# 5.02 CARFILZOMIB, Injection, 60 mg/50 mL injection 1 x 50 mL vial, 30 mg/30 mL injection 1 x 30 mL vial, Kyprolis®, Amgen Australia Pty Ltd.

## Purpose of Application

* 1. Section 100 (Efficient Funding of Chemotherapy – Public and Private Hospital) Authority Required listing of carfilzomib for the treatment of relapsed or refractory multiple myeloma.

## Requested listing

* 1. The requested (abridged) restrictions for the Cd and CLd regimens, including initial and continuing treatment, are presented below. Suggestions and additions proposed by the Secretariat to the requested listing are added in italics and suggested deletions are crossed out with strikethrough.

Initial treatment: dual therapy (carfilzomib with dexamethasone)

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| Name, Restriction,  Manner of administration and form | | Max.  Amt | №.of  Rpts | Dispensed Price for Max. Amt | Proprietary Name and Manufacturer | |
| CARFILZOMIB  Powder for injection, 30 mg  Powder for injection, 60 mg | | 120 mg | 17 | Published  Public: $'''''''''''''''''''  Private: $''''''''''''''''''''  Effective  Public: $''''''''''''''''''''''  Private: $''''''''''''''''''''''' | Kyprolis | [AN] |
| **Category /**  **Program** | Section 100 – Efficient funding of Chemotherapy | | | | | |
| **Prescriber type:** | Dental Medical Practitioners Nurse practitioners Optometrists  Midwives | | | | | |
| **Condition:** | Multiple myeloma | | | | | |
| **PBS Indication:** | *Progressive* multiple myeloma | | | | | |
| **Treatment phase:** | ~~Treatment of Progressive disease -~~ Initial treatment | | | | | |
| **Restriction Level / Method:** | Authority Required - In Writing | | | | | |
| **Clinical criteria:** | The condition must be confirmed by a histological diagnosis,  AND  The treatment must be in combination with dexamethasone,  AND  Patient must have progressive disease after at least one prior therapy,  AND  Patient must have undergone or be ineligible for a ~~primary~~ stem cell transplant,  AND  Patient must not be receiving concomitant PBS-subsidised thalidomide, lenalidomide, bortezomib, or pomalidomide  *AND*  *Patient must not receive more than four cycles of treatment under this restriction.* | | | | | |
| **Prescriber Instructions** | *Progressive disease is defined as at least 1 of the following:*  *(a) at least a 25% increase and an absolute increase of at least 5 g per L in serum M protein (monoclonal protein); or*  *(b) at least a 25% increase in 24-hour urinary light chain M protein excretion, and an absolute increase of at least 200 mg per 24 hours; or*  *(c) in oligo-secretory and non-secretory myeloma patients only, at least a 50% increase of the difference between involved free light chain and uninvolved free light chain; or*  *(d) at least a 25% relative increase and at least a 10% absolute increase in plasma cells in a bone marrow aspirate or on biopsy; or*  *(e) an increase in the size or number of lytic bone lesions (not including compression fractures); or*  *(f) at least a 25% increase in the size of an existing or the development of a new soft tissue plasmacytoma (determined by clinical examination or diagnostic imaging); or*  *(g) development of hypercalcaemia (corrected serum calcium greater than 2.65 mmol per L not attributable to any other cause).*  *Oligo-secretory and non-secretory patients are defined as having active disease with less than 10 g per L serum M protein.*  *The authority application must be made in writing and must include:*  *(1) a completed authority prescription form; and*  *(2) a completed Multiple Myeloma carfilzomib Authority Application - Supporting Information Form, which includes details of the histological diagnosis of multiple myeloma, prior treatments including name(s) of drug(s) and date of most recent treatment cycle and record of prior stem cell transplant or ineligibility for prior stem cell transplant; details of the basis of the diagnosis of progressive disease or failure to respond; and nomination of which disease activity parameters will be used to assess response.*  *(3) a signed patient acknowledgment.*  *To enable confirmation of eligibility for treatment, current diagnostic reports of at least one of the following must be provided:*  *(a) the level of serum monoclonal protein; or*  *(b) Bence-Jones proteinuria - the results of 24-hour urinary light chain M protein excretion; or*  *(c) the serum level of free kappa and lambda light chains; or*  *(d) bone marrow aspirate or trephine; or*  *(e) if present, the size and location of lytic bone lesions (not including compression fractures); or*  *(f) if present, the size and location of all soft tissue plasmacytomas by clinical or radiographic examination i.e. MRI or CT-scan; or*  *(g) if present, the level of hypercalcaemia, corrected for albumin concentration.*  *As these parameters will be used to determine response, results for either (a) or (b) or (c) should be provided for all patients. Where the patient has oligo-secretory or non-secretory multiple myeloma, either (c) or (d) or if relevant (e), (f) or (g) should be provided. Where the prescriber plans to assess response in patients with oligo-secretory or non-secretory multiple myeloma with free light chain assays, evidence of the oligo-secretory or non-secretory nature of the multiple myeloma (current serum M protein less than 10 g per L) must be provided.* | | | | | |
| **Administrative Advice** | *No increase in the maximum number of repeats may be authorised.*  *No increase in the maximum amount or number of units may be authorised.*  *Special Pricing Arrangements apply.* | | | | | |

Continuing treatment: dual therapy (carfilzomib with dexamethasone)

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| **Category /**  **Program** | Section 100 – Efficient funding of Chemotherapy | | | | | |
| **Prescriber type:** | Dental Medical Practitioners Nurse practitioners Optometrists  Midwives | | | | | |
| **Severity:** | *Progressive* | | | | | |
| **Condition:** | Multiple myeloma | | | | | |
| **PBS Indication:** | *Progressive* multiple myeloma | | | | | |
| **Treatment phase:** | ~~Treatment of Progressive disease –~~ Continuing treatment | | | | | |
| **Restriction Level / Method:** | *Authority Required - In Writing*  ~~Authority Required - Telephone~~  ~~Authority Required - Emergency~~  ~~Authority Required - Electronic~~ | | | | | |
| **Clinical criteria:** | Patient must have previously received an authority prescription for this condition with this drug ~~in combination with dexamethasone.~~  AND  The treatment must be in combination with dexamethasone,  AND  Patient must not have progressive disease while receiving treatment with this drug, | | | | | |
| **Prescriber Instructions** | *Same definition for progressive disease as per previous restriction*  ~~Authority applications for continuing therapy must be made every 3 months by telephone by contacting Medicare Australia on 1800 700 270.~~  *Same requirements for the authority application to be made in writing as per previous restriction* | | | | | |
| **Administrative Advice** | ~~A maximum of 17 repeats will be provided for use every 3 months until progression.~~  *No increase in the maximum number of repeats may be authorised.*  *No increase in the maximum amount or number of units may be authorised.*  *Special Pricing Arrangements apply* | | | | | |

Initial treatment (cycles 1-3): triple therapy (carfilzomib with lenalidomide and dexamethasone)

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| **Category / Program** | Section 100 – Efficient funding of Chemotherapy | | | | | |
| **Prescriber type:** | Dental Medical Practitioners Nurse practitioners Optometrists  Midwives | | | | | |
| **Severity:** | *Progressive* | | | | | |
| **Condition:** | Multiple myeloma | | | | | |
| **PBS Indication:** | *Progressive* multiple myeloma | | | | | |
| **Treatment phase:** | ~~Treatment of Progressive disease -~~ Initial treatment | | | | | |
| **Restriction Level / Method:** | Authority Required - In Writing | | | | | |
| **Clinical criteria:** | The condition must be confirmed by a histological diagnosis,  AND  The treatment must be in combination with lenalidomide and dexamethasone.  AND  Patient must have progressive disease after at least one prior therapy  AND  Patient must have undergone or be ineligible for a ~~primary~~ stem cell transplant  AND  Patient must have previously received lenalidomide,\*  AND  Patient must not have progressed within three months of commencing lenalidomide  AND  Patient must not be receiving concomitant PBS-subsidised thalidomide, bortezomib, or pomalidomide  *AND*  *Patient must not receive more than four cycles of treatment under this restriction.* | | | | | |
| **Prescriber Instructions** | *<Same definition for progressive disease as per previous restriction>* | | | | | |
| **Administrative Advice** | ~~A maximum of 17 repeats will be provided for use every 3 months until progression.~~  *No increase in the maximum number of repeats may be authorised.*  *No increase in the maximum amount or number of units may be authorised.*  *Special Pricing Arrangements apply* | | | | | |

\*Secretariat notes that this restriction wording should be removed and updated to reflect that if a patient has had previous lenalidomide, they must not have progressed within three months of commencing treatment. A criteria requiring previous treatment with lenalidomide is not proposed

Continuing treatment 1 (cycles 4+): triple therapy (carfilzomib with lenalidomide and dexamethasone)

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| Name, Restriction,  Manner of administration and form | | Max.  Amt | №.of  Rpts | Dispensed Price for Max. Amt | Proprietary Name and Manufacturer | |
| CARFILZOMIB  Powder for injection, 30 mg  Powder for injection, 60 mg | | 60 mg | 17 | Published  Public $'''''''''''''''''''''''  Private: $'''''''''''''''''''  Effective  Public: $''''''''''''''''  Private: $''''''''''''''''' | Kyprolis | [AN] |
| **Category / Program** | Section 100 – Efficient funding of Chemotherapy | | | | | |
| **Prescriber type:** | Dental Medical Practitioners Nurse practitioners Optometrists  Midwives | | | | | |
| **Severity:** | *Progressive* | | | | | |
| **Condition:** | Multiple myeloma | | | | | |
| **PBS Indication:** | *Progressive* multiple myeloma | | | | | |
| **Treatment phase:** | ~~Treatment of Progressive disease -~~ Continuing treatment | | | | | |
| **Restriction Level / Method:** | Authority Required - In Writing  ~~Authority Required - Telephone~~  ~~Authority Required - Emergency~~  ~~Authority Required - Electronic~~ | | | | | |
| **Clinical criteria:** | Patient must have previously received an authority prescription for carfilzomib in combination with lenalidomide and dexamethasone under the initial criteria.  AND  Patient must not have progressive disease while receiving treatment this drug | | | | | |
| **Prescriber Instructions** | *<Same definition for progressive disease as per previous restriction>*  ~~Authority applications for continuing therapy must be made every 3 months by telephone by contacting Medicare Australia on 1800 700 270.~~  *<Same requirements for the authority application to be made in writing as per previous restriction>* | | | | | |
| **Administrative Advice** | ~~A maximum of 17 repeats will be provided for use every 3 months until progression.~~  *No increase in the maximum number of repeats may be authorised.*  *No increase in the maximum amount or number of units may be authorised.*  *Special Pricing Arrangements apply.* | | | | | |

* 1. The PSCR (p5) disagreed with the Secretariat’s comments regarding whether a written Authority Required restriction should apply to carfilzomib for continuing treatment on the basis that the lenalidomide restriction requires a telephone authority for continuing treatment. However, the PBS listing for bortezomib for continuing treatment requires a written authority.
  2. The PSCR (p5) argued that the PBS restriction for carfilzomib should not include a criterion for performance status, on the basis that the PBS restrictions for bortezomib and lenalidomide do not comment to performance status.
  3. The submission indicated that some patients were currently receiving carfilzomib through a compassionate use program. However, the PSCR (p1) indicated that the sponsor is not aware of the dosage regimen or concomitant therapy of patients currently receiving carfilzomib through this program, and that the criteria for access is different to the requested PBS listings. As such, it is unclear how many patients currently accessing treatment through the program would be eligible for PBS‑subsidised treatment, and therefore what the associated costs to the PBS would be.
  4. The requested PBS listings were for the two regimens of carfilzomib:
* carfilzomib plus dexamethasone (Cd); and
* carfilzomib plus lenalidomide and dexamethasone (CLd).
  1. The submission appeared to propose two scenarios for PBS-listing:
* Scenario 1: carfilzomib would be PBS-subsidised for use as part of the Cd regimen only; and
* Scenario 2: carfilzomib would be PBS-subsidised for use as part of both regimens (Cd and CLd).

