

7.10 SELINEXOR, Tablet 20 mg, Xpovio[®], Antengene (Aus) Pty. Ltd.

1 Purpose of submission

- 1.1 The standard re-entry resubmission requested a Section 100 (Highly Specialised Drug), Authority Required (Telephone, Electronic) listing of selinexor in combination with bortezomib and dexamethasone (SBd) for the treatment of adult patients with relapsed and/or refractory multiple myeloma (RRMM) who have received at least one prior therapy.
- 1.2 Listing was requested on the basis of a cost-minimisation analysis (CMA) versus carfilzomib + dexamethasone (Cd).

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

Component	Description
Population	Adult patients with relapsed and/or refractory multiple myeloma who have received at least one prior therapy
Intervention	Selinexor in combination with bortezomib and dexamethasone (SBd)
Comparator ^a	Main comparator: carfilzomib + dexamethasone (Cd)
Outcomes	PFS; Safety
Clinical claim ^b	In patients with MM who have received at least one prior therapy, treatment with selinexor in combination with bortezomib and dexamethasone is non-inferior compared to Cd with respect to efficacy with a different safety profile.

Source: Table 1-2, p29 of the resubmission.

Abbreviations: Cd = carfilzomib + dexamethasone; MM = multiple myeloma; PFS = progression free survival; SBd = selinexor + bortezomib + dexamethasone.

a. The July 2021 submission nominated Bd as primary comparator and Cd as secondary comparator.

b. The July 2021 submission claimed comparable effectiveness and different safety profile of SBd compared with Cd.

Blue shading indicates data previously seen by the PBAC.

2 Background

Registration status

- 2.1 Selinexor was TGA registered on 8 March 2022 for the following indication:
- In combination with bortezomib and dexamethasone for the treatment of adult patients with multiple myeloma who have received at least one prior therapy.
- 2.2 The requested PBS restriction is consistent with the TGA indication.

Previous PBAC consideration

- 2.3 A summary of the key matters of concern from the previous PBAC consideration is presented in Table 2. As distinct from the July 2021 submission, the resubmission did

Public Summary Document – March 2022 PBAC Meeting

not include bortezomib + dexamethasone (Bd) as a comparator and did not make a clinical claim or present evidence of the cost-effectiveness of SBd relative to Bd.

Table 2: Summary of key matters of concern

Component	Matter of concern	How the resubmission addresses it
Comparator	The submission nominated Bd as the primary comparator and Cd as a secondary comparator. However, PBAC considered that SBd was most likely to replace and/or displace Cd, lenalidomide plus dexamethasone, pomalidomide plus dexamethasone and some bortezomib-based regimens including Bd (para 7.3, July 2021 PBAC PSD).	The resubmission nominated Cd as the primary comparator. The resubmission did not include Bd as a comparator and did not make a clinical claim or present evidence of the cost-effectiveness of SBd relative to Bd. The resubmission did not adequately justify the exclusion of Bd as a comparator and also did not address the potential for SBd to substitute Ld, Pd, ELd and PBd.
Clinical place in therapy	DBd was available on the PBS as a second line treatment only, SBd would likely be used as a third or later line treatment (para 7.3, July 2021 PBAC PSD).	The clinical management algorithm remained unchanged, and presented SBd as a second or third line therapy.
Clinical effectiveness	<ul style="list-style-type: none"> There were differences that might have impacted the transitivity of BOSTON and ENDEAVOR trials (para 7.9, July 2021 PBAC PSD). The claim that SBd was non-inferior compared to Cd in terms of efficacy was not supported given the numerically superior PFS results for Cd versus Bd and the lack of a significant gain in OS for SBd versus Bd (para 7.11, July 2021 PBAC PSD). 	<ul style="list-style-type: none"> An adjusted ITC and STC which accounted for differences between trials in terms of ECOG status and age was presented. However, differences that may have impacted the transitivity of the trials remained. Not addressed. No new trials were identified, and the results from the BOSTON updated data cut-off (February 2021) showed no significant OS gain for SBd versus Bd.
Safety	The comparison between SBd and Cd was difficult to interpret due to the transitivity issues between the trials and the absence of data presented for the Bd common reference arms (para 7.10, July 2021 PBAC PSD)	Not adequately addressed. The resubmission provided a formal ITC for SBd versus Cd, via Bd, for key safety outcomes. However, the unadjusted ITC presented was confounded by the underlying transitivity issues between the studies.
Economic evaluation (CUA)	In the CUA comparing SBd to Bd, the ICER was likely underestimated, and the PBAC considered the economic model should conservatively estimate any survival advantage for SBd due to the lack of demonstrated OS benefit in the clinical trial (para. 7.13, July 2021 PBAC PSD).	Not addressed. CUA versus Bd has been removed from the resubmission.
Economic evaluation (CMA)	<ul style="list-style-type: none"> The CMA should incorporate adverse event costs, particularly haematological events related to SBd use (para 7.15, July 2021 PBAC PSD). Within the CMA the duration of treatment of SBd was made equivalent to that of Cd (9.18 months of treatment, i.e. 7.98 SBd cycles and 9.98 Cd cycles)" (para 7.15, July 2021 PBAC PSD). The duration of SBd treatment applied in the CMA (7.98 cycles) was considerably higher than that observed in the BOSTON trial (6.67 cycles) (para 7.16, July 2021 PBAC PSD). 	<ul style="list-style-type: none"> Addressed. Cost of haematological AEs was included in the CMA. Unchanged. The treatment duration was similar between SBd and Cd. The duration of SBd treatment of 9.87 cycles was still considerably higher than that observed in BOSTON.
Predicted use of the medicine in practice	<ul style="list-style-type: none"> A market share approach may have been more appropriate to estimate market size (para 6.84, July 2021 PBAC PSD). The utilisation estimates for SBd were overestimated (para 7.17, July 2021 PBAC PSD). 	Addressed. The resubmission adopted a market share approach to estimate the market size. The utilisation estimates may be overestimated given the uncertain efficacy and toxicity of SBd compared to existing treatment regimens.

Source: Table E.1, pp13-14 of the resubmission.

Abbreviations: AEs = adverse events; Bd = bortezomib + dexamethasone; Cd = carfilzomib + dexamethasone; CUA = cost utility analysis; CMA = cost minimisation analysis; DBd = daratumumab in combination with bortezomib and dexamethasone; ECOG = Eastern Cooperative

Public Summary Document – March 2022 PBAC Meeting

Oncology Group; ELd = Elotuzumab + lenalidomide + dexamethasone; ICER = incremental cost-effectiveness ratio; ITC = indirect treatment comparison; Ld = lenalidomide + dexamethasone; mg = milligrams; OS = overall survival; PFS = progression free survival; Pd = pomalidomide + dexamethasone; PBd = pomalidomide + bortezomib + dexamethasone; PBAC = pharmaceutical benefits advisory committee; PSD = Public Summary Document; SBd = selinexor + bortezomib+ dexamethasone; STC = simulated treatment comparison.

2.4 A submission seeking listing of selinexor plus dexamethasone (Sd) for use in adult patients who have received at least four prior lines of therapy and whose disease is refractory to at least two proteasome inhibitors (PIs), at least two immunomodulatory agents (IMiDs) and an anti-CD38 monoclonal antibody (mAb); described as triple-class-refractory and penta-refractory multiple myeloma (TCR/PR MM) was also considered at the March 2022 PBAC meeting.

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

3 Requested listing

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

Name, Restriction, Manner of administration and form	Max. Qty	No. of Repeats	DPMQ	Proprietary Name and Manufacturer
SELINEXOR, TABLETS, 20 mg	16	2	Published price: \$11,525.44 (HSD Public) \$11,573.22 (HSD Private) Effective price: TBC	XPOVIO ANTENGENE Pty Ltd
SELINEXOR, TABLETS, 20 mg	20	2	Published price: \$14,406.80 (HSD Public) \$14,454.58 (HSD Private) Effective price: TBC	XPOVIO ANTENGENE Pty Ltd

Category/Program: Section 100 (Highly Specialised Drugs Program)
Prescriber type: <input checked="" type="checkbox"/> Medical Practitioners
Restriction type: <input checked="" type="checkbox"/> Authority Required – immediate/real-time assessment by Services Australia (telephone/online)
Episodicity: Relapsed and/or refractory
Severity: [blank]
Condition: Multiple Myeloma
PBS Indication: Relapsed and/or refractory multiple myeloma
Treatment phase: Initial treatment: Initial treatment following at least one prior line of drug therapy
Treatment criteria: Initial treatment
Clinical criteria:
The condition must be confirmed by a histological diagnosis
AND
Clinical criteria:
The treatment must be in combination with bortezomib and dexamethasone
AND
Clinical criteria:

Public Summary Document – March 2022 PBAC Meeting

	Patient must have progressive disease after at least one prior therapy for this condition
	AND
	Clinical criteria:
	Patient must not have previously received this drug for this condition
	AND
	Patient must not be receiving concomitant PBS-subsidised treatment with any of the following: (i) proteasome inhibitors, (ii) immunomodulators, (iii) anti-CD38 monoclonal antibody
	Definitions: 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).
	Prescriber 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: 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: No increase in the maximum number of repeats may be authorised.
	Administrative Advice: Special Pricing Arrangements apply
	Caution: This drug is a category D drug and must not be given to pregnant women. If selinexor is taken during pregnancy, a teratogenic effect of selinexor in humans cannot be ruled out.

	Category/Program: Section 100 (Highly Specialised Drugs Program)
	Prescriber type: <input checked="" type="checkbox"/> Medical Practitioners
	Restriction type: <input checked="" type="checkbox"/> Authority Required – immediate/real-time assessment by Services Australia (telephone/online)
	Episodicity: Relapsed and/or refractory
	Severity: [blank]
	Condition: Multiple Myeloma
	PBS Indication: Relapsed and/or refractory multiple myeloma
	Treatment phase: Continuing treatment
	Treatment criteria: Continuing treatment
	Clinical criteria:
	Patient must have previously received PBS-subsidised treatment with an authority prescription for this drug for this condition
	AND
	Clinical criteria:
	The treatment must be in combination with bortezomib and dexamethasone
	AND
	Clinical criteria:

Public Summary Document – March 2022 PBAC Meeting

	Patient must not have developed disease progression while receiving treatment with this drug for this condition
	AND
	Clinical criteria:
	<i>Patient must not be receiving concomitant PBS-subsidised treatment with any of the following: (i) proteasome inhibitors, (ii) immunomodulators, (iii) anti-CD38 monoclonal antibody</i>
	Definitions: 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).
	Prescriber 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: <i>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.</i>
	Administrative Advice: <i>No increase in the maximum number of repeats may be authorised.</i>
	Administrative Advice: <i>Special Pricing Arrangements apply</i>
	Caution: <i>This drug is a category D drug and must not be given to pregnant women. If selinexor is taken during pregnancy, a teratogenic effect of selinexor in humans cannot be ruled out.</i>

	Category/Program: Section 100 (Highly Specialised Drugs Program)
	Prescriber type: <input checked="" type="checkbox"/> Medical Practitioners
	Restriction type: <input checked="" type="checkbox"/> Authority Required – immediate/real-time assessment by Services Australia (telephone/online)
	Episodicity: <i>Relapsed and/or refractory</i>
	Severity: <i>Multiple Myeloma [blank]</i>
	Condition: <i>Relapsed and/or refractory m/Multiple myeloma</i>
	PBS Indication: Initial treatment <i>Initial treatment following at least one prior line of drug therapy Relapsed and/or refractory multiple myeloma</i>
	Treatment phase: Grandfather treatment - Transitioning from non-PBS to PBS-subsidised supply
	Clinical criteria:
	Patient must have received non-PBS-subsidised treatment with this drug for this condition prior to [date of selinexor PBS listing].
	AND
	Clinical criteria
	Patient must have met all initial treatment PBS eligibility criteria applying to a non-grandfathered patient prior to having commenced treatment with this drug.
	<i>The condition must be confirmed by a histological diagnosis</i>
	AND
	Clinical criteria:

Public Summary Document – March 2022 PBAC Meeting

	<i>The treatment must be in combination with bortezomib and dexamethasone</i>
	AND
	Clinical criteria:
	<i>Patient must have progressive disease after at least one prior therapy for this condition</i>
	AND
	Clinical criteria:
	<i>Patient must not have previously received this drug for this condition</i>
	AND
	<i>Patient must not be receiving concomitant PBS-subsidised treatment with any of the following: (i) proteasome inhibitors, (ii) immunomodulators, (iii) anti-CD38 monoclonal antibody</i>
	AND
	Clinical criteria:
	<i>Patient must not have developed disease progression while receiving treatment with this drug for this condition.</i>
	<p>Definitions: Prescriber instructions: <i>Progressive disease is defined as at least 1 of the following:</i> <i>(a) at least a 25% increase and an absolute increase of at least 5 g per L in serum M protein (monoclonal protein); or</i> <i>(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</i> <i>(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</i> <i>(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</i> <i>(e) an increase in the size or number of lytic bone lesions (not including compression fractures); or</i> <i>(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</i> <i>(g) development of hypercalcaemia (corrected serum calcium greater than 2.65 mmol per L not attributable to any other cause).</i></p>
	<p>Prescriber instructions: <i>Oligo-secretory and non-secretory patients are defined as having active disease with less than 10 g per L serum M protein.</i></p>
	<p>Prescriber instructions: <i>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, must be in the patient's medical records.</i> <i>Confirmation of eligibility for treatment with current diagnostic reports of at least one of the following must be documented in the patient's medical records:</i> <i>(a) the level of serum monoclonal protein; or</i> <i>(b) Bence-Jones proteinuria - the results of 24-hour urinary light chain M protein excretion; or</i> <i>(c) the serum level of free kappa and lambda light chains; or</i> <i>(d) bone marrow aspirate or trephine; or</i> <i>(e) if present, the size and location of lytic bone lesions (not including compression fractures); or</i> <i>(f) if present, the size and location of all soft tissue plasmacytomas by clinical or radiographic examination i.e. MRI or CTscan; or</i> <i>(g) if present, the level of hypercalcaemia, corrected for albumin concentration.</i> <i>As these parameters must be used to determine response, results for either (a) or (b) or (c) should be documented for all patients. Where the patient has oligo-secretory or non-secretory multiple myeloma, either (c) or (d) or if relevant (e), (f) or (g) must be documented in the patient's medical records. Where the prescriber plans to assess response in patients with oligo-secretory or non-secretory multiple myeloma with free light chain assays, evidence of the oligo-secretory or nonsecretory nature of the multiple myeloma (current serum M protein less than 10 g per L) must be documented in the patient's medical records.</i></p>
	Administrative Advice:

