15, 16, 22 and 23 Cd weekly (Cd70 QW) *Carfilzomib:* Cycle 1: 20 mg/m^2 on Day 1, 70 mg/m^2 on Days 8 and 15 Cycle 2+: 70 mg/m^2 IV on Days 1, 8 and 15. *Dexamethasone:* Cycles 1-9: 40 mg orally or IV on Days 1, 8, 15 and 22 Cycles 9+: 40 mg orally or IV on Days 1, 8 and 15
	Secondary **Elotuzumab in combination with lenalidomide and dexamethasone (ELd)[a]** 28-day cycles: *Elotuzumab:* Cycles 1-2: 10 mg/kg IV on Days 1, 8, 15, and 22 Cycles 2+: 10 mg/kg IV on Days 1 and 15 *Lenalidomide*: 25 mg orally on Days 1-21 *Dexamethasone:* Cycles 1-2: 28 mg orally on Days 1, 8, 15 and 22 Cycles 3+: 40 mg on Days 8 and 22

Component	Description
	Pomalidomide in combination with bortezomib and dexamethasone (PBd) 21-day cycles *Pomalidomide:* 4 mg orally on Days 1-14 *Bortezomib:* Cycles 1-8: 1.3 mg/m^2 on Days 1, 4, 8 and 11 Cycle 9+: 10 mg/kg IV+: 1.3 mg/m^2 on Days 1 and 8. *Dexamethasone:* Cycles 1-8: 20 mg orally on days 1, 2, 4, 5, 8, 9, 11 and 12, Cycle 9+: 20 mg on Days 1, 2, 8 and 9
Outcomes	Main outcomes assessed are PFS, OS and safety for each of the following comparisons: Indirect treatment comparison of CLd vs Ld (ASPIRE) vs: Main comparator: • Cd (ENDEAVOR – Cd56 BIW vs Bd) • Cd (ARROW – Cd70 QW vs Cd27 BIW) Secondary comparators: • ELd (ELOQUENT-2 – ELd vs Ld) • PBd (OPTIMISMM – PBd vs Bd)
Clinical claim	CLd is non-inferior in terms of efficacy compared to Cd, ELd and PBd; CLd is non-inferior in terms of safety compared to Cd, ELd and PBd with different side-effect profiles

Source: Table 1.1-2 p8 of the resubmission.

Bd = bortezomib and dexamethasone; Cd = carfilzomib and dexamethasone; Cd27 BIW = carfilzomib 27 mg/m^2 twice weekly and dexamethasone; Cd56 BIW = carfilzomib 56 mg/m^2 twice weekly and dexamethasone; Cd70 = carfilzomib 70 mg/m^2 weekly and dexamethasone; CLd = carfilzomib, lenalidomide and dexamethasone; IV = intravenous, Ld = lenalidomide and dexamethasone; ELd = elotuzumab, lenalidomide and dexamethasone; OS = overall survival; PBd = pomalidomide, bortezomib and dexamethasone; PFS = progression free survival; QW= once weekly; RRMM = relapsed and/or refractory multiple myeloma

Blue shading represents information presented in carfilzomib November 2016 submission

a. The original carfilzomib (November 2016) submission also included an indirect comparison of CLd versus ELd. However, these results were not discussed at the ESC or PBAC meetings because elotuzumab was not TGA-registered, PBS-listed, or being considered at the November 2016 PBAC meeting

2 Background

Registration status

2.1 CLd was TGA registered on 19 December 2016 for the treatment of patients with multiple myeloma who have received at least one prior therapy. The product information, the TGA Delegate's Overview and the Clinical Evaluation Report were provided in the resubmission.

Previous PBAC consideration

2.2 CLd was previously considered by the PBAC in November 2016 based on a cost-utility analysis (CUA) versus lenalidomide plus dexamethasone (Ld). It was not recommended due to a high and uncertain cost-effectiveness ratio (paragraph 7.1, carfilzomib public summary document (PSD), November 2016).

2.3 The resubmission stated that the approach proposed in this submission (i.e. a CMA compared to Cd) was based on the fact that Cd has been a comparator for most triplet therapy submissions considered by the PBAC regardless of the backbone therapy (bortezomib plus dexamethasone (Bd) or Ld). The resubmission further suggested Cd as a comparator for CLd allows the PBAC to have a consistent frame of reference for decision-making for treatments for RRMM.

2.4 The resubmission presented an indirect treatment comparison (ITC) to support the therapeutic claim of non-inferior effectiveness and a non-inferior, yet different, safety profile compared to Cd and a CMA of CLd versus Cd accordingly. A comparison with the previous submission is provided in Table 2.

Table 2: Key differences between submissions

PBAC Meeting	November 2016 PBAC submission	March 2022 PBAC re-submission
Authority level	Written and telephone Authority	Streamlined (consistent with current Cd listing)
Patient population	RRMM after one prior therapy	RRMM after one prior therapy
PBS item codes	New PBS codes (public and private Hospital)	Cd is PBS listed for twice weekly and weekly use New CLd PBS codes (Public and Private Hospital): Separate codes for Cycles 1 – 12 (17 repeats) and Cycles 13+ (11 repeats)
Comparator	Main comparator: Ld Near term comparator: ELd and ILd- indirect treatment comparison (ITC)	Main: Cd – (ITC) for clinical and economic claim Secondary: ELd and PBd (ITC) Main comparators for estimation of expenditure caps: Cd, PBd and ELd
Price	AEMP list price = $21.49/mg Net price: $[redacted]/mg. SPA requested	AEMP list price = $21.49 per mg Current Cd rebate is [redacted]%, resulting in a net price of $[redacted]/mg An SPA is requested. The specific effective price not known until lenalidomide price is revealed
Pivotal clinical evidence	Main comparison: ASPIRE (CLd vs Ld) Secondary comparison[a] (ITC): ELd (ELOQUENT-2 –ELd vs Ld) ILd (TOURMALINE MM-1 - ILd vs Ld)	Main comparison: ITC CLd vs Cd: ASPIRE (CLd vs Ld) vs ENDEAVOR (Cd vs Bd) Secondary comparisons: ITC of CLd (ASPIRE) vs: ELd (ELOQUENT-2 - ELd vs Ld) PBd (OPTIMISMM - PBd vs Bd)
Clinical Claim	CLd has superior efficacy and inferior safety compared to Ld	CLd is non-inferior in terms of efficacy compared to Cd, ELd and PBd CLd is non-inferior in terms of safety compared to ELd and PBd and Cd with a different side-effect profile compared to Cd
Economic evaluation	CUA vs Ld. ICER was in excess of $[redacted][1]/QALY	CMA vs Cd
Budget impact	Submission presented combined estimates for both Cd and CLd. The submission assumed 20% of patients would use Cd and 80% would use CLd Estimated net cost to PBS/RPBS: • Year 1: $[redacted][2] • Year 2: $[redacted][3] • Year 3: $[redacted][2] • Year 4: $[redacted][4] • Year 5: $[redacted][4]	The resubmission requested a revision to the carfilzomib RSA expenditure caps to allow for other regimens which have been cost-minimised to Cd to share these caps based on a precedent set with PBd. The resubmission stated that the proposed expenditure caps will not result in an increase overall PBS/RPBS cost to the RRMM market. However, the financial estimates presented by the resubmission resulted in a positive net cost. The resubmission presented the financial estimates for the base case scenario with Cd + PBd + ELd + CLd: • 2022: $[redacted][5] • 2023: $[redacted][6] • 2024: $[redacted][6] • 2026: $[redacted][6] • 2026: $[redacted][6] • 2027: $[redacted][6]
Reason for rejection	High and uncertain ICERs.	-

Source: Table 1.1.1 p3-4 of the resubmission, carfilzomib PSD November 2016

AEMP = approved ex-manufacturer price; Bd = bortezomib and dexamethasone; Cd = carfilzomib and dexamethasone; CLd = carfilzomib and lenalidomide and dexamethasone; CMA = cost-minimisation approach; CUA = cost-utility analysis; ELd = elotuzumab, lenalidomide and dexamethasone; ICER = incremental cost-effectiveness ratio; ILd = ixazomib, lenalidomide and dexamethasone; ITC = indirect treatment comparison; Ld = lenalidomide and dexamethasone; PBS = Pharmaceutical Benefits Scheme; PBd = pomalidomide, lenalidomide

and dexamethasone; QALY = quality adjusted life year; RPBS = Repatriation Pharmaceutical Benefits Scheme; RRMM = relapsed and/or refractory multiple myeloma; RSA = risk sharing arrangement; SPA = special pricing arrangement
Blue shading represents information presented in carfilzomib November 2016 submission.
a. The ITC was presented in the initial submission but not considered by the ESC or PBAC.
The redacted values correspond to the following ranges
[1]*$135,000 to < $155,000*
[2]*$30 million to < $40 million*
[3]*$20 million to < $30 million*
[4]*$40 million to < $50 million*
[5]*$60 million to < $70 million*
[6]*$80 million to < $90 million*

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

3 Requested listing

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

MEDICINAL PRODUCT Medicinal product pack	Dispensed price for Max. Amount	PBS item code	Max. Amount	№.of Rpts	Manufacturer
CARFILZOMIB injection	Published: Public: $1,355.22 Private: $1,414.02 Effective[1] Public $[redacted] Private $[redacted]	NEW (Public) NEW (Private)	60 mg	17	Amgen Australia Pty Ltd
Available brands					
Kyprolis (carfilzomib 10 mg injection, 1 vial)					
Kyprolis (carfilzomib 30 mg injection, 1 vial)					
Kyprolis (carfilzomib 60 mg injection, 1 vial)					

1. The effective price per milligram, corresponding to the published price times the agreed [redacted]% rebate, used to estimate the effective DPMA was presented by the resubmission in the economic model in Section 3 but not in the main body of the resubmission.

Restriction Summary [new] / Treatment of Concept: [new]

	Category/Program: Section 100 (Efficient Funding of Chemotherapy)
	Prescriber type: ☒Medical Practitioners
	Restriction type / Method: ☒Authority Required - STREAMLINED
	Episodicity: Relapsed and/or refractory
	Condition: Multiple myeloma
	PBS Indication: Relapsed and/or refractory multiple myeloma
	Treatment phase: Initial treatment for Cycles 1 to ~~12~~ *3*
	Clinical criteria:
	The condition must be confirmed by a histological diagnosis,
	AND
	Clinical criteria:
	The treatment must be in combination with lenalidomide and dexamethasone,

	AND
	Clinical criteria:
	Patient must have progressive disease after at least one prior therapy,
	~~**AND**~~
	~~**Clinical criteria:**~~
	~~Patient must not be receiving concomitant PBS-subsidised *treatment with any of (i)* bortezomib, *(ii)* pomalidomide, *(iv)* thalidomide, or *(v)* daratumumab~~
	Prescribing 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 in 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).
	Prescribing instructions Oligo-secretory and non-secretory patients are defined as having active disease with less than 10 g per L serum M protein.
	Prescribing Instructions: *Provide details of the histological diagnosis of multiple myeloma, prior treatments including name(s) of drug(s) and date of most recent treatment cycle; the basis of the diagnosis of progressive disease or failure to respond; and which disease activity parameters will be used to assess response once only through the Authority application for lenalidomide.*
	Administrative Advice: *No increase in the maximum number of repeats may be authorised.*
	Administrative Advice: *Special Pricing Arrangements apply*

	Category/Program: Section 100 (Efficient Funding of Chemotherapy)
	Prescriber type: ☒Medical Practitioners
	Restriction type / Method: ☒Authority Required - STREAMLINED
	Episodicity: Relapsed and/or refractory
	Condition: Multiple myeloma
	PBS Indication: Relapsed and/or refractory multiple myeloma
	Treatment phase: ~~Initial~~ *Continuing* treatment for Cycles ~~1~~ *3* to 12
	Clinical criteria:
	Patient must have previously received PBS-subsidised treatment with this drug for this condition
	AND
	Clinical criteria:
	The treatment must be in combination with lenalidomide and dexamethasone,
	AND
	Clinical criteria:
	Patient must not have developed progressive disease while receiving treatment with this drug for this condition,

	~~**AND**~~
	~~**Clinical criteria:**~~
	~~Patient must not be receiving concomitant PBS-subsidised *treatment with each of (i)* bortezomib, *(ii)* pomalidomide, *(iv)* thalidomide, or *(v)* daratumumab~~
	Prescribing 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 in 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).
	Prescribing instructions 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.*
	Administrative Advice: *Special Pricing Arrangements apply*

Restriction Summary [new] / Treatment of Concept: [new]

	Category/Program: Section 100 (Efficient Funding of Chemotherapy)
	Prescriber type: ☒Medical Practitioners
	Restriction type / Method: ☒Authority Required - STREAMLINED
	Episodicity: Relapsed and/or refractory
	Condition: Multiple myeloma
	PBS Indication: Relapsed and/or refractory multiple myeloma
	Treatment phase: Continuing treatment for Cycles 13 onwards
	Clinical criteria:
	Patient must have previously received PBS-subsidised treatment with this drug for this condition
	AND
	Clinical criteria:
	The treatment must be in combination with lenalidomide and dexamethasone,
	AND
	Clinical criteria:
	Patient must not have developed progressive disease while receiving treatment with this drug for this condition,
	~~**AND**~~
	~~**Clinical criteria:**~~
	~~Patient must not be receiving concomitant PBS-subsidised *treatment with each of (i)* bortezomib, *(ii)* pomalidomide, *(iv)* thalidomide, or *(v)* daratumumab~~
	Prescribing 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 in 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).
	Prescribing instructions 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.*
	Administrative Advice: *Special Pricing Arrangements apply*

3.2 Add new lenalidomide Treatment phase listing to permit use in carfilzomib + lenalidomide + dexamethasone triple combination therapy as follows:

MEDICINAL PRODUCT medicinal product pack	**PBS item code**	**Max. Qty (units)**	**Max. Qty (packs)**	**No. of Rpts**	**Available brands**	**Sponsor**
LENALIDOMIDE						
lenalidomide 5 mg capsule, 21	New (Public) / (Private)	21	1	2	Revlimid	Celgene Pty Ltd
lenalidomide 10 mg capsule, 21	New (Public) / (Private)	21	1	2	Revlimid	Celgene Pty Ltd
lenalidomide 15 mg capsule, 21	New (Public) / (Private)	21	1	2	Revlimid	Celgene Pty Ltd
lenalidomide 25 mg capsule, 21	New (Public) / (Private)	21	1	2	Revlimid	Celgene Pty Ltd

Restriction Summary [new] / Treatment of Concept: [new]	
	Category/Program: *Section 100 (Highly Specialised Drugs Program) – Public/Private hospitals*
	Prescriber type: ☒*Medical Practitioners*
	Restriction type: ☒*Authority Required (telephone/online PBS Authorities system)*
	PBS Indication: *Relapsed and/or refractory multiple myeloma*
	Treatment phase: *Triple combination therapy consisting of carfilzomib, lenalidomide and dexamethasone*
	Treatment criteria:
	Patient must be undergoing concurrent treatment with carfilzomib obtained through the PBS
	AND
	Treatment criteria:
	Patient must not be undergoing simultaneous treatment with this drug obtained under another PBS listing
	Administrative advice: *Applications for authorisation under this restriction may be made in real time using the Online PBS Authorities system (see www.servicesaustralia.gov.au/HPOS) or by telephone by contacting Services Australia on 1800 888 333.*
	Administrative Advice: *Special Pricing Arrangements apply*

3.3 The resubmission requested listing of carfilzomib at a maximum amount of 60 mg when used in combination with Ld, based on the maximum dose recommended in ASPIRE of 27 mg/m^2. The current PBS listing of carfilzomib (used in combination with dexamethasone) has an approved maximum quantity of 120 mg.