The submission did not appear to request PBS listing of carfilzomib for use as part of the CLd regimen only. This was considered reasonable during the evaluation as listing carfilzomib for use in only the CLd regimen might result in leakage to the Cd regimen in patients who are not suitable for triple therapy with CLd.

* 1. The Cd regimen used a higher dose of carfilzomib (56 mg/m2 per dose) than the CLd regimen (27 mg/m2 per dose) after the initial two doses (both regimens used 20 mg/m2 for doses 1 and 2 of Cycle 1).
  2. Thus the submission proposed five different restrictions for carfilzomib:
* two for use as part of the Cd regimen - initial and continuing; and
* three for use as part of the CLd regimen - initial, Cycles 2 to 12, and Cycles 13 onwards.

The Secretariat’s proposed wording for the (abridged) restrictions are presented above. For simplicity in implementation, the Secretariat proposed a single restriction for the continuing treatment with carfilzomib as part of the CLd regimen.

* 1. Carfilzomib was proposed to be used until disease progression in both regimens.
* For Cd, this was consistent with the key clinical trial (ENDEAVOR).
* For CLd, this was inconsistent with the key clinical trial (ASPIRE), where carfilzomib was ceased after 18 cycles, while lenalidomide and dexamethasone could be continued until disease progression.

The ESC considered that treatment until disease progression was standard clinical practice for multiple myeloma.

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

## Background

* 1. TGA status at the time of PBAC consideration: the submission was made under the TGA‑PBAC parallel process. At the time of PBAC consideration, the delegate’s overview was available. The delegate recommended the approval of carfilzomib as proposed: “*(*Carfilzomib), as part of combination therapy with dexamethasone or lenalidomide and dexamethasone, is indicated for the treatment of patients with relapsed or refractory multiple myeloma who have received at least one prior therapy” (TGA Delegates overview, p1). This is consistent with the proposed PBS restriction.
  2. The PBAC has not previously considered carfilzomib.
  3. In March 2016, the PBAC recommended listing of lenalidomide for first-line use in transplant-ineligible patients. The PBAC recommended amending the lenalidomide restriction to enable re-use following disease progression in patients who previously discontinued when the disease was stable. At the same meeting, the PBAC also recommended amending the bortezomib restriction to enable use in patients with progressive disease after initial therapy with lenalidomide or thalidomide. The submission appropriately included these changes in the treatment algorithm.

## Clinical place for the proposed therapy

* 1. Multiple myeloma is considered incurable with approximately one third of patients not responding to first-line therapy, and eventual relapse occurring in virtually all patients who obtain an initial response.
  2. The submission requested listing of carfilzomib in second- and later-line treatment of multiple myeloma. The submission considered that:
* Cd would replace Bd; and
* CLd would replace Ld.

However, the submission did not propose separate target populations for the two carfilzomib-containing regimens. The ESC considered that both the Cd and CLd regimens would represent a new treatment option in addition to the existing treatments for multiple myeloma, and that either Bd or Ld could be used before or after treatment with Cd or CLd. The PBAC agreed with the ESC’s view.

* 1. If both regimens were subsidised (Scenario 2), CLd would likely be used in all patients able to tolerate triple therapy. Thus Cd would mainly be used in patients who are unsuitable for CLd, such as patients who cannot take lenalidomide (because of contraindication, intolerance or other clinical factors, or patients who are refractory to lenalidomide).
  2. Noting a number of issues with the assessment of the cost-effectiveness of the CLd regimen, the pre-PBAC response (p2) requested that the PBAC consider the proposed listings for the Cd and CLd regimens separately. On this basis it was considered in the pre-PBAC response that the scenario where both Cd and CLd are listed to be hypothetical. The PBAC noted both regimens are included in the indication proposed by the TGA Delegate and that the appropriate clinical positioning of each regimen needs to be considered in this light.

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

## Comparator

Scenario 1 (Cd only)

* 1. The submission nominated Bd as the main comparator. The submission noted that Cd might also substitute for Ld but it assumed that the extent of this substitution would be small and that Ld would have the same benefits and patient costs as Bd because lenalidomide was listed on a cost-minimisation basis to bortezomib. However, the clinician survey provided in the submission indicated that there might be significant substitution of Cd for Ld. The evaluation considered that while lenalidomide was listed on a cost-minimisation basis to bortezomib in November 2008, in the absence of new data, it might not be reasonable to assume non-inferior efficacy between these two drugs.
  2. The PSCR argued that there was no basis for assuming that the non-inferiority between bortezomib and lenalidomide was no longer valid. The ESC considered that in the absence of new data, it might not be reasonable to assume non-inferior efficacy between these two drugs. Furthermore, the ESC considered that while there may be a theoretical basis to assume that lenalidomide was non-inferior to bortezomib, in the absence of a direct head-to-head comparison of Cd versus Ld, there was insufficient evidence to conclude that Cd was also of superior efficacy over Ld.
  3. The PBAC recalled that at the time of considering the cost minimisation of lenalidomide to bortezomib, it noted that overall survival (OS) may possibly favour lenalidomide with dexamethasone (Lenalidomide November 2008 Public Summary Document). Therefore, the PBAC considered that it might not be reasonable to assume non‑inferior efficacy between Bd and Ld.

Scenario 2 (Cd and CLd available)

* 1. The submission nominated Bd as the main comparator for Cd. With CLd available, Cd would mainly be used in patients unsuitable for lenalidomide, thus Bd was an appropriate main comparator. The PBAC considered that an appropriate secondary comparator for patients unsuitable for triple therapy (but able to tolerate lenalidomide) might be Ld.
  2. The submission nominated placebo plus Ld as the main comparator for CLd, because carfilzomib was being added-on to Ld. The PBAC considered that this was appropriate.
  3. The PBAC considered that if both regimens were subsidised, CLd would likely be used in all patients able to tolerate triple therapy and Cd would mainly be used in patients who could not take CLd (such as lenalidomide-refractory patients).
  4. The submission nominated elotuzumab and ixazomib as secondary comparators. Although these drugs are not TGA approved or PBS-listed, they might be used in combination with Ld in relapsed/refractory multiple myeloma in the future because they have been used in clinical trials in this setting.

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

## Consideration of the evidence

### Sponsor hearing

* 1. There was no hearing for this item.

### Consumer comments

* 1. The PBAC noted and welcomed the input from individuals (168), and health care professionals (2) via the Consumer Comments facility on the PBS website. The comments described a range of benefits of treatment with carfilzomib, including availability of an additional treatment option, fewer side effects related to neuropathy, slowed disease progression, and improved quality of life.

### Clinical trials

* 1. The submission was based on two head-to-head trials comparing:
* Cd versus Bd (the ENDEAVOR trial, N = 929); and
* CLd versus Ld (the ASPIRE trial, N = 792).

The PBAC noted that the trials were open-label, but that the assessment of progression free survival (PFS) and OS was blinded.

* 1. The submission also included an indirect comparison of CLd versus elotuzumab+Ld and ixazomib+Ld. However, these results were not discussed at the ESC or PBAC meetings because elotuzumab and ixazomib were not TGA-registered, PBS-listed, or being considered at the November 2016 PBAC meeting.
  2. Details of the randomised controlled trials used to inform the direct comparisons presented in the submission are provided in Table 1.

**Table 1: Trials and associated reports presented in the submission**

| **Trial ID** | **Protocol title/ Publication title** | **Publication citation** |
| --- | --- | --- |
| ENDEAVOR  NCT01568866 | A Randomised, Open-label, Phase 3 Study of Carfilzomib Plus Dexamethasone vs. Bortezomib Plus Dexamethasone in Patients with Relapsed Multiple Myeloma.  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. | 26 May 2015  *Lancet Oncol* 2016.17:27–38. |
| ASPIRE  NCT0108039 | A Randomised, Multicenter, Phase 3 Study Comparing Carfilzomib, Lenalidomide, and Dexamethasone vs. Lenalidomide and  Dexamethasone in Patients with Relapsed Multiple Myeloma.  Stewart K, Rajkumar V, Dimopoulos M, *et al*. Carfilzomib, lenalidomide, and dexamethasone for relapsed multiple myeloma | 14 October 2014  *N Engl J Med*; 2015.372(2):142-52 |

Source: Table B.2.1.1-1, p58 of the submission

* 1. The key features of the direct randomised trials are summarised in Table 2.

**Table 2: Key features of the included evidence**

| **Trial** | **N** | **Design/ duration** | **Risk of bias** | **Patient population** | **Outcomes** | **Use in modelled evaluation** |
| --- | --- | --- | --- | --- | --- | --- |
| **Cd vs Bd** | | | | | | |
| ENDEAVOR | 929 | MC, R, OL,  11.5 months | Low to unclear a | R/R MM, after 1-3 lines of prior therapy | PFS, OS, ORR | PFS  OS |
| **CLd vs Ld** | | | | | | |
| ASPIRE | 792 | MC, R, OL,  30.8 months | Low to unclear a | R/R MM, after 1-3 lines of prior therapy | PFS, OS, ORR | PFS  OS |

Source: compiled during the evaluation

Bd = bortezomib + dexamethasone; Cd = carfilzomib + dexamethasone; CLd = carfilzomib + lenalidomide + dexamethasone; Ld = lenalidomide + dexamethasone; MC = multi-centre; MM = multiple myeloma; OL = open label; ORR = overall response rate; OS = overall survival; PFS = progression-free survival; R = randomised; R/R = relapsed/refractory

a Due to: a risk of performance bias as the trial was open-label to patients and investigators; and imbalances in discontinuation rates and reasons between the trials.

* 1. ENDEAVOR and ASPIRE were both open-label, multicentre, randomised controlled trials. The ASPIRE trial had longer-term follow-up data than the ENDEAVOR trial (an additional 20 months). Thus, more mature data were available for the CLd regimen than for the Cd regimen.

### Comparative effectiveness

Cd versus Bd (ENDEAVOR)

* 1. The key results of the ENDEAVOR trial (Cd versus Bd) are presented in Table 3.