Public Summary Document – March 2022 PBAC Meeting

	<i>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.</i>
	Administrative Advice: <i>No increase in the maximum number of repeats may be authorised.</i>
	Administrative Advice: <i>Special Pricing Arrangements apply</i>
	Caution: <i>This drug is a category D drug and must not be given to pregnant women. If selinexor is taken during pregnancy, a teratogenic effect of selinexor in humans cannot be ruled out.</i>

- 3.2 The resubmission proposed restrictions for initial treatment, continuing treatment, and grandfathering with a restriction level of Authority Required (Telephone, Electronic) as opposed to the July 2021 submission which proposed Authority Required (STREAMLINED). This was consistent with previous advice (para 3.1, Selinexor (RRMM), PBAC Public Summary Document [PSD], July 2021 PBAC meeting).
- 3.3 The requested clinical criteria were consistent with those applied to other RRMM therapies (including ELd, PBd, DBd, Cd, Ld and Bd). However, the PBAC previously considered that SBd would likely be used as a third or later line treatment (Para. 7.3, Selinexor (RRMM), PBAC PSD, July 2021 PBAC meeting). The resubmission presented clinical evidence for the use of SBd after 1-3 prior therapies, and a subgroup analysis in patients with ≥ 2 prior lines of therapy.
- 3.4 The resubmission proposed a new published price, which reflected a 7% increase relative to the July 2021 submission because of a decrease in the published bortezomib price. The resubmission also requested special pricing, with the effective pricing to be informed by the carfilzomib effective pricing.
- 3.5 The requested published dispensed price for maximum amount (DPMA) reflected the median dose of selinexor used in the trial (BOSTON); 80 mg. This was inconsistent with the SBd equi-effective dose calculation applied in the CMA which was based on 100 mg of selinexor per dose, as per the Product Information. The proposed published price (\$720.34 per tablet) was therefore higher than the cost-minimised price per tablet presented as the base case in Section 3 (\$1 per tablet).
- 3.6 The resubmission requested two pack sizes, one containing 16 tablets and one containing 20 tablets. The dose of selinexor, as per the Product Information, is 100 mg (5 x 20 mg tablets) orally on Days 1, 8, 15, 22 and 29 of each 35 day cycle (i.e. 5 tablets per week). Thus, the 20 tablet pack would provide treatment for 28 days treatment at the recommended dose. The 16 tablet pack would provide 28 days treatment at the lower dose of 80 mg (4 x 20 mg), which was consistent with the median dose received in the BOSTON trial. The proposed pack sizes are not consistent with the proposed 35 day treatment cycle, since they reflect 28 days of treatment. Previously in June 2021, DUSC considered it was unclear as to when a 16-pack would be prescribed over the 20-pack, given that the proposed restriction for the 16-pack and the 20-pack are the same, and at a dose intensity of 80%, the 20-pack would provide a full cycle's requirement of selinexor. DUSC noted that prescribers would likely still prescribe the larger pack-size despite the lower dose intensity for patient convenience (Para. 6.86, Selinexor (RRMM), PBAC PSD, July 2021 PBAC meeting).

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

4 Population and disease

- 4.1 MM is a relatively uncommon cancer of the plasma cells, accounting for approximately 1-2% of all cancers, and approximately 17% of haematological malignancies. MM may remain asymptomatic until later stages of disease, however several signs and symptoms may be clinically identifiable at diagnosis. Those with MM may also be at increased risk of infection due to immune dysfunction.
- 4.2 The clinical management algorithms presented in the resubmission were primarily based on recommendations by the Australian Medical Scientific Advisory Group (MSAG) MM clinical practice guidelines, which were updated in October 2019. The resubmission noted that these guidelines do not make specific recommendations for treatment regimens to be used in first and subsequent lines rather, the guideline provides recommendations for various protocols, with these being based on a specific 'backbone' agent, and the treatment should be catered to the specific need of the individual patient.
- 4.3 The proposed clinical management algorithm presented by the resubmission including SBd, was updated to include recent PBS listing of daratumumab and elotuzumab. The ESC considered that the algorithm did not reflect Australian clinical practice. The ESC noted that the resubmission presented SBd as a second or third line therapy, and considered this was inappropriate as it did not reflect previous PBAC advice. The ESC considered daratumumab to be the most common treatment in the second line setting, and therefore SBd would likely be used in third line or later lines.
- 4.4 The proposed clinical algorithm was mostly consistent with the proposed PBS restriction; product information; and clinical evidence presented in the resubmission. The ESC noted the availability of a growing number of treatment options on the PBS and considered that a preferred treatment order has not yet been established. The ESC considered it was difficult to predict where clinicians would use SBd in the management of relapsed MM, and that treatment decisions would likely consider comorbidity profiles of individual patients and adverse event profiles of the therapeutic options. The pre-PBAC response acknowledged that a preferred treatment order in the RRMM setting has not yet been established and stated that the selection of regimen is based on a broad range of parameters including current clinical status, treatment history, previous toxicities, duration of previous response, and patient preference. The PBAC considered this was reasonable.
- 4.5 The ESC also considered that the proposed algorithm was incomplete because it did not include the proposed listing of Sd for TCR/PR MM. The ESC considered there appears to be overlap between the proposed populations if it is assumed that SBd will be used after multiple earlier lines of treatment. The resubmission did not discuss reasons for a clinician to choose SBd rather than Sd, or vice versa, for patients eligible for both. The ESC considered this information is needed to understand the place in

therapy and may have implications for the financial estimates. The pre-PBAC response provided an updated clinical management algorithm which positioned SBd as a treatment option in the second, third and fourth line settings, and Sd as a treatment option in fifth or sixth line settings. The updated algorithm was not consistent with the requested patient population for SBd which would allow use in any line after first line (see paragraph 3.1).

- 4.6 Selinexor is an oral, first-in-class, potent, selective inhibitor of nuclear export (SINE) compound that specifically blocks exporting 1 (XPO1). Inhibition of XPO1 leads, amongst other mechanisms, to the nuclear accumulation and activation of tumour suppressor proteins (TSPs), which then initiate apoptosis in cancer cells. The ESC noted that selinexor is an oral therapy, however the SBd regimen requires bortezomib to be administered by subcutaneous injection once weekly. The intervention remained unchanged from the July 2021 submission.

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

5 Comparator

- 5.1 The resubmission nominated Cd as the main comparator. The resubmission stated that Cd was the most appropriate comparator to SBd on the basis of being the regimen most likely to be replaced and being consistent with other recommendations for listing of new regimens in the proposed patient population on the basis of cost-minimisation versus Cd.
- 5.2 The July 2021 submission nominated Bd as the primary comparator and Cd as the secondary comparator. The resubmission did not include Bd as a comparator.
- 5.3 Given that the PBAC considered that SBd was most likely to replace and/or displace Cd, lenalidomide plus dexamethasone (Ld), pomalidomide plus dexamethasone (Pd) and some bortezomib-based regimens including Bd (para. 7.3, Selinexor (RRMM), PBAC PSD, July 2021 PBAC meeting), the exclusion of Bd, as well as Ld and Pd as comparators, was not adequately justified by the resubmission. The resubmission also did not address the potential for SBd to substitute elotuzumab in combination with lenalidomide and dexamethasone (ELd) and pomalidomide in combination with bortezomib and dexamethasone (PBd), which was not justified given that both regimens are likely to be used in the same RRMM setting, and they were recommended based on CMA relative to Cd.

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

6 Consideration of the evidence

Sponsor hearing

- 6.1 The sponsor provided a hearing for this item. The clinician discussed the Australian treatment landscape and noted that most patients will be lenalidomide refractory, but not bortezomib refractory at first relapse. The clinician described the benefits of SBd

therapy, particularly in patients who are refractory to lenalidomide, have high risk cytogenetics (including 17 p deletion) or extramedullary disease, and those who can't receive Cd due to cardiac comorbidities. The clinician described the potential adverse events associated with treatment as manageable and non-cumulative, in contrast to cardiac toxicity associated with carfilzomib which is known to be cumulative. The clinician also spoke about the importance of having a choice of treatments available for Australian patients. The PBAC considered that the hearing was informative as it provided a clinical perspective on the utilisation of SBd.

Consumer comments

- 6.2 The PBAC noted and welcomed the input from individuals (11) and organisations (3) via the Consumer Comments facility on the PBS website. The comments from individuals described the debilitating impact of relapsed myeloma and discussion regarding a range of treatments that the patients had personal experience with. The comments supported the proposed listing on the basis of it providing an additional treatment option, and also noted that selinexor is a tablet that may be taken at home.
- 6.3 The PBAC noted the advice received from (i) Myeloma Australia, (ii) the Leukaemia Foundation, and (iii) Myeloma Australia's Medical and Scientific Advisory Group (MSAG), which described an ongoing need for new treatment options and supported the proposed listing for SBd. Myeloma Australia described selinexor as highly effective, and noted that Australian patients want access to medicines that are available to myeloma patients in other parts of the world. The Leukemia Foundation noted that selinexor belongs to a new drug class and supported the listing based on the BOSTON trial, noting that the SBd regimen was associated with high response rates and low rates of peripheral neuropathy (the main dose-limiting toxicity of bortezomib). Myeloma Australia's MSAG referred to results from the BOSTON trial and stated that SBd would provide a significant alternative for RRMM patients. The PBAC noted this advice was supportive of the evidence provided in the submission.

Clinical trials

- 6.4 The resubmission presented indirect treatment comparisons (ITCs) of SBd and Cd via Bd informed by two head-to-head trials: study KCP-330-023 (BOSTON); and the ENDEAVOR study. Both BOSTON and ENDEAVOR were presented in the July 2021 submission. The resubmission presented longer follow-up duration for efficacy from BOSTON, with a data-cut from 15 February 2021 (13.5 months median follow-up in the SBd arm and 24.5 months in the Bd arm) compared to the data cut from 18 February 2020 (13.2 months median follow-up in the SBd arm and 16.5 months in the Bd arm) presented in the July 2021 submission. Both efficacy and safety data from ENDEAVOR remained unchanged from July 2021 submission.
- 6.5 Results of the updated data cut (February 2021) from BOSTON informed the adjusted ITC and the simulated treatment comparison (STC) for the efficacy outcome progression free survival (PFS). The ITC for safety outcomes relied on the original data cut (February 2020).

6.6 Details of the two trials presented in the resubmission are provided in the Table 3.

Table 3: Trials and associated reports presented in the resubmission

Trial ID	Protocol title/ Publication title	Publication citation
Direct trials (SBd versus Bd)		
BOSTON	KCP-330-023 A PHASE 3 RANDOMISED, CONTROLLED, OPEN-LABEL STUDY OF SBD (SBd) VERSUS BORTEZOMIB AND DEXAMETHASONE (Bd) IN PATIENTS WITH RELAPSED OR REFRACTORY MULTIPLE MYELOMA (RRMM). Grosicki S, Simonova M, Spicka I, et al. Once-per-week SBd versus twice-per-week bortezomib and dexamethasone in patients with multiple myeloma (BOSTON): a randomised, open-label, phase 3 trial.	May 2020 Lancet 2020 Nov; 14;396(10262):1563-1573.
Direct trials (Cd versus Bd)		
ENDEAVOR	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. Dimopoulos MA, Goldschmidt H, Niesvizky R, et al. Carfilzomib or bortezomib in relapsed or refractory multiple myeloma (ENDEAVOR): an interim overall survival analysis of an open-label, randomised, phase 3 trial. Correction: Carfilzomib or bortezomib in relapsed or refractory multiple myeloma (ENDEAVOR): an interim overall survival analysis of an openlabel, randomised, phase 3 trial. Orlowski RZ, Moreau P, Niesvizky R, et al. Carfilzomib-Dexamethasone Versus Bortezomib-Dexamethasone in Relapsed or Refractory Multiple Myeloma: Updated Overall Survival, Safety, and Subgroups.	The Lancet Oncology 2016; 17(1): 27-38. The Lancet Oncology 2017; 18(10): 1327-1337. The Lancet Oncology. 18(10): e562. Clin Lymphoma Myeloma Leuk. 2019 Aug; 19(8):522-530.e1.

Source: Table 2-5, pp64-66 and Table 2-7, pp66-68 of the resubmission.

Abbreviations: Bd = bortezomib + dexamethasone; Cd = carfilzomib + dexamethasone; N/A = not applicable; OS = overall survival; PFS = progression free survival; SBd = selinexor + bortezomib + dexamethasone.

Note: Blue shading indicates data previously seen by the PBAC.