3.4 The resubmission's proposed published dispensed price per maximum amount (DPMA) of carfilzomib was $1,355.22 (public) and $1,414.02 (private). The DPMAs were based on cost-minimisation at the approved ex-manufacturer prices (AEMPs). See *Economic analysis* in section 6 below for issues regarding the calculations of the effective price. The published AEMP for carfilzomib remained unchanged from the initial submission in November 2016.

3.5 The proposed restrictions were consistent with the TGA approved indication, the clinical evidence presented in the resubmission, the CMA and the estimation of use in clinical practice. The trial eligibility criteria for ASPIRE, the pivotal trial, included restrictions on patients' prior response to treatment, including achieving at least a partial response and not being refractory to prior lenalidomide. The proposed PBS restrictions do not include these criteria.

3.6 The treatment duration in ASPIRE differed from the proposed PBS listing. Patients in ASPIRE received 18 cycles of CLd followed by Ld until disease progression, whereas the proposed restriction was for treatment with CLd until disease progression.

3.7 The submission requested an Authority Required (Streamlined) listing for initial and continuing treatment. This was consistent with the approved restriction for Cd in the RRMM setting. The initial submission (November 2016) had requested restriction as 'Authority Required – In writing'.

3.8 The resubmission requested a separate restriction for lenalidomide use in CLd. This was consistent with the requested restriction for lenalidomide when used in combination with elotuzumab and dexamethasone (ELd; paragraph 6.12, elotuzumab PSD, July 2021).

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

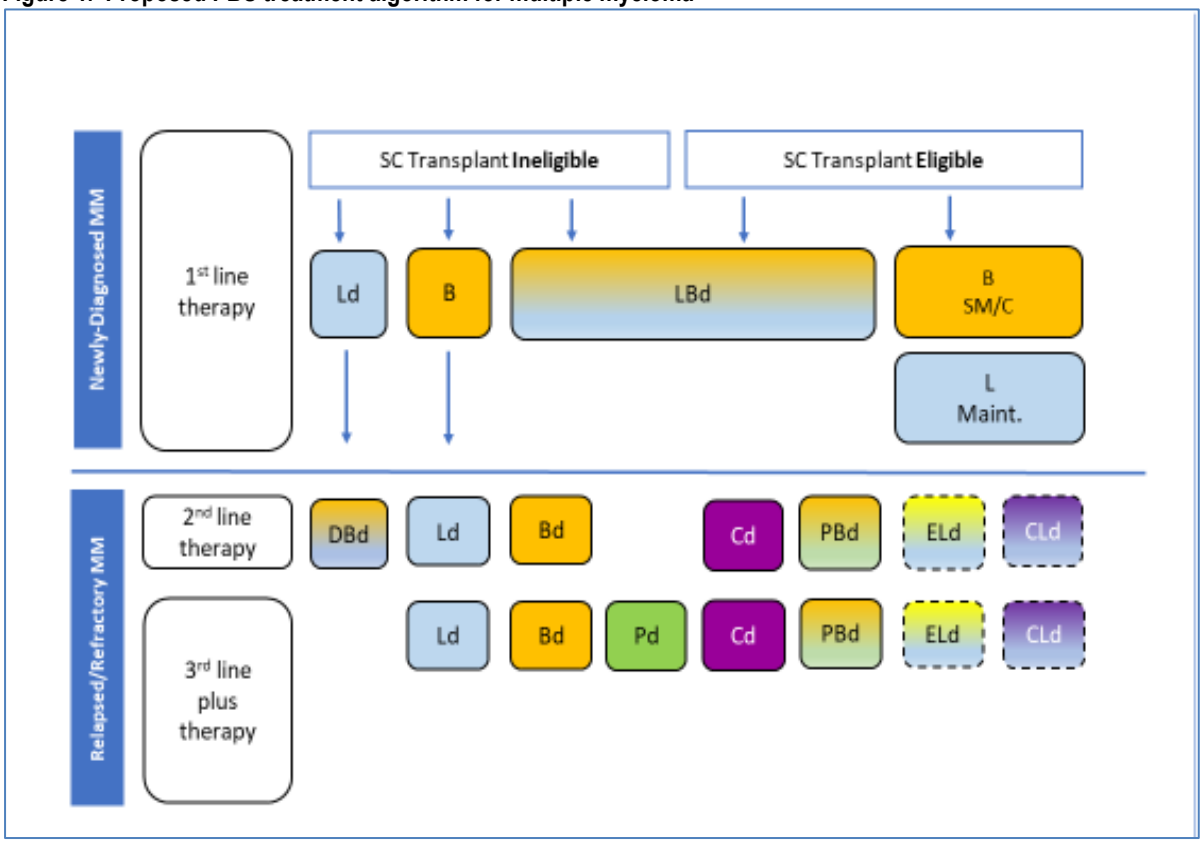
4 Population and disease

4.1 Multiple myeloma (MM) is a B-cell malignancy characterised by the clonal proliferation of malignant plasma cells within the bone marrow. The natural history of the disease includes disruption of normal bone marrow function (reflected by anaemia and/or low counts of white blood cells and platelets), progressive destruction and invasion of bone surrounding the bone marrow cavity leading to skeletal complications and fractures, hypercalcaemia, production and release of monoclonal protein (M-protein) by myeloma cells into the blood and/or urine, organ dysfunction (particularly involving the kidneys), and compromised immune function (reflected in decreased levels of normal immunoglobulins and increased susceptibility to infection).

MM remains incurable; with diminishing duration of response to subsequent lines of therapy with each relapse that tends to be progressively more aggressive.

4.2 The resubmission requested PBS listing of CLd for the treatment of patients with RRMM who had received at least one prior treatment. The clinical algorithm (Figure 1) presented in the resubmission proposed that CLd would substitute for Cd and Ld. The ESC noted that daratumumab in combination with bortezomib and dexamethasone (DBd) is PBS listed for use in the second line setting only, and considered that other treatments, including CLd, will be displaced to the third line in clinical practice.

Figure 1: Proposed PBS treatment algorithm for multiple myeloma



Source: Figure 1.2-2 p14 of the resubmission

B = bortezomib; Bd = bortezomib and dexamethasone; Cd = carfilzomib and dexamethasone; CLd = carfilzomib, lenalidomide and dexamethasone; DBd = daratumumab, bortezomib and dexamethasone; ELd = elotuzumab, lenalidomide and dexamethasone; LBd = lenalidomide, bortezomib and dexamethasone; Ld = lenalidomide and dexamethasone; Maint = maintenance; MM = multiple myeloma; PBd = pomalidomide, bortezomib and dexamethasone; PBS = Pharmaceutical Benefits Scheme; Pd = pomalidomide and dexamethasone; SC = stem cell; SM/C = steroid and melphalan or cyclophosphamide

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

5 Comparator

5.1 The resubmission nominated Cd as the primary comparator for CLd. The choice of comparator was different from the initial submission in November 2016 where CLd

was compared to Ld on a cost effectiveness basis. Cd has been a comparator (either main or secondary) for most triplet therapies (e.g. pomalidomide plus bortezomib and dexamethasone (PBd), ELd, and ixazomib plus lenalidomide and dexamethasone (ILd)) that have been considered by the PBAC on a cost-minimisation basis, regardless of the backbone therapy (Bd or Ld). Thus, it was argued Cd as a comparator for CLd allows the PBAC to have a consistent frame of reference for decision-making about treatments for RRMM. The PBAC considered the nomination of Cd as main comparator was reasonable.

5.2 The resubmission nominated PBd and ELd as secondary and near market comparators respectively. At the time of the resubmission, these represented the most recent therapies to be PBS listed (PBd) and recommended for listing (ELd) for the treatment of RRMM. The PBAC considered the nomination of PBd as a secondary comparator and ELd as a near market comparator was reasonable.

5.3 The ESC noted that the CMA presented by the resubmission was conducted based on the primary comparator Cd only, while the financial estimates presented by the resubmission assumed different scenarios in which CLd, Cd, PBd and ELd were available.

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

6 Consideration of the evidence

Sponsor hearing

6.1 The sponsor requested a hearing for this item. The hearing discussed the sponsor's request to increase the RSA expenditure caps for carfilzomib to accommodate the treatment regimens that have been cost minimised to Cd and recommended to join the Cd RSA. The sponsor representative described that the current caps were not intended to reflect the overall market, and that financial estimates of the market provided in the resubmission were developed based on utilisation data of the prevalent patient lines obtained from the DUSC Secretariat and the sponsor's projected market share. It was also stated that there is a risk that other triplet therapies will be unable to list if the caps are not increased.

Consumer comments

6.2 The PBAC noted and welcomed the input from individuals (12) and organisations (3) via the Consumer Comments facility on the PBS website. The comments described the impact of multiple myeloma on patients and their families, and a desire for access to additional treatments for patients with RRMM.

6.3 The PBAC noted the comments from Myeloma Australia's Medical and Scientific Advisory Group (MSAG), which supported the proposed listing of CLd on the basis of the safety and efficacy results from the ASPIRE trial. The PBAC noted the comments from Myeloma Australia, which strongly supported the proposed listing and

highlighted the importance of providing patients with the best possible opportunity to achieve and stay in remission. The PBAC noted the comments from the Leukemia Foundation in support of the proposed listing. The PBAC also noted the input from consumers with personal experience with carfilzomib treatment contained in the Leukemia Foundation submission, and that some cases of cardiac toxicity were reported in this sample.

Clinical trials

6.4 The resubmission presented three ITCs comparing CLd with Cd, PBd and ELd.

6.5 The ITC of CLd and Cd was informed by two randomised controlled trials (RCTs): ASPIRE which compared CLd with Ld (N=792) and ENDEAVOR which compared Cd with Bd (N=929). In forming this comparison, the resubmission utilised Ld and Bd as the common reference, assuming their equivalence and did not adjust for any potential difference in their outcomes. The PBAC has previously stated that it may not be reasonable to assume non-inferior efficacy between Ld and Bd (paragraph 5.3, carfilzomib PSD, November 2016), noting at the time of considering Ld versus Bd that overall survival (OS) may possibly favour Ld (Lenalidomide PSD, November 2008).

6.6 The ITC of CLd versus PBd was informed by two RCTs: ASPIRE and OPTIMISMM, which compared PBd with Bd (N=559). In forming this comparison, the resubmission utilised Ld and Bd as the common reference, assuming therapeutic equivalence. However, as stated above, this assumption may not be appropriate.

6.7 The ITC of CLd versus Eld was informed by two RCTs: ASPIRE and ELOQUENT-2, which compared ELd with Ld (N=646). In forming this comparison, the resubmission utilised Ld as the common comparator arm.

6.8 Details of the trials presented in the resubmission are provided in Table 3 below.

Table 3: Trials and associated reports presented in the submission

Trial ID	Protocol title/ Publication title	Publication citation
ASPIRE NCT0108039	A Randomised, Multicenter, Phase 3 Study Comparing Carfilzomib, Lenalidomide, and Dexamethasone vs. Lenalidomide and Dexamethasone in Patients with Relapsed Multiple Myeloma	14 October 2014 24 September 2017 [data cut-off 28 April 2017
	Stewart K, Rajkumar V, Dimopoulos M, *et al*. Carfilzomib, lenalidomide, and dexamethasone for relapsed multiple myeloma	N Engl J Med 2015; 372(2):142-52
	Siegel DS et al. Improvement in Overall Survival With Carfilzomib, Lenalidomide, and Dexamethasone in Patients With Relapsed or Refractory Multiple Myeloma.	J Clin Oncol 2018;36:728-34
	Secondary publications	
	Weisel K, Mateos MV, Gay F, Delforge M, Cook G, Szabo Z, Desgraz R, DeCosta L, Moreau P. Efficacy and safety profile of deep responders to carfilzomib-based therapy: a subgroup analysis from ASPIRE and ENDEAVOR.	Leukemia. 2021 Jun;35(6):1732-1744
	Siegel DS, Dimopoulos MA, Ludwig H, Facon T, Goldschmidt H, Jakubowiak A, San-Miguel J, Obreja M, Blaedel J, Stewart AK. Improvement in overall survival with carfilzomib, lenalidomide, and dexamethasone in patients with relapsed or refractory multiple myeloma.	Journal of Clinical Oncology (2018) 36:8 (728-734)
	Mateos M-V, Goldschmidt H, San-Miguel J, Mikhael J, DeCosta L, Zhou L, Obreja M, Blaedel J, Szabo Z, Leleu X. Carfilzomib in relapsed or refractory multiple myeloma patients with early or late relapse following prior therapy: A subgroup analysis of the randomized phase 3 ASPIRE and ENDEAVOR trials.	Hematological Oncology (2018) 36:2 (463-470)
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	Avet-Loiseau H, Fonseca R, Siegel D, Dimopoulos MA, Špička I, Masszi T, Hájek R, Rosiñol L, Goranova-Marinova V, Mihaylov G, Maisnar V, Mateos M-V, Wang M, Niesvizky R, Oriol A, Jakubowiak A, Minarik J, Palumbo A, Bensinger W, Kukreti V, Ben-Yehuda D, Stewart AK, Obreja M, Moreau P. Carfilzomib significantly improves the progression-free survival of high-risk patients in multiple myeloma.	Blood (2016) 128:9 (1174-1180)
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	Lancet Oncol 2016; 17:27–38.
	Dimopoulos MA, 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	Lancet Oncol 2017;18:1327-37
ARROW	A Randomized, Open-label, Phase 3 Study in Subjects With Relapsed and Refractory Multiple Myeloma Receiving Carfilzomib in Combination With Dexamethasone, Comparing Once-weekly Versus Twice-weekly Carfilzomib Dosing	June 2019

Trial ID	Protocol title/ Publication title	Publication citation
	Moreau P, et al. Once weekly versus twice weekly carfilzomib dosing in patients with relapsed and refractory multiple myeloma (A.R.R.O.W.): interim analysis results of a randomised, phase 3 study.	Lancet Oncol 2018;19:953-64
ELOQUENT-2	Lonial S, et al. Elotuzumab Therapy for Relapsed or Refractory Multiple Myeloma.	N Engl J Med 2015;373:621-31
	Dimopoulos MA, et al. Elotuzumab, lenalidomide, and dexamethasone in RRMM: final overall survival results from the phase 3 randomized ELOQUENT-2 study	Blood Cancer Journal 2020;10:91
OPTIMISMM	Richardson PG, et al. Pomalidomide, bortezomib, and dexamethasone for patients with relapsed or refractory multiple myeloma previously treated with lenalidomide (OPTIMISMM): a randomised, open-label, phase 3 trial.	Lancet Oncol 2019;20:781-94

Source: Table 2.2.2 p27-30, Table 2.2.3 p32 of the resubmission.
Blue shading represents information presented in carfilzomib November 2016 submission

6.9 The key features of the direct randomised trials included in the ITC are summarised in the Table 4 below. Of the trials listed above, ARROW was the only trial not used to inform the ITC. ARROW was used to inform the CMA and to account for differences in the available dose regimens of carfilzomib and was previously considered by the PBAC in relation to the once weekly (QW) regimen of Cd submission.

Table 4: Key features of the included evidence to inform the indirect treatment comparison

Trial	N	Design/duration	Risk of bias	Patient population	Outcomes
CLd vs Cd					
ASPIRE	792	Phase III, R, OL PFS: 48 months OS: 67 months (cut-off 28 April 2017)[a]	Low	RRMM patients who had received 1-3 prior lines of therapy	Primary: PFS Secondary: OS, ORR, Safety, HRQoL
Cd vs Bd					
ENDEAVOR	929	Phase III, R, OL, MC PFS: 16.6 months (cut-off 3 Mar 2016) OS: 44.3 months (Cd) and 43.7 months (Bd) (cut-off 19 July 2017)[a]	Low	RRMM patients who had received 2-3 prior lines of therapy and achieved at least a partial response to at least 1 previous treatment	Primary: PFS Secondary: OS, ORR and Safety
Eld vs Ld					
ELOQUENT-2[b]	646	Phase III, R, OL PFS: 46.8 months OS: 70.6 months (cut-off 3 Oct 2018)[a]	Low	RRMM patients who had received ≥ 1 prior line of therapy	Co-primary endpoints: PFS and ORR Secondary: OS and BPI-SF Exploratory: Safety, HRQoL
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 ≥ 1 prior treatment regimen including lenalidomide for at least 2 consecutive cycles	Primary: PFS, Secondary: OS, ORR, DOR, Safety

Source: Compiled by the commentary based on the resubmission.