**Table 3: Results of the ENDEAVOR trial of Cd versus Bd**

| **Regimen** | **Cd**  **N = 464** | **Bd**  **N = 465** | **Difference** |
| --- | --- | --- | --- |
| **Progression free survival** | | | |
| Median duration of follow-up for PFS, months | 11.9 (11.2, 12.4) | 11.1 (10.2, 11.4) |  |
| Median PFS a, months (95% CI) | 18.7 (15.6, NE) | 9.4 (8.4, 10.4) | 9.3 months |
| Hazard Ratio for PFS (95% CI) | | | **0.53 (0.44, 0.65)** |
| **Overall survival** | | | |
| Median duration of follow-up for OS, months | 12.5 (11.9, 13.2) | 11.9 (11.2, 12.6) |  |
| Patients who died; n (%) | 75 (16.2%) | 88 (18.9%) |  |
| OS duration, months (95% CI)  25th percentilec | 22.8 (17.0, NE) | 16.1 (14.7, 18.5) |  |
| Median OS a | NE (NE, NE) | 24.3 (24.3, NE) |  |
| Hazard Ratio (95% CI) | | | Stratified: 0.79 (0.58, 1.08)b |

Source: Table B.6.1-1, p95 of the submission; Table 20, p112-113 of CSR for ENDEAVOR

Bd = bortezomib + dexamethasone; Cd = carfilzomib + dexamethasone; CI = confidence interval; NE = not estimable; OS = overall survival; PFS = progression free survival; **bold** = statistically significant

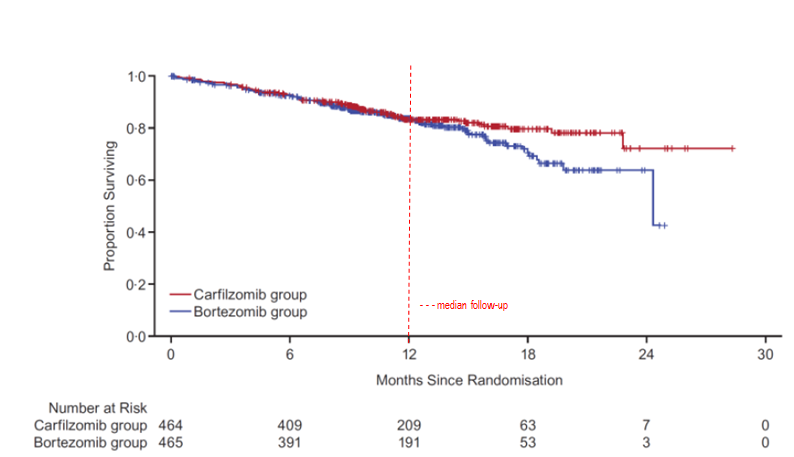
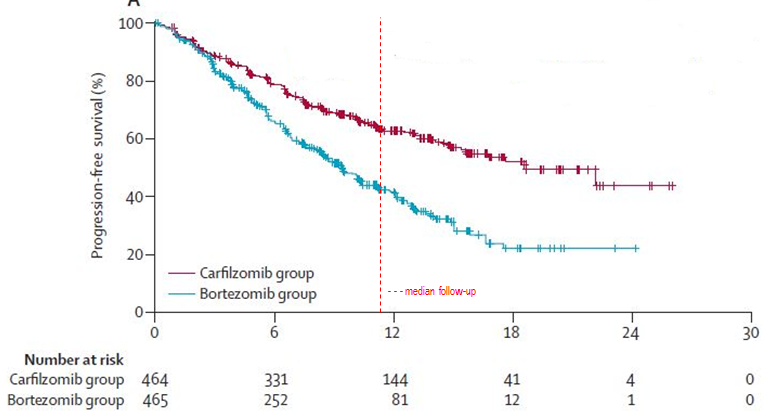
a Note that median PFS was not reached in Cd arm, value is estimated using the Kaplan-Meier method

b Stratification factors were ß2 microglobulin levels, prior bortezomib and prior lenalidomide. The unstratified OS HR was 0.78 (95% CI: 0.57, 1.06).

c values were extracted during evaluation

* 1. The Kaplan-Meier curves for Cd versus Bd for PFS (left panel) and OS (right panel) are presented in Figure 1.

**Figure 1: Kaplan-Meier curves: ENDEAVOR trial (Cd versus Bd) for PFS (left panel) and OS (right panel)**



Source: Dimopoulos et al, 2016 Figure 2 and Figure S2 in Supplementary appendix to publication

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

* 1. For Cd versus Bd the hazard ratio (HR) for PFS was 0.53 (95% confidence interval (CI): 0.44 to 0.65). The median PFS was estimated to be 18.7 months for Cd. This was compared with a PFS of 9.4 months in the Bd arm. However, the evaluation noted that these data were immature and might not be a reliable estimate of the true median. Further, it was unclear whether PFS was a good surrogate for OS in multiple myeloma, particularly given it is a relapsing condition. The PSCR argued that PFS was accepted by the Food and Drug Administration (FDA) and the European Medicines Agency (EMA) as an appropriate primary endpoint for the carfilzomib trials. The ESC considered that using PFS to extrapolate OS was reasonable. However the ESC considered that the issues relating to the extrapolation of PFS to OS in the economic model were not adequately addressed in the PSCR (see Paragraph 6.38 for more detail). The PBAC agreed with the ESC that the data were immature and that although it may be reasonable to extrapolate OS from the PFS, the method of extrapolation was inadequately justified.
  2. The improvement in OS with Cd was not statistically significant (HR = 0.79; 95% CI: 0.58 to 1.08), based on approximately 12 months of follow-up. The PBAC noted that at median follow-up there was no separation in the Kaplan-Meier OS curves for Cd versus Bd.
  3. The PBAC noted that for the subgroup of patients from the ENDEAVOUR trial who were refractory to lenalidomide, PFS was not statistically significant (HR = 0.80; 95% CI: 0.57 to 1.11). While acknowledging the limitations of this subgroup analysis (e.g. a large number of subgroup analyses were conducted), the PBAC considered that in Scenario 2 this was the group of patients most likely to take Cd (rather than CLd) in clinical practice. The PBAC therefore considered that the evidence indicated that in patients likely to take the Cd regimen in scenario 2, Cd did not confer any advantage over the Bd regimen for PFS.

CLd versus Ld (ASPIRE)

* 1. A summary of the key results of the ASPIRE trial is presented in Table 4.

**Table 4: Results of the ASPIRE trial of CLD vs Ld**

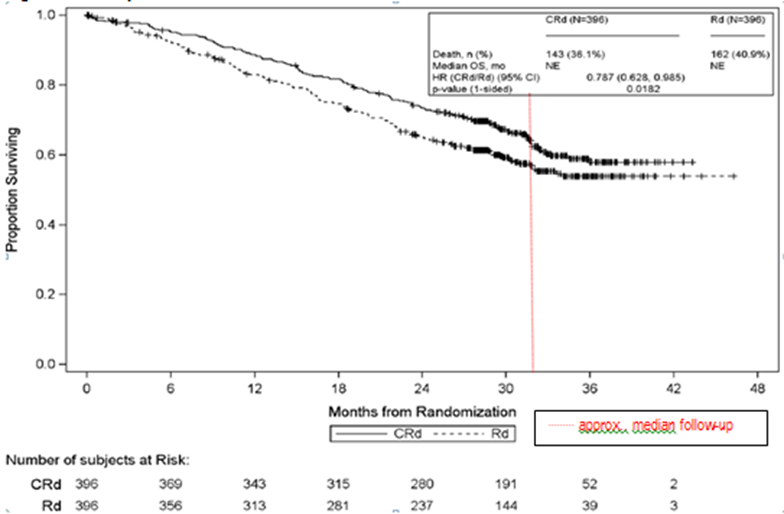
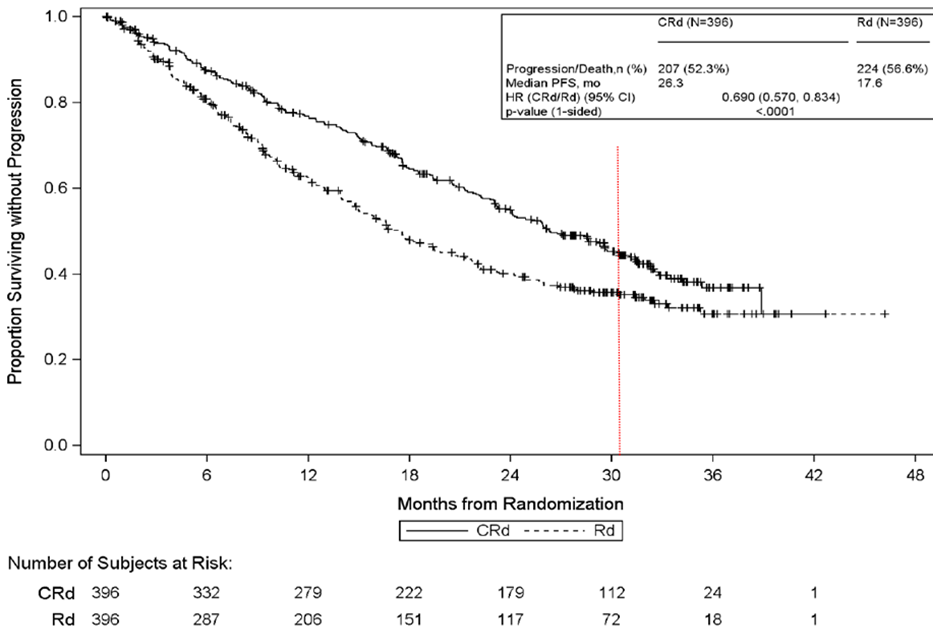
| **Regimen** | **CLd**  **N = 396** | **Ld**  **N = 396** | **Difference** |
| --- | --- | --- | --- |
| **Progression free survival** | | | |
| Median duration of follow-up for PFS, months | 31.4 (30.7, 31.9) | 30.1 (28.8,31.4) |  |
| Median PFS, months (95% CI) | 26.3 (23.3, 30.5) | 17.6 (15.0, 20.6) | 8.7 months |
| PFS Hazard Ratio (95% CI) | | | **0.69 (0.57, 0.83)** |
| **Overall survival** | | | |
| Median duration of follow-up, months | 32.3 (31.7, 33.2) | 31.5 (30.8, 32.5) | NA |
| OS duration, months (95% CI)  25th percentile\* | 22.9 (19.1, 27.0) | 17.6 (14.6, 20.3) | NA |
| Median OS | NE (NE, NE) | NE (32.1, NE) |  |
| Hazard Ratio (95% CI) | 0.79 (0.63, 0.99) p value (1 sided) = 0.0182  (p value required for significance [1-sided] = 0.0051) | | |

Source: Table B.6.1-1, p95; Table B.6.2-1, p98 of the submission; *Table 14.2.3.1, pp491-2 of the CSR for ASPIRE*

CI = confidence interval; CLd = carfilzomib + lenalidomide + dexamethasone; Ld = lenalidomide + dexamethasone; NE = not estimable; OS = overall survival; PFS = progression free survival; **bold** = statistically significant; *\** = values extracted during evaluation

* 1. The Kaplan-Meier curves for progression free and OS from the ASPIRE trial are presented in Figure 2.

**Figure 2: Kaplan-Meier curves: ASPIRE trial (CLd versus Ld) for PFS (left panel) and OS (right panel)**

****

Source: Figure B.6.2-2, p97; Figure B.6.2-4, p97 of the submission; red dotted line indicates median follow-up

CI = confidence interval; CRd = carfilzomib + lenalidomide + dexamethasone; HR = hazard ratio; mo = months; NE = not estimable; OS = overall survival; PFS = progression free survival; Rd = lenalidomide + dexamethasone;

* 1. The median PFS increased by 8.7 months when carfilzomib was added to Ld (HR = 0.69; 95% CI: 0.57 to 0.83). Median OS was not reached in either arm (HR = 0.79; 95% CI: 0.63 to 0.99, p [1-sided] = 0.018). The result for OS was not considered to be statistically significant as it did not meet the pre-specified p-value (1-sided p-value of 0.0051).