6.7 The key features of the direct randomised trials are summarised in the Table 4.

Table 4: Key features of the included evidence

Trial	N	Design	Risk of bias	Patient population	Outcome(s)	Use in modelled evaluation
SBd vs. Bd						
BOSTON ¹	402	R, OL, phase 3, 2-arm, global, active comparator-controlled, multicentre study	Low	Patients with RRMM who had 1-3 prior treatments	Primary: PFS Secondary: ORR, ≥VGPR, PN, OS, DOR, TTNT, safety and tolerability.	PFS and safety
Cd vs. Bd						
ENDEAVOR	929	R, OL, phase 3, multicentre study	Low	Patients with RRMM who had 1-3 prior treatments	Primary: PFS Secondary: OS, ORR, DOR, incidence of Grade ≥ 2 PN, safety.	PFS and safety

Source: Figure 2-5, p70, and p69 of the resubmission.

Abbreviations: Bd = bortezomib + dexamethasone; Cd = carfilzomib + dexamethasone; OL = open-label; ORR = overall response rate; OS = overall survival; PFS = progression free survival; R = randomised; SBd = selinexor + bortezomib + dexamethasone;.

Notes: Blue shading indicates data previously seen by the PBAC.

1. Crossover from the Bd arm to a treatment that included selinexor was allowed at the point of IRC-confirmed objective disease progression per the IMWG criteria for patients in the Bd arm.

- 6.8 The overall risk of bias in BOSTON and ENDEAVOR was considered low.
- 6.9 Baseline demographic, disease, and clinical characteristics in BOSTON were balanced across the two treatment arms. Similarly, baseline characteristics of the ENDEAVOR population were also generally balanced between treatment arms. Differences between the trials which may impact the transitivity of the trials included:
- that patients in BOSTON were slightly older, appeared to have more advanced/severe disease compared to ENDEAVOR, with a greater proportion of patients with higher stages of R-ISS (stage II and III) disease and higher average ECOG performance status;
 - the time difference of 5 years from the recruitment of patients into ENDEAVOR (2012) and BOSTON (2017). The submission stated that this partly explained the fact that patients in BOSTON had more advanced disease and were exposed to a wider range of prior therapies (5 prior unique therapies compared with 3 in ENDEAVOR); and
 - that the bortezomib dosing regimen differed between the trials. In BOSTON bortezomib was administered twice weekly for the first eight cycles and once per week thereafter; whereas in ENDEAVOR it was administered twice weekly for the entire treatment duration.
- 6.10 As of the updated data cut-off (15 February 2021), the median follow-up for OS was 28.7 months for both SBd and Bd arms, while median follow-up for PFS was 13.5 months in the SBd arm and 24.5 months in the Bd arm. The median follow-up for PFS observed in the updated data (February 2021) was substantially different between treatment arms, likely due to the imbalance in censoring between SBd and Bd (52.8% in the SBd arm and 33.8% in the Bd arm). As of the original data cut-off (February 2020), the median follow-up time for PFS was 13.2 months in the SBd arm and 16.5 months in the Bd arm.
- 6.11 The median follow-up for OS for patients in ENDEAVOR was reported by the resubmission as 44.3 month for Cd and 43.7 months for Bd (19 July 2017 data cut-off). The median follow-up time for PFS was 11.9 months in the Cd arm and 11.1 months in the Bd arm (data cut-off date of 10 November 2014). Based on these data cut-off dates, the median follow-up time for PFS in BOSTON was longer than ENDEAVOR, whilst the median follow-up time for OS in BOSTON (data cut-off date of 15 February 2021) was shorter than ENDEAVOR (data cut-off date of 19 July 2017).

Comparative effectiveness

BOSTON (SBd versus Bd)

- 6.12 As of data cut-off date of February 2021, the median PFS was 13.2 months in the SBd arm and 9.5 month in the Bd arm (HR = 0.71; 95% CI: 0.54, 0.93; p=0.006; see Table 5 and Figure 1).
- 6.13 The resubmission noted that in the interim data (February 2020) the median PFS was 4.4 months longer in the SBd arm than in the Bd arm. In the updated data (February 2021) the median PFS gain had reduced to 3.7 months between the SBd arm and Bd arm (see Table 5). The PBAC previously considered that SBd provided, for some patients, an improvement in PFS compared to Bd but noted that the data for overall survival (OS) were immature and difficult to interpret (Para.7.1, Selinexor (RRMM), PBAC PSD, July 2021 PBAC meeting). The clinical claim of non-inferior efficacy of SBd compared to Cd presented by the resubmission was based on the PFS outcome.

Table 5: Progression free survival by treatment arm (ITT population)

	BOSTON (original data cut-off Feb 2020)		BOSTON (updated data cut-off Feb 2021)	
	SBd arm (N=195)	Bd arm (N=207)	SBd arm (N=195)	Bd arm (N=207)
Median follow-up (months)	13.2	16.5	13.5	24.5
Progression-free survival (months), Median	13.9	9.5	13.2	9.5
Difference in median PFS (months)	4.4		3.7	
95% CI	(11.73, NE)	(8.11, 10.78)	(11.73, 23.43)	(8.11, 10.78)
Stratified log-rank test ^a One sided P-value	0.0075		0.0064	
Hazard ratio ^{a,b} (95% CI)	0.70 (0.53, 0.93)		0.71 (0.54, 0.93)	
Patients with events, n (%)	80 (41.0)	124 (59.9)	92 (47.2)	137 (66.2)
PD	69 (35.4)	111 (53.6)	79 (40.5)	122 (58.9)
Death	11 (5.6)	13 (6.3)	13 (6.7)	15 (7.2)
Patients censored, n (%)	115 (59.0)	83 (40.1)	103 (52.8)	70 (33.8)

Source: Table 2-19, p92 of the resubmission.

Abbreviations: Bd = bortezomib + dexamethasone; CI = confidence interval; ITT = intent to treat; IRC = independent review committee; NE = not estimable; PD = progressive disease; SBd = selinexor + bortezomib + dexamethasone.

Notes: **Bold** indicates a statistically significant difference.

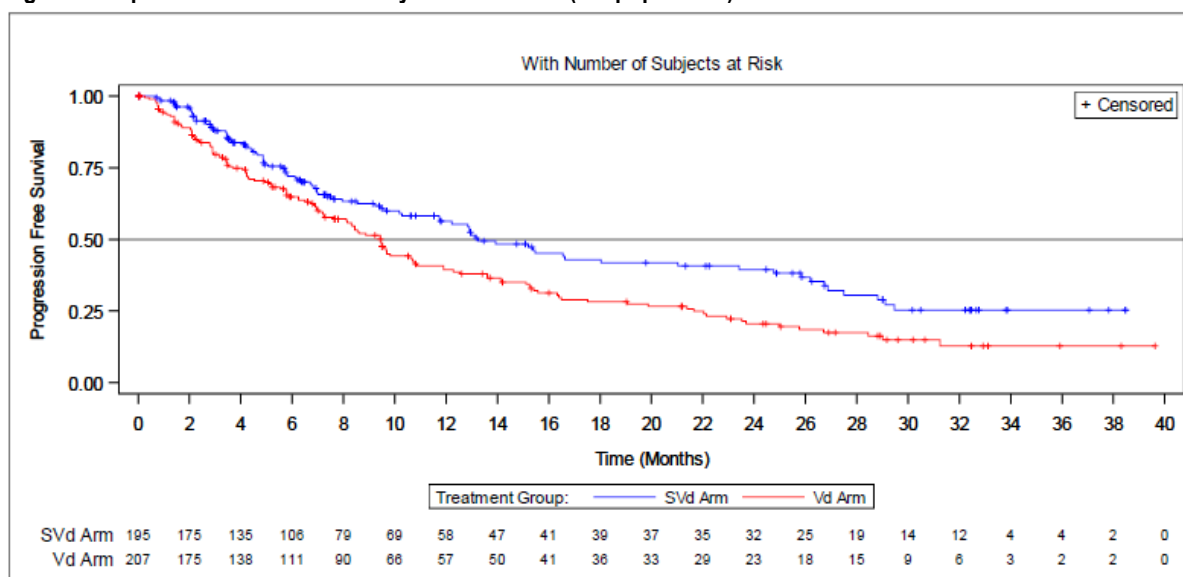
Progression-free survival is calculated from date of randomisation until the first date of IRC-confirmed PD per International Myeloma Working Group response criteria, or death due to any cause, whichever occurs first.

Blue shading indicates data previously seen by the PBAC.

a. Stratified for prior proteasome inhibitor therapies, number of prior anti-MM regimens and R-ISS Stage at study entry.

b. Based on stratified Cox Proportional Hazard model with Efron's Method of handling ties.

Figure 1: Kaplan-Meier curve of PFS by treatment arm (ITT population)



Source: Figure 2-9, p93 of the resubmission.

Abbreviations: CI = confidence interval; HR = hazard ratio; ITT = intent to treat; IRC = independent review committee; PFS = progression free survival.

Notes: The abbreviation of SVd was referred to as SBd (selinexor, bortezomib plus dexamethasone) in this commentary.

The abbreviation of Vd was referred to as Bd (bortezomib plus dexamethasone) in this commentary.

6.14 As of the February 2021 data cut-off date, at a median follow-up of 28.7 months, the Kaplan Meier estimate of median OS for patients in the SBd and Bd arms was 36.7 (95% CI: 30.19, NE) and 32.7 (95% CI: 27.83, NE) months respectively (see Table 6 and Figure 2).

Table 6: Overall survival by treatment arm (ITT population)

Patients with events, n (%)	BOSTON (original data cut-off Feb 2020)		BOSTON (updated data cut-off Feb 2021)	
	SBd arm (N=195)	Bd arm (N=207)	SBd arm (N=195)	Bd arm (N=207)
Death	47 (24.1)	62 (30.0)	68 (34.9)	80 (38.6)
Patients Censored, n (%)	148 (75.9)	145 (70.0)	127 (65.1)	127 (61.4)
Median Follow-up Time (Months), 95% CI	17.28 (16.56, 18.27)	17.51 (17.08, 18.23)	28.71 (27.24, 29.90)	28.65 (27.63, 29.67)
Overall Survival (Months)				
Median, 95% CI	NE (NE, NE)	24.97 (23.49, NE)	36.7 (30.19, NE)	32.7 (27.83, NE)
Stratified log-rank test ^a				
One Sided P-value		0.1852		0.2152
Hazard Ratio ^{a,b}		0.84		0.88
95% CI		(0.57, 1.23)		(0.63, 1.22)

Source: Table 2-22, pp95-96 of the resubmission.

Abbreviations: Bd = bortezomib + dexamethasone; CI = confidence interval; ITT = intention to treat; NE = not evaluable; SBd= selinexor + bortezomib + dexamethasone.

Notes: Overall survival is calculated from date of randomisation to date of death.

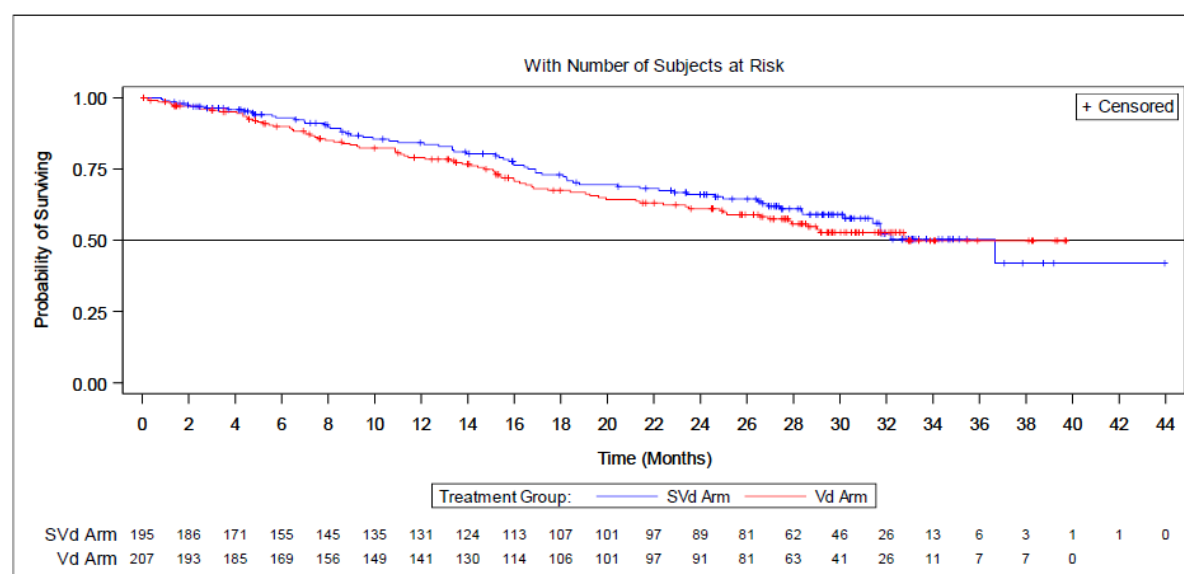
Patients without events were censored at the date of study discontinuation or date of last participating visit, whichever occurred first.

Blue shading indicates data previously seen by the PBAC.

a. Stratified for prior PI therapies, number of prior anti-MM regimens and R-ISS Stage at screening.

b. Based on stratified Cox Proportional Hazard model with Efron's Method of handling ties.

Figure 2: Kaplan-Meier curve of OS by treatment arm (ITT population)



Source: Figure 2-10, p96 of the resubmission.

Abbreviations: HR = hazard ratio; ITT = intention to treat; OS = overall survival; Bd = bortezomib + dexamethasone; SBd = selinexor + bortezomib + dexamethasone.