Bd = bortezomib and dexamethasone; BPI-SF = Brief Pain Inventory-Short Form; Cd = carfilzomib and dexamethasone; CLd = carfilzomib, lenalidomide and dexamethasone; DOR = duration of response; ELd = elotuzumab, lenalidomide and dexamethasone; HRQoL=health related quality of life; MC = multi-centre; OL = open label; OS = overall survival; ORR = overall response rate, PBd = pomalidomide, bortezomib and dexamethasone; PFS = progression-free survival; R = randomised; RRMM = relapsed and/or refractory multiple myeloma
Blue shading represented information presented in carfilzomib November 2016 submission
a. The details of the follow-up are provided for the latest data cut-off available.
b. ELOQUENT-2 was presented in the original submission but not considered by ESC or the PBAC.

6.10 The demographic characteristics across the trials were similar, with the following exceptions: more patients in ASPIRE had an Eastern Cooperative Oncology Group (ECOG) performance status of 2 (10.1%), compared with ENDEAVOR (6.9%), ARROW (0.4%) and OPTIMISMM (3.9%). Patients in ASPIRE had higher levels of creatinine clearance compared to ENDEAVOR, ELOQUENT-2 and OPTIMISMM. The ESC noted that demographics were similar across the trials and considered that the differences were minor and were not anticipated to affect the comparability of these trials.

6.11 The ESC noted that the trials included in the ITC had different durations of follow-up for both progression free survival (PFS) and OS. The follow-up time for PFS in ASPIRE was 31 months, compared with 11.5 months in ENDEAVOR, 24.5 months in ELOQUENT-2 and 15.9 months in OPTIMISMM. Similarly, the follow-up time for OS was 32 months in ASPIRE, compared with 37 months in ENDEAVOR, 38.7 months in ELOQUENT-2 and 26.2 months in OPTIMISMM. The comparability of the trials may be impacted by the differences in follow-up.

6.12 The key differences between the eligibility criteria of the trials with respect to prior exposure to either lenalidomide or bortezomib were:

- In ASPIRE, patients were allowed prior lenalidomide unless either the patient (i) progressed during the first 3 months of initiating Ld treatment, or (ii) progressed at any time during Ld treatment if that was the most recent therapy;
- In ARROW, patients received 2-3 prior regimens including proteasome inhibitor and an immunomodulatory imide drug (IMiD);
- In ENDEAVOR, patients had to have at least a partial response to bortezomib, had discontinued bortezomib therapy due to toxicity, and were to have had at least a 6-month bortezomib free period prior to study initiation;
- In ELOQUENT-2, patients had to have achieved at least a partial response, not be refractory, not having discontinued due to a grade ≥3 related adverse event (AE) and not received more than 9 cycles of lenalidomide, and had at least 9 months between the last dose of lenalidomide and progression;
- In OPTIMISMM, all patients were required to have received prior treatment with lenalidomide; patients with prior bortezomib use, were included provided they did not have progressive disease during therapy or within 60 days of the last dose of bortezomib containing therapy.

The noted differences in eligibility criteria specific to prior use of lenalidomide (ASPIRE and ELOQUENT-2) and bortezomib (ENDEAVOR and OPTIMISMM) may impact on the exchangeability of the trials for the quantitative ITC.

6.13 The differences in prior exposure to lenalidomide and bortezomib across the trials are presented in Table 5.The ESC noted that prior exposure to lenalidomide was the most significant difference between the trials.

Table 5: Prior treatment exposure in the included trials

	ASPIRE		ENDEAVOR		ARROW		ELOQUENT-2		OPTIMISMM	
	CLd	Ld	Cd 56 BIW	Bd	Cd70 QW	Cd27 BIW	ELd	Ld	PBd	Bd
Number of patients	396	396	464	465	240	238	321	325	281	278
Prior exposure to lenalidomide; n (%)	79 (19.9)	78 (19.7)	177 (38.1)	177 (38.1)	207 (86.3)	194 (81.5)	16 (5.0)	21 (6.5)	281 (100)	278 (100)
Prior exposure to bortezomib; n (%)	261 (65.9)	260 (65.7)	250 (53.9)	252 (54.2)	236 (98.3)	237 (99.6)	219 (68.2)	231 (71.1)	201 (71.8)	203 (73.0)

Source: Table 2.4.3 p45-46 of the resubmission

Bd = bortezomib and dexamethasone; Cd27 BIW = carfilzomib 27 mg/m^2 twice weekly and dexamethasone; Cd56 BIW = carfilzomib 56 mg/m^2 twice weekly and dexamethasone; Cd70 = carfilzomib 70 mg/m^2 weekly and dexamethasone; CLd = carfilzomib, lenalidomide and dexamethasone; ELd = elotuzumab, lenalidomide and dexamethasone; Ld = lenalidomide and dexamethasone; PBd = pomalidomide, lenalidomide and dexamethasone

Comparative effectiveness

6.14 The ASPIRE and ENDEAVOR trials were presented in the November 2016 submission. Updated data was presented for both ASPIRE (28 April 2017 data cut; median follow up 67 months) and ENDEAVOR (July 2017 data cut; median follow-up 44 months) in the resubmission. The data informing the PFS ITC was not updated in the resubmission. For the OS ITC data from the original submission was presented and compared with updated data-cut offs for ASPIRE and ENDEAVOR.

<u>CLd versus Ld (ASPIRE trial)</u>

6.15 The summary of PFS and OS results from ASPIRE are presented in Table 6, with the corresponding Kaplan-Meier plots reported in Figure 2. Patients in the CLd arm had statistically significantly longer PFS and OS compared to Ld. The efficacy estimates for the OS did not change substantially between the two data-cuts (16 June 2014, median follow up = 32 months and 28 April 2017 data cut, median follow up = 67 months).

Table 6: PFS and OS results from ASPIRE

	Median time to follow up (months)	CLd (N=396)		Ld (N=396)		Difference in median	P value (log rank test)	Hazard ratio (95% CI)
		Patients with events, n (%)	Median months (95% CI)	Patients with events, n (%)	Median months (95% CI)			
PFS								
16 Jun 2014 IRC	31	207 (52.3%)	26.3 (23.3, 30.5)	224 (56.6%)	17.6 (15.0, 20.6)	8.7	<0.0001	**0.69 (0.57, 0.83)**
16 Jun 2014 INV Interim analysis	31	209 (52.8%)	26.1 (23.2, 29.7)	240 (60.6%)	16.6 (14.5, 19.4)	9.5	<0.0001	**0.65 (0.54, 0.76)**
28 Apr 2017 INV Final analysis	67	244 (61.6%)	26.1 (23.2, 30.3)	272 (68.7%)	16.6 (14.5, 19.4)	9.5	<0.001	**0.66 (0.55, 0.78)**
OS								
16 Jun 2014 Interim analysis	32	143 (36.1%)	NE	162 (40.9%)	NE	-	0.0182	**0.79 (0.63, 0.99)**
28 Apr 2017 Final analysis	67	246 (62.1%)	48.3 (42.4, 52.8)	267 (67.4%)	40.4 (33.6, 44.4)	7.9	0.0045	**0.79 (0.67, 0.95)**

Source: Table 2.5-4 p62 of the resubmission

CI = confidence interval; CLd = carfilzomib, lenalidomide and dexamethasone; INV = investigator-assessed; IRC = independent review committee; Ld = lenalidomide and dexamethasone; NE = not estimable; OS = overall survival; PFS = progression free survival

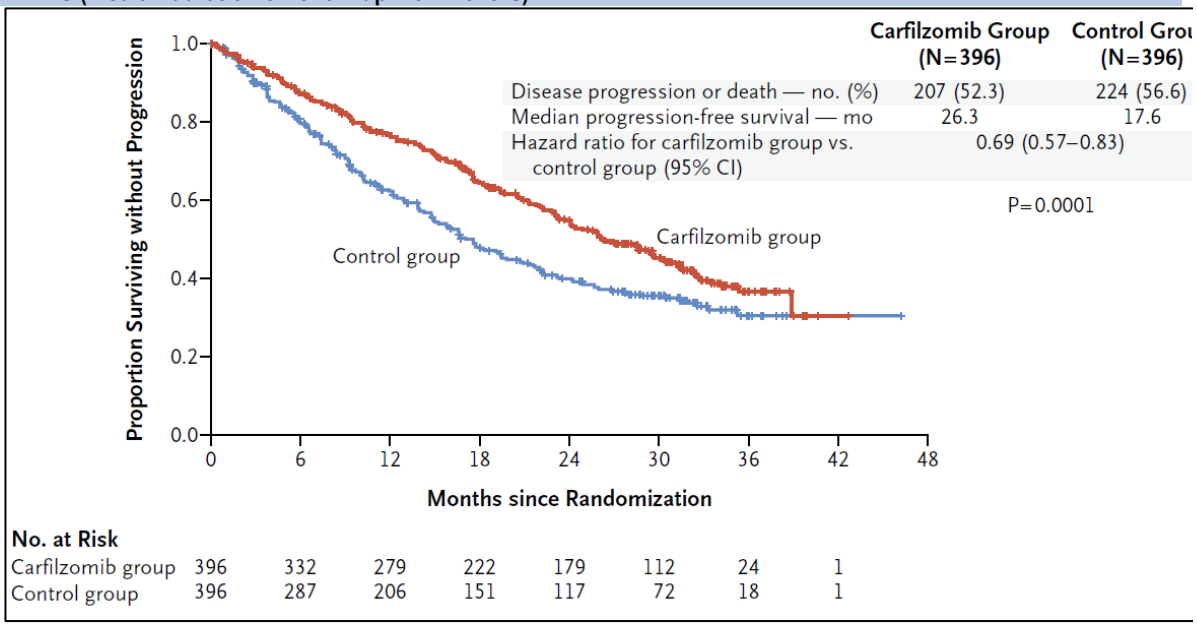
Note: ASPIRE median follow for PFS: 31 months (data cut 16 Jun 2014); OS: 32 months (data cut 16 Jun 2014); 67 months (data cut 28 April 2018).

Bold = statistically significant

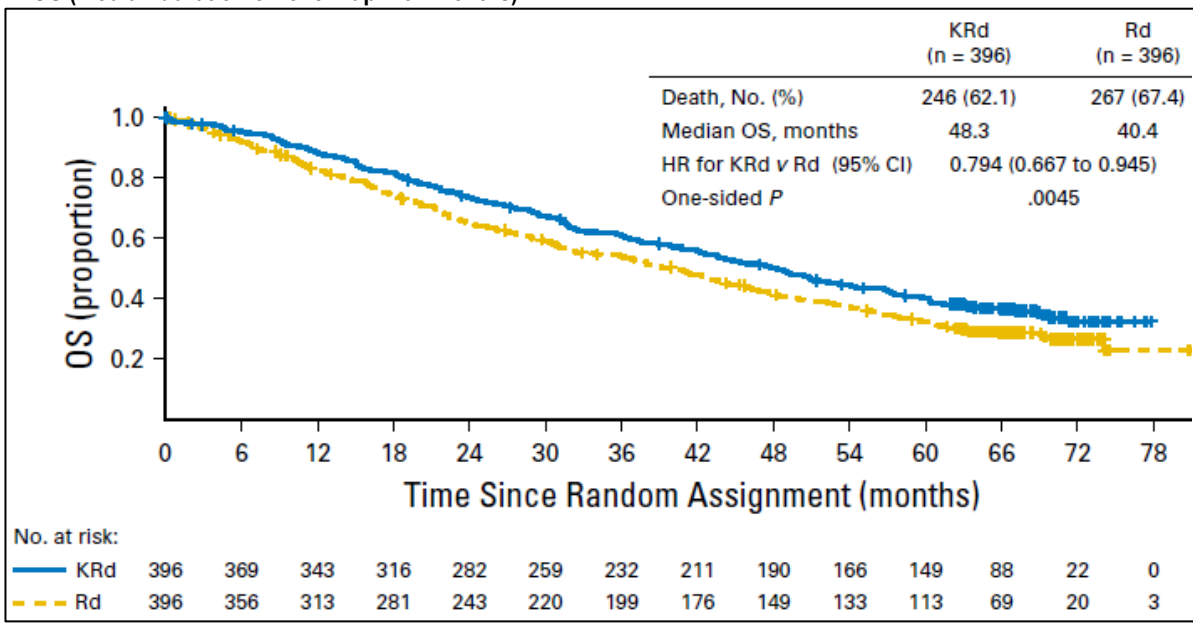
Blue shading represents information presented in carfilzomib November 2016 submission

Figure 2: Kaplan-Meier curves for (A) PFS and (B) OS, ASPIRE

A: PFS (median duration of follow-up = 31 months)



B: OS (median duration of follow-up = 67 months)



Source: Figure 2.5.1 p59, Figure 2.5.2 p62 of the resubmission
CI = confidence interval; HR = hazard ratio; KRd = carfilzomib, lenalidomide, and dexamethasone; mo = months; OS = overall survival; PFS = progression free survival; Rd = lenalidomide and dexamethasone
Notes: Medians were estimated using the Kaplan-Meier method. HRs and p-values were obtained from stratified Cox regression and stratified log-rank test, respectively
Blue shading represents information presented in carfilzomib November 2016 submission

6.16 The results for objective response rate (ORR) are presented in Table 7. Patients in the CLd arm had a statistically significantly higher ORR compared to Ld.

Table 7: ORR results from ASPIRE

	CLd (N=396)		Ld (N=396)		Difference in median, months	P value (log rank test)	Odds ratio (95% CI)
	n/N (%)	Median, months	n/N (%)	Median, months			
16 June 2014 IRC	345/396 (87.1)	NR	264/396 (66.7)	NR	NR	**<0.0001**	**3.47 (2.41, 5.00)**

Source: Table 2.5-8 p64-65 of the resubmission.
CI = confidence interval; CLd = carfilzomib, lenalidomide and dexamethasone; IRC = Independent Review Committee; Ld = lenalidomide and dexamethasone; NR = not reported; ORR = objective response rate
Bold = statistically significant
Blue shading represented information presented in carfilzomib November 2016 submission

6.17 The results for health-related quality of life (HRQoL) in ASPIRE showed that the minimal clinically important difference (MCID) for between-group differences on the QLQ-C30 Global Health Status and Quality of Life scale of 5.0 points was met at Cycle 12 (5.6 points) and approached at Cycle 18 (4.8 points).

Cd versus Bd (ENDEAVOR trial)

6.18 The summary of survival outcomes from ENDEAVOR are presented in Table 8.

Table 8: Results of PFS and OS in ENDEAVOR

	Median time to follow up (months)	Cd 56 BIW (N=464)		Bd (N=465)		Difference in median	P value (log rank test)	Hazard ratio (95% CI)
		Patients with events, n (%)	Median, months (95% CI)	Patients with events, n (%)	Median, months (95% CI)			
PFS								
10 Nov 2014 IRC	11.5	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	11.5	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	12.2	75 (16.2)	NE	88 (18.9)	24.3 (24.3, NE)	NE	**0.0650**	0.79 (0.58, 1.08)
3 Jan 2017	37	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)**
19 July 2017	44	214 (46.1%)	47.8 (41.9, NE)	248 (53.3%)	38.8 (31.7, 42.7)	9.0	**0.0017**	**0.76 (0.63, 0.92)**

Source: Table 2.5.5 p62 of the resubmission
Bd = bortezomib and dexamethasone; Cd56 BIW = carfilzomib 56 mg/m^2 twice weekly and dexamethasone; CI = confidence interval; IRC = Independent Review Committee; NE = not estimable; ORCA = Onyx response computation assessment; OS = overall survival; PFS = progression free survival.
Note: ENDEAVOR median follow for PFS: 11.5 months (data cut 10 Nov 2014); 16.6 months (data cut 3 March 2016); OS: 37 months (data cut 3 Jan 2017); 44 months (data cut 19 July 2017).
Bold = statistically significant
Blue shading represented information presented in carfilzomib November 2016 submission

6.19 The patients in the Cd arm of ENDEAVOR had statistically significant improvements in PFS and OS compared to Bd. The PBAC previously considered that Cd demonstrated

a statistically significant improvement in PFS and OS compared to Bd (paragraph 6.12, carfilzomib PSD, July 2017).