### Comparative harms

* 1. A summary of the treatment related adverse events from the two carfilzomib trials are presented in Table 5.

**Table 5: Summary of treatment-related adverse events, ENDEAVOR and ASPIRE**

| **Trial** | | **ENDEAVOR** | | | **ASPIRE** | | |
| --- | --- | --- | --- | --- | --- | --- | --- |
| **Regimen, (n safety set)** | | **Cd (463)** | | **Bd (456)** | **CLd (392)** | | **Ld (389)** |
| Median duration of treatment, months a | | 9.2 a | | 6.2 a | 20.2 b | | 13.1 |
| **Treatment-related AEs, number of patients with events (%)** | | | | | | | |
| ≥1 treatment‑related AE | | 404 (87.3%) | | 406 (89.0%) | 332 (84.7%) | | 329 (84.6%) |
| ≥ Grade 3 | | 248 (53.6%) | | 230 (50.4%) | 263 (67.1%) | | 234 (60.2%) |
| SAE | | 110 (23.8%) | | 69 (15.1%) | 117 (29.8%) | | 104 (26.7%) |
| Leading to discontinuation of any study drug | | 60 (13.0%) | | 76 (16.7%) | 54 (13.8%)\* | | 65 (16.7%)\* |
| Leading to death\* | | 23 (5.0%) | | 18 (3.9%) | 32 (8.2%) | | 29 (7.5%) |

Source: Table B.6.7-1, p104 of the submission; Table 53, p192; Table 61, p208 of the ASPIRE CSR; Table 46, p192; Table 14.3.1 p692 of the ENDEAVOR CSR

AE = adverse event; Bd = bortezomib + dexamethasone; Cd = carfilzomib + dexamethasone; CLd = carfilzomib + lenalidomide + dexamethasone; SAE = serious adverse event; \* = values extracted during evaluation

a Note this was censored, as many patients continued to receive treatment after the data-cut reported.

b While carfilzomib use was capped at 18 cycles in the ASPIRE trial, the lenalidomide and dexamethasone components could be continued beyond 18 cycles.

* 1. Almost all patients experienced at least one treatment-related adverse event (AE). In ENDEAVOR, Cd was associated with more serious treatment-related AEs than Bd (23.8% versus 15.1%, respectively). In ASPIRE, more patients experienced Grade 3 or higher treatment-related AEs with CLd compared with Ld (67.1% versus 60.2%, respectively).

### Benefits/harms

* 1. A summary of the comparative benefits and harms for Cd versus Bd, and for CLd versus Ld is presented in Table 6.

**Table 6: Summary of comparative benefits and harms for Cd versus Bd, and for CLd versus Ld**

|  | **ENDEAVOR** | | | | **ASPIRE** | | |
| --- | --- | --- | --- | --- | --- | --- | --- |
|  | **Cd a** | **Bd a** | | **Difference** | **CLd b** | **Ld b** | **Difference** |
| **N** | 464 | 465 | |  | 396 | 396 |  |
| **PFS** | | | | | | | |
| Progressed, n (%) | 171 (36.9%) | 243 (52.3%) | |  | 207 (52.3%) | 224 (56.6%) |  |
| Median PFS, months (95% CI)a | 18.7  (15.6, NE) | 9.4  (8.4, 10.4) | | 9.3 | 26.3  (23.3, 30.5) | 17.6  (15.0, 20.6) | 8.7 |
| PFS HR (95% CI) |  |  | | **0.53 (0.44, 0.65)** |  |  | **0.69 (0.57, 0.83)** |
| **OS** | | | | | | | |
| Died; n (%) | 75 (16.2%) | 88 (18.9%) | | RD\*: -2.8%  (-7.6%, 2.1%) | 143 (36.1%) | 162 (40.9%) | RD\*: -4.8%  (-11.6%, 2.0%)- |
| OS\*, mo (95% CI)  25th percentile | 22.8  (17.0, NE) | 16.1  (14.7, 18.5) | |  | 22.9  (19.1, 27.0) | 17.6  (14.6, 20.3) |  |
| Median OS | NE (NE, NE) | 24.3  (24.3, NE) | |  | NE (NE, NE) | NE (32.1, NE) |  |
| OS HR (95% CI) |  |  | | 0.79 (0.58, 1.08) |  |  | 0.79 (0.63, 0.99) c |
| **Harms - ENDEAVOR trial of Cd versus Bd** | | | | | | | |
|  | **Cd a** | **Bd a** | **RR\***  **(95% CI)** | | **Event rate/100 patients a** | | **RD\***  **(95% CI)** |
|  | |
| **Cd** | **Bd** |
| Any ≥ Grade 3treatment related AE | 248 / 463 | 230 / 456 | 1.06 (0.94, 1.20**)** | | 53.6 | 50.4 | 3.1 (-3.3%, 9.6%) |
| **Treatment emergent adverse events ≥ Grade 3, number of patients** | | | | | | | |
| Hypertension | 41 / 463 | 12 / 456 | **3.37 (1.79, 6.32)** | | 8.9 | 2.6 | **6.2% (3.2%, 9.2%)** |
| Decreased lymphocytes | 26 / 463 | 8 / 456 | **3.20 (1.46, 7.00)** | | 5.6 | 1.8 | **3.9% (1.4%, 6.3%)** |
| Peripheral neuropathy | 6 / 463 | 24 / 456 | **0.25 (0.1, 0.6)** | | 1.3 | 5.3 | **-4.0% (-6.3%, -1.7%)** |
| **Harms - ASPIRE trial of CLd versus Ld** | | | | | | | |
|  | **CLd b** | **Ld b** | **RR**  **(95% CI)** | | **Event rate/100 patients b** | | **RD**  **(95% CI)** |
| **CLd** | **Ld** |
| Any ≥ Grade 3treatment related AE | 263 / 392 | 234 / 389 | 1.12 (1.00, 1.24**)** | | 67.1 | 60.2 | **6.9% (0.2%, 13.7%)** |
| **Treatment emergent adverse events ≥ Grade 3, number of patients** | | | | | | | |
| Hypertension | 17 / 392 | 7 / 389 | **2.41 (1.01, 5.75)** | | 4.3 | 1.8 | **2.5% (0.1%, 4.9%)** |
| Thrombocytopenia | 65 / 392 | 48 / 389 | 1.34 (0.95, 1.90) | | 16.6 | 12.3 | 4.2% (-0.7%, 9.2%) |
| Hypokalemia | 37 / 392 | 19 / 389 | **1.93 (1.13, 3.3)** | | 9.4 | 4.9 | **4.6% (1.0%, 8.2%)** |

Source: Compiled during evaluation based on TableB.6.1-1, p95; Table B.6.2-1, p98; Table B.6.7-1, p104; Table B.6.10-1, p111; of the submission; Table 21, p113; Table 50, pp187-188; Table 14.2.2.1, p458 of the CSR for ASPIRE

AE = adverse event; Bd = bortezomib + dexamethasone; Cd = carfilzomib + dexamethasone; CI = confidence interval; CLd = carfilzomib + lenalidomide + dexamethasone; HR = hazard ratio; Ld = lenalidomide + dexamethasone; mo = months; NE = not estimable; OS = overall survival; PFS = progression free survival; RD = risk difference; RR = relative risk; **bold** = statistically significant; \* = values with \* were extracted or calculated during evaluation

a Median duration of follow-up for PFS was 11.9 months in the Cd arm, 11.1 months in the Bd arm; Median duration of follow-up for OS was 12.5 months in the Cd arm and 11.9 months in the Bd arm.

b Median duration of follow-up for PFS was 31.4 months in the CLd arm, 30.1 months in the Ld arm; Median duration of follow-up for OS was 32.3 months in the CLd arm and 31.5 months in the Ld arm.

c Not significant when adjusted for multiplicity. p value (1 sided) = 0.0182 (p value required for significance [1-sided] = 0.0051)

* 1. The ESC considered that the incremental benefit of CLd over Cd was unclear and that data using a common reference, preferably Ld, would be useful to establish the difference in efficacy between the dual and triple therapy regimens. The PBAC acknowledged that the sponsor was not making any clinical claim in the submission relating to the efficacy of CLd in comparison to Cd, but noted that ensuring triple therapy conferred additional benefit for the additional cost would be relevant for assessing cost-effectiveness of the regimen. However, the PBAC also noted that a naïve comparison between two trials with different populations and follow-up time was an insufficient basis upon which to draw conclusions regarding comparative efficacy between the dual and triple therapy regimens.
  2. The PBAC noted that although Cd was associated with more serious treatment related adverse events than Bd, there was a significantly lower rate of peripheral neuropathy, which is an important side effect from a patient perspective.

Cd versus Bd

* 1. On the basis of direct evidence presented by the submission, there would be approximately a 9.3 month increase in median progression-free survival in patients treated with Cd in comparison with Bd, however, there would be no improvement in OS between these two groups. For every 100 patients treated with Cd in comparison with Bd, over a median follow-up of around 12 months:
* Approximately three additional patients would experience a Grade 3 or higher treatment-related adverse event; and
* Approximately four fewer patients would experience Grade 3 or higher peripheral neuropathy.

CLd versus Ld

* 1. On the basis of direct evidence presented by the submission, there would be approximately an 8.7 month increase in median progression-free survival in patients treated with CLd in comparison with Ld, however, there would be no improvement in OS between these two groups. For every 100 patients treated with CLd in comparison with Ld over a median follow-up of around 31 months:
* Approximately seven additional patients would experience a Grade 3 or higher treatment-related adverse event; and
* Approximately five additional patients would experience Grade 3 or higher hypokalaemia.

### Clinical claim

Scenario 1 (Cd only)

* 1. The submission claimed that Cd was superior in terms of comparative efficacy over Bd, and has a different safety profile. The claim of superior efficacy may be reasonable, although there was some degree of uncertainty because:
* Lenalidomide was also a relevant comparator.
* There was no statistically significant gain in OS, which was based on immature data. The ESC considered that the magnitude of OS gain was uncertain and was likely to have been overestimated; and
* There were higher rates of discontinuations without an event in the Bd arm. In the context of an open-label trial, this might bias the results in favour of Cd. The PSCR (p5) argued that discontinuations are not at random and the suggestion that this biased the results in favour of carfilzomib was unreasonable.
  1. The claim of a different safety profile between Cd and Bd was adequately supported by the evidence presented in the submission.

Scenario 2 (Cd and CLd available)

* 1. Cd versus Bd: in addition to the above comments, the patient population who might benefit from Cd (if CLd is also available) was unclear. If both regimens were available, the PBAC considered that Cd would predominantly be used in patients who could not take CLd (e.g. lenalidomide‑refractory patients). However, the PBAC noted that in the relevant subgroup analysis of the ENDEAVOUR trial (patients who were refractory to lenalidomide), Cd was not associated with a significant improvement in PFS compared with Bd.
  2. CLd versus Ld: The submission claimed that CLd is superior in terms of comparative efficacy and inferior in terms of comparative safety over Ld. The evaluation considered that the claim of superior efficacy was not adequately supported because OS was not statistically significantly superior in the carfilzomib arm when adjusted for multiplicity; the claim of inferior comparative safety was reasonable.