Notes: The abbreviation of SVd was referred to as SBd (selinexor, bortezomib plus dexamethasone) in this commentary.

The abbreviation of Vd was referred to as Bd (bortezomib plus dexamethasone) in this commentary.

- 6.15 Despite the longer follow-up, the survival data was still immature with an event rate of 35% and 39% for SBd and Bd arms, respectively (Table 6). The difference in OS based on the updated data cut-off (February 2021) was still not statistically significant between the two trial arms, a result that was consistent with the February 2020 data cut-off as presented in the July 2021 submission. The PBAC previously noted that the OS data based on the February 2020 data cut-off were immature, with median OS not reached for the SBd arm (HR = 0.84; 95% CI: 0.57, 1.23, and the claim of superior efficacy of SBd compared to Bd could not be supported due to the immaturity of the data from the BOSTON trial (Para. 7.6 and 7.8, Selinexor (RRMM), PBAC PSD, July 2021 PBAC meeting).
- 6.16 The resubmission did not provide updated crossover data based on the February 2021 data cut-off. At the February 2020 data cut-off, the submission noted that seventy-four (36%) patients from the Bd arm crossed over after confirmed progressive disease to receive a regimen that included selinexor. The proportion of patients on Bd who crossed over to either SBd or Sd was 36% (74 patients); with 30.4% (63 patients) crossing over to SBd, and 5.3% (11 patients) crossing over to Sd. The resubmission stated no adjustment for cross over was made given that an economic model of SBd versus Bd was not provided.
- 6.17 The Pre-Sub-Committee Response (PSCR) noted that the OS data from the first data cut was numerically in favour of SBd (HR = 0.84; 95% CI: 0.57, 1.23), and when adjusted for crossover using the two-stage estimation method (TSEM) to account for the 36%

of patients in the Bd arm who received either SBd or selinexor plus dexamethasone (Sd) following disease progression, the numerical benefit improved in favour of SBd (HR = 0.77; 95% CI: 0.52, 1.14). The last data-cut continues to support a positive treatment effect of SBd on OS.

- 6.18 The ESC noted that OS data for BOSTON remained immature despite the updated OS data provided by the resubmission, and that while the HR numerically favoured SBd compared with Bd, the result was not statistically significant (HR = 0.88; 95% CI: 0.63, 1.22). The ESC considered although this result may be due to the impact of crossover within the Bd treatment arm to SBd treatment, the impact of SBd on OS was very uncertain.
- 6.19 Overall response rate (ORR) results from the updated BOSTON data cut-off (February 2021) were similar to those observed in the interim data cut-off (February 2020), with ORR significantly higher in the SBd group (76.9%; 95% CI: 70.4, 82.6) than in the Bd group (63.3%; 95% CI: 56.3, 69.9); with an odds ratio (OR) = 1.94 (95% CI: 1.25, 3.03); p=0.0016 (see Table 7).

Table 7: ORR by treatment arm (ITT population)

	BOSTON (original data cut-off Feb 2020)		BOSTON (updated data cut-off Feb 2021)	
	SBd arm (N=195)	Bd arm (N=207)	SBd arm (N=195)	Bd arm (N=207)
ORR, n (%) ^a	149 (76.4)	129 (62.3)	150 (76.9)	131 (63.3)
Exact 95% CI	(69.8, 82.2)	(55.3, 68.9)	(70.4, 82.6)	(56.3, 69.9)
Cochran-Mantel-Haenszel Test (SBd vs. Bd) ^b				
OR (95% CI)	1.96 (1.26, 3.05)		1.94 (1.25, 3.03)	
One Sided P-value	0.0012		0.0016	
Breslow-Day Test for homogeneity				
P-value	0.2430		0.4154	

Source: Table 2-21, p94 of the resubmission.

Abbreviations: Bd = bortezomib + dexamethasone; CI = confidence interval; ITT = intention to treat; IRC = Independent Review Committee; ORR = overall response rate; OR = odds ratio; PD = progressive disease; SBd = selinexor + bortezomib + dexamethasone.

Notes: **Bold** indicates a statistically significant difference.

Blue shading indicates data previously seen by the PBAC.

a. Overall response rate is the proportion of patients who achieve a partial response or better, before IRC-confirmed PD or initiating a new MM treatment or crossover.

b. Analysis using Cochran-Mantel-Haenszel test stratified by prior PI therapies, number of prior anti-MM regimens, and R-ISS stage at screening.

ENDEAVOR (Cd versus Bd)

- 6.20 As of the data cut-off date of 10 November 2014, median PFS was 18.7 months in the Cd arm versus 9.4 months in Bd arm; HR= 0.53 (0.44–0.65); p<0.0001 (see Table 8). Results from a later data cut-off (3 March 2016 data cut-off) with a median follow-up for PFS of 16.6 months, were consistent with the first interim PFS analysis. The median PFS was longer by 7.4 months in the Cd arm (16.8 months; 95% CI: 14.8, 20.3) compared to Bd (9.3 months; 95% CI: 8.3, 10.4; HR = 0.55 (95% CI: 0.46-0.65); p < 0.001; Table 6, Carfilzomib PSD, July 2017 PBAC Meeting).

Table 8: Results of PFS in ENDEAVOR

Treatment arm	Patients with event, n/N (%)	Median, months (95% CI)	Difference in median, months	P value (log rank test)	HR (95% CI)
Cd	171/464 (36.9%)	18.7 (15.6, NE)	9.3	< 0.0001	0.53 (0.44, 0.65)
Bd	243/465 (52.3%)	9.4 (8.4, 10.4)			

Source: Table 2-25, p103 of the resubmission.

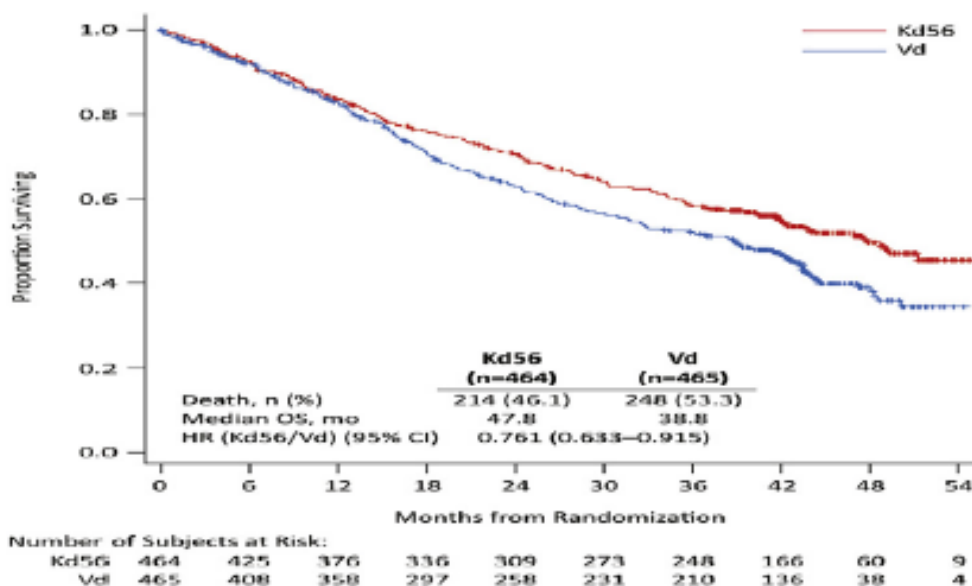
Abbreviations: Bd = bortezomib + dexamethasone; CI = confidence interval; Cd = carfilzomib + dexamethasone; HR = hazard ratio; n= number of patients; N = total number of patients; NE = not estimable; PFS = progression free survival.

Notes: **Bold** indicates statistically significant results.

Blue shading indicates data previously seen by the PBAC.

6.21 As of the data cut-off date of 19 July 2017, there were 214 (46.1%) patients alive in the Cd arm and 168 (36.1%) in the Bd arm (see Figure 3). Median follow-up time for OS was 44.3 months in the Cd arm and 43.7 months in the Bd arm. The median OS for the ITT population was 9.0 months longer for Cd than Bd, resulting in an HR = 0.76 (95% CI: 0.63-0.92); 1-sided p= 0.0017. The results with the updated OS data were consistent with those of the interim analysis. Previously, the ESC considered that although the improvement in OS was statistically significant (data from interim analysis), the upper confidence interval was close to the null; HR = 0.79 (95% CI: 0.65-0.96) (paragraph 6.11, Carfilzomib PSD, July 2017). However, the OS analysis from the data cut-off date of 19 July 2017 has demonstrated ongoing OS benefits with Cd and the upper confidence interval is distancing from the null (95% CI: 0.63, 0.92).

Figure 3: Kaplan Meier curve of OS (ITT)



Source: Figure 2-15, p106 of the resubmission.

Abbreviations: CI = confidence interval; Cd56 = carfilzomib + dexamethasone; n= number of patients; OS = overall survival.

Notes: Kd56 was referred to using the abbreviation Cd (carfilzomib plus dexamethasone) in this Commentary.

Vd was referred to using the abbreviation Bd (bortezomib plus dexamethasone) in this Commentary.

Blue shading indicates data previously seen by the PBAC.

Efficacy ITC (SBd versus Cd)

- 6.22 The resubmission presented an ITC as the basis of the clinical claim of non-inferior effectiveness and different safety profile of SBd compared with Cd. The key outcomes presented by the resubmission in the ITC were PFS and safety. The resubmission justified that the ITCs were only performed for PFS for the reason that OS data were immature in BOSTON and that PFS was not influenced by cross-over.
- 6.23 The resubmission stated that an adjusted ITC and STC was performed to address the concerns raised by the PBAC during the evaluation of the July 2021 submission. The July 2021 submission presented a naïve ITC (non-matched) comparing SBd with Cd for the efficacy outcome of PFS. The PBAC considered that the ITCs presented in the July 2021 submission between SBd and the secondary comparator Cd, did not adequately support non-inferiority (Para.7.1, Selinexor (RRMM), PBAC PSD, July 2021 PBAC meeting). The PBAC also noted that although the eligibility criteria of the BOSTON and ENDEAVOR trials were generally similar, there were differences that might have impacted the transitivity of the trials including differences in the baseline disease characteristics of patients, differences in the time at which the trials were conducted and differences in the maturity of the data (Para. 7.9, Selinexor (RRMM), PBAC PSD, July 2021 PBAC meeting).
- 6.24 The resubmission stated that the analyses relied on individual patient data (IPD) for BOSTON (15 February 2021 data cut-off), BOSTON interim clinical study report (CSR) (18 February 2020), and published evidence for ENDEAVOR (10 November 2014).
- 6.25 The resubmission presented the results of four different ITC models as presented below:
- Unadjusted ITCs were performed based on the methods outlined for the primary analysis of PFS in the BOSTON trial – reference base case (as per that previously considered by the PBAC and based on the BOSTON February 2020 data cut-off).
 - Unadjusted ITCs, matching the statistical methods utilised in the estimation of PFS in BOSTON to those of ENDEAVOR, with respect to stratification variables, to calculate a new base case HR (95% CI). The resubmission stated that the difference was not only on the variable used (ISS versus Revised ISS), but more specifically on the grouping of the stages (I-II/III versus I/II-III), and a different definition of stratification variables is likely to lead to different results for the Cox model. Given the differences in the variable used (ISS versus Revised ISS), but also the grouping of the stages (I-II/III versus I/II-III), reanalysing the BOSTON data was reasonable in adjusting for the differences in the application of staging in the stratification of the Cox model.
 - Adjusted ITCs were conducted including the selected variables, age and ECOG, (multivariate) as covariates in the Cox model with methods matching that used in ENDEAVOR. The resubmission identified characteristics which were significantly

different between BOSTON and ENDEAVOR at baseline and that had a significant impact on PFS.

- STCs were used to produce estimates of SBd versus Bd HRs in a population with the characteristics of the ENDEAVOR population for the selected adjustment variables. These estimates were derived from the adjusted models using the baseline ECOG status and age (<65 and ≥65) distributions as per ENDEAVOR in the ITT population and for the subgroup of patients with ≥2 prior lines of treatment (including and excluding India).
- 6.26 The submission did not provide model fit statistics to assess the fit of the adjusted and STC models. While the adjusted ITCs and STCs account for differences in the baseline disease characteristics of patients the transitivity of the trials is still affected by the differences in the time at which the trials were conducted and differences in the maturity of the data.
- 6.27 The ITC models described above were performed on ITT population, ITT population excluding Indian centres, patients with ≥2 prior lines of MM therapies, and patients with ≥2 prior lines of MM therapies excluding Indian centres.
- 6.28 The resubmission noted that 43 patients (10.7%) in BOSTON were from India whereas no patients from India were included in ENDEAVOR. Moreover, a disproportionately high proportion of SBd patients died because of a TEAE in India compared with no deaths in the Bd arm, versus that observed in the other countries. As it was clear that those events that led to death in India in the SBd arm were infections (sepsis and pneumonia) that could most likely have been avoided with appropriate care, and given that deaths influence PFS, ITC analyses excluding the population from India were also presented. The ESC considered this was reasonable.
- 6.29 The key results of the adjusted ITC of SBd versus Cd in terms of PFS (ITT population) via Bd are presented in Table 9.