6.20 The ORR was statistically significantly higher for patients receiving Cd compared with Bd (Table 9).

Table 9: Summary of efficacy results: ORR, ENDEAVOR (10 Nov 2014 data-cut; median follow up = 11.5 months)

	Cd56 BIW (N=464)		Bd (N=465)		Difference in median, months	P value (log rank test)	Odds ratio (95% CI)
	Patients with events, n (%)	Median, months	Patients with events, n (%)	Median, months			
ORR	357 (76.9%)	1.1	291 (63.0%)	1.1	0	**<0.0001**	**2.03 (1.52, 2.72)**

Source: Table 2.5.8, pp64-65 of the resubmission.
Bd = bortezomib and dexamethasone; Cd56 BIW = carfilzomib 56 mg/m^2 twice weekly and dexamethasone; CI = confidence interval; ORR = objective response rate.
Bold = statistically significant
Blue shading representes information presented in carfilzomib November 2016 submission

6.21 In ENDEAVOR, treatment with Cd resulted in statistically but not clinically significant improvements in mean global health status (GHS)/quality of life (QoL) scores versus Bd. Treatment with Cd also significantly prolonged time to deterioration in GHS/QoL (median 3.7 versus 2.8 months, p = 0.0046), physical function (5.6 versus 3.7 months, p = 0.0390), nausea/vomiting (17.6 versus 8.2 months, p = 0.0358), side effects (6.4 versus 3.7 months, p < 0.0001), and FACT/GOG-Ntx (11.1 versus 5.5 months, p = 0.0004) compared with Bd.

ELd versus Ld (ELOQUENT-2 trial)

6.22 The summary of survival outcomes in ELOQUENT-2 is presented in Table 10. Patients in the ELd arm had significantly longer PFS and OS compared to Ld.

Table 10: Results of PFS and OS in ELOQUENT-2

	Median time to follow-up (months)	ELd (N=321)		Ld (N=325)		Difference in median, months	P value (log rank test)	Hazard ratio (95% CI)
		Patients with events, n (%)	Median, months (95% CI)	Patients with events, n (%)	Median, months (95% CI)			
PFS								
29 Oct 2014 – ITT (IRC)	24.5	192 (59.8%)	18.5 (16.5, 21.4)	231 (71.1%)	14.3 (12.0, 16.0)	4.2	**0.0001**	**0.68 (0.56, 0.83)**
3 Oct 2018 – ITT (IRC)	46.8	268 (83.5%)	19.4 (16.6, 22.2)	290 (89.2%)	14.8 (12.1, 16.6)	4.6	**0.0001**	**0.72 (0.61, 0.85)**
OS								
29 Oct 2015	38.7	136 (42.4%)	43.7 (40.3, NE)	159 (48.9%)	39.6 (33.3, NE)	4.1	**0.0257**	**0.77 (0.61, 0.97)**
3 Oct 2018	70.6	212 (66.0%)	48.3 (40.3, 51.9)	225 (69.2%)	39.6 (33.3, 45.3)	8.7	**0.0408**	**0.82 (0.68, 0.99)**

Source: Table 2.5.6, p63 of the resubmission.
CI = confidence interval; ELd = elotuzumab, lenalidomide and dexamethasone; IRC = independent review committee; ITT = intention to treat; Ld = lenalidomide and dexamethasone; NE = not estimable; OS = overall survival; PFS = progression free survival
Note: ELOQUENT-2 median follow for PFS: 24.5 months (data cut 29 Oct 2014); 46.8 months (data cut 3 Oct 2018); OS: 38.7 months (data cut 29 Oct 2015); 70.6 months (data cut 3 Oct 2018).
Bold = statistically significant

PBd vs Bd (OPTIMISMM trial)

6.23 The summary of survival outcomes in OPTIMISMM are presented in Table 11. Patients in the PBd arm had statistically significantly longer PFS compared to Bd. The resubmission indicated that the updated data suggested an emerging OS benefit for patients in the PBd arm compared with the Bd arm. However, the results were not statistically significant and did not change substantially between the two data-cuts cuts (where the median time to follow-up increased from 15.9 to 26.2 months, respectively).

Table 11: Results of PFS and OS in OPTIMISMM

	Median time to follow-up (months)	PBd (N=281)		Bd (N=278)		Difference in median, months	P value (log rank test)	Hazard ratio (95% CI)
		Patients with events, n (%)	Median, months (95% CI)	Patients with events, n (%)	Median, months (95% CI)			
PFS								
26 Oct 2017	15.9	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)**
OS								
26 Oct 2017	15.9	87 (31.0%)	NE (28.4, NE)	89 (32.0%)	31.2 (27.0, NE)	NE	0.894	0.98 (0.73, 1.32)
15 Sep 2018	26.2	116 (41.3%)	40.5 (29.8, NE)	126 (45.3%)	30.5 (24.6,35.9)	10.1	0.476	0.91 (0.70, 1.18)

Source: Table 2.5.7, p63 of the resubmission.
Bd = bortezomib and dexamethasone; CI = confidence interval; NE = not estimable; OS = overall survival; PBd = pomalidomide, lenalidomide and dexamethasone; PFS = progression free survival
Note: OPTIMISMM median follow for PFS: 15.9 months (data cut 26 Oct 2017); OS: 26.2 months (data cut 15 Sept 2018)
Bold = statistically significant

Indirect treatment comparison - CLd vs Cd

6.24 The results of the ITC of CLd and Cd for the outcomes of PFS and OS are presented in Table 12. The ITC compared CLd to Cd assuming that the efficacy results for Ld and Bd were the same for the purposes of anchoring a common comparator in the ITC. As noted in paragraph 6.5, this required consideration as Ld and Bd are different treatment regimens and, although the PBAC has previously considered Ld and Bd to be non-inferior, the results of the ITC could be confounded by any differences in the efficacy of these two therapies, as well as potential issues of transitivity between the trials. The submission did not adjust the ITC for differences in efficacy between Ld and Bd.

Table 11: Summary of results of the indirect comparison for PFS and OS, between ASPIRE and ENDEAVOR

	Median duration of follow-up (months)	CLd or Cd56 BIW		Ld or Bd		Difference in median, months	HR[c] (95% CI)
		Events, n/N (%)	Median, months (95% CI)	Events n/N (%)	Median, months (95% CI)		
PFS							
ASPIRE CLd vs Ld 16 Jun 2014[a]	31	207/396 (52.3%)	26.3 (23.3, 30.5)	224/396 (56.6%)	17.6 (15.0, 20.6)	8.7	**0.69 (0.57, 0.83)**
ENDEAVOR Cd vs Bd 10 Nov 2014[b]	11.5	171/464 (36.9%)	18.7 (15.6, NE)	243/465 (52.3%)	9.4 (8.4, 10.4)	9.3	**0.53 (0.44, 0.65)**
Indirect comparison CLd vs. Cd							1.29 (0.98, 1.71)
OS							
ASPIRE CLd vs Ld 16 Jun 2014	32	143/396 (36.1%)	NE	162/396 (40.9%)	NE	NE	**0.79 (0.63, 0.99)**
ENDEAVOR Cd vs Bd 3 Jan 2017	37	189/464 (40.7%)	47.6 (42.5, NE)	209/465 (44.9%)	40.0 (32.6, 42.3)	7.6	**0.79 (0.65, 0.96)**
Indirect comparison CLd vs. Cd							0.99 (0.74, 1.34)

Source: Table 2.6.1, p87 of the resubmission

Bd = bortezomib and dexamethasone; Cd56 BIW = carfilzomib 56 mg/m^2 twice weekly and dexamethasone; CI = confidence interval; CLd = carfilzomib, lenalidomide, and dexamethasone; HR = hazard ratio; IRC = independent review committee; ITC = indirect treatment comparison; ITT = intention to treat; Ld = lenalidomide and dexamethasone; nNE = not estimable; OS = overall survival; PFS = progression free survival

a. IRC assessed; ITT definition of PFS

b. IRC generated; ITT population

c. Performed using the Bucher ITC method

Bold = statistically significant

6.25 The results of the ITC demonstrated that there were no statistically significant differences between CLd and Cd in terms of PFS or OS. The results of the ITC demonstrated a numerical advantage in PFS in favour of Cd relative to CLd (HR = 1.29; 95% CI: 0.98, 1.71). A numerical advantage in OS for CLd relative to Cd was not observed (HR = 0.99; 95% CI: 0.74, 1.34). A non-inferiority margin was not nominated by the resubmission.

Indirect treatment comparisons - CLd vs PBd and ELd

6.26 The results of the ITCs between CLd and PBd and Eld for the outcomes of PFS and OS are presented in Table 13. The ITC compared CLd to PBd assuming that the efficacy results for Ld and Bd were the same for the purposes of anchoring as a common comparator in the ITC. As noted in paragraphs 6.5 and 6.24, this required consideration as Ld and Bd are different treatment regimens. The common comparator in the comparison with ELd was Ld. The results of the ITCs for both PFS and OS were not statistically different.

Table 12: Summary of results of the indirect comparison for PFS and OS, between ASPIRE and OPTIMISMM

	Median duration of follow-up	CLd or PBd		Ld or Bd		Difference in median, months	HR[c] (95% CI)
		Events n/N (%)	Median, months (95% CI)	Events n/N (%)	Median, months (95% CI)		
PFS							
ASPIRE CLd vs Ld 16 Jun 2014[a]	31	207/396 (52.3%)	26.3 (23.3, 30.5)	224/396 (56.6%)	17.6 (15.0, 20.6)	8.7	**0.69 (0.57, 0.83)**
OPTIMISMM PBd vs Bd 26 Oct 2017[b]	15.9	154/281 (54.8%)	11.2 (9.66, 13.73)	162/278 (58.3%)	7.1 (5.88, 8.48)	4.1	**0.61 (0.49, 0.77)**
ELOQUENT-2 ELd vs Ld 29 Oct 2014[b]	24.5	192/321 (59.8%)	18.5 (16.5,21.4)	231/325 (71.1%)	14.3 (12.0,16.0)	4.2	**0.68 (0.56, 0.83)**
Indirect comparison CLd vs. PBd							1.13 (0.84, 1.52)
Indirect comparison CLd vs. ELd							1.01 (0.77, 1.33)
OS							
ASPIRE CLd vs Ld 16 Jun 2014	32	143/396 (36.1%)	NE	162/396 (40.9%)	NE	NE	**0.79 (0.63, 0.99)**
OPTIMISMM PBd vs Bd 15 Sep 2018[b]	26.2	116/281 (41.3%)	40.5 (29.8, NE)	126/278 (45.3%)	30.5 (24.6, 35.9)	10.1	0.91 (0.70, 1.18)
ELOQUENT-2 ELd vs Ld 29 Oct 2015	38.7	136/321 (42.4%)	43.7 (40.3, NE)	159/321 (48.9%)	39.6 (33.3, NE)	4.1	**0.82 (0.68, 0.99)**
Indirect comparison CLd vs. PBd							0.86 (0.61, 1.22)
Indirect comparison CLd vs. ELd							1.02 (0.74, 1.41)

Source: Table 2.6.3, p93 of the resubmission

Bd = bortezomib and dexamethasone; CI = confidence interval; CLd = carfilzomib, lenalidomide and dexamethasone; ELd = elotuzumab, lenalidomide and dexamethasone; HR = hazard ratio; IRC = independent review committee; ITC = indirect treatment comparison; ITT = intention to treat; Ld = lenalidomide and dexamethasone; NE = not estimable; OS = overall survival; PBd = pomalidomide, bortezomib and dexamethasone; PFS = progression free survival

a. IRC assessed; ITT definition of PFS

b. IRC generated; ITT population

c. Performed using the Bucher ITC method

Bold = statistically significant

Comparative harms

CLd versus Ld (ASPIRE trial)

6.27 The summary of key safety outcomes from ASPIRE is presented in Table 14. Treatment with CLd was associated with more serious adverse events (AEs) and Grade 3-4 AEs compared to Ld.

Table 13: Summary of key adverse events in the ASPIRE (28 April 2017 data cut-off; median follow-up of 67 months).

	CLd n with event/N (%)	Ld n with event/N (%)	RR (95% CI)
Median treatment duration	**88 weeks**	**57 weeks**	
Patients with any AE	384/392 (98.0)	381/389 (97.9)	1.00 (0.98, 1.02)
Patients with Grade 3-4 AE	341/392 (87.0)	324/389 (83.3)	1.04 (0.99, 1.11)
Patients with SAE	256/392 (65.3)	221/389 (56.8)	1.15 (1.03, 1.28)
Patients with AE leading to discontinuation	131/392 (33.4)	118/389 (30.3)	1.10 (0.90, 1.35)
Deaths	45/392 (11.5)	42/389 (10.8)	1.06 (0.72, 1.58)
TEAEs ≥ Grade 3			
Neutropenia	122/392 (31.1)	107/389 (27.5)	1.13 (0.91, 1.41)
Anaemia	73/392 (18.6)	68/389 (17.5)	1.07 (0.79, 1.44)
Thrombocytopenia	66/392 (16.8)	51/389 (13.1)	1.28 (0.92, 1.80)
Pneumonia	63/392 (16.1)	47/389 (12.1)	1.33 (0.94, 1.89)
Hypokalaemia	41/392 (10.5)	23/389 (5.9)	1.77 (1.08, 2.89)
Hypertension	25/392 (6.4)	9/389 (2.3)	2.76 (1.30, 5.83)
Fatigue	32/392 (8.2)	26/389 (6.7)	1.22 (0.74, 2.01)
Diarrhoea	18/392 (4.6)	17/389 (4.4)	1.05 (0.55, 2.01)

Source: Table 2.5-10 p p68-69 of the resubmission, Table 2 p732 Siegel et al 2018

AE = adverse event; CI = confidence interval; CLd = carfilzomib, lenalidomide and dexamethasone; Ld = lenalidomide and dexamethasone; RR = relative risk; SAE = serious adverse event; TEAE = treatment emergent adverse event

6.28 The most frequently reported Grade 3-4 AEs in ASPIRE (CLd versus Ld) were neutropenia (31.1%, 27.5%), anaemia (18.6%, 17.5%), pneumonia (16.1%, 12.1%), thrombocytopenia (16.8%, 13.1%) and hypokalaemia (10.5%, 5.9%). However, no statistically significant differences were noted.

6.29 The resubmission included the costs of using growth-colony stimulating factors (G-CSF) for the treatment of neutropenia in the CMA. This was appropriate.

Cd versus Bd (ENDEAVOR trial)

6.30 The summary of AEs reported in ENDEAVOR is presented in Table 15. Treatment with Cd was associated with more Grade ≥ 3 and serious AEs compared to Bd.