PBAC consideration

* 1. The PBAC considered that the claim of superior comparative effectiveness of Cd over Bd in Scenario 1, where only the Cd regimen was available, was reasonable. In Scenario 2, where the Cd regimen would likely be used in the subgroup of patients who could not use CLd, while the PBAC acknowledged the limitations of the subgroup analysis, the committee nevertheless considered that there was insufficient evidence to support a claim of superior comparative effectiveness of Cd over Bd. The PBAC considered that the claim of superior efficacy of CLd over Ld was adequately supported by the data for the PFS outcome but not for the OS outcome as the difference was not statistically significant when adjusted for multiplicity.
  2. The PBAC considered that the claim of a different safety profile between Cd and Bd was adequately supported by the data, and that the claim of inferior comparative safety of CLd to Ld was reasonable.

### Economic analysis

* 1. The submission presented two cost-utility analyses:
* Cd versus Bd (based on the ENDEAVOR trial); and
* CLd versus Ld (based on the ASPIRE trial).
  1. The economic model was a decision analytic model that used area under the curve methods to estimate PFS and OS. The model included three health states: progression free, progressed disease, and dead. No post-progression costs were included. Patients with multiple myeloma have subsequent relapses and lines of treatment. The ESC considered that a three-state model was insufficient to capture all of the disease states, the potentially displaced therapies and post-progression treatment costs. The pre-PBAC response (p2) stated that subsequent therapies were included in an alternative version of the model but they were excluded on the basis of not being a key driver of the cost-effectiveness. The PBAC agreed with the ESC, and considered that the three-state model did not adequately reflect the nature of multiple myeloma, as patients have initial and subsequent relapses and are usually prescribed various lines of treatments as the disease progress.
  2. The structure of the economic model was the same for both analyses, however the inputs differed. The submission considered the results of the two economic analyses in isolation without taking into account variations in the patient populations caused by the availability of the other regimen. The ESC considered that this may not have been appropriate, as the same population will be eligible for treatment but take different pathways depending on the suitable treatment (Cd or CLd), as such it may have been more appropriate to have structured the two scenarios as branches of the same model. The PBAC agreed with the ESC’s views, and noted that the model has not accounted for the effect of one regimen when the other regimen is also available.
  3. A summary of the model structure is presented in Table 7.

**Table 7: Summary of model structure and rationale**

|  |  |
| --- | --- |
| **Component** | **Summary** |
| Time horizon | 15 years in the base case, versus median follow-up of 11.5 months in ENDEAVOR and 31 months in ASPIRE. |
| Outcomes | Life years gained and QALYs. |
| Methods used to generate results | Decision analytic model that used area under the curve methods to estimate progression free survival and overall survival (Markov model). |
| Health states | Progression free, progressed disease, dead. |
| Cycle length | 28-days, with half-cycle correction. |
| Transition probabilities | Partitioned survival method, rather than explicit transition probabilities. |

Source: Text, pp 217-219 of the submission

QALY = quality adjusted life years

* 1. The ESC considered that the 15 year time horizon was not reasonable, given the patients’ age and that patients are required to have relapsed after stem cell transplantation or be transplant ineligible to be eligible for PBS-subsidised treatment, and are therefore more likely to be at later stages of multiple myeloma. The ESC considered that applying a 10 year time horizon would be more appropriate and noted that doing so increased the incremental cost‑effectiveness ratio (ICER) to $75,000 - $105,000 quality-adjusted life-year (QALY) for scenario 1 and to $105,000 - $200,000 per QALY for scenario 2. The pre-PBAC response (p3) argued that the time horizon was reasonable given that approximately a quarter of patients treated with Cd or Bd are still alive at 15 years in the model’s base case. However, this justification was based on patient numbers that have been derived from the extrapolation of the Kaplan-Meier OS curves and application of consistent treatment effects, which the PBAC considered to be highly uncertain. The PBAC agreed with the ESC and noted that the ICER was sensitive to the time horizon; and applying a 10 year time horizon significantly increased the ICER.

Scenario 1 (Cd only)

* 1. The key drivers of the economic model for Cd versus Bd are presented in Table 8.

**Table 8: Key drivers of the model of Cd vs Bd**

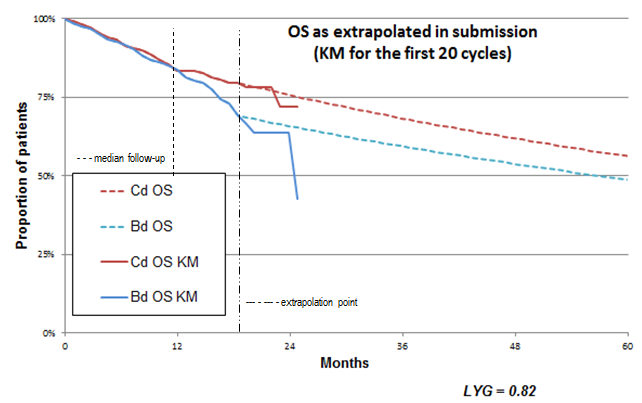
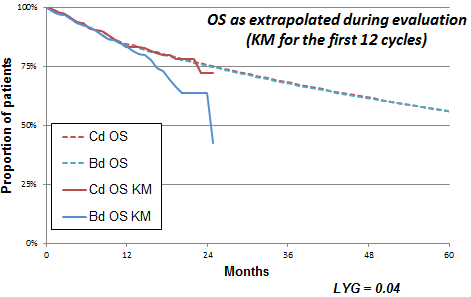
| **Description** | **Method/Value** | **Impact** |
| --- | --- | --- |
| Extrapolation of PFS and OS | Used the KM curve from ENDEAVOR for the first 20 cycles, despite a median follow-up of ~12 cycles. After this, for OS, UK registry data were adjusted and fitted with a parametric curve. Thus a persistent treatment effect was assumed and the OS curves did not converge. Overall, this resulted in 0.82 LYG. Extrapolation from 12 cycles resulted in 0.04 LYG (see Figure 3 below). | High, favoured Cd |
| Carfilzomib drug costs | No carfilzomib drug costs were included beyond ''''' cycles. The rationale provided in the submission was that Cd was used for longer than Bd in ENDEAVOR, and therefore the modelled duration of Cd use should also be longer than Bd (note that the maximum Bd cost was adjusted to reflect the maximum duration on the PBS).  The rationale for selecting ''''' cycles was unclear and the exclusion of carfilzomib drug costs beyond '''''' cycles was poorly justified. As carfilzomib was used until progression in the trial (mean PFS in the model was 21.6 cycles for Cd) and PBS-listing was proposed until progression, Cd costs should have been included until progression. | High, favoured Cd |
| Bortezomib treatment duration (costs and outcomes) | Bortezomib drug costs were included for 22 cycles (of 21-days) to align with the maximum duration under the PBS (favoured carfilzomib). On the other hand, this would underestimate the incremental effect of carfilzomib in Australian clinical practice (favoured bortezomib). | Unclear, direction of bias unclear |
| Post-progression costs & subsequent therapies | No post-progression costs were included. The 3 health-state model structure did not appropriately reflect the relapsing nature of multiple myeloma. | Unclear direction of bias unclear |
| Utilities | 0.81 for the progression free and 0.64 for the progressed health state (from van Agthoven 2004). These were not applicable to relapsed multiple myeloma, and the methods used to derive the progressed disease utilities were inappropriate. | Medium, direction of bias unclear |

Source: compiled during the evaluation

Bd = bortezomib + dexamethasone; Cd = carfilzomib + dexamethasone; KM = Kaplan-Meier; LYG = life years gained; OS = overall survival; PBS = Pharmaceutical Benefits Scheme; PFS = progression free survival; *ital.* = values in italics were calculated or interpreted during evaluation

* 1. Figure 3 (left panel) shows the OS curves from the submission’s base case (i.e. using the first 20 cycles of the Kaplan-Meier curve then extrapolation based on UK registry data). The right panel shows a sensitivity analysis conducted during the evaluation, which used the first 12 cycles of the Kaplan-Meier curve (which equated to the median follow-up, and then extrapolation was based on UK registry data per the submission).

**Figure 3: Cd vs Bd: Overall survival as extrapolated in the submission (left panel) and as extrapolated in a sensitivity analysis during evaluation (right panel)**

Source: Constructed during evaluation based on Carfilzomib\_Section D\_Economic Model.xlsm

Bd = bortezomib + dexamethasone; Cd = carfilzomib + dexamethasone; KM = Kaplan-Meier; LYG = life years gained; OS = overall survival; ital. = values in italics were calculated during evaluation

* 1. A key issue with the economic evaluation of Cd versus Bd was that the Kaplan-Meier curves from the ENDEAVOR trial were used for 20 cycles, which was well beyond the median follow-up in the trial (~12 cycles), The point from which the trial data was extrapolated was informed by a small number of patients, and was a point where there was a large difference in survival between the two arms (as shown in Figure 3).
  2. The PSCR (p2) argued that since entry to the ENDEAVOR trial was staggered, there was a distribution of potential follow-up ranges as opposed to a single value for follow-up. Therefore the PSCR suggested that the method to determine the time for which the Kaplan-Meier curves be used be determined through the effective number of patients remaining in the trial for which the same standard error applied had there been no censoring.
  3. The ESC considered that the PSCR did not adequately justify the current point of extrapolation used in the economic model and that the point of extrapolation overestimated the difference between Cd and Bd, favouring Cd. The ESC also noted that in the clinical trial, there was no separation between the survival curves at median follow-up. The PBAC agreed with the ESC and noted that the ICER was highly sensitive to the point of extrapolation from the Kaplan-Meier OS curve. Furthermore, the PBAC noted that the sensitivity analysis conducted during the evaluation extrapolating OS from the point of median follow-up conferred minimal survival benefit for carfilzomib, and resulted in an ICER of over $200,000 per QALY for scenario 1 (refer to Table 12 “OS KM duration”).
  4. Other key issues with the economic evaluation of Cd versus Bd were:
* No carfilzomib drug costs were included beyond '''''' cycles. The PBAC considered that this was inappropriate because carfilzomib was used until disease progression in the key trial (ENDEAVOR), the proposed restriction would enable use until disease progression, and this was the likely use in clinical practice in patients who have not progressed.
* UK registry data were used to extrapolate OS beyond the trial. The same probabilities (from the registry data) were applied to each arm of the comparison. Thus, a persistent treatment effect of carfilzomib was assumed (i.e. the survival curves did not converge during the modelled time horizon). The probabilities from the UK registry data were applied from the nominated last data-point from the Kaplan-Meier curve. Thus the choice of this last data-point had a large impact on the ICER.
* The PBAC considered that as per previous PBAC advice (Lenalidomide Public Summary Document (PSD), November 2015; Pomalidomide PSD, July 2014) the utilities from van Agthoven 2004 were not applicable to the relapsed/refractory multiple myeloma population. These utilities have previously not been accepted by the PBAC due to the inappropriate methods used to derive the progressed disease health state utilities.

Scenario 2 (Cd and CLd available)

* 1. For CLd versus Ld, the key drivers of the economic model are presented in Table 9.