Table 9: Results of the unadjusted, adjusted indirect comparison and simulated treatment comparison for PFS (ITT population)

Population / Analysis method used to derive BOSTON estimates	Covariate p-value	SBd vs Bd (BOSTON) HR (95% CI)	Cd vs Bd (ENDEAVOR) HR (95% CI)	IEE: SBd vs Cd via Bd HR (95% CI)
ITT – base case				
Unadjusted: As per BOSTON CSR method,	NA	0.70 (0.53, 0.93)	0.53 (0.44, 0.65)	1.32 (0.94, 1.86)
Unadjusted: matching methods in BOSTON with ENDEAVOR		0.68 (0.51, 0.9)	0.53 (0.44, 0.65)	1.28 (0.91, 1.81)
Adjusted model: Multivariate (ECOG 0 vs 1 vs 2 & age < 65 vs ≥ 65 years)	0.036, 0.036	0.65 (0.49, 0.87)	0.53 (0.44, 0.65)	1.23 (0.87, 1.75)
STC: Multivariate (ECOG and age)	NA	0.57 (0.40, 0.82)	0.53 (0.44, 0.65)	1.08 (0.72, 1.63)

Source: Table 2-47, pp141 of the resubmission.

Abbreviations: Bd = bortezomib + dexamethasone; Cd = carfilzomib + dexamethasone; CI = confidence interval; HR = hazard ratio; IEE = indirect estimate of effect; ITT = intent to treat; PFS = progression free survival; SBd = selinexor + bortezomib + dexamethasone; STC = simulated treatment comparison.

- 6.30 The resubmission appropriately used BOSTON IPD to conduct adjusted ITC analyses and STCs. The adjusted ITCs and STCs accounted for some differences in patient characteristics between BOSTON and ENDEAVOR, thereby potentially producing more robust estimates of efficacy than the unadjusted models. The methodology described by the resubmission was appropriate.
- 6.31 While the results from all of the ITT comparisons did not demonstrate a significant difference between SBd and Cd in terms of PFS, these results also showed a numeric difference in favour of Cd and wide CIs. Furthermore, a lack of a statistically significant difference between SBd and Cd does not adequately establish non-inferiority; this would have required that the confidence limits of the difference in treatment effect does not include an a priori stated clinically meaningful difference favouring the comparator (PBAC Guidelines, Section 2.4.5, p 39). In addition, the PBAC has previously noted the large difference in median PFS between the SBd (13.9 months) and Cd (18.7 months) arms; whereas the results were similar in the Bd common comparator arms (9.5 months in the Bd arm of BOSTON compared to 9.4 months in the Bd arm of ENDEAVOR) (Para. 7.9, selinexor (RRMM), PBAC PSD, July 2021 PBAC meeting).
- 6.32 While the adjusted ITC and STC accounted for differences between trials in terms of ECOG status and age, differences that may have impacted the transitivity of the trials remained. These included the time period during which the studies were conducted (a difference of 5 years between the recruitment of the ENDEAVOR and BOSTON), differences in the maturity of the data and differences in dosing regimen of bortezomib. These underlying transitivity issues associated with the ITCs impact the certainty of any conclusion that can be drawn from these analyses.
- 6.33 The results from the unadjusted ITC (with statistical methods matched to those of ENDEAVOR), the adjusted ITC and STC of SBd vs Cd via Bd on PFS for the three subgroups identified by the resubmission are presented in Table 10. The results from these analyses were consistent with the results based on the ITT population with the

Public Summary Document – March 2022 PBAC Meeting

exception of the STC for the subgroup in patients with ≥ 2 prior lines of therapy and the unadjusted ITC (matched methods), adjusted ITC and STC for the subgroup in patients with ≥ 2 prior lines of therapy and excluding India, in which the indirect estimates of effect favoured SBd. The subgroup of patients who had received at least 2 prior lines of therapy was consistent with the previous PBAC advice that SBd would likely be used as a third or later line treatment (Para. 7.3, Selinexor (RRMM), PBAC PSD, July 2021 PBAC meeting).

Table 10: Results of the unadjusted and adjusted indirect comparisons and STC for PFS (subgroup analyses)

Population / Analysis method used to derive BOSTON estimates	Covariate p-value	SBd vs Bd (BOSTON) HR (95% CI)	Cd vs Bd (ENDEAVOR) HR (95% CI)	IEE: SBd vs Cd via Bd HR (95% CI)
ITT – excluding India				
Unadjusted: As per BOSTON CSR method	NA	0.66 (0.48, 0.89)	0.53 (0.44, 0.65)	1.24 (0.86, 1.78)
Unadjusted: matching methods in BOSTON with ENDEAVOR		0.63 (0.46, 0.86)	0.53 (0.44, 0.65)	1.19 (0.83, 1.72)
Adjusted model: Multivariate (ECOG 0 vs 1 vs 2 & age < 65 vs ≥ 65 years)	0.123, 0.058	0.62 (0.45, 0.84)	0.53 (0.44, 0.65)	1.16 (0.81, 1.68)
STC: Multivariate (ECOG and age)	NA	0.54 (0.37, 0.80)	0.53 (0.44, 0.65)	1.02 (0.66, 1.57)
Subgroup ≥ 2 prior lines				
Unadjusted: As per BOSTON CSR method	NA	0.74 (0.5, 1.08)	0.60 (0.47, 0.78)	1.22 (0.77, 1.93)
Unadjusted: matching methods in BOSTON with ENDEAVOR		0.68 (0.46, 0.99)	0.60 (0.47, 0.78)	1.12 (0.71, 1.77)
Adjusted model: Multivariate (ECOG 0 vs 1 vs 2 & age < 65 vs ≥ 65 years)	0.028, 0.138	0.65 (0.45, 0.95)	0.60 (0.47, 0.78)	1.08 (0.68, 1.71)
STC: Multivariate (ECOG and age)	NA	0.57 (0.36, 0.91)	0.60 (0.47, 0.78)	0.94 (0.55, 1.60)
Subgroup ≥ 2 prior lines & excluding India				
Unadjusted: As per BOSTON CSR method	NA	0.67 (0.44, 1.01)	0.60 (0.47, 0.78)	1.10 (0.67, 1.8)
Unadjusted: matching methods in BOSTON with ENDEAVOR		0.59 (0.39, 0.89)	0.60 (0.47, 0.78)	0.97 (0.6, 1.58)
Adjusted model: Multivariate (ECOG 0 vs 1 vs 2 & age < 65 vs ≥ 65 years)	0.165, 0.233	0.58 (0.38, 0.88)	0.60 (0.47, 0.78)	0.96 (0.59, 1.56)
STC: Multivariate (ECOG and age)	NA	0.51 (0.31, 0.85)	0.60 (0.47, 0.78)	0.85 (0.48, 1.49)

Source: Table 2-47, p141 of the resubmission.

Abbreviations: Bd = bortezomib + dexamethasone; Cd = carfilzomib + dexamethasone; CI = confidence interval; HR = hazard ratio; IEE = indirect estimate of effect; ITT = intent to treat; PFS = progression free survival; SBd = selinexor + bortezomib + dexamethasone.

6.34 The Commentary stated that results from the adjusted ITC and STC in the subgroups should be interpreted with caution given the wide confidence intervals observed and the absence of a stated non-inferiority margin.

Comparative harms

SBd versus Bd

Treatment emergent adverse events (TEAEs)

- 6.35 The resubmission presented a summary of TEAEs in the safety population (N= 399) based on the February 2021 data cut-off along with the interim data cut-off (February 2020; see Table 11).
- 6.36 The resubmission stated that given there were no differences observed in the overall rates of AEs between the original and updated data cuts, the rates of individual events will not differ either. The resubmission did not provide any safety data for individual adverse events from the updated data cut-off (February 2021). The difference between the treatment arms for overall TEAEs was not statistically significant in terms of relative risk (RR), odds ratio (OR), or risk difference (RD). The difference in serious adverse events (SAEs); Grade 3/4 TEAEs; and TEAEs leading to either dose modification, reduction, or interruption, was statistically significant in terms of RR, OR and RD in favour of the Bd arm, which may be anticipated given that SBd is adding a third therapy to the existing Bd regimen.

Public Summary Document – March 2022 PBAC Meeting

Table 11: Summary of TEAEs (safety population)

Patients with at least one n (%)	BOSTON (original data cut-off Feb 2020)					BOSTON (updated data cut-off Feb 2021)				
	SBd arm (N=195)	Bd arm (N=204)	OR (95% CI) ^a	RR (95% CI)	RD (95% CI) ^a	SBd arm (N=195)	Bd arm (N=204)	OR (95% CI) ^a	RR (95% CI) ^a	RD (95% CI)
TEAE	194 (99.5)	198 (97.1)	5.88 (0.7, 49.28)	1.03 (1.00, 1.05)	0.02 (0, 0.05)	194 (99.5)	198 (97.1)	5.88 (0.70, 49.29)	1.03 (1.00, 1.05)	0.02 (0.00, 0.05)
Grade 3/4 TEAE ^b	154 (79.0)	114 (55.9)	2.97 (1.91, 4.61)	1.41 (1.23, 1.63)	0.23 (0.14, 0.32)	153 (78.5)	115 (56.4)	2.82 (1.82, 4.38)	1.39 (1.21, 1.60)	0.22 (0.13, 0.31)
Grade 4 TEAE ^b	34 (17.4)	22 (10.8)	1.75 (0.98, 3.11)	1.62 (0.98, 2.66)	N/A	37 (19.0)	22 (10.8)	1.94 (1.10, 3.42)	1.76 (1.08, 2.87)	0.08 (0.01, 0.15)
SAE	101 (51.8)	77 (37.7)	1.77 (1.19, 2.64)	1.37 (1.10, 1.71)	0.14 (0.04, 0.24)	106 (54.4)	79 (38.7)	1.88 (1.27, 2.81)	1.40 (1.13, 1.74)	0.16 (0.06, 0.25)
TEAE Leading to Dose Modification in Study Treatment ^c	173 (88.7)	156 (76.5)	2.42 (1.40, 4.19)	1.16 (1.06, 1.27)	0.12 (0.05, 0.20)	173 (88.7)	156 (76.5)	2.42 (1.40, 4.19)	1.16 (1.06, 1.27)	0.12 (0.05, 0.20)
TEAE Leading to Dose Reduction in Study Treatment	141 (72.3)	104 (51.0)	2.51 (1.65, 3.81)	1.42 (1.21, 1.66)	0.21 (0.12, 0.31)	141 (72.3)	106 (52.0)	2.41 (1.59, 3.66)	1.39 (1.19, 1.63)	0.20 (0.11, 0.30)
TEAE Leading to Dose Interruption in Study Treatment	167 (85.6)	139 (68.1)	2.79 (1.70, 4.58)	1.26 (1.13, 1.40)	0.18 (0.09, 0.26)	167 (85.6)	139 (68.1)	2.79 (1.70, 4.58)	1.26 (1.13, 1.40)	0.18 (0.09, 0.26)
TEAE Leading to Study Treatment Discontinuation	41 (21.0)	32 (15.7)	1.43 (0.86, 2.39)	1.34 (0.88, 2.04)	0.05 (-0.02, 0.13)	41 (21.0)	34 (16.7)	1.33 (0.80, 2.20)	1.26 (0.84, 1.90)	0.04 (-0.03, 0.12)
TEAE Leading to Death	12 (6.2)	11 (5.4)	1.15 (0.5, 2.67)	1.14 (0.52, 2.53)	0.01 (-0.04, 0.05)	14 (7.2)	13 (6.4)	1.14 (0.52, 2.48)	1.13 (0.54, 2.34)	0.01 (-0.04, 0.06)

Source: Table 2-28, p109 of the resubmission.

Abbreviations: Bd = bortezomib + dexamethasone; CI = confidence interval; OR = odds ratio; RD = risk difference; SBd = selinexor + bortezomib + dexamethasone; SAE = serious adverse event; TEAE = treatment emergent adverse events.

Notes: Study treatment is selinexor with bortezomib and dexamethasone for the SBd arm and bortezomib with dexamethasone for the Bd arm.

Bold indicates statistically significant results.

Blue shading indicates data previously seen by the PBAC.

Italics indicates results calculated during evaluation.

a. Calculated by the resubmission using Review Manager version 5.4.1.

b. Based on maximum severity grade of each patient.

c. The number of patients with dose modification(s) is not necessarily equal to the sum of the number of patients who had a modified dose or a drug interruption since the same patient could fall into more than one of these categories.

Individual TEAEs

6.37 A summary of TEAEs occurring in $\geq 10\%$ of patients in both treatment arms is presented in Table 12 and shows that thrombocytopenia, fatigue, nausea, anaemia, decreased appetite, weight decreased, cataract, asthenia, neutropenia, nasopharyngitis, dizziness and vomiting occurred statistically significantly more in the SBd arm compared to the Bd arm. The resubmission stated that these AEs are consistent with the known safety profile of SBd alone or in combination. Peripheral neuropathy (PN) occurred statistically significantly more in the Bd arm. This is likely due to the difference in bortezomib exposure between the two treatment arms. The lower rates of PN with once weekly bortezomib in the SBd arm compared with those in the twice weekly bortezomib in the Bd arm were consistent with the mostly sensory nature of bortezomib-induced PN. These results were previously seen by the PBAC as the current resubmission did not present individual TEAE data based on the updated data cut-off (February 2021). The ESC agreed with the Commentary that the lower rate of peripheral neuropathy seen in the SBd arm was likely due to the lower bortezomib exposure in the SBd arm compared with the Bd arm.