Table 15: Summary of safety outcomes from ENDEAVOR (3 January 2017 data cut-off; follow up 37 months)

	Cd n with event/N (%)	Bd n with event/N (%)	RR (95% CI)
Median treatment duration	**48 weeks**	**27 weeks**	
Patients with any AE	457/463 (98.7)	451/456 (98.9)	1.00 (0.98, 1.01)
Patients with Grade 3+ AE	377/463 (81.4)	324/456 (71.1)	1.15 (1.07, 1.24)
Patients with SAE	273/463 (59.0)	182/456 (39.9)	1.48 (1.29, 1.69)
Patients with AE leading to discontinuation	133/463 (28.7)	118/456 (25.9)	1.11 (0.90, 1.37)
Patients with AE leading to death	32/463 (6.9)	21/456 (4.6)	1.50 (0.88, 2.56)
TEAEs ≥ Grade 3			
Neutropenia	11/463 (2.4)	10/456 (2.2)	1.08 (0.46, 2.53)
Anaemia	76/463 (16.4)	46/456 (10.1)	1.63 (1.16, 2.29)
Thrombocytopenia	41/463 (8.9)	43/456 (9.4)	0.94 (0.62, 1.41)
Pneumonia	42/463 (9.1)	39/456 (8.6)	1.06 (0.70, 1.61)
Hypokalaemia	11/463 (2.4)	17/456 (3.7)	0.64 (0.30, 1.35)
Hypertension	67/463 (14.5)	15/456 (3.3)	4.40 (2.55, 7.58)
Fatigue	31/463 (6.7)	35/456 (7.7)	0.87 (0.55, 1.39)

Source: Table 2.5-10 pp68-69, Table 2.5-13 p74-75 of the resubmission

AE = adverse events; Bd = bortezomib and dexamethasone; CI = confidence interval; Cd = carfilzomib and dexamethasone; RR = relative risk; SAE = serious adverse event; TEAE = treatment emergent adverse event

6.31 The most frequently reported Grade ≥ 3 AEs in ENDEAVOR were anaemia, hypertension, and pneumonia. All were observed at a higher frequency in the Cd arm compared to the Bd arm.

6.32 At the latest data-cut (19 July 2017), AEs (all grades) of special interest which occurred in a higher proportion of patients in the Cd arm compared with Bd included: hypertension (32.4% vs. 10.1%), cardiac failure (11.0% vs. 3.5%); acute renal failure (10.8% vs. 6.4%) and infections and infestations (79.5% vs. 70.0%). Peripheral neuropathy was more common in the Bd arm compared with Cd (54.6% vs. 21.0%).

6.33 The PBAC has previously accepted that Cd has a different safety profile compared with Bd (paragraph 7.7, carfilzomib PSD, November 2016 and paragraph 6.13, carfilzomib PSD, July 2017). The PBAC has also noted that based on the 3rd Jan 2017 data cut-off, the clinical data indicate a reduction in the rates of peripheral neuropathy, but an increase in serious cardiovascular AEs for Cd compared to Bd (paragraph 7.4, carfilzomib PSD, July 2017). This was supported by the data from the 19th July 2017 cut-off.

<u>Safety naïve ITC - CLd vs Cd, PBd and ELd</u>

6.34 The resubmission presented a naïve indirect comparison of safety outcomes between CLd and Cd, ELd and PBd (Table 16). It should be noted that the median duration of treatment differed between the trials. The ESC considered that the comparisons may bias against CLd due to the longer duration of exposure, and hence potential to accumulate more toxicity events within ASPIRE.

Table 16: Naïve comparison of safety outcomes in CLd (ASPIRE) and Cd (ENDEAVOR)

	ASPIRE	ENDEAVOR	ELOQUENT-2	OPTIMISMM
Treatment arm	**CLd (N=392)**	**Cd56 BIW (N=463)**	**ELd (N=318)**	**PBd (N=278)**
Data-cut	**28 April 2017**	**3 Jan 2017**	**3 Oct 2018**	**26 Oct 2017**
Median duration of treatment in respective treatment arm	**88 weeks**	**48 weeks**	**73 weeks**	**38 weeks**
Any TEAE, n (%)	384 (98.0)	457 (98.7)	316 (99.4)	NR
≥ Grade 3	341 (87.0)	377 (81.4)	244 (76.7)	NR
SAE	256 (65.3)	273 (59.0)	238 (74.8)	159 (57.2)
TEAE leading to discontinuation of study drug	131 (33.4)	133 (28.7)	114 (35.8)	66 (23.7)
TEAE leading to death	45 (11.5)	32 (6.9)	45 (14.2)	27 (9.7)
TEAEs ≥ Grade 3, n (%)				
Neutropenia	122 (31.1)	11 (2.4)	115 (36)	116 (42)
Anaemia	73 (18.6)	76 (16.4)	64 (20)	38 (14)
Thrombocytopenia	66 (16.8)	41 (8.9)	67 (21)	76 (27)
Pneumonia	63 (16.1)	42 (9.1)	45 (14)	32 (11)
Hypokalaemia	41 (10.5)	11 (2.4)	NR	17 (6)
Hypertension	25 (6.4)	67 (14.5)	NR	8 (3)
Lymphocytopenia	NR	NR	250 (79)	NR
Infections	NR	NR	105 (33)	2 (<1)
Fatigue	32 (8.2)	31 (6.7)	32 (10)	23 (8)
Hyperglycaemia	NR	22 (4.8)	NR	25 (10)
Diarrhoea	18 (4.6)	NR	18 (6)	20 (7)

Source: Table 2.5.10 p70, Table 2.5.11 p71, Table 2.5.12 p72-73, Table 2.5-13 p74-75; Table 2.5-16 p82 of the resubmission, Table 8-5 carfilzomib abbreviated CSR April 2017; Table 1 p4037, Dimopoulos et al., 2018; Supplementary Table 4 p12, Table 2 p732 Siegel et al 2018; Table 3 p289 Richardson et al., 2019

Cd56 BIW = carfilzomib 56 mg/m^2 twice weekly and dexamethasone; CLd = carfilzomib, lenalidomide, and dexamethasone; ELd = elotuzumab, lenalidomide, and dexamethasone; NR = not reported; PBd = pomalidomide, bortezomib, and dexamethasone; SAE = serious adverse event; TEAE = treatment emergent adverse event

6.35 The proportion of patients experience events was similar across the CLd and Cd arms in terms of patients experiencing at least one AE (98% vs. 98.7%); serious AE (65.3% vs. 59.0%); Grade 3 AE (87% vs. 81.4%) and AE leading to discontinuation (33.4% vs 28.7%). Similar rate of discontinuations may suggest that the AE profile of CLd was manageable.

6.36 The reported Grade 3-4 AEs that occurred in a higher proportion of CLd patients compared with Cd patients (≥ 5% difference in either treatment arm) were: neutropenia (31.1% vs 2.4%); pneumonia (16.1% vs. 9.1%) and hypokalaemia (10.5% vs. 2.4%). Conversely, the following Grade 3-4 AEs were reported in a higher proportion of Cd patients compared with CLd patients (≥ 5% difference in either treatment arm): hypertension (14.5% vs 5.4%).

6.37 The proportions were similar across the CLd and PBd arms in terms of the incidence of patients experiencing serious AE (65.3% vs. 57.2%) and AE leading to death (11.5% vs. 9.7%). However, the incidence of AE leading to discontinuation was higher in CLd (33.4% vs 23.7%) which may suggest that the AE profile of CLd was less manageable compared to PBd.

6.38 The reported Grade 3-4 AEs that occurred in a higher proportion of CLd patients compared with PBd patients were anaemia (18.6% vs. 14%), pneumonia (16.1% vs. 12%) and hypokalaemia (10.5% vs. 6%). Conversely, the following Grade 3-4 AEs were reported in a higher proportion of (≥ 5% difference in either treatment arm) in PBd patients compared with CLd patients was neutropenia (42% vs. 31.1%) and thrombocytopenia (27% vs. 16.8%).

6.39 The proportions were similar across the CLd and ELd arms in terms of the incidence of patients experiencing at least one AE (98% vs. 99.4%); serious AE (65.3% vs. 74.8%); and AE leading to discontinuation (33.4% vs 35.8%). However, the incidence of Grade 3 AE (87% vs. 76.7%) was higher for ELd. The reported Grade 3-4 AEs that occurred in ELd patients was lymphocytopenia (79%).

Benefits/harms

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

Clinical claim

Indirect treatment comparison - CLd vs Cd

6.41 On the basis of the ITC, the resubmission claimed that CLd was non-inferior in terms of effectiveness compared to Cd.

6.42 The ESC considered that the clinical claim in terms of comparative effectiveness was likely supported, noting that there were uncertainties relating to:

- The results from the ITCs for both PFS and OS. The lack of a statistically significant difference did not adequately establish non-inferiority. This would have required that the confidence limits of the difference in treatment effect do not include an a priori stated clinically meaningful difference favouring the comparator (PBAC Guidelines, Section 2.4.5, p39). In addition, PFS was numerically in favour of Cd (HR > 1);
- The potential transitivity issues between the ASPIRE and ENDEAVOR trials which may have affected their comparability (see paragraphs 6.10 to 6.13); and
- The assumption that Ld and Bd were the same in terms of efficacy and could be used as a common comparator may not have been appropriate (see paragraphs 6.5 and 6.24).

6.43 The resubmission claimed, based on a naïve ITC, that CLd has a different, yet non-inferior, safety profile relative to Cd. The ESC considered that this claim was likely supported, noting that the durations of follow-up differed between the trials and may have favoured Cd. The ESC noted that CLd resulted in a higher frequency of Grade 3-4 AEs (87.0% vs. 81.4%) compared to Cd and ESC considered that the higher occurrence of neutropenia (31% vs 2.4%) was of particular concern given that 30% of

CLd patients were receiving G-CSF concomitant medication in ASPIRE. The neutropenia was accounted for in the economic evaluation and financial estimates.

Indirect treatment comparisons - CLd vs PBd and ELd

6.44 On the basis of the ITC, the resubmission claimed that CLd was non-inferior in terms of effectiveness compared to PBd. The results of the ITC for both PFS and OS were not statistically significantly different. The clinical claim was uncertain due to the lack of a nominated non-inferiority margin, potential transitivity issues between the ASPIRE and OPTIMISMM trials (see paragraphs 6.10 to 6.13) and as the assumption that Ld and Bd were the same in terms of efficacy and could be used as a common comparator may not have been appropriate (see paragraph 6.5).

6.45 On the basis of the ITC, the resubmission claimed that CLd was non-inferior in terms of effectiveness compared to ELd. The results of the ITC for both PFS and OS were not statistically significantly different. The clinical claim was uncertain due to the lack of a nominated non-inferiority margin and potential transitivity issues between the ASPIRE and ELOQUENT-2 trials (see paragraphs 6.10 to 6.13).

6.46 The resubmission claimed that on the basis of a naïve ITC that CLd has a non-inferior, but different, safety profile compared to PBd and ELd.

6.47 Regarding the secondary comparators, the ESC considered that the resubmission's claims that CLd was non-inferior to both PBd and ELd in terms of effectiveness and safety, were likely to be supported by the data presented, noting that there were some uncertainties relating to the lack of a non-inferiority margin and transitivity issues between the trials.

6.48 The PBAC considered that the claims of non-inferior comparative effectiveness for the comparisons between CLd vs Cd, ELd and PBd and were reasonable and adequately supported by the data.

6.49 The PBAC considered that the claims of non-inferior comparative safety for the comparisons between CLd vs Cd, ELd and PBd and were reasonable and adequately supported by the data.

Economic analysis

6.50 The resubmission presented a CMA comparing CLd to Cd.

6.51 The CMA applied mean carfilzomib doses per infusion calculated using individual patient data (IPD) from ASPIRE (for CLd dosing), ENDEAVOR (for twice weekly (BIW) Cd dosing) and ARROW (for once weekly (QW) Cd dosing). To account for wastage, the doses were rounded up to the nearest 10 mg. The CMA applied a mean relative dose intensity (RDI) for lenalidomide calculated using IPD from ASPIRE. The IPD analysis from the ENDEAVOR and ARROW trials, from which the Cd mean doses per infusions were derived, were not provided in the resubmission. Based on the IPD analysis supplied with the PSCR, the dose intensity (DI) data applied in the calculation of the

equi-effective doses of BIW Cd (ENDEAVOR trial) could be verified. However, the IPD data from ARROW, which informed the use of the QW Cd regimen, were not included in the analysis supplied by the PSCR and therefore could not be verified. The calculated doses are summarised in Table 17.

6.52 The number of infusions per course of treatment for Cd was calculated using PBS data for July and August 2021, resulting in a weighted average of Cd QW (55%) and Cd BIW (45%) regimens.

6.53 The resubmission did not include dexamethasone in the calculation of equi-effective dose for CLd and Cd.

6.54 The resultant equi-effective doses per course of treatment (15 cycles), as estimated by the resubmission, were:

4,478 mg carfilzomib + 6,213 mg lenalidomide (given as CLd) =

9,076 mg carfilzomib BIW (given as Cd) OR 5,603 mg carfilzomib QW (given as Cd)

6.55 The resubmission presented the CMA based on the mean treatment duration of 15 cycles from ENDEAVOR for Cd (equivalent to 62.53 weeks/13.8 months) – see Table 18. This was consistent with the | cap applied in the current risk sharing arrangement (RSA) for carfilzomib; however, differed from the maximum treatment duration of carfilzomib in ASPIRE which was 18 cycles and the treatment duration applied in the November 2020 submission for the QW Cd regimen of 13.3 cycles. The PSCR stated that the treatment duration of 15 cycles assumed in the base case was appropriate, referencing a Kaplan-Meier analysis of PBS utilisation data provided by the DUSC Secretariat that indicated a mean treatment time of 339.9 days for carfilzomib (equivalent to 12.1 x 28-day cycles, or 11.2 months). Sensitivity analyses revealed reductions in the calculated price of carfilzomib when shorter durations of Cd were assumed.

6.56 The resubmission included additional costs associated with differences in the administration of CLd and Cd and management of AEs. The cost of AE management was based on the incidence of neutropenia in CLd in ASPIRE with the effective price for pegfilgrastim ($346.39/dose) applied in 15% of cycles.

6.57 The CMA presented by the resubmission was based on the effective AEMP for carfilzomib. The effective price of lenalidomide was not known to the sponsor and was estimated based on the dispensed price per maximum quantity (DPMQ) adjusted to an estimated 55% rebate in the resubmission. The resubmission stated that the rebate applied to lenalidomide was derived based on the effective price for bortezomib in August 2017 disclosed to the sponsor, and further adjusted to accommodate the 10% price reduction offered by the sponsor of lenalidomide (paragraph 5.18, elotuzumab PSD, July 2021) and the expected 25% F2 price reduction in 2022.

6.58 The 10% price reduction applied to the estimated effective price of lenalidomide in CLd was consistent with the price rebate offered by the sponsor in elotuzumab

resubmission (paragraph 5.18, elotuzumab PSD, July 2021). However, the 10% price reduction proposed by the elotuzumab sponsor was specific to the use of lenalidomide in combination with elotuzumab. Moreover, elotuzumab was not PBS listed at the time of PBAC consideration.