**Table 9: Key drivers of the model of CLd vs Ld**

| **Description** | **Method/Value** | **Impact** |
| --- | --- | --- |
| Lenalidomide drug costs | The submission did not include lenalidomide drug costs in either arm. This favoured CLd due to a longer treatment duration for CLd than for Ld. | High, favoured CLd |
| Carfilzomib drug costs | No carfilzomib drug costs were included beyond ''''''' cycles. The submission proposed an RSA to cover the full carfilzomib drug costs beyond '''''' cycles for CLd. | High, favoured CLd |
| Extrapolation of OS | Used the KM curve from ASPIRE trial for the first 26 cycles vs median follow-up of around 35 cycles. This was appropriate as the data were reasonably more mature and this made little impact on the ICER. Per the Cd vs Bd model, UK registry data were then applied (adjusted and fitted with a parametric curve). Per the Cd vs Bd model, the OS curves did not converge and the registry data might not reflect current OS. | Unclear, favoured CLd |
| Post-progression costs & subsequent therapies | No post-progression costs were included. Further the 3 health-state model structure might not appropriately reflect the relapsing nature of multiple myeloma. | Unclear, direction of bias unclear |
| Utilities | 0.81 for the progression free and 0.64 for the progressed health state (from van Agthoven 2004). These were not applicable to relapsed multiple myeloma, and the methods used to derive the progressed disease utilities were inappropriate. | Medium, direction of bias unclear |

Source: compiled during the evaluation

Bd = bortezomib + dexamethasone; Cd = carfilzomib + dexamethasone; CLd = carfilzomib + lenalidomide + dexamethasone; ICER = incremental cost-effectiveness ratio; KM = Kaplan-Meier; Ld = lenalidomide + dexamethasone; OS = overall survival; RSA = Risk Sharing Arrangement; vs = versus

CLd versus Ld

* 1. The key issues for the comparison of CLd versus Ld were:
* The cost of lenalidomide was not included. The ESC considered that this was insufficiently justified in the PSCR and inappropriate because lenalidomide was used until disease progression in both arms, with a longer duration of use in the CLd arm compared with the Ld arm. The PBAC agreed with the ESC and also noted that treatment until progression is consistent with expected clinical practice. Although the treatment cost was excluded the treatment effect of prolonged lenalidomide use was included in the economic evaluation. The PBAC therefore considered that the cost of the CLd regimen was underestimated in the economic evaluation and noted that inclusion of lenalidomide costs (weighted price based on PBS utilisation data and using published prices) in both arms increased the ICER to more than $200,000 for CLd versus Ld and more than $200,000 for the weighted ICER[[1]](#footnote-2).
* The ICER relied on a RSA '''' '''''''''''' ''''''' ''''''' ''''''''''' ''''''''''' ''''' '''''''''''''''''''''''' '''''''''''''''''' '''''' ''''''''''''''' ''''''''' '''''' '''''''''''''''''''''''' '''''''''''' '''''''''''''' ''''''''''' ''''''''''''''''''' '''''''''''''''' ''''' '''''''''''''''' ''''' ''''''' ''''''''''''''''' ''''''''' '''''''''''' ''''''''' '''''''''''''''''''''''' ''''' ''''''''' '''''''''''''''''' ''''''''''''''''''' '''' ''''''''''''''''''''' ''''' ''''''''''''''''''''' ''''' ''''''''''''''''''''''''''' ''''''''''' '''''''''''' ''''' '''''''' '''''''' ''''''''''' '''''''''''''''''''' '''' '''''''' ''''''''''''''''''''''''' '''''''' ''''''''''''''''''' ''''''''' ''''''''''''''''''''''' '''''' '''''''''' '''''''''' '''' ''''''' '''''''''''''''' '''''''''''''' '''''' '''''''''''''''' '''''' '''''''' ''''''''''' '''''''''''''''''''' ''''''''' '''''''''''''''''''''''' ''''''''''''''''''''' '''''''''' ''''''''''''''''''''' ''' ''''''''''''''''''''''''' ''''' ''''''''''''''''''' ''' '''''''''''''' '''''''''''''''''''''' ''''''' ''''''' ''''''' ''''''''''''''''''''' '''''''' ''''''' ''''''' '''''''''''''''''' ''''''''' '''''''''''''''' ''''''''''''''''.
* Per the Cd versus Bd model, UK registry data were used to extrapolate OS beyond the trial and a persistent treatment effect of carfilzomib was assumed. The PBAC considered that the assumption of a persistent treatment effect of carfilzomib was inappropriate.
* Per the Cd versus Bd model, the utilities were not applicable.

Both models

* 1. Table 10 summarises the results of the two modelled economic evaluations. Drug costs for carfilzomib and bortezomib were updated during the evaluation to reflect: the weighted number of vials per infusion for carfilzomib; the number of doses required per cycle for bortezomib; and the 1 August 2016 drug prices. The ICERs were corrected during the evaluation to account for these amendments, and then further updated based on the revised Special Pricing Arrangement (SPA) proposal for Cd in the PSCR. The ESC further noted that using the effective price for bortezomib and lenalidomide increased the ICER for both regimens.

**Table 10: Results of the economic evaluation for the two models (values were recalculated based on the new SPA proposal in the PSCR)**

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
|  | **Cd vs Bd** | | | **CLd vs Ld** | | |
|  | **Cd** | **Bd** | **Incremental outcome** | **CLd** | **Ld** | **Incremental outcome** |
| Cost (per submission)  Corrected costa | $'''''''''''''''''''''  $''''''''''''''''''' | $74,999  $72,420 | $''''''''''''''''  $''''''''''''''' | $'''''''''''''''  $'''''''''''''''' | $5,256  $5,256 | $'''''''''''''''  $''''''''''''''' |
| LYG | 5.83 | 5.21 | 0.61 | 5.73 | 5.18 | 0.55 |
| **Incremental cost/extra LYG (submission)**  **Corrected incremental cost/extra LYGa** | | | **$''''''''''''''**  **$''''''''''''''** |  |  | **$''''''''''''''''**  **$''''''''''''''''** |
| QALYs | 4.01 | 3.51 | 0.49 | 4.10 | 3.66 | 0.45 |
| **Incremental cost/extra QALY gained**  **Corrected incremental cost/ QALY gaineda** | | | **$''''''''''''**  **$''''''''''''** |  |  | **$'''''''''''''''''**  **$'''''''''''''''''** |

Source: Tables D.5-1 to D.5-4, pp233-6 of the submission; Carfilzomib\_Section D\_Economic Model.xlsm

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

a The drug costs were updated/corrected for carfilzomib and bortezomib to appropriately estimate the cost per infusion and revised based on the new SPA proposed in the PSCR (pg 4)

* 1. During evaluation the ICERs for each of the scenarios were calculated. For Scenario 2 a weighted ICER was calculated based on 20% of patients taking Cd and 80% taking CLd (per the financial estimates, based on a clinician survey). The resulting ICERs for each of the two scenarios are presented in Table 11.

**Table 11: ICER for each scenario (values were recalculated based on the new SPA proposal in the PSCR)**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Scenario** | **Comparison** | **Δ cost** | **Δ QALY** | **ICER** |
| **1 (only Cd subsidised)** | Cd vs. Bd | **$''''''''''''** | **0.492** | **$'''''''''''''** |
| **2 (Cd and CLd subsidised)** | Cd vs. Bd | $''''''''''''''''' | 0.492 | $''''''''''''''''' |
| CLd vs Ld | $'''''''''''''''''' | 0.445 | $'''''''''''''''''''' |
| **Weighted (20% Cd and 80% CLd) a** | **$''''''''''''''** | **0.454** | **$'''''''''''''''''** |

Source: Table D.5-1, p233; Table D.5-2, p235 of the submission; Carfilzomib\_Section D\_Economic Model.xlsm

Bd = bortezomib + dexamethasone; Cd = carfilzomib + dexamethasone; CLd = carfilzomib + lenalidomide + dexamethasone; ICER = incremental cost-effectiveness ratio; Ld = lenalidomide + dexamethasone; QALY = quality-adjusted life year; vs = versus

a The weighted ICER was calculated by dividing the weighted mean difference in costs by the weighted mean difference in QALYs. The weightings used were: 20% Cd and 80% CLd (per the financial estimates)

* 1. The economic evaluation for Scenario 1 resulted in an ICER of $45,000 - $75,000 per QALY for Cd versus Bd.
  2. The economic evaluation for Scenario 2 resulted in an ICER of $45,000 - $75,000 QALY for Cd versus Bd (i.e. the same as Scenario 1); and an ICER of $105,000 - $200,000 per QALY for CLd versus Ld. The resulting weighted ICER was $105,000 - $200,000 per QALY. The ICERs for both scenarios were likely to be underestimated.
  3. The ESC noted that the PSCR (p5) argued against using a weighted ICER on the basis that this would disadvantage the Cd regimen. The ESC considered that both the individual and weighted ICERs were uncertain and likely to be underestimated, and that rather than applying a weighted ICER, a more appropriate approach would be to include both treatment arms in the same model, given that the proposed eligible populations are identical.
  4. Table 12 presents the results of univariate sensitivity analyses presented in the submission and additional analyses performed during the evaluation.

**Table 12: Results of selected sensitivity analyses calculated during the evaluation (does not reflect updated prices per the new SPA)**

|  | **Cd vs Bd** | | | **CLd vs Ld** | | | **Weighted ICER a**  **Scenario 2** |
| --- | --- | --- | --- | --- | --- | --- | --- |
|  | **Δ**  **cost** | **Δ**  **QALY** | **ICER**  **Scenario 1** | **Δ**  **cost** | **Δ**  **QALY** | **ICER** |
| **Base case (submission)** | **$''''''''''''** | **0.492** | **$'''''''''''''** | **$''''''''''''** | **0.445** | **$'''''''''''''''** | **$''''''''''''''''** |
| **Corrected base case b** | **$''''''''''''''** | **0.492** | **$''''''''''''** | **$'''''''''''''** | **0.445** | **$''''''''''''''''** | **$''''''''''''''''** |
| **Univariate analyses (base case values are presented in brackets)** | | | | | | | |
| PFS KM duration (20 cycles)   * 12 cycles for Cd vs Bd * 34 cycles for CLd vs Ld | $''''''''''''''''' | 0.457 | $''''''''''''''' | $'''''''''''''''' | 0.438 | $'''''''''''''''''' | $''''''''''''''''''' |
| OS KM duration (20 cycles)   * 12 cycles for Cd vs Bd * 34 cycles for CLd vs Ld | $''''''''''''''''' | 0.119 | $''''''''''''''''''' | $'''''''''''''''' | 0.464 | $''''''''''''''''' | $''''''''''''''''''''' |
| Utilities (PFS 0.81, PD 0.64)   * 0.7 and 0.4 | $''''''''''''''' | 0.421 | $'''''''''''''''' | $''''''''''''''' | 0.383 | $''''''''''''''''''' | $'''''''''''''''''''' |
| **Costs** |  |  |  |  |  |  |  |
| Max cycles of Carf paid (''''''')   * Until progression for Cd * Until progression for Cd & CLd | $''''''''''''''''''''  $''''''''''''''''''' | 0.492  0.492 | $''''''''''''''''''''  $''''''''''''''''''''' | $'''''''''''''''''  $'''''''''''''''''''' | 0.445  0.445 | $''''''''''''''''''  $''''''''''''''''''' | $''''''''''''''''''''  $''''''''''''''''''' |
| Ld costs included ($0)   * $6,156 c for len, $21 for dexa per cycle (86.9% of doses taken) using published price | $''''''''''''''''' | 0.492 | $'''''''''''''''''' | $''''''''''''''''''''' | 0.445 | $''''''''''''''''''''' | $''''''''''''''''''''' |
| Time horizon (15 years)   * 10 years | $''''''''''''''' | 0.423 | $'''''''''''''''' | $'''''''''''''''' | 0.385 | $''''''''''''''''''''' | $''''''''''''''''' |
| **Multivariate sensitivity analyses** | | | | | | | |
| PFS +OS KM duration (20 cycles)   * 12 cycles for both for Cd vs Bd * 34 cycles for both for CLd vs Ld | $'''''''''''''''' | 0.083 | $''''''''''''''''' | $'''''''''''''''' | 0.458 | $'''''''''''''''''''''' | $'''''''''''''''''' |
| PFS + OS KM duration of 12 cycles + carf costs until progression   * Until progression for Cd * Until progression for Cd & CLd | $''''''''''''''''  $'''''''''''''''' | 0.083  0.083 | $''''''''''''''''''''''''  $''''''''''''''''''''''' | $'''''''''''''''''  $''''''''''''''''' | 0.458  0.458 | $''''''''''''''''''  $''''''''''''''''''' | $'''''''''''''''''''''  $''''''''''''''''' |
| Carf, Bort and Len costs included, and until progression (max cycles of Carf = 18; Bort = 22; Len = 0)   * Until progression | $'''''''''''''''''' | 0.492 | $'''''''''''''''''' | $''''''''''''''''' | 0.445 | $''''''''''''''''''' | $'''''''''''''''''''' |