Table 12: TEAEs occurring in $\geq 10\%$ of patients in either treatment arm (safety population)

MedDRA preferred term n (%)	BOSTON (original data cut-off Feb 2020)			
	SBd arm (N=195)	Bd arm (N=204)	RR (95% CI) ^a	RD (95% CI) ^a
Patients with ≥ 1 TEAE	194 (99.5)	198 (97.1)	1.03 (1.00, 1.05)	0.02 (0.00, 0.05)
Thrombocytopenia	117 (60.0)	55 (27.0)	2.23 (1.73, 2.87)	0.33 (0.24, 0.42)
Peripheral neuropathy	63 (32.3)	96 (47.1)	0.69 (0.53, 0.88)	-0.15 (-0.24, -0.05)
Fatigue	82 (42.1)	37 (18.1)	2.32 (1.66, 3.24)	0.24 (0.15, 0.33)
Nausea	98 (50.3)	20 (9.8)	5.13 (3.30, 7.95)	0.41 (0.32, 0.49)
Anaemia	71 (36.4)	47 (23.0)	1.58 (1.16, 2.16)	0.13 (0.05, 0.22)
Decreased appetite	69 (35.4)	11 (5.4)	6.56 (3.58, 12.02)	0.30 (0.23, 0.37)
Weight decreased	51 (26.2)	25 (12.3)	2.13 (1.38, 3.30)	0.14 (0.06, 0.22)
Asthenia	48 (24.6)	27 (13.2)	1.86 (1.21, 2.86)	0.11 (0.04, 0.19)
Cataract	42 (21.5)	13 (6.4)	3.38 (1.87, 6.10)	0.15 (0.09, 0.22)
Vomiting	40 (20.5)	9 (4.4)	4.65 (2.32, 9.33)	0.16 (0.10, 0.22)
Neutropenia	29 (14.9)	12 (5.9)	2.53 (1.33, 4.81)	0.09 (0.03, 0.15)
Nasopharyngitis	23 (11.8)	10 (4.9)	2.41 (1.18, 4.92)	0.07 (0.02, 0.12)
Dizziness	24 (12.3)	8 (3.9)	3.14 (1.44, 6.82)	0.08 (0.03, 0.14)

Source: Table 2-30, p111 of the resubmission.

Abbreviations: Bd = bortezomib + dexamethasone; CI = confidence interval; MedDRA = Medical Dictionary for Regulatory Activities; RD = risk difference; RR = relative risk; SBd = selinexor + bortezomib + dexamethasone; TEAE = treatment emergent adverse events.

Notes: **Bold** indicates statistically significant results.

For patients who crossed over, AEs that occurred after the crossover were not included.

This table uses MedDRA version 22.0.

Preferred Terms are recoded to aggregate medically similar preferred terms.

Blue shading indicates data previously seen by the PBAC.

a. RD and RR was calculated during the evaluation.

Grade ≥ 3 TEAEs

6.38 The occurrence of Grade ≥ 3 TEAEs is presented in Table 13 and shows statistically significantly more thrombocytopenia (39.5% versus 17.2%), fatigue (13.3% versus

Public Summary Document – March 2022 PBAC Meeting

1.0%), neutropenia (8.7% versus 3.4%), nausea (7.7% versus 0.0%), cataract (8.7% versus 1.5%), and diarrhoea (6.2% versus 0.5%) for SBd compared with Bd.

Table 13: Treatment-emergent Grade 3 or higher adverse events occurring in ≥5% of patients in either treatment arm (safety population)

MedDRA preferred term	BOSTON (original data cut-off Feb 2020)				
	SBd arm (N=195) n (%)	Bd arm (N=204) n (%)	OR (95% CI) ^b	RR (95% CI) ^a	RD (95% CI) ^a
Patients with ≥1 Grade 3+ TEAE	166 (85.1)	125 (61.3)	3.62 (2.23, 5.87)	1.39 (1.23, 1.57)	0.24 (0.16, 0.32)
Thrombocytopenia	77 (39.5)	35 (17.2)	3.15 (1.98, 5.01)	2.30 (1.63, 3.26)	0.22 (0.14, 0.31)
Fatigue	26 (13.3)	2 (1.0)	15.54 (3.64, 66.42)	13.60 (3.27, 56.53)	0.12 (0.07, 0.17)
Neutropenia	17 (8.7)	7 (3.4)	2.69 (1.09, 6.63)	2.54 (1.08, 5.99)	0.05 (0.01, 0.10)
Cataract	17 (8.7)	3 (1.5)	6.40 (1.84, 22.20)	5.93 (1.76, 19.91)	0.07 (0.03, 0.12)
Nausea	15 (7.7)	0	NE	NE	0.08 (0.04, 0.11)
Diarrhoea	12 (6.2)	1 (0.5)	13.31 (1.71, 103.38)	12.55 (1.65, 95.64)	0.06 (0.02, 0.09)

Source: Table 2-31, p112 of the resubmission.

Abbreviations: Bd = bortezomib + dexamethasone; CI = confidence interval; MedDRA = Medical Dictionary for Regulatory Activities; NE = not estimable; RD = risk difference; RR = relative risk; SBd = selinexor + bortezomib + dexamethasone; TEAE = treatment emergent adverse events.

Notes: **Bold** indicates statistically significant results.

Blue shading indicates data previously seen by the PBAC.

Italics indicates results calculated during evaluation.

a. RD and RR was calculated during the evaluation.

b. Calculated by the resubmission using Review Manager version 5.4.1.

Cd versus Bd

6.39 Overall, 457 (98.7%) patients in the Cd arm and 451 (98.9%) patients in the Bd arm experienced an AE (see Table 14). Results were statistically significant for Grade 3/4 and any serious AE in favour of Bd. Previously PBAC considered that the overall safety profile of carfilzomib was inferior to bortezomib (para 7.5, carfilzomib PSD, July 2017).

Table 14: Summary of adverse events (safety population)

	Cd (N=463) n (%)	Bd (N=456) n (%)	OR (95% CI)^a	RR (95% CI)	RD (95% CI)^a
Any AE	457 (98.7)	451 (98.9)	0.84 (0.26, 2.79)	1.00 (0.98, 1.01)	0.00 (-0.02, 0.01)
Grade 3 and 4 AEs	379 (81.9)	324 (71.1)	1.84 (1.35, 2.51)	1.15 (1.07, 1.24)	0.11 (0.05, 0.16)
Any serious AE	279 (60.3)	183 (40.1)	2.26 (1.74, 2.95)	1.50 (1.31, 1.72)	0.20 (0.14, 0.26)
Any Adverse Event Leading to carfilzomib or bortezomib dose reduction	138 (29.8)	226 (49.6)	0.43 (0.33, 0.57)	0.60 (0.51, 0.71)	-0.20 (-0.26, -0.14)
Any AE leading to discontinuation of study treatment	137 (29.6)	121 (26.5)	1.16 (0.87, 1.55)	1.12 (0.91, 1.37)	0.03 (-0.03, 0.09)
Any adverse event leading to death	32 (6.9)	22 (4.8)	1.46 (0.84, 2.56)	1.43 (0.85, 2.43)	0.02 (-0.01, 0.05)

Source: Table 2-40, p125 of the resubmission.

Abbreviations: AE = adverse event; Bd = bortezomib + dexamethasone; Cd= carfilzomib + dexamethasone; CI = confidence interval; N = total number of patients; n = number of patients; OR = odds ratio; RD = risk difference.

Notes: **Bold** indicates statistically significant results.

Blue shading indicates data previously seen by the PBAC.

RR was calculated during the evaluation.

a. Calculated by the resubmission using Review Manager version 5.4.1.

6.40 The most commonly experienced Grade ≥ 3 AE in the Cd arm were anaemia (17.3%) and hypertension (14.9%). Compared with Bd, a statistically significantly higher proportion of Cd patients experienced anaemia, pyrexia, hypertension, dyspnoea, and cardiac failure with the absolute risk of 6% of cardiac failure with Cd (see Table 15).

Table 15: Treatment-emergent adverse events of Grade 3 or higher (safety population)

Event	Cd (N = 195), n (%)	Bd (N=204), n (%)	OR (95% CI) ^a	RR (95% CI)	RD (95% CI) ^a
Anaemia	80 (17.3)	46 (10.1)	1.86 (1.26, 2.75)	1.71 (1.22, 2.40)	0.07 (0.03, 0.12)
Diarrhoea	19 (4.1)	40 (8.8)	0.45 (0.25, 0.78)	0.47 (0.28, 0.80)	-0.05 (-0.08, -0.02)
Pyrexia	14 (3.0)	3 (0.7)	4.71 (1.34, 16.5)	4.60 (1.33, 15.89)	0.02 (0.01, 0.04)
Hypertension	69 (14.9)	15 (3.3)	5.15 (2.9, 9.15)	4.53 (2.63, 7.80)	0.12 (0.08, 0.15)
Dyspnoea	29 (6.3)	10 (2.2)	2.98 (1.44, 6.19)	2.86 (1.41, 5.79)	0.04 (0.01, 0.07)
Cardiac failure	28 (6.0)	9 (2.0)	3.2 (1.49, 6.85)	3.06 (1.46, 6.42)	0.04 (0.02, 0.07)
Peripheral neuropathy (PN)	11 (2.4)	44 (9.6)	0.23 (0.12, 0.45)	0.25 (0.13, 0.47)	-0.07 (-0.1, -0.04)

Source: Table 2-41, p126 of the resubmission.

Abbreviations: Bd = bortezomib + dexamethasone; Cd= carfilzomib + dexamethasone; CI = confidence interval; N = total number of patients; n = number of patients; OR = odds ratio; RD = risk difference.

Notes: **Bold** indicates statistically significant results.

Blue shading indicates data previously seen by the PBAC.

RR was calculated during the evaluation.

a. Calculated by the resubmission using Review Manager version 5.4.1.

Safety ITC (SBd versus Cd)

- 6.41 The resubmission presented an unadjusted ITC with respect to safety outcomes for SBd versus Cd via Bd as a common reference based on BOSTON and ENDEAVOR. Events for inclusion in the ITC were based on the original data cut of BOSTON (February 2020) and the latest data cut of ENDEAVOR (July 2017).
- 6.42 Results of safety ITCs with respect to overall AEs showed no statistically significant differences were observed between SBd and Cd with respect to any AE, Grade 3 or higher TEAEs, any SAE, AEs leading to discontinuation and AEs resulting in death when the analyses were performed on the OR. However, a statistically significant difference in Grade 3 or higher TEAEs in favour of Cd was observed when the RD was considered (see Table 16).
- 6.43 Results obtained on the basis of the unadjusted ITC are confounded by the underlying transitivity issues between the studies (BOSTON and ENDEAVOR) such as the unknown effects of the differences in baseline disease characteristics between the trials, differences in the time at which the studies were conducted and differences in the maturity of the data. The resubmission did not present safety analyses for overall AEs based on an adjusted ITC or STC.
- 6.44 The PBAC noted the limitations of the unadjusted ITC and considered that underlying transitivity issues between the studies had potential to confound the results.

Table 16: Results of indirect comparison for overall AEs (SBd versus Cd)

Adverse event, n (%) Grade	BOSTON (SBd versus Bd)		ENDEAVOR (Cd versus Bd)		Indirect estimate of effect (SBd versus Cd)	
	OR (95% CI) ^a	RD (95% CI) ^a	OR (95% CI) ^a	RD (95% CI) ^a	OR (95% CI); p-value	RD (95% CI); p-value
Any AE	5.88 (0.7, 49.28)	0.02 (0, 0.05)	0.84 (0.26, 2.79)	0 (-0.02, 0.01)	7.00 (0.61, 79.96); 0.117	0.02 (-0.01, 0.05); 0.179
Grade 3 and 4 AEs	2.97 (1.91, 4.61)	0.23 (0.14, 0.32)	1.84 (1.35, 2.51)	0.11 (0.05, 0.16)	1.61 (0.94, 2.77); 0.082	0.12 (0.01, 0.23); 0.026
Any serious AE	1.77 (1.19, 2.64)	0.14 (0.04, 0.24)	2.26 (1.74, 2.95)	0.2 (0.14, 0.26)	0.78 (0.49, 1.26); 0.316	-0.06 (-0.18, 0.06); 0.313
Any AE leading to discontinuation of study treatment	1.43 (0.86, 2.39)	0.05 (-0.02, 0.13)	1.16 (0.87, 1.55)	0.03 (-0.03, 0.09)	1.23 (0.69, 2.22); 0.485	0.02 (-0.08, 0.12); 0.683
AE leading to Deaths	1.15 (0.5, 2.67)	0.01 (-0.04, 0.05)	1.46 (0.84, 2.56)	0.02 (-0.01, 0.05)	0.79 (0.29, 2.15); 0.642	-0.01 (-0.06, 0.04); 0.717

Source: Table 2-45, pp137 of the resubmission.

Abbreviations: AE = adverse events; Bd = bortezomib + dexamethasone; Cd = carfilzomib + dexamethasone; CI = confidence interval; OR = odds ratio; RD = risk difference; SBd = selinexor + bortezomib + dexamethasone.

Note: a. Calculated by the resubmission using Review Manager version 5.4.1.