Table 17: Input parameters of the cost-minimisation model applied in the resubmission

Parameter	Base case	Source
Proportion of Cd patients using the weekly regimen	0.55	PBS data July and August 2021
Known or assumed rebates for: Carfilzomib in Cd (twice weekly) Carfilzomib in Cd (weekly) Lenalidomide	 0.[redacted] 0.[redacted] 0.55	 Carfilzomib SPA Estimated from pricing history
Mean duration of a course of treatment (28-day cycles)	15 cycles	Mean treatment duration in ENDEAVOR
Cd regimen twice weekly, 28-day cycles 2 infusions at 20 mg/m^2 Cycle 1 only 88 infusions at 56 mg/m^2	 41.2 mg 102.2 mg	 ENDEAVOR IPD; 15 cycles at 6 doses per cycle
Cd regimen once weekly, 28-day cycles 1 infusion at 20 mg/m^2 Cycle 1 only 44 infusions at 70 mg/m^2	 41.2 mg 126.4 mg	 ARROW IPD; 15 cycles at 3 doses per cycle
CLd regimen, carfilzomib 2 infusions at 20 mg/m^2 Cycle 1 only 70 infusions (after Day 2; 27 mg/m^2; 6/cycle) 12 infusions (after Cycle 12; 27 mg/m^2; 4/cycle)	 41.2 mg 53.6 mg 53.6 mg	 ENDEAVOR ASPIRE ASPIRE
CLd regimen, lenalidomide 28-day cycles of 21 x 25 mg tablets Relative dose intensity	 0.789	 ASPIRE / Product Information ASPIRE
Cost for treating Grade ≥ 3 neutropenia (CLd) Patients Cycles Cost per treatment (pegfilgrastim)	 30% 15% of 15 $346.39	 ASPIRE ASPIRE PBS AEMP Oct 21
Cost per infusion	$112.40	MBS item 13950

Source: Table 3.4.1, pp106 of the resubmission

AEMP = approved ex-manufacturer price; Cd = carfilzomib and dexamethasone; CLd = carfilzomib, lenalidomide and dexamethasone; IPD = individual patient data; MBS = Medicare Benefits Schedule; PBS = Pharmaceutical Benefit Scheme; SPA = special pricing arrangement

Table 18: Estimated cost-minimised price of carfilzomib presented in the resubmission

Parameter	Inputs	Source/calculation
Total amount of carfilzomib (Cd twice weekly)	9,076 mg	Sum product of infusions and doses
Total amount of carfilzomib (Cd once weekly)	5,603 mg	Sum product of infusions and doses
CLd regimen, total amount of carfilzomib	4,478 mg	Sum product of infusions and doses
CLd regimen, total amount of lenalidomide	6,213 mg	15 x 21 x 25 mg x 0.789
Cost for treating Grade ≥ 3 neutropenia (CLd)	$233.81	30% x 15% x 15 cycles x $346.39
Cost for infusions Cd BIW, 90 infusions Cd QW, 45 infusions CLd, 84 infusions	 $10,116 $5,058 $9,442	 90 x $112.40 45 x $112.40 84 x $112.40
Cost of Cd Cd BIW (including [redacted]% rebate) Cd QW (including [redacted]% rebate)	 $[redacted] $[redacted]	 9,076 mg x $[redacted]/mg + $10,116 6,197 mg x $[redacted]/mg + $5,058
Weighted cost of Cd QW or BIW	$[redacted]	Costs above with weighting by infusions (0.55 QW)
Cost minimised treatment course cost of CLd Lenalidomide Infusions Adverse events Remaining for carfilzomib Cost per mg SPA (Rebate on published price of carfilzomib)	$98,404 $31,575 $9,442 $234 $[redacted] $[redacted] [redacted]%	 $70,167 x [redacted]% rebate 84 x $112.40 $346.39 x [redacted]% x [redacted]% Subtraction from total cost $[redacted] / 4,478 mg Rebate vs. $21.15/mg

Source: Table 3.4-2, p107-108 of the resubmission

BIW = twice weekly; Cd = carfilzomib and dexamethasone; CLd = carfilzomib, lenalidomide and dexamethasone; QW = once weekly; SPA = special pricing arrangement

6.59 The results of sensitivity analyses are presented in Table 19.

Table 19: Sensitivity analyses

Analyses	Price per course of treatment	Change from base case
Base case (DOT = 15 cycles; Cd 55% QW and 45% BIW)	**$**	-
Lenalidomide	$31,575	-
Remaining for carfilzomib	$	-
Carfilzomib price per mg	$	-
SPA (estimated rebate on published price)	%	-
DOT = 12 cycles (based on the November 2016 submission)	**$**	**-20%**
Lenalidomide	$	-20%
Remaining for carfilzomib	$	-21%
Carfilzomib price per mg	$	-8%
SPA (estimated rebate on published price)	45%	5%
DOT = 18 cycles (maximum permitted in ASPIRE)	**$**	**20%**
Lenalidomide	$37,890	20%
Remaining for carfilzomib	$	21%
Carfilzomib price per mg	$	6%
SPA (estimated rebate on published price)	36%	-4%
CLd vs Cd 100% QW	**$**	**-23%**
Lenalidomide	$31,575	0%
Remaining for carfilzomib	$	-39%
Carfilzomib price per mg	$	-39%
SPA (estimated rebate on published price)	63%	58%
CLd vs Cd 100% BIW	**$**	**27%**
Lenalidomide	$31,575	0%
Remaining for carfilzomib	$	47%
Carfilzomib price per mg	$	47%
SPA (estimated rebate on published price)	11%	-73%
Revised pre-PBAC case case (DOT = 15 cycles; Cd 60% QW and 40% BIW)	**$**	**-3%**
Lenalidomide	$31,575	0%
Remaining for carfilzomib	$	-5%
Carfilzomib price per mg	$	-5%
SPA (estimated rebate on published price)	42%	5%

Source: Prepared by the Commentary during the evaluation and during preparation of the ESC ADV
BIW = twice weekly; Cd = carfilzomib and dexamethasone; CLd = carfilzomib, lenalidomide and dexamethasone; DOT = duration of treatment; QW = once weekly; SPA = special pricing arrangement

6.60 The ESC noted the cost-minimised price of carfilzomib when used as CLd was substantially different when based on the comparison with Cd QW ($ per mg) versus Cd BIW ($ per mg). The ESC noted the reasons for this large difference were not clear, but considered that the difference may in part be due to:

- The proposed equi-effective doses for the BIW and QW Cd regimens (9,076 mg: 5,603 mg = 1.62 mg: 1mg) being different to those previously accepted by the PBAC (7,278 mg: 4,969 mg = 1.46 mg: 1 mg). The doses applied for carfilzomib in the Cd regimen were consistent with those applied in the July 2020 PBAC submission for the listing of the QW regimen (initial dose of 41.2 mg versus 40.6 in the July 2020 submission; 126.4 mg for subsequent QW dose in both current and July 2020 submissions; 102.2 mg versus 100.0 mg for subsequent BIW doses in the July 2020 submission). However, there was a difference in the number of

infusions in the current submission versus the July 2020 submission. The current submission assumed a total of 90 infusions for the BIW regimen (2 + 88) and 45 infusions for the QW regimen (1 + 44) (i.e. a ratio of 2:1) whereas the PBAC accepted equi-effective doses were based on a total of 74 infusions for the BIW regimen (2 + 72) and 40 infusions for the QW regimen (1 + 39) (i.e. a ratio of 1.85:1) (Table 5, carfilzomib PSD, July 2020).

- The current per mg price for carfilzomib price was applied for both the BIW and QW regimens; whereas, the cost-effective price for the BIW regimen is and the cost-effective price for the QW regimen is .

6.61 The ESC noted, given the large difference in price based on the comparison between Cd QW and Cd BIW, that the relative use of these regimens was a driver for the analysis. The ESC further noted the assumed 55% use of the QW regimen was inconsistent with the estimates included in the July 2020 submission (% in Year 1 increasing to % in Year 6; paragraph 5.16, carfilzomib PSD, July 2020).

6.62 The pre-PBAC response (p1) stated that when Cd QW was PBS listed a weighted average rebate was calculated assuming 60% Cd QW versus 40% Cd BIW. If 60% QW is assumed within the current submission, the rebate for carfilzomib in CLd would be %, compared with % in the submission's base case (see Table 19).

Drug cost/patient/course

6.63 Applying the equi-effective doses estimated in the resubmission, the cost of CLd per course, based on the CMA, was estimated to be $, with the cost of carfilzomib equal to $ and the cost of lenalidomide equal to $31,575. The cost minimised price for CLd per course of treatment was based on an estimated effective AEMP for carfilzomib of $/mg and of $11.29/mg for lenalidomide (as estimated in the resubmission).

Table 140: Drug cost per patient for proposed and comparator drugs

	CLd			Cd		
	Trial dose and duration	**CMA**	**Financial estimates**	**Trial dose and duration**	**CMA**	**Financial estimates**
Mean dose	Carf: 41.20 mg[a]; 53.6mg[b] Len: RDI 78.9%[c]	Carf: 41.20 mg[a]; 53.6mg[b] Len: RDI 78.9%[c]	Carf: 41.20 mg[a]; 53.6mg[b] Len: RDI 78.9%[c]	Carf QW: 41.2 mg; 126.4 mg Carf BIW: 41.2 mg; 102.2 mg	Carf QW: 41.2 mg[d]; 126.4 mg[e] Carf BIW: 41.2 mg[d]; 102.2 mg[e]	Carf QW: 41.2 mg[d]; 126.4 mg[e] Carf BIW: 41.2 mg[d]; 102.2 mg[e]
Frequency/ cycle	Carf: 20 mg/m^2 (Days 1 and 2 of Cycle 1) 27 mg/m^2 (after Day 2 of Cycle 1; 6/cycle); 27 mg/m^2 (after Cycle 12; 4/cycle) Len: 25 mg orally on Days 1 to 21 of 28 day cycles			Carf BIW: 20 mg/m^2 (Days 1 and 2 of Cycle 1) 56 mg/m^2 (after Day 2 of Cycle 1; 6/cycle) Carf QW: 20 mg/m^2 (Day 1 of C1;) 70 mg/m^2 (after Day 2 of Cycle 1; 3/cycle)		
Mean duration	18 cycles[f]	15 cycles	4.12 cycles/year	15 cycles	15 cycles	4.12 cycles/year
Cost/course[g]	CLd: $[redacted] Carf: $[redacted] Len: $37,890 Dex: NA	CLd: $[redacted] Carf: $[redacted] Len: $31,575 Dex: NA	CLd: $[redacted] Carf: $[redacted] Len: $8,673 Dex: NA	Cd: $[redacted] Carf: $[redacted] Dex: NA	Cd: $[redacted] Carf: $[redacted] Dex: NA	Cd: $[redacted] Carf: $[redacted] Dex: NA

Source: Compiled by the Commentary based on the resubmission

BIW = twice weekly; Carf = carfilzomib; Cd = carfilzomib and dexamethasone; CLd = carfilzomib, lenalidomide and dexamethasone CMA = cost minimisation approach; Dex = dexamethasone; IPD = individual patient data; Len = lenalidomide; NA = not applied; RDI = relative dose intensity; QW = once weekly

a. mg/infusion in Cycle 1 (Day 1 and 2) based on ASPIRE IPD data

b. mg/infusion in from Day 8, Cycle 1 onwards based on ASPIRE IPD data

c. 19.73 mg/infusion

d. mg/infusion in Cycle 1 (Days 1 and 2) based on ENDEAVOR IPD and ARROW IPD data

e. mg/infusion in Day 8, Cycle 1 onwards based on ENDEAVOR IPD and ARROW IPD data

f. In the CLd arm of ASPIRE, carfilzomib was administered for up to a maximum of 18 cycles, after which patients continued on lenalidomide and dexamethasone until disease progression or unacceptable toxicity.

g. Cost per year is presented for the financial estimates

Estimated PBS usage & financial implications

6.64 This resubmission was not considered by DUSC.

6.65 The resubmission also requested an increase to the RSA expenditure caps to accommodate the treatment regimens that have been cost minimised to Cd (PBd and ELd) and recommended by the PBAC to join the Cd RSA (see paragraphs 6.84 to 6.86).

6.66 The resubmission presented four scenarios for the financial estimates which included PBd, ELd and CLd:

1. Cd + PBd (current scenario);
2. Cd + PBd + ELd (ELd is anticipated to join the current carfilzomib expenditure cap as it received a positive PBAC recommendation at the July 2021 PBAC meeting. The PBAC previously stated that it would be appropriate to include ELd in the RSA for carfilzomib (paragraph 6.11, elotuzumab PSD, July 2021);

3. Cd + PBd + CLd (scenario reflecting the current scenario plus the requested CLd listing);
4. Cd + PBd + ELd + CLd (base case presented by the resubmission).

6.67 The resubmission presented a mixed model approach combining epidemiology and market share data to estimate the financial implications of the proposed listing. The evaluation considered this approach was reasonable given that the resubmission was requesting a change to the current RSA caps, although a market share approach would usually be more appropriate for submissions presenting a CMA. The PBAC noted the net costs associated with listing CLd were not separately provided in the resubmission.

6.68 The estimated CLd eligible population was based on historical prevalence data (100% PBS data supplied by the DUSC Secretariat from 2016-2021) of carfilzomib.

6.69 The estimated treatment durations of CLd and Cd were assumed to be equal and were based on the mean number of Cd scripts utilised in the period between 2018-2020 (DUSC Secretariat data). The mean number of scripts derived from 100% PBS utilisation data was based on Cd BIW administration only. However, the resubmission adjusted the financial estimates and the CMA to the proportion of Cd QW (55%) and Cd BIW (45%). The CLd regimen is currently only available BIW (a QW CLd regimen is being evaluated in the ARROW2 clinical study due for completion in 2023 (NCT03859427)). The equi-effective doses of CLd and Cd were based on ASPIRE, ARROW and ENDEAVOR as presented in the CMA. The treatment duration applied in the financial estimates (4.12 cycles per patient per year) could not be easily compared to the duration applied in the CMA (total of 15 cycles).

6.70 The estimated market share of CLd was adjusted to reflect the utilisation of DBd in the second-line setting (first line RRMM setting) and substitution from Cd and Ld. The ESC considered that CLd was likely to be used in patients currently receiving Ld or Cd.

6.71 The resubmission estimated the market share of DBd based on the PBAC recommendation indicating a linear increase of 50% in Year 1 to 90% uptake in Year 6 (paragraph 7.15, daratumumab PSD, November 2019) which translated to a 12.5% annual increase in the uptake. Based on 10% PBS data for April 2021, the resubmission estimated that the market share of DBd in the second-line setting was 35%. The market share of treatments that were initially listed to be used in patients that had progressed after at least one prior therapy (e.g. Cd), would have likely reduced following the listing of DBd. As patients progress, they are less likely to be treated with a subsequent line. Overall, the listing of DBd is expected to displace the use of therapies such as Cd, PBd, ELd and CLd to the third-line setting.

6.72 The resubmission assumed that CLd would substitute for 20% of Cd use, 20% of Ld use and 20% of ELd use. The proposed substitution rates were not justified in the resubmission. It was expected that, as the requested maximum quantity of carfilzomib

in CLd is lower than in Cd (60 mg vs 120 mg, respectively), the PBS listing of CLd would result in a reduction in the utilisation of carfilzomib.

6.73 The key inputs for the financial estimates are presented in Table 21.

Table 151: Key inputs for financial estimates

Parameter	Value applied and source	Comment
Eligible patients	Year 1: 581 to Year 6: 1,014 Estimated based on prevalent number of RRMM patients based on DUSC Secretariat utilisation data (2016-2021) and extrapolated based on forecast change in number of patients treated with the relevant medicines (Cd, PBd, ELd and CLd) and their substitution rates.	-
Assumed substitution to CLd	Cd: 20% Ld: 20% ELd: 20%	The proposed substitution rates were not justified in the resubmission, the uptake may be higher or lower.
Assumed maximum rates of substitution for Cd, Ld and ELd to CLd	65% (Year 1) – 85% (Year 2)	
Assumed substitution to PBd	Bd: 5% Pd: 60% Ld: 15% Cd:15%	
Assumed substitution to ELd	Ld: 30% Cd:15%	
Market growth	5.7% (Year 1) – 3.0% (Year 6); based on DUSC Secretariat utilisation data	-
Patients treated with CLd	Year 1: 581 to Year 6: 1,014	The estimated number of patients eligible for treatment with CLd is uncertain as the resubmission applied assumed substitution rates between the therapies.
DOT	4.12 cycles per year for both CLd and Cd. Based on mean number of scripts in using DUSC Secretariat utilisation data (2018-2020) (24.7= 16.47 weeks)	Equal DOTs across regimens was consistent with the assumption in the CMA.
Scripts per course of treatment	Based on DUSC Secretariat data (100% PBS data). CLd Carf = 24.7, Len = 4.12 Cd Carf BIW = 24.7 Carf QW = 12.35 PBd = 5.5 ELd = 12.24	-
Carfilzomib	Carfilzomib 60mg - Published: $1,268.94 Effective: $[redacted]	The drug price was consistent with the CMA.
Other medicine included in therapy	Lenalidomide 25 mg - Published: $5,928.74 Effective: $2,667.93 (estimated by sponsor)	Effective AEMP price for lenalidomide was calculated based on an estimated 55% rebate. This was also applied in the CMA.
Comparator	Carfilzomib (120mg) - Published: $2,537.88 Effective: $[redacted] Carfilzomib (160mg) - Published: $3,383.84 Effective: $[redacted]	The split between the carfilzomib QW and BIW administration was 55% and 45%, respectively. This is inconsistent with the estimates included in the July 2020 PBAC submission for QW Cd ([redacted]% increasing to [redacted]%).
MBS items	MBS Item 13950 (parenteral administration of one or more antineoplastic agents, which is used for infusion of carfilzomib and elotuzumab): $112.40	MBS Item was appropriate.