Source: Tables D.6-1 to D.6-4 pp241-247 of the submission; Carfilzomib\_Section D\_Economic Model.xlsm; Bd = bortezomib + dexamethasone; Bort = bortezomib; Carf = carfilzomib; Cd = carfilzomib + dexamethasone; CLd = carfilzomib with lenalidomide and dexamethasone; dexa = dexamethasone; ICER = incremental cost-effectiveness ratio; Ld = lenalidomide + dexamethasone; len = lenalidomide; KM = Kaplan-Meier; OS = overall survival; PFS = progression free survival; PD = progressed disease; PFS = progression free survival; QALY = quality-adjusted life year

a The weighted ICER was calculated by first calculating the weighted incremental costs and incremental QALYs. The weightings used were: 20% Cd and 80% CLd. These were the weights that the submission used for the financial estimates.

b The drug costs were updated and corrected for carfilzomib and bortezomib to estimate the cost per infusion

c The weighted lenalidomide price was based on utilisation from PBS data (March 2015 to February 2016).

* 1. Cd versus Bd: the results of the sensitivity analyses indicated that the ICER for Cd versus Bd was most sensitive to the extrapolation of OS, utility values applied, and the exclusion of carfilzomib drug costs after ''''''' cycles. In the sensitivity analysis of Cd versus Bd, the ICER ranged from $75,000 - $105,000 per QALY to over $200,000 per QALY.
  2. CLd versus Ld: the sensitivity analyses indicated that the ICER for CLd versus Ld was most sensitive to the exclusion of lenalidomide costs, the exclusion of carfilzomib drug costs after '''''' cycles, and the utility values applied. In the sensitivity analysis of CLd versus Ld, the ICER ranged from $105,000 - $200,000 per QALY to over $200,000 per QALY.
  3. Overall for Scenario 2, the ICER was most sensitive to the extrapolation of PFS and OS, the exclusion of carfilzomib drug costs after 18 cycles and the exclusion of lenalidomide costs. In the sensitivity analysis of Scenario 2, the ICER ranged from $105,000 - $200,000 per QALY to over $200,000 per QALY.
  4. Other uncertainties that could not be tested during evaluation, as they would require structural changes to the model, included the impact of a three-state model and the persistent OS benefit (i.e. the OS curves did not converge over the modelled time horizon).
  5. The PBAC noted that the sensitivity analyses using a 10 year time horizon, including carfilzomib drug costs beyond '''''' cycles, and including lenalidomide drug costs for the CLd regimen, increased the ICERs considerably. The PBAC considered that this indicated that the submission’s base case ICER was highly uncertain and likely underestimated.

### Drug cost/patient/course: (the following costs were not updated to reflect the new SPA price proposed in the PSCR)

**The cost of carfilzomib in the Cd regimen was: $''''''''''''''**.

* 1. This was based on a mean treatment of '''''' doses (''''''''''' cycles with six infusions a cycle, and '''''''% of doses given) and an average cost of $'''''''''''' per dose (based on the distribution of vials per infusion from the ENDEAVOR trial, in which '''''''% of infusions used the 60 mg vial, ''''''% used a 30 mg plus a 60 mg vial, and '''''''% used two 60 mg vials).

**The cost of carfilzomib in the CLd regimen was $''''''''''''''.**

* 1. This cost did not include the additional costs for the prolonged duration of lenalidomide.
  2. The estimated drug cost was based on a mean treatment of '''''' doses (''''''''''' cycles with six infusions a cycle for Cycles 1 to 12 and four infusions a cycle for Cycles 13+, and ''''''% of doses given) and an average cost of $'''''''''' per dose (based on one 60 mg vial required per infusion in the ASPIRE trial). The PBAC noted that the lower cost of carfilzomib in the CLd regimen was because the carfilzomib dose is lower in CLd than in Cd.

### Estimated PBS usage & financial implications

* 1. This submission was not considered by DUSC. The submission used a mixed epidemiological and market share approach to estimate the utilisation and financial impact of listing carfilzomib.

Scenario 1 (Cd only)

* 1. The estimated use and financial implications of listing carfilzomib on the PBS for use as part of the Cd regimen (Scenario 1) are presented in Table 13. The redacted table below shows that at year 5 the estimated number of patients was less than 10,000 per year and the net cost to the PBS would be $10 - $20 million per year.

**Table 13: Estimated use and financial implications- Scenario 1 (Cd listed only)**

|  | **Year 1** | **Year 2** | **Year 3** | **Year 4** | **Year 5** |
| --- | --- | --- | --- | --- | --- |
| **Estimated extent of use** | | | | | |
| Number treated | '''''''''' | '''''''''' | '''''''''' | '''''''''' | ''''''''' |
| Doses dispensed | ''''''''''''''''' | ''''''''''''''''' | '''''''''''''''' | '''''''''''''''''' | ''''''''''''''' |
| **Estimated net cost to PBS/RPBS/MBS\*** | | | | | |
| Net cost to PBS/RPBS | $''''''''''''''''''''''''''' | $'''''''''''''''''''''''' | $'''''''''''''''''''''''' | $'''''''''''''''''''''''' | $'''''''''''''''''''''''' |
| Net cost to MBS | $''''''''''''''''''''' | $'''''''''''''''''' | $''''''''''''''''''' | $''''''''''''''''''''' | $'''''''''''''''''' |
| **Estimated total net cost** | | | | | |
| **Net cost to PBS/RPBS/MBS\*** | **$'''''''''''''''''''''''** | **$''''''''''''''''''''** | **$'''''''''''''''''''''''** | **$'''''''''''''''''''''** | **$'''''''''''''''''''''** |

Source: Table E.1-8, p262; Table E.4-1, p265 of the submission; Section E spreadsheet

Cd = carfilzomib + dexamethasone; MBS = Medicare Benefits Schedule; PBS = Pharmaceutical Benefits Scheme; RPBS = Repatriation Pharmaceutical Benefits Scheme; Values with \* were updated during evaluation to reflect 1 August 2016 prices and apply the co-payments per initial prescription for Efficient Funding of Chemotherapy drugs

* 1. The submission estimated, for Scenario 1, a total net cost to PBS/RPBS and MBS of $60 - $100 million over five years. The PBAC considered that this was an underestimate of the cost to the PBS/RPBS because:
* Carfilzomib costs were only included for up to ''''''' cycles, while listing was sought until disease progression. No RSA was proposed for Cd. Although the PSCR stated that carfilzomib treatment (in Cd) is not expected to continue beyond '''''' cycles, the ESC did not believe that this was sufficiently justified and that clinicians are likely to continue to use carfilzomib while the patient is not progressing;
* The number of eligible patients was underestimated because the number of patients initiating bortezomib each year was underestimated (it was assumed that almost half the patients were continuing from the previous year) and not all item codes were included;
* There might be higher uptake in the eligible population treated with lenalidomide;
* The submission overestimated bortezomib cost offsets due to possible overestimation of the number of bortezomib doses used on the PBS;
* Cost offsets are unlikely to be realised because carfilzomib is likely to add another line of therapy. The PSCR argued that additional costs are likely to be offset by reduced costs since patients treated with carfilzomib are less likely to progress and move to alternative therapies. The PBAC considered that this was unlikely, because while treatment with carfilzomib may delay progression, it does not prevent it, and therefore drug costs from alternative therapies will still be incurred; and
* The number of patients with relapsed multiple myeloma might have increased at a higher rate than estimated due to the survival benefits of newer treatments.

Scenario 2 (Cd and CLd available)

* 1. The estimated use and financial implications of listing carfilzomib on the PBS for use as part of the Cd and CLd regimens (Scenario 2) are presented in Table 14. For Scenario 2, the submission used the total patient numbers from Scenario 1 then increased this by 30% to estimate utilisation of both Cd and CLd. The submission then assumed that 20% of patients would use Cd and 80% would use CLd.

**Table 14: Estimated use and financial implications- Scenario 2 (Cd and CLd both listed)**

|  | **Year 1** | **Year 2** | **Year 3** | **Year 4** | **Year 5** |
| --- | --- | --- | --- | --- | --- |
| **Estimated extent of use** | | | | | |
| Number treated with Cd | ''''''''' | '''''''''' | ''''''''' | '''''''''' | '''''''''' |
| Number treated with CLd | '''''''''' | '''''''' | ''''''''' | '''''''''' | '''''''''' |
| Doses dispensed for Cd | ''''''''''''' | ''''''''''''''' | '''''''''''' | '''''''''''''' | '''''''''''' |
| Doses dispensed for CLd | '''''''''''''''' | ''''''''''''''''' | '''''''''''''''''' | '''''''''''''''' | ''''''''''''''''' |
| **Estimated net cost to PBS/RPBS/MBS** | | | | | |
| Net cost to PBS/RPBS\* | $''''''''''''''''''''''''' | $''''''''''''''''''''''''' | $''''''''''''''''''''''''''''' | $''''''''''''''''''''''' | $''''''''''''''''''''''''''' |
| Net cost to MBS | $''''''''''''''''''''''''' | $''''''''''''''''''''''' | $'''''''''''''''''''''' | $'''''''''''''''''''''''' | $''''''''''''''''''''''''' |
| **Estimated total net cost** | | | | | |
| **Net cost to PBS/RPBS/MBS\*** | **$'''''''''''''''''''''** | **$'''''''''''''''''''''** | **$''''''''''''''''''''''** | **$'''''''''''''''''''''** | **$'''''''''''''''''''''** |

Source: Table E.1-8, p262; Table E.4-1, p265 of the submission; Section E spreadsheet

Cd = carfilzomib + dexamethasone; CLd = carfilzomib + lenalidomide + dexamethasone; MBS = Medicare Benefits Schedule; PBS = Pharmaceutical Benefits Scheme; RPBS = Repatriation Pharmaceutical Benefits Scheme; Values with \* were updated during evaluation to reflect 1 August 2016 prices and apply the co-payments per initial prescription for Efficient Funding of Chemotherapy drugs, but does not reflect the new SPA price.

,

The redacted table above shows that at year 5 the estimated number of patients was less than 10,000 per year and the net cost to the PBS would be $30 - 60 million per year.