- 6.45 Results of safety ITCs with respect to individual Grade ≥ 3 TEAEs for SBd vs Cd showed statistically significant differences in favour of SBd with respect to hypertension (OR= 0.27 (95% CI: 0.08, 0.93) and dyspnoea (OR= 0.07 (95% CI: 0.01, 0.74). Conversely, statistically significant differences in favour of Cd were observed for fatigue (OR= 17.46 (95% CI: 3.76, 81.12), diarrhoea (OR= 29.58 (95% CI: 3.52, 248.49) and thrombocytopaenia (OR= 3.80 (95% CI: 2.09, 6.9) (see Table 17).
- 6.46 These results should be interpreted with caution given the indirect nature of the evidence and the underlying transitivity issues between the studies. The resubmission did not present safety analyses for TEAEs of Grade 3 or higher based on an adjusted ITC or STC. The PBAC previously noted that SBd was associated with higher rates of haematological events compared to Cd; whereas Cd was associated with higher rates of cardiac failure, and considered that the comparison was difficult to interpret due to the transitivity issues between the trials and the absence of data presented for the Bd common reference arms (para. 7.10, selinexor, PBAC PSD, July 2021 PBAC meeting) (see Table 13 and Table 15).
- 6.47 The PSCR stated that whilst the safety analyses were not adjusted for differences in baseline characteristics, the results were intuitive and broadly consistent with the known safety profile of SBd and Cd. The resubmission sought to address any remaining uncertainty in the analyses of safety, by including the cost of the AEs that were more prevalent with SBd in the CMA, but not including those more prevalent with Cd.

Table 17: Results of indirect comparison for TEAE of Grade 3 or higher (SBd versus Cd)

Adverse event	BOSTON (SBd versus Bd)		ENDEAVOR (Cd versus Bd)		Indirect estimate of effect	
	OR (95% CI) ^a	RD (95% CI) ^a	OR (95% CI) ^a	RD (95% CI) ^a	OR (95% CI)	RD (95% CI)
Anaemia	1.65 (0.91, 2.98)	0.06 (-0.01, 0.12)	1.86 (1.26, 2.75)	0.07 (0.03, 0.12)	0.89 (0.44, 1.8)	-0.01 (-0.09, 0.07)
Diarrhoea	13.31 (1.71, 103.38)	0.06 (0.02, 0.09)	0.45 (0.25, 0.78)	-0.05 (-0.08, -0.02)	29.58 (3.52, 248.49)	0.11 (0.06, 0.16)
Pyrexia	1.58 (0.26, 9.55)	0.01 (-0.02, 0.03)	4.71 (1.34, 16.5)	0.02 (0.01, 0.04)	0.34 (0.04, 3.02)	-0.01 (-0.04, 0.02)
Hypertension	1.41 (0.48, 4.15)	0.01 (-0.02, 0.05)	5.15 (2.9, 9.15)	0.12 (0.08, 0.15)	0.27 (0.08, 0.93)	-0.11 (-0.16, -0.06)
Fatigue	15.54 (3.64, 66.42)	0.12 (0.07, 0.17)	0.89 (0.54, 1.47)	-0.01 (-0.04, 0.03)	17.46 (3.76, 81.12)	0.13 (0.07, 0.19)
Dyspnoea	0.21 (0.02, 1.77)	-0.02 (-0.04, 0)	2.98 (1.44, 6.19)	0.04 (0.01, 0.07)	0.07 (0.01, 0.74)	-0.06 (-0.1, -0.02)
Cardiac failure	0.52 (0.05, 5.79)	0 (-0.02, 0.01)	3.2 (1.49, 6.85)	0.04 (0.02, 0.07)	0.16 (0.01, 1.97)	-0.04 (-0.07, -0.01)
Ischaemic heart disease	0.35 (0.01, 8.57) ^b	0 (-0.02, 0.01) ^b	1.71 (0.67, 4.37)	0.01 (-0.01, 0.03)	0.2 (0.01, 6.81)	-0.01 (-0.04, 0.02)
Peripheral neuropathy	0.5 (0.22, 1.14)	-0.04 (-0.09, 0.01)	0.23 (0.12, 0.45)	-0.07 (-0.1, -0.04)	2.17 (0.76, 6.24)	0.03 (-0.03, 0.09)
Acute renal failure	1.58 (0.26, 9.55)	0.01 (-0.02, 0.03)	1.7 (0.9, 3.21)	0.02 (0, 0.05)	0.93 (0.14, 6.28)	-0.01 (-0.05, 0.03)
Thrombocytopenia	3.15 (1.98, 5.01)	0.22 (0.14, 0.31)	0.83 (0.57, 1.21)	-0.02 (-0.07, 0.02)	3.8 (2.09, 6.9)	0.24 (0.14, 0.34)
Neutropenia	2.69 (1.09, 6.63)	0.05 (0.01, 0.1)	1.19 (0.51, 2.77)	0 (-0.02, 0.02)	2.26 (0.66, 7.79)	0.05 (0, 0.1)

Source: Table 2-46, pp138 of the resubmission.

Abbreviations: AE = adverse events; Bd = bortezomib + dexamethasone; Cd = carfilzomib + dexamethasone; CI = confidence interval; OR = odds ratio; RD = risk difference; SBd = selinexor + bortezomib + dexamethasone; TEAE = treatment emergent adverse event.

Notes: a. Calculated by the resubmission using Review Manager version 5.4.1.

b. Referred to as 'myocardial ischaemia'.

Benefits/harms

6.48 The resubmission presented a non-inferiority claim. Accordingly, a summary of comparative benefits and harms has not been presented.

Clinical claim

6.49 On the basis of the ITC, the resubmission claimed that SBd is non-inferior in terms of efficacy and has a different safety profile compared to Cd. The clinical claim of comparable efficacy was based on PFS, and the clinical claim of non-inferior but different safety profiles for SBd compared with Cd was based on a comparison of the overall AEs and individual TEAE of Grade 3 or higher. The clinical claim of non-inferior efficacy of SBd versus Cd based on PFS remained unchanged from the previous

submission, while for safety, the July 2021 submission claimed SBd had a comparable but different safety profile compared to Cd.

- 6.50 While the adjusted ITCs addressed some concerns relating to differences in baseline disease characteristics between BOSTON and ENDEAVOR, the ability to draw conclusions from the results of the adjusted ITCs for the efficacy outcomes remained limited given the remaining underlying transitivity issues associated with the ITCs (period of conduct, differences in comparator regimen and differences in the maturity of the data). The Commentary stated that given the submission did not include a stated clinically meaningful difference, the indirect nature of the comparison and the potential transitivity issues, the clinical claim with respect to Cd was not supported. Furthermore, a statistically significant improvement in OS was demonstrated for Cd versus Bd (in ENDEAVOR), but not for SBd versus Bd (in BOSTON) potentially due to both immature OS data and cross-over.
- 6.51 In terms of comparative safety of SBd versus Cd, the Commentary stated that the claim of comparable but different safety profile was not supported by the evidence given the unadjusted nature of the analyses presented by the resubmission which was confounded by the underlying transitivity issues between the studies. The ESC considered that in terms of comparative safety of SBd versus Cd, a claim of comparable but different safety profile was possibly supported by the evidence, however this was uncertain due to the limitations of the unadjusted analysis. The ESC considered that similar numbers of overall adverse events were noted for SBd and Cd (paragraph 6.45), however SBd patients were more likely to experience haematological adverse events, such as thrombocytopenia and fatigue; while Cd patients were more likely to have cardiovascular related toxicities such as hypertension, and dyspnoea.
- 6.52 The PBAC considered that the claim of non-inferior comparative effectiveness was not adequately supported by the data. The PBAC noted the additional analyses of PFS provided by the resubmission (Table 9 and Table 10), however considered that a lack of a statistically significant difference between SBd and Cd did not adequately establish non-inferiority. Secondly, the PBAC noted that a statistically significant improvement in OS was demonstrated for Cd versus Bd (in ENDEAVOR), but not for SBd versus Bd (in BOSTON).
- 6.53 The PBAC considered that the claim of non-inferior comparative safety was reasonable, noting that SBd is associated with a different safety profile compared with Cd. The PBAC considered that in general, the types of adverse associated with SBd are more easily managed than those experienced with Cd.

Economic analysis

- 6.54 The resubmission presented a CMA comparing SBd and Cd based on an ITC of BOSTON and ENDEAVOR. The resubmission noted that other regimens in this setting (ELd and

Public Summary Document – March 2022 PBAC Meeting

PBd) were recommended by the PBAC on the basis of a CMA against Cd. The key components and assumptions of the CMA are presented in Table 18.

6.55 The July 2021 submission included both a cost-utility analysis (CUA) for SBd versus Bd; and a CMA for SBd versus Cd. However, the resubmission presented an economic evaluation based on a CMA only (SBd versus Cd).

Table 18: Key components and assumptions of the cost-minimisation analysis

Component	July 2021 submission claim or assumption	Resubmission claim or assumption	PBAC concern	Comment
Therapeutic claim: effectiveness	Effectiveness is assumed to be non-inferior to Cd	Effectiveness is assumed to be non-inferior to Cd	N/A	Remained unchanged
Therapeutic claim: safety	Safety is assumed to be different	Safety is assumed to be different	N/A	Remained unchanged
Evidence base	A naive ITC comparing SBd and Cd using data from the BOSTON and ENDEAVOR trials.	An adjusted ITC comparing SBd and Cd in the ITT population using data from the BOSTON and ENDEAVOR trials as presented in Section 2.6. AE rates were based on an indirect comparison of SBd and Cd presented in Section 2.6.	There were differences that might have impacted the transitivity of BOSTON and ENDEAVOR The claim that SBd was non-inferior compared to Cd in terms of efficacy was not supported given the numerically superior PFS results for Cd versus Bd and the lack of a significant gain in OS for SBd versus Bd.	Not adequately addressed. While the evidence base for the effectiveness claim was based on an adjusted ITC, and the safety claim was based on an unadjusted ITC in the current resubmission, differences that may have impacted the transitivity of the trials remained. No new trials were identified, and the results from the BOSTON updated data cut-off (February 2021) showed no significant OS gain for SBd versus Bd.

Public Summary Document – March 2022 PBAC Meeting

Component	July 2021 submission claim or assumption	Resubmission claim or assumption	PBAC concern	Comment
Equi-effective doses	The equi-effective doses for SBd and Cd were estimated based on the key clinical trials (BOSTON and ENDEAVOR) and PIs for selinexor and carfilzomib.	<p><u>Cd (100% dose intensity):</u></p> <ul style="list-style-type: none"> Carfilzomib (twice weekly dosing): 7278 milligrams over 74 infusions (carfilzomib, July 2020 PSD) <p><u>SBd (100% dose intensity):</u></p> <ul style="list-style-type: none"> Selinexor (once weekly dosing): 4933 milligrams (246.67 x 20 mg tablets) (see Table 3.2.2) Bortezomib (once weekly dosing): 116 milligrams (inclusive of wastage)^a (see Table 3.2.1 and Table 3.2.2) 	N/A	Equi-effective doses in the current resubmission were estimated based on Cd equi-effective dose established in the carfilzomib July 2020 PBAC submission.
Duration of treatment	The treatment duration of SBd was made equivalent to that of Cd (39.9 weeks).	The treatment duration of SBd was made equivalent to that of Cd (49.3 weeks).	<p>The PBAC noted that the duration of treatment of SBd was made equivalent to that of Cd and considered that was not reasonable.</p> <p>The PBAC considered that the duration of SBd treatment applied in the CMA (7.98 cycles; 39.9 weeks) was considerably higher than that observed in the BOSTON trial (6.67 cycles; 26.7 weeks).</p>	<p>The duration of SBd treatment was assumed to be the same as Cd (49.3 weeks) and was still considerably higher than that observed in BOSTON (26.7 weeks).</p> <p>The ESC noted this was consistent with a non-inferiority claim, but that the relative treatment durations were uncertain.</p>

Public Summary Document – March 2022 PBAC Meeting

Component	July 2021 submission claim or assumption	Resubmission claim or assumption	PBAC concern	Comment
Other costs or cost offsets	Infusion administration costs with carfilzomib. Adverse effect-related costs, leading to an incremental cost savings result.	<ul style="list-style-type: none"> • Infusion administration costs with carfilzomib. • Costs of haematological AEs that are slightly more prevalent with SBd. In order to be conservative, the analysis does not include AEs which are more prevalent with Cd. This is biased against SBd. • The cost of dexamethasone was not included in the CMA. • The costs of diarrhoea and fatigue events were not incorporated. • The costs of concomitant treatments were not considered. 	The PBAC considered that adverse event costs should be incorporated, particularly haematological events related to SBd use.	Addressed. Costs of haematological AEs were included in the CMA.

Source: Table 3-1, p156 of the resubmission.

Abbreviations: AEs = adverse events; Cd = carfilzomib + dexamethasone; CMA = cost minimisation analysis; mg = milligram; ITC = indirect treatment comparison; ITT = intent to treat; PSD = public summary document; SBd = selinexor + bortezomib + dexamethasone.

Notes: Blue shading indicates data previously seen by the PBAC.

a. Bortezomib is available on the PBS in 1 mg, 3 mg and 3.5 mg formulations which means doses to the nearest 1 mg or a dose of 3.5 mg can be dispensed.

- 6.56 The equi-effective dose for SBd was estimated by the resubmission based on the carfilzomib equi-effective dose established in the July 2020 PBAC submission which compared Cd once weekly dosing with Cd twice weekly dosing. The base case assumed the use of the Cd twice weekly regimen only as per the ENDEAVOR trial. The assumption that use of Cd was twice-weekly only was inconsistent with the utilisation applied in the financial estimates, in which the resubmission assumed that 20% of carfilzomib utilisation would be the twice weekly regimen and 80% of would be the once weekly regimen (based on the uptake rate of both scripts since the PBS listing of once weekly scripts in February 2021). The PBAC considered that the assumption that Cd would always be used twice weekly in the CMA was not justified, and that further consideration was required with respect to the carfilzomib dose assumed in the CMA.
- 6.57 The cost of dexamethasone was not included in the CMA. The PBAC considered this was reasonable given the low cost associated with dexamethasone treatment and similar dosage regimen (20 mg twice weekly).
- 6.58 The resubmission applied a dose intensity of 100% to both Cd and SBd in the base case. The dose intensity for Cd applied in the July 2021 submission was 87%, sourced

from the ENDEAVOR trial. The dose intensity applied to SBd was 80%, sourced from the BOSTON trial. The ESC previously considered that the lower dose intensity for selinexor represented the high rate of adverse events associated with SBd and the required dose modifications (i.e. dose reductions and interruptions)' (para 6.64, selinexor (RRMM), PBAC PSD, July 2021 PBAC meeting). The application of a lower dose intensity for SBd than Cd increases the price of selinexor (see Table 23).