Source: Compiled by the Commentary based on the resubmission
AEMP = approved ex-manufacturer price; Bd = bortezomib and dexamethasone; BIW = twice weekly; Carf = carfilzomib; Cd = carfilzomib and dexamethasone; CLd = carfilzomib, lenalidomide and dexamethasone; CMA = cost minimisation approach; DOT = duration of treatment; DUSC = Drug Utilisation Sub Committee; ELd = elotuzumab, lenalidomide and dexamethasone; Ld = lenalidomide and dexamethasone; Len = lenalidomide; MBS = Medicare Benefits Schedule; PBd = pomalidomide, lenalidomide and dexamethasone; PBS = Pharmaceutical Benefits Scheme; Pd = pomalidomide and dexamethasone; QW = once weekly; RRMM = relapsed and/or refractory multiple myeloma

6.74 The resubmission claimed that the emergence of triplet combinations will continue to replace doublet combinations (i.e. Bd, Ld, Pd, and Cd). The ESC considered this was reasonable and consistent with the NCCN International Guidelines for MM that recommend triplet regimens as standard therapy in patients with MM.

6.75 The resubmission estimated the prevalent patient lines of treatment based on PBS utilisation data provided by the DUSC Secretariat. The prevalent patient lines of treatment were then extrapolated over six years with the average growth rate for 2016 to 2020 of 5.7% being applied to 2021 together with a 10% reduction in the growth rate for each subsequent year. The market share of each RRMM treatment regimen was forecasted based on assumed substitution within the market. The estimated overall market share of therapies proposed to be included in the carfilzomib expenditure caps (Cd, PBd, ELd, CLd) was 40.8% in Year 1, increasing to 48.4% in Year 6 of listing (Table 162).

6.76 PBd is currently the only PBS-listed treatment added to the carfilzomib RSA (PBd was PBS listed 1 October 2021). The inclusion of ELd was recommended by the PBAC in July 2021; however, the listing has not yet occurred. The listing of DBd in the first line RRMM setting was based on cost-effectiveness analysis versus Bd and it is therefore not included in the current carfilzomib RSA.

Table 162: Current and projected market share of RRMM prevalent lines of treatment 2021 to 2027

RRMM treatment	2021	2022 Year 1	2023 Year 2	2024 Year 3	2025 Year 4	2026 Year 5	2027 Year 6
Thalidomide	3.2%	1.5%	0.4%	0	0	0	0
Bortezomib	5.7%	4.9%	3.7%	3.0%	3.0%	3.0%	3.0%
Lenalidomide	44.2%	24.7%	18.7%	14.5%	14.0%	13.4%	13.4%
Pomalidomide	15.1%	8.4%	6.3%	5.1%	4.6%	4.0%	4.0%
Daratumumab as DBd	13.2%	19.7%	22.1%	24.9%	28.0%	31.5%	31.5%
Carfilzomib as Cd	18.6%	11.7%	9.6%	8.3%	7.8%	7.2%	7.2%
Pomalidomide as PBd	-	11.4%	14.8%	17.8%	17.3%	16.7%	16.7%
Elotuzumab as ELd	-	8.3%	12.1%	11.9%	11.4%	10.8%	10.8%
Carfilzomib as CLd	-	9.4%	12.3%	14.8%	14.3%	13.7%	13.7%
Resubmission's estimated proportion of market to be to be included in carfilzomib caps (Cd + PBd + ELd + CLd)	18.6%	40.8%	48.8%	52.8%	50.8%	48.4%	48.4%

Source: Table 4.2.5 p116 of the resubmission
Cd = carfilzomib and dexamethasone; CLd = carfilzomib, lenalidomide and dexamethasone; DBd = daratumumab, bortezomib and dexamethasone; ELd = elotuzumab, lenalidomide and dexamethasone; PBd = pomalidomide, bortezomib and dexamethasone; RRMM = relapsed and/or refractory multiple myeloma

6.77 A summary of the use and financial implications for the four scenario analyses as presented in the submission are presented in Table 23.

Table 23: Cost (minus patient co-payments) to the health budget (at known or assumed effective PBS prices)

	2022	2023	2024	2025	2026	2027
Scenario 1: Cd + PBd						
Estimated patients	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]
PBS/RPBS cost ($)	[redacted][2]	[redacted][5]	[redacted][5]	[redacted][5]	[redacted][5]	[redacted][5]
MBS cost ($)	[redacted][3]	[redacted][3]	[redacted][3]	[redacted][3]	[redacted][3]	[redacted][3]
Total ($)	$[redacted][2]	$[redacted][5]	$[redacted][5]	$[redacted][5]	$[redacted][4]	$[redacted][4]
Scenario 2: Cd + PBd + ELd						
Estimated patients	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]
PBS/RPBS cost ($)	$[redacted][4]	$[redacted][6]	$[redacted][7]	$[redacted][6]	$[redacted][6]	$[redacted][7]
MBS cost ($)	[redacted][3]	[redacted][3]	[redacted][3]	[redacted][3]	[redacted][3]	[redacted][3]
Total ($)	$[redacted][4]	$[redacted][6]	$[redacted][7]	$[redacted][7]	$[redacted][7]	$[redacted][7]
Scenario 3: Cd + PBd + CLd						
Estimated patients	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]
PBS/RPBS cost ($)	$[redacted][5]	$[redacted][4]	$[redacted][4]	$[redacted][4]	$[redacted][4]	$[redacted][4]
MBS cost ($)	[redacted][3]	[redacted][3]	[redacted][3]	[redacted][3]	[redacted][3]	[redacted][3]
Total ($)	$[redacted][5]	$[redacted][4]	$[redacted][4]	$[redacted][4]	$[redacted][4]	$[redacted][4]
Scenario 4: Cd + PBd + ELd + CLd (resubmission's base case)						
Estimated patients	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]
PBS/RPBS cost ($)	$[redacted][6]	$[redacted][7]	$[redacted][8]	$[redacted][8]	$[redacted][8]	$[redacted][8]
MBS cost ($)	[redacted][3]	[redacted][3]	[redacted][3]	[redacted][3]	[redacted][3]	[redacted][3]
Total ($)	$[redacted][6]	$[redacted][8]	$[redacted][8]	$[redacted][8]	$[redacted][8]	$[redacted][8]

Source: Table 4.5.4 p130-131 of the resubmission, Section 4 workbook 2b. Patient-prevalent,
Cd = carfilzomib and dexamethasone; CLd = carfilzomib, lenalidomide and dexamethasone; ELd = elotuzumab, lenalidomide and dexamethasone; MBS = Medicare Benefits Schedule; PBd = pomalidomide, lenalidomide and dexamethasone; PBS = Pharmaceutical Benefits Scheme; RPBS = Repatriation Pharmaceutical Benefits Scheme

The redacted values correspond to the following ranges:
[1]500 <5,000
[2]$30 million to < $40 million
[3]$0 to < $10 million
[4]$50 million to < $60 million
[5]$40 million to < $50 million
[6]$60 million to < $70 million
[7]$70 million to < $80 million
[8]$80 million to < $90 million

6.78 The resubmission estimated the cost to the PBS/RPBS in the base case scenario, which assumed the PBS listings of Cd, PBd, ELd and CLd, was $60 million to < $70 million in Year 1 increasing to $80 million to < $90 million in Year 6. The estimated cost to the PBS/RPBS in the in the scenario in which Cd, PBd and CLd are listed, was $40 million to < $50 million in Year 1 increasing to $50 million to < $60 million in Year 6.

6.79 The resubmission stated that the increase in the estimated net cost to the PBS/RPBS over six years could be explained by the greater use of triple therapies, enabled by the listing of PBd (and potentially ELd and CLd), which will result in shifting the utilisation of Pd to PBd (and from Ld to ELd and Cd/Ld to CLd).

6.80 The resubmission acknowledged the uncertainties associated with the substitution rates between the therapies, proportion of market share in first and second line

RRMM setting, market growth rate, duration of treatments, number of therapies listed in the second line RRMM setting and proportion of weekly dosing of Cd.

6.81 An estimate of the net cost of listing CLd on the PBS/RPBS was not included in the resubmission. An approximation of the costs was estimated during evaluation based on the total net cost for the base case scenario (listing of Cd, PBd, ELd and CLd) and the market share for CLd. It was estimated that the net cost would be approximately $0 to < $10 million in Year 1, increasing to approximately $10 million to < $20 million in Year 3 and subsequent years.

6.82 The PSCR stated that the cost of the CLd listing, including cost offsets, could be determined from the Excel model using the cost of carfilzomib and lenalidomide in CLd for the current scenario (Scenario 3, Cd, PBd and CLd listed). For the cost offsets, PBd was estimated to substitute 15% of Ld and CLd was estimated to substitute 20% of Ld; therefore, the lenalidomide cost offsets attributed to CLd (20% of 35%) could be determined. Compared with the approach taken during the evaluation, this approach resulted in a similar net cost to PBS/RPBS for the CLd listing in Year 1 but lower estimates in Years 3 to 6 (Table 24). The sponsor's estimates included in the PSCR were not able to be verified. The PBAC noted these costs were based on the assumed effective prices utilised in the financial estimates and that the net cost to the PBS/RPBS will change once the confidential effective prices are applied.

Table 24: Net cost to PBS/RPBS for listing CLd as estimated in the PSCR at known or assumed effective PBS prices

	2022	2023	2024	2025	2026	2027
Net cost to PBS/RPBS estimated by the PSCR, reflects Scenario 3: Cd + PBd + CLd[a]						
C+L in CLd ($)	[1]	[1]	[2]	[2]	[2]	[2]
Cost offsets (C+L) ($)	[3]	[3]	[1]	[1]	[1]	[1]
Net cost to PBS/RPBS ($)	[3]	[3]	[1]	[3]	[3]	[3]

C=carfilzomib; L=lenalidomide; d=dexamethasone; PBd=pomalidomide + bortezomib + dexamethasone.

a. Costs from 'Results' worksheet referencing '3c. Impact - proposed (eff)'; lenalidomide offsets from sums of reduced lenalidomide codes in '4c. Impact - affected (eff)'

The redacted values correspond to the following ranges:
[1]$10 million to < $20 million
[2]$20 million to < $30 million
[3]$0 to < $10 million

Quality Use of Medicines

6.83 The resubmission did not identify any potential quality use of medicines issues. The PBAC previously stated that as different doses of carfilzomib are used in the Cd and CLd regimens (the carfilzomib dose in Cd regimen was 56 mg/m^2 while for the CLd regimen was 27 mg/m^2 for most cycles), this might potentially lead to inappropriate doses being given (paragraph 6.62, carfilzomib PSD, July 2016).

Financial Management – Risk Sharing Arrangements

6.84 An RSA was established at the time of carfilzomib listing in January 2018. At this time, the therapies available in the RRMM setting were doublet therapies (i.e. Bd, Ld, and Pd). The resubmission stated the expenditure caps for carfilzomib were intended to solely reflect Cd specific use and as such, represented a subset of the overall RRMM treatment algorithm (replacing Bd and to a lesser extent Ld) and it was assumed that separate expenditure caps would be recommended for separate therapies. Since then, the PBAC has recommended that PBd and ELd join the carfilzomib RSA (paragraph 5.34, pomalidomide PSD, November 2019; paragraph 5.31, elotuzumab PSD, July 2021). The PSCR (p3) noted that this assumes that the triplet therapies will only replace Cd, which will not be the case as ELd will likely replace some Ld use and PBd will likely replace some Bd use.

6.85 The resubmission stated that the use of Cd has been as high as approximately [redacted]% of the expenditure cap – see Table 25.

Table 25: Carfilzomib expenditure caps and net PBS/RPBS benefits

	2018	2019	2020	2021	2022
Expenditure Caps ($)	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]
Commonwealth Payments ($)	[redacted][2]	[redacted][2]	[redacted][2]	[redacted][2]	NA
% of expenditure cap	[redacted]				NA

Source: Table 4.1-1 p111 of the resubmission.
NA = not available; PBS = Pharmaceutical Benefits Schedule; RPBS = Repatriation Pharmaceutical Benefits Scheme

The redacted values correspond to the following ranges:
[1]$30 million to < $40 million
[2]$20 million to < $30 million

6.86 The ESC considered that although cost neutrality may not be realised in practice, the resubmission's request to increase the expenditure caps was not well supported, noting that (i) usage currently was at approximately [redacted]% of the expenditure cap; (ii) a lower dose of carfilzomib is used as part of CLd as compared with Cd; and (iii) carfilzomib is now likely to be used in the third and later line settings due to the listing of daratumumab in the second line setting. The ESC did note that there was little risk of leakage of RRMM treatments to other diseases or to other lines of therapy. The PBAC agreed with the ESC that these considerations are relevant.

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

7 PBAC Outcome

7.1 The PBAC recommended the listing of carfilzomib in combination with lenalidomide and dexamethasone (CLd) for the treatment of relapsed or refractory multiple myeloma (RRMM), on the basis that it should be available only under special arrangements under Section 100 (Efficient Funding of Chemotherapy). Listing was recommended on the basis of a cost-minimisation approach (CMA) versus carfilzomib

in combination with dexamethasone (Cd), and inclusion in the existing carfilzomib risk sharing arrangement (RSA) without an increase in the expenditure caps. The PBAC noted the resubmission also requested an increase in the expenditure caps established in the Deed of Agreement in place since carfilzomib was PBS listed in January 2018. The PBAC considered the estimates included in the resubmission were not a reliable basis on which to revise the existing RSA expenditure caps. However, the PBAC acknowledged that future revision to the caps may be appropriate given the changing treatment algorithm for multiple myeloma with the availability of multiple new therapies.

7.2 The PBAC noted and welcomed the input from consumers and organistions via the Consumer Comments facility which supported the CLd resubmission and described the desire for alternate RRMM therapies.

7.3 Noting that daratumumab in combination with bortezomib and dexamethasone (DBd) is PBS listed for use in the second line setting only, the PBAC considered CLd would likely be used in the third and later lines of therapy.

7.4 The PBAC recalled in its consideration of ELd at the July 2021 meeting that it noted that the use of lenalidomide was increasing in the first line setting as maintenance therapy and as part of triple therapy in combination with bortezomib and dexamethasone (LBd). On this basis the PBAC accepted Cd as the primary comparator for ELd in the RRMM setting. Similarly, the PBAC considered the nomination of Cd as the primary comparator for CLd to be appropriate. The PBAC considered that the nomination of pomalidomde plus bortezomib and dexamethasone (PBd) as a secondary comparator and elotuzumab plus lenalidomide and dexamethasone (ELd) as a near market comparator was reasonable.

7.5 The PBAC noted that the primary clinical comparison presented in the submission was an indirect treatment comparison (ITC) between CLd and Cd, based on the ASPIRE (CLd versus Ld, N = 792) and ENDEAVOR (Cd versus Bd, N = 929) trials. The ITC utilised Ld and Bd as the common reference based on an assumption of equivalence and did not adjust for any potential differences. The PBAC has previously stated it may not be reasonable to assume non-inferior efficacy between Ld and Bd (see paragraph 5.3, carfilzomib PSD, November 2016 and Lenalidomide PSD, November 2008), and this was considered a limitation of the available evidence.