* 1. The submission estimated, for Scenario 2, a total net cost to the PBS/RPBS and MBS of more than $100 million. The PBAC considered that total net cost to the PBS/RPBS may have been underestimated because:
* Lenalidomide costs were not included for the CLd regimen and treatment with lenalidomide would be extended when used in CLd compared with Ld (see economic model). Insufficient justification was provided for this exclusion;
* Carfilzomib costs were only included for a maximum of '''''' cycles, while listing was sought until progression and although the sponsor '''''''''''''''''''' '''' ''''''''''''''''''''''''''' ''''' '''''''''''''''''''''' '''' '''''''''''''''' '''''''''''''''''''' '''''' ''''''''' ''''''' ''''''''''' '''''''''''''''''''' ''''''''' ''''''' '''''''''' ''''' ''''''''''''''''''''''' ''''''''''' ''''''' ''''''''''''' '''''''''' ''''''''''' '''''''''''''''''''' ''''''' ''''''''' '''''''''' ''''''''''''''''''';
* Uptake from patients currently being treated with lenalidomide was significantly underestimated;
* Cost offsets are unlikely to be realised because carfilzomib is likely to add another line of therapy and the number of patients with relapsed multiple myeloma might have increased due to the survival benefits of newer treatments; and
* The effective price of other therapies has not been taken into account in calculating the cost offsets.
  1. In a sensitivity analysis, the submission used the PBS 10% sample data to estimate the number of patients who started bortezomib or lenalidomide each year. A more reliable method would have been to estimate the total eligible population per year, that is, the total number of patients who started any PBS-listed treatment for second or later lines of multiple myeloma therapy. Uptake assumptions (e.g. from the market research survey) could then be applied to determine the number of patients likely to use carfilzomib.

### Quality Use of Medicines

* 1. The submission did not identify any potential quality use of medicines issues. Different doses of carfilzomib were used in the Cd and CLd regimens (the carfilzomib dose in Cd regimen was 56 mg/m2, while for the CLd regimen was 27 mg/m2 for most cycles). This might potentially lead to inappropriate doses being given.

### Financial Management – Risk Sharing Arrangements

* 1. The submission proposed a '''''''''% rebate for carfilzomib use beyond '''''' cycles for the CLd regimen. This was because in the ASPIRE trial (CLd versus Ld), ''''''''''''''''''''''''''' ''''''''' '''''''''''''''' ''''''''''' ''''''' '''''''''''''''' ''''''' '''''''' '''''''''''''''''''''''''''' '''''''''''''''''''''''' '''''''''''' ''''' '''''''''''''''''''''''''''' '''''''''' '''''''''''''''''' '''''''''''''''''''''''''. This was included in the economic model and the financial estimates. However, it was not certain whether a RSA based on '''''''''''''' '''' '''''''''''''''''''''''' could be implemented as it would require data at the individual patient level.
  2. No rebate was proposed for the Cd regimen, but no drug costs for carfilzomib use beyond '''''' cycles were included in the economic evaluation or financial estimates. Therefore, the cost of treatment with carfilzomib as part of the Cd regimen was likely underestimated. The PSCR (p1) stated that carfilzomib treatment as part of the Cd regimen was not anticipated to extend beyond '''''' months and that the sponsor was ''''''''''''''' ''''' ''''''''''''''''' ''''''''''' '''' ''''''''''''''''''' ''''''''' '''''''''''''''' ''''' '''''''''. However, no rationale was provided in the PSCR for this assumption on treatment duration or details on how the risk of extended treatment beyond ''''' months might be mitigated. The rationale for this was not well justified, and the ESC considered that both the economic and financial models should include drug costs beyond '''''' cycles. The pre-PBAC response (p3) indicated that the sponsor was willing to explore “various possibilities” for Cd, but did not provide a specific proposal for a RSA.
  3. The submission also stated that the sponsor would be open to considering market or financial caps in line with those for other multiple myeloma medicines.

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

1. **PBAC Outcome**
   1. The PBAC did not recommend the listing of carfilzomib for the treatment of relapsed or refractory multiple myeloma in combination with dexamethasone (Cd) or in combination with lenalidomide and dexamethasone (CLd) on the basis of high and uncertain incremental cost-effectiveness ratios (ICERs). The PBAC considered the role of CLd versus Cd in clinical practice was unclear and noted clinical data comparing these two regimens are not available. The PBAC considered the modelled overall survival gains with carfilzomib to be uncertain because the data from the clinical trials are immature and the differences were not statistically significant. The PBAC noted a number of assumptions in the economic model which favoured carfilzomib and hence considered that the base case ICERs were likely to be substantially underestimated.
   2. The PBAC noted the consumer comments received in support of a PBS listing for carfilzomib, and considered that these reflected the clinical need for additional treatment options for patients with relapsed or refractory multiple myeloma.
   3. The submission requested listings for Cd alone (Scenario 1) and for both Cd and CLd (Scenario 2), but not for CLd alone. The PBAC noted the submission did not address the different patient populations likely to be treated with CLd versus Cd if both were available, and further considered the role of CLd versus Cd in clinical practice was unclear, especially given a lower dose of carfilzomib is used in the CLd regimen and clinical data comparing the two regimens are not available. The PBAC noted the request in the sponsor’s Pre-PBAC response to separately consider the Cd and CLd regimens, however noted both regimens are included in the indication proposed by the TGA Delegate and that the appropriate clinical positioning of each regimen needs to be considered in this light.
   4. The PBAC considered that Bd, as nominated by the submission, was an appropriate comparator for Cd, but that Ld was also a relevant comparator. The PBAC also accepted that placebo plus Ld was an appropriate comparator for CLd.
   5. The PBAC noted that the submission was based on two head-to-head trials, one comparing Cd with Bd (ENDEAVOR) and one comparing CLd with Ld (ASPIRE). The PBAC noted that although the trials were open-label, the assessment of PFS was blinded and was based on objective measures of response. The PBAC also noted that although ASPIRE had 20 months more follow-up than ENDEAVOR, the data from both trials were immature.
   6. The PBAC considered that the claim of superior comparative effectiveness of Cd over Bd for Scenario 1 (Cd only) was reasonable. The PBAC did not accept this claim for Scenario 2 (both Cd and CLd) because the population most likely to receive Cd would be the subgroup of patients who could not tolerate or were refractory to lenalidomide, and noted that a subgroup analysis of ENDEAVOR participants who were refractory to lenalidomide showed no significant difference in PFS between the Cd and Bd arms. Whilst the PBAC acknowledged the limitations of the subgroup analysis, it considered that there was no conclusive evidence that Cd was of superior efficacy over Bd in patients who would not be able to tolerate or were refractory to lenalidomide. The PBAC considered that the claim of superior efficacy of CLd over Ld was adequately supported by the data for the PFS outcome but not for the OS outcome as the difference was not statistically significant when adjusted for multiplicity.
   7. The PBAC accepted the claim that Cd had a different safety profile compared to Bd, and that CLd was of inferior safety compared to placebo plus Ld. The PBAC noted that patients taking Cd had a significantly lower rate of peripheral neuropathy related adverse events, but that the rate of any grade 3 or higher treatment-related adverse events was not significantly different to Bd. The PBAC also noted that patients taking CLd had significantly higher rates of hypertension and hypokalaemia adverse events, but that the rate of any Grade 3 or higher treatment-related adverse events was not significantly different to Ld.
   8. The PBAC noted that the structure of the economic model was the same for both scenarios, hence issues relating to the model structure related to both scenarios. The PBAC considered that it may be appropriate for the model to include multiple lines of therapy and post-progression treatment costs. The PBAC further considered that the model was not appropriately structured to account for the effect of one regimen while the other regimen is also available, rather, the submission presented an economic analysis for the Cd and CLd regimens in isolation.
   9. The PBAC considered the modelled overall survival gains with carfilzomib to be uncertain because the data from the clinical trials are immature and the differences were not statistically significant. The PBAC considered that this uncertainty was increased by assuming a persistent treatment effect for the model duration (i.e. the survival curves did not converge)and using a time horizon of 15 years. The PBAC considered a persistent treatment effect was not adequately supported and a time horizon of 10 years would be more appropriate. The PBAC also noted its previous advice that the utilities from van Agthoven 2004 were not applicable to the relapsed/refractory multiple myeloma population, and therefore considered that its use was inappropriate in this submission.
   10. The PBAC considered that the ICERs presented in the submission’s base case of $45,000 - $75,000 for Cd and $105,000 - $200,000 for CLd were high, and likely to be significantly underestimated due to concerns with the economic model, additional to the above mentioned, including:

Cd

* The method of extrapolation: OS was based on the Kaplan-Meier curves up until 20 cycles (beyond the median trial follow-up of 12 cycles), after which UK registry data were applied to extrapolate over the time horizon. The ICER was highly sensitive to the point of extrapolation from the Kaplan-Meier OS curves. When the Kaplan-Meier OS curves were used until median follow-up (12 cycles), the modelled life years gained decreased to 0.04, and ICER increased to over $200,000 per QALY.
* Cost of carfilzomib beyond '''''' cycles: this was not included despite PBS-listing being sought until disease progression, and no specific RSA was proposed by the sponsor for Cd.

CLd

* Cost of lenalidomide: the PBAC considered that it was inappropriate for the lenalidomide drugs costs to be excluded from the model, as treatment in combination with carfilzomib extended the treatment time, and therefore cost, with lenalidomide. The PBAC noted that inclusion of lenalidomide costs (based on published prices) increased the ICER to over $200,000/QALY gained.
  1. The PBAC noted that the estimated net cost of carfilzomib was approximately $60 - $100 million and more than $100 million over five years, for Scenario 1 and 2, respectively. The PBAC considered that the estimated financial impacts to the PBS of listing carfilzomib were underestimated. For Cd, the PBAC considered that carfilzomib drug costs beyond '''''' cycles should have been included as although the sponsor has indicated willingness for a RSA, no clear proposal was provided. The PBAC further considered that the number of eligible patients was underestimated, and cost offsets are unlikely to be realised because bortezomib use has been overestimated, and carfilzomib is likely to displace rather than replace other treatment options. In addition to the issues relating to Cd costs, the drug costs for longer treatment with lenalidomide as part of the CLd regimen were not included.
  2. The PBAC noted that the sponsor was unable to provide details of the number of patients currently receiving carfilzomib through the compassionate use program that would be eligible for PBS subsidy, and therefore these patients were not included in the estimates. The sponsor also did not propose a practical approach to grandfathering these patients.
  3. The PBAC considered that any resubmission must be a major submission and should address the issues raised by the PBAC, particularly in relation to clinical place of CLd versus Cd, the issues with the economic model, and financial forecasts.
  4. The PBAC noted that this submission is eligible for an Independent Review.

**Outcome:**

Rejected

1. **Context for Decision**

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

1. **Sponsor’s Comment**

Amgen is committed to working with the PBAC to address any areas of uncertainty and ensure that patients are able to access carfilzomib through the PBS at the earliest possible opportunity.

Amgen is pleased with the PBAC’s acknowledgement of the clinical need for additional treatment options for patients with relapsed or refractory multiple myeloma and regard carfilzomib - either Cd or CLd - as an important therapeutic option for Australian myeloma patients.

Amgen believe that triplet combination therapy represents an important advance for myeloma patients and whilst it presents unique challenges with regard to assessing cost-effectiveness, Amgen look forward to working with the PBAC and the broader haematology community to identify solutions to this complex funding issue.

1. ICERs do not reflect the updated prices per the new SPA proposed in the PSCR [↑](#footnote-ref-2)