7.6 The submission also presented secondary ITCs between CLd and ELd based on the ASPIRE and ELOQUENT-2 (ELd versus Ld, N = 646) trials and between CLd and PBd based on the ASPIRE and OPTIMISMM (PBd versus Bd, N = 559) trials. The PBAC noted that patient demographics were similar across the trials and although there were minor differences in trial durations and eligibility criteria, the differences were not anticipated to affect the comparability. The ITC between CLd and ELd utilised Ld as the common reference. The ITC between CLd and PBd utilised Ld and Bd as the common reference based on an assumption of equivalence and did not adjust for any potential

differences, which may not have been reasonable (see paragraph 6.5).

7.7 The PBAC noted that the ITCs did not demonstrate statistically significant differences between CLd and Cd in terms of PFS (HR = 1.29; 95% CI: 0.98, 1.71) and OS (HR = 0.99; 95% CI: 0.74, 1.34). The PBAC noted that there were also no statistically significant differences found in terms of PFS and OS between CLd and ELd or CLd and PBd. The PBAC noted that a non-inferiority margin was not nominated by the resubmission.

7.8 With regards to comparative harms, the PBAC considered that interpretation of the naïve ITC was impacted by different durations of follow-up and hence treatment (see paragraph 6.34). The PBAC noted that although for the CLd arm of ASPIRE and the Cd arm of ENDEAVOR the incidence of patients experiencing at least one adverse event (AE; 98% vs. 98.7%); serious AE (65.3% vs. 59.0%); Grade 3 AE (87% vs. 81.4%) and AE leading to discontinuation (33.4% vs 28.7%) were similar, CLd appeared to be associated with higher rates of Grade ≥ 3 neutropenia (31.1% vs. 2.4%), thrombocytopenia (16.8% vs. 8.9%), pneumonia (16.1% vs. 9.1%) and hypokalaemia (10.5% vs. 2.4%) than Cd.

7.9 Overall, the PBAC considered that the submission's claim of non-inferior comparative effectiveness and safety was reasonable for the primary comparison between CLd and Cd, and for the secondary comparisons between CLd and ELd and PBd. The PBAC noted although there were some uncertainties relating to the clinical claims, the evidence base was similar to that which had supported other multiple myeloma listings based on a CMA.

7.10 The PBAC noted that the resubmission presented a CMA between CLd and Cd based on 15 cycles of treatment. The PBAC considered that the equi-effective doses derived from the clinical evidence (ASPIRE, ENDEAVOR and ARROW trials) and based on 15 cycles of treatment were reasonable:

4,478 mg carfilzomib + 6,213 mg lenalidomide (given as CLd) =

9,076 mg carfilzomib BIW (given as Cd) OR 5,603 mg carfilzomib QW (given as Cd)

7.11 The PBAC noted that the proposed equi-effective doses for the BIW and QW Cd regimens (9,076 mg: 5,603 mg = 1.62 mg: 1mg) were different to those previously accepted by the PBAC (7,278 mg: 4,969 mg = 1.46 mg: 1 mg) which assumed more treatment cycles for the QW regimen (40/3 = 13.3) compared with the BIW regimen (74/6 = 12.3) (see paragraph 6.60). The PBAC noted in the context of the CMA for CLd versus Cd assuming the same (shorter) treatment duration for the QW regimen as for the BIW regimen was potentially conservative and hence considered the equi-effective doses as presented in the resubmission reasonable.

7.12 The PBAC noted the cost of the QW Cd regimen ($[redacted] over 15 cycles; Table 19) was substantially less than the cost of the BIW Cd regimen ($[redacted] over 15 cycles, Table 19), but noted this was based on the current "weighted" price for carfilzomib, which assumes 60% of Cd use is QW and 40% is BIW, rather than regimen specific prices in which the

cost per mg of carfilzomib would be | for the QW regimen and | for the BIW regimen. However, the PBAC noted even when the regimen specific prices were used ($| for BIW and $|/mg for QW, back calculated from the BIW price [$|/mg] and the weighted price [$|/mg]), the cost of the QW Cd regimen was still less than that for the BIW Cd regimen ($| versus $| respectively). The PBAC acknowledged the lower cost associated with the QW regimen was at least in part due to the assumed equi-effective doses (paragraph 7.11). The PBAC noted the weighting of 60% QW Cd plus 40% BIW Cd proposed in the pre-PBAC response for the cost-minimisation analysis aligned with the weighting applied in the Cd QW submission recommended by the PBAC in July 2020 and hence reflected the current price of carfilzomib.

7.13 The PBAC considered that inclusion of costs for treating Grade ≥ 3 neutropenia (with CLd), and costs for infusions (for Cd and CLd) in the CMA was appropriate, with unit costs as specified in Table 17.

7.14 The PBAC noted that an estimate of the net cost of listing CLd on the PBS/RPBS was not included in the resubmission. The PBAC noted that the estimates provided in the PSCR suggested that the listing of CLd would result in an annual net cost of up to $| (based on known or assumed effective prices). The PBAC noted that the additional cost was due to CLd replacing Ld which is less expensive than Cd and ELd; however, the proposed substitution rates, and in particular the extent of substitution of Ld relative to Cd, were not adequately justified in the resubmission. As noted in paragaraph 7.4 above, the PBAC considered it is likely that the use of lenalidomide is increasing in the first line setting, and there would be a corresponding decrease in use in the relapsed and refractory setting. This would be expected to reduce the replacement of Ld relative to the replacement of Cd.

7.15 The PBAC acknowledged that the treatment algorithm for MM has changed substantially since the listing of Cd, including additional listings for first line treatments, DBd as a second line treatment and the listing of triplet combinations. More specifically, the RRMM treatment algorithm is changing with there being an increasing preference for triplet therapies, and there being the potential for increasing sequential use of therapies (and combinations), due to the availability of new treatments with different mechanisms of action. In some cases, such as younger or fitter patients, the PBAC noted that patients may receive many lines of therapy.

7.16 The PBAC noted that the current RSA for carfilzomib is entering its final year and the resubmision requested PBAC consider an increase to the current expenditure caps. The PBAC noted that a mixed modelling approach (epidemiological and market share) was presented in the resubmission to estimate the increased financial caps for a RSA including Cd and triplet therapies. Four senarios were presented which included the current scenario (Cd and PBd listed), and scenarios with the listing of ELd (recommended July 21) and/or CLd. The PBAC noted the estimated cost to the PBS/RPBS for the scenario which assumed the PBS listings of Cd, PBd, ELd and CLd was $60 million to < $70 million in Year 1 increasing to $80 million to < $90 million in Year

6 (based on known or assumed effective prices). For the scenario in which Cd, PBd and CLd are listed the estimated cost was $40 million to < $50 million in Year 1 increasing to $50 million to < $60 million in Year 6. The PBAC noted that the proposed caps were substantially higher than the existing caps, with the Year 5 cap for the current RSA being $30 million to < $40 million. The PBAC noted that the additional cost was stated to be due to the replacement of doublet combinations; however, the proposed substitution rates, including extent of substitution from doublet combinations versus triplet combinations, were not adequately justified in the resubmission. Further, the PBAC considered it was unclear whether the impact of more effective first and second line treatments being available had been adequately accounted for. The PBAC considered the estimates included in the resubmission were not a reliable basis on which to revise the existing RSA caps.

7.17 The PBAC requested that the Department work with the relevant sponsors to elicit projections across the RRMM recommended and PBS listed therapies that would inform a RSA including Cd and triplet therapies and provide the Committee with revised estimates of financial caps which consider the issues noted above regarding substitution rates and extent of doublet combinations versus triplet combinations, as well as displacement to the third-line treatment setting.

7.18 Acknowleding the sponsor's concerns regarding the addition of the triplet therapies to the existing RSA for Cd, at this time the PBAC considered a listing for CLd in which the expenditure for the carfilzomib component of CLd was included in the existing carfilzomib RSA without an increase in the expenditure caps was reasonable, noting that the current RSA expires in January 2023. The PBAC also noted that in its recommendation of ELd in July 2021, it had advised that expenditure on both elotuzumab and lenalidomide be included in the RSA for carfilzomib. The PBAC considered that it would also be appropriate for lenalidomide as part of CLd to be included in the RSA; however, noting that it was sponsored by another company, advised the Department to negotiate these arrangements as appropriate. The PBAC noted the clarification provided in the pre-PBAC response (p1) that stated that when Cd was recommended by the PBAC (July 2017 PBAC meeting), a [redacted] cap was applied in the economic evaluation and used to derive the cost-effective price and expenditure caps. This was implemented by including [redacted].

7.19 The PBAC noted that the financial estimates would need to be revised to present the cost of listing CLd versus Cd only on the PBS with the inclusion of all relevant cost offsets. The PBAC considered that the revised financial estimates should also apply a duration of treatment that aligned with the CMA.

7.20 In terms of the restriction, the PBAC considered that a streamlined authority for carfilzomib would be appropriate when used as part of CLd, consistent with the current Cd listing. The PBAC considered it would be appropriate to include a criterion stating that 'Patient must not have previously received this drug for this condition' to prevent patients being retreated with carfilzomib. Including this criterion would be

consistent with the current restriction for carfilzomib for use in combination with dexamethasone.

7.21 The PBAC noted that flow on restriction changes would be required to create a separate lenalidomide listing to enable use in combination with carfilzomib and dexamethasone. For lenalidomide, the PBAC considered that an immediate/real-time assessment authority required listing (telephone/online) would be appropriate when used as part of CLd, consistent with the proposed listing for ELd.

7.22 The PBAC noted that the submission did not propose a grandfathering restriction.

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

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

Outcome:
Recommended

8 Recommended listing

8.1 Amend existing carfilzomib listing as follows:

MEDICINAL PRODUCT Medicinal product pack	PBS item code	Max. Amount	№.of Rpts	Manufacturer
CARFILZOMIB injection	NEW (Public) NEW (Private)	60 mg	17	Amgen Australia Pty Ltd
Available brands				
Kyprolis (carfilzomib 10 mg injection, 1 vial)				
Kyprolis (carfilzomib 30 mg injection, 1 vial)				
Kyprolis (carfilzomib 60 mg injection, 1 vial)				

Restriction Summary [new] / Treatment of Concept: [new]

	Category/Program: Section 100 (Efficient Funding of Chemotherapy)
	Prescriber type: ☒Medical Practitioners
	Restriction type / Method: ☒Authority Required - STREAMLINED
	Episodicity: Relapsed and/or refractory
	Condition: Multiple myeloma
	PBS Indication: Relapsed and/or refractory multiple myeloma

	Treatment phase: Initial treatment for Cycles 1 to ~~12~~ 3
	Clinical criteria:
	The condition must be confirmed by a histological diagnosis,
	AND
	Clinical criteria:
	The treatment must be in combination with lenalidomide and dexamethasone,
	AND
	Clinical criteria:
	Patient must have progressive disease after at least one prior therapy,
	AND
	Patient must not have previously received this drug for this condition.
	Prescribing 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 in 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).
	Prescribing instructions Oligo-secretory and non-secretory patients are defined as having active disease with less than 10 g per L serum M protein.
	Prescribing Instructions: Provide details of the histological diagnosis of multiple myeloma, prior treatments including name(s) of drug(s) and date of most recent treatment cycle; the basis of the diagnosis of progressive disease or failure to respond; and which disease activity parameters will be used to assess response once only through the Authority application for lenalidomide.
	Administrative Advice: No increase in the maximum number of repeats may be authorised.
	Administrative Advice: Special Pricing Arrangements apply

	Category/Program: Section 100 (Efficient Funding of Chemotherapy)
	Prescriber type: ☒Medical Practitioners
	Restriction type / Method: ☒Authority Required - STREAMLINED
	Episodicity: Relapsed and/or refractory
	Condition: Multiple myeloma
	PBS Indication: Relapsed and/or refractory multiple myeloma
	Treatment phase: ~~Initial~~ Continuing treatment for Cycles ~~1~~ 3 to 12
	Clinical criteria:
	Patient must have previously received PBS-subsidised treatment with this drug for this condition
	AND
	Clinical criteria:
	The treatment must be in combination with lenalidomide and dexamethasone,

	AND
	Clinical criteria:
	Patient must not have developed progressive disease while receiving treatment with this drug for this condition,
	Prescribing 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 in 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).
	Prescribing instructions 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.
	Administrative Advice: Special Pricing Arrangements apply

Restriction Summary [new] / Treatment of Concept: [new]

	Category/Program: Section 100 (Efficient Funding of Chemotherapy)
	Prescriber type: ☒Medical Practitioners
	Restriction type / Method: ☒Authority Required - STREAMLINED
	Episodicity: Relapsed and/or refractory
	Condition: Multiple myeloma
	PBS Indication: Relapsed and/or refractory multiple myeloma
	Treatment phase: Continuing treatment for Cycles 13 onwards
	Clinical criteria:
	Patient must have previously received PBS-subsidised treatment with this drug for this condition
	AND
	Clinical criteria:
	The treatment must be in combination with lenalidomide and dexamethasone,
	AND
	Clinical criteria:
	Patient must not have developed progressive disease while receiving treatment with this drug for this condition,

	Prescribing 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 in 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).
	Prescribing instructions 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.
	Administrative Advice: Special Pricing Arrangements apply

8.2 Add new lenalidomide Treatment phase listing to permit use in carfilzomib + lenalidomide + dexamethasone triple combination therapy as follows:

MEDICINAL PRODUCT medicinal product pack	PBS item code	Max. Qty (units)	Max. Qty (packs)	No. of Rpts	Available brands	Sponsor
LENALIDOMIDE						
lenalidomide 5 mg capsule, 21	New (Public) / (Private)	21	1	2	Revlimid	Celgene Pty Ltd
lenalidomide 10 mg capsule, 21	New (Public) / (Private)	21	1	2	Revlimid	Celgene Pty Ltd
lenalidomide 15 mg capsule, 21	New (Public) / (Private)	21	1	2	Revlimid	Celgene Pty Ltd
lenalidomide 25 mg capsule, 21	New (Public) / (Private)	21	1	2	Revlimid	Celgene Pty Ltd

Restriction Summary [new] / Treatment of Concept: [new]	
	Category/Program: Section 100 (Highly Specialised Drugs Program) – Public/Private hospitals
	Prescriber type: ☒Medical Practitioners
	Restriction type: ☒Authority Required (telephone/online PBS Authorities system)
	PBS Indication: Relapsed and/or refractory multiple myeloma
	Treatment phase: Triple combination therapy consisting of carfilzomib, lenalidomide and dexamethasone
	Treatment criteria:
	Patient must be undergoing concurrent treatment with carfilzomib obtained through the PBS
	AND
	Treatment criteria:
	Patient must not be undergoing simultaneous treatment with this drug obtained under another PBS listing
	Prescribing Instructions: Patients receiving this drug under the PBS listing must be registered in the i-access risk management program
	Caution: This drug is a category X drug and must not be given to pregnant women. If lenalidomide is taken during pregnancy, a teratogenic effect of lenalidomide in humans cannot be ruled out.
	Administrative advice:

	Applications for authorisation under this restriction may be made in real time using the Online PBS Authorities system (see www.servicesaustralia.gov.au/HPOS) or by telephone by contacting Services Australia on 1800 700 270.
	Administrative Advice: Special Pricing Arrangements apply

9 Context for Decision

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

10 Sponsor's Comment

Amgen are pleased that the PBAC have recommended carfilzomib, lenalidomide and dexamethasone as triplet therapy. In accordance with the PBAC's recommendation we will now work closely with the Department to ensure that the carfilzomib RSA is appropriately amended to reflect carfilzomib and triplet therapy use.