- 6.59 The duration of treatment with SBd was made equivalent to that of Cd (49.3 weeks) within the CMA. The assumption of equivalent treatment duration between SBd and Cd might not be reasonable given the shorter median PFS observed for SBd in BOSTON (13.5 months) from the updated data cut-off (Feb 2021) compared to the median PFS of 18.7 months observed for Cd in ENDEAVOR. The median duration of treatment for Cd applied in the July 2021 submission was 9.18 months (39.9 weeks), sourced from the ENDEAVOR trial and the duration of treatment with SBd was made equivalent to that of Cd. The ESC noted this was consistent with a non-inferiority claim, but that the relative treatment durations were uncertain.
- 6.60 The SBd regimen consists of selinexor 100 mg every week and bortezomib administered subcutaneously 1.3 mg/m² once weekly for 4 out of 5 weeks (this is equivalent to 9.87 treatment cycles at full compliance (49.3/5). Therefore, each SBd patient will receive the equivalent of 246.67 tablets of 20 mg selinexor (9.87 cycles x 5 tablets per dose x 5 doses per cycle) and 39.47 doses of bortezomib (9.87 cycles x 4 doses per cycle). The resubmission stated that based on a mean (\pm SD) BSA of 1.8 m² (\pm 0.18) and after incorporating wastage, each dose of bortezomib is 2.93 mg.
- 6.61 Administration costs were included in the CMA to account for the variance in administration between SBd and Cd. The source used for the carfilzomib administration cost was appropriate. This remained unchanged from the July 2021 submission. No cost was assumed for subcutaneous administration of bortezomib, as part of SBd, however the PBAC considered that this should be included, noting that MBS Item 13950 would apply.
- 6.62 The CMA included costs of AEs consistent with previous PBAC advice. The following issues were noted:
- The CMA included the costs of haematological AEs that are more prevalent with SBd. The PBAC previously considered that the CMA should incorporate adverse event costs, particularly haematological events related to SBd use (para. 7.15, selinexor (RRMM), PBAC PSD, July 2021 PBAC meeting). The haematological AEs included in the CMA were anaemia, thrombocytopenia, and neutropenia. These were inconsistent with the safety results presented in Section 2.6 which showed that thrombocytopenia and neutropenia were more prevalent with SBd, while anaemia was more prevalent with Cd (although not statistically significant). The inclusion of costs relating to anaemia was conservative (decreasing the cost of selinexor).

- The CMA included TEAEs of Grade ≥ 3 based on data availability in ENDEAVOR for AEs of Grade 3 or higher (all Grade ≥ 3 AEs reported in ENDEAVOR were included in the CMA). The resubmission estimated the cost of AEs by assuming all Grade 3 AEs to receive hospital care. Given not all grade ≥ 3 AEs are likely to receive hospital care, this assumption is conservative, decreasing the cost-minimised price of selinexor. The inclusion of these AEs in the CMA relies on the acceptance of the unadjusted nature of the ITC performed with respect to safety outcomes.
 - The resubmission did not incorporate costs of diarrhoea and fatigue events which both occurred more frequently with SBd than Cd with a statistically significant difference in terms of OR and RD. However, inclusion of costs relating to treatment of diarrhoea and fatigue (as estimated by the resubmission) was tested in the sensitivity analyses conducted during evaluation, and their impact on the selinexor cost-minimising price was found to be minimal (see Table 23).
 - The median follow-up time at which the incidences of AEs were observed was shorter for SBd (17.3 months) than Cd (44.3 months). This is likely biased in favour of SBd.
- 6.63 The resubmission did not include the costs of any concomitant treatments. In BOSTON, prophylactic concomitant treatment with a 5-HT3 antagonist and/or other anti-nausea agents is recommended prior to and during treatment with selinexor. The PBAC considered that recommended concomitant treatments should have been included in the CMA.
- 6.64 The resubmission presented a CMA based on the published AEMP of Cd and Bd (see Table 19). The total cost per course of Cd (inclusive of infusion administration costs) was estimated to be \$162,240 per patient (at published PBS prices), while the cost per patient of the selinexor was estimated to be \$1 (after removing the costs of additional haematological AEs with SBd and the costs of bortezomib). The equi-effective dosing of selinexor was 4,933 milligrams per patient meaning the cost-minimising price of selinexor was calculated as \$1 per milligram, or \$1 per 20 mg tablet (see Table 19).

Public Summary Document – March 2022 PBAC Meeting

Table 19: Results of cost-minimisation analysis (Cd and SBd)

Row	Parameter	Value	Reference
A	Cd: equi-effective dose (mg)	7,278	Table 4, July 2020 PSD, carfilzomib
B	Cd: cost per mg (AEMP)	\$21.1490	PBS items 11229B, 11230C, 12243J, 12244K
C	Cd: total drug costs	\$153,922.42	A x B
D	Cd: infusions	74	Table 5, July 2020 PSD, carfilzomib
E	Cd: cost per infusions	\$112.40	MBS item 13950
F	Cd: total infusion costs	\$8,317.60	D x E
G	Cd: total cost per patient per course	\$162,240.02	C + F
H	SBd: additional AE costs per patient	\$█	Calculated by the resubmission
I	SBd: bortezomib equi-effective dose (mg)	115.56	Calculated by the resubmission
J	SBd: bortezomib cost per milligram (AEMP)	\$172.9100	PBS items 12219D, 12227M
K	SBd: bortezomib drug costs	\$19,981.79	I x J
L	SBd: cost-minimising selinexor costs per patient	\$█	G - H (AE costs) – K (bortezomib costs)
M	SBd: selinexor equi-effective dose	4,933.33	Calculated by the resubmission (see Table 3.2.2)
N	SBd: selinexor cost per milligram	\$█	L / M
O	SBd: selinexor cost per 20 mg tablet	\$█	N x 20

Source: Table 3-6, p161 of the resubmission.

Abbreviations: AEMP = approved ex-manufacturer price; Cd = carfilzomib + dexamethasone; CMA = cost-minimisation analysis; mg = milligram; MBS = Medicare Benefits Schedule; PSD = public summary document; SBd = selinexor + bortezomib + dexamethasone.

Blue shading indicates data previously seen by the PBAC.

6.65 The results of the key sensitivity are summarised in Table 20.

Table 20: Results of sensitivity analyses using Cd published price (conducted during evaluation)

Parameter	Total cost of Cd	Total cost of Bd ^a	Total cost of selinexor	Selinexor AEMP estimation
Base case	\$162,240.02	\$19,981.79	\$█	\$█
48-week treatment duration for Cd and SBd	\$157,853.10	\$19,441.74	\$█	\$█
Cd utilisation (100% Cd 70/20 mg/m ²)	109,585.38	\$19,981.79	\$█	\$█
Cd utilisation; 50% Cd 56/20 mg/m ² ^b . 50% Cd 70/20 mg/m ^{2c}	\$137,823.50	\$19,981.79	\$█	\$█
Cd utilisation; 20% Cd 56/20 mg/m ² ^b . 80% Cd 70/20 mg/m ^{2c}	\$148,651.81	\$19,981.79	\$█	\$█
SBd utilisation (80%) ^d	\$162,240.02	\$19,981.79	\$█	\$█
Cost of diarrhoea and fatigue (included)	\$162,240.02	\$19,981.79	\$█	\$█
Cost of diarrhoea and fatigue (included); cost of anaemia excluded	\$162,240.02	\$19,981.79	\$█	\$█

Source: Conducted during evaluation.

Abbreviations: Cd = carfilzomib + dexamethasone; SBd = selinexor + bortezomib + dexamethasone.

Notes: a. As part of SBd backbone.

b. Twice weekly (Cd56).

c. Once weekly (Cd70).

d. Assuming median dose of 80 mg instead of full dose of 100 mg (4,933.33 x 80/100). 80 mg dose intensity was the basis of the proposed published price.

Drug cost/patient/course

6.66 A summary of the drug cost per patient for SBd and Cd is presented in Table 21.

Table 21: Drug cost per patient for proposed and comparator drugs

	SBd			Cd		
	Trial dose and duration	CMA	Financial estimates	Trial dose and duration	CMA	Financial estimates
Mean dose	NR ^a	4933 mg	4933 mg	NR	7278 mg	7278 mg
Mean duration	26.68 weeks ^b	49.33 weeks	49.33 weeks	39.9 weeks ^c	49.33 weeks	49.33 weeks
Cost/patient/course	NE	\$	\$	NE	\$	\$

Source: Table 3-6, p161 of the resubmission.

Abbreviations: Cd = carfilzomib + dexamethasone; CMA = cost-minimisation analysis; mg = milligram; SBd = selinexor + bortezomib + dexamethasone; NE = not estimated; NR = not reported by the resubmission.

Notes: a. Selinexor median dose was 80 mg once weekly.

b. Based on BOSTON February 2020 data cut-off.

c. Based on ENDEAVOR November 2014 data cut-off (Dimopoulos et al. 2016).

Estimated PBS usage & financial implications

6.67 This resubmission was not considered by DUSC.

6.68 The resubmission used a market share approach to estimate the market size and financial implications of listing SBd based on assumed substitution of the comparator; Cd. This was consistent with the PBAC’s consideration of the July 2021 submission, that a market share approach may have been more appropriate to estimate the market size of selinexor (Para 6.84, Selinexor (RRMM), PBAC PSD, July 2021 PBAC meeting). The July 2021 submission used an epidemiological approach to estimate the financial implications of listing selinexor.

6.69 The resubmission provided financial estimates based on the proposed published prices for selinexor (16 pack and 20 pack). In addition, the resubmission provided financial estimates using an assumed effective price for carfilzomib (assuming a 40% rebate) and the consequent cost-minimising price of selinexor based on 100% dose intensity (assumed effective price of selinexor used in the financial estimates).

6.70 A summary of key inputs for the financial estimates is provided in Table 22.

Public Summary Document – March 2022 PBAC Meeting

Table 22: Key inputs for financial estimates

Parameter	Value applied	Source	Comment
Historical utilization of comparator			
Number of twice weekly carfilzomib scripts occupying the RRMM market per annum	23,753 scripts	Estimated by the resubmission	The resubmission assumed a constant twice weekly regimen scripts across the six-year analysis period by reasoning carfilzomib has achieved its optimal market share.
Treatment utilisation			
Assumed market share of twice and once weekly carfilzomib	20% for twice weekly script and 80% for once weekly script	The resubmission made this assumption based on the six-month uptake rate of both scripts since the PBS listing of once weekly scripts in February 2021.	This appears reasonable however, the data upon which this assumption was made was for only the first six-month of once weekly script listing. The resubmission assumed it is likely that the uptake rate will continue to increase before plateauing as observed with the monthly twice weekly scripts carfilzomib use presented by the resubmission. This was reasonable, however the extent to which uptake will continue to increase is uncertain.
Uptake (substitution) rate of selinexor	Yr 1: 20% Yr 2: 35% Yr 3: 50% Yr 4: 50% Yr 5: 50% Yr 6: 50%	Assumption made by the resubmission	The proposed substitution rate was unsupported. The uptake rates provided by the resubmission may be overestimated, given the toxicity associated with SBd. Of note, the resubmission assumes substitution of only Cd whereas the July 2021 submission assumed substitution of Bd, Cd and DBd. In addition, the current substitution rate of SBd for Cd is lower than assumed in the July 2021 submission; 35% in Year 1 increasing to 60% in Year 6 (a 5% incremental increase per year).
Proportion of carfilzomib scripts substituted by selinexor 20 and 16 pack formulation	53.97% for the 20 pack and 46.03% for the 16 pack.	This was calculated by the resubmission as the per tablet basis equivalence of the assumed proportions of 48.4% for 20 pack and 51.6% for 16 pack.	This was appropriate.
Costs			
Proposed medicine: Selinexor	AEMP 20 X 20 mg = \$ 16 X 20 mg = \$	Selinexor 20 X 20 mg tablets and 16 X 20 mg tablets Requested price, weighted AEMP for Public and Private	The resubmission did not propose an effective AEMP. The applied published AEMP was consistent with that requested, however was not based on the cost-minimised price presented in the CMA. The proposed published AEMP was based on an alternate cost-minimised price based on a dose intensity of selinexor of 80% rather than 100% as applied in the base case. In addition, the resubmission provided financial estimates using an assumed effective price for carfilzomib (assuming a % rebate) and the consequent cost-minimising price of selinexor based on 100% dose intensity (assumed effective price of selinexor used in financial estimates).
Other medicine included in therapy	Bortezomib (1,3 and 3.5 mg) Dispensed price - \$592.57, \$640.69 (below current published DPMA: \$605.00, \$653.29)	Bortezomib 12219D, 12227M – AEMP for Public and DPMQ for Private	B as part of SBd. The resubmission did not include the costs attributable to dexamethasone as part of the SBd regimen, due to the low cost associated with dexamethasone treatment and similar dosage regimen in SBd and Cd.

Public Summary Document – March 2022 PBAC Meeting

Parameter	Value applied	Source	Comment
Comparator	Carfilzomib twice and once weekly (10, 30, 60 mg) Published - \$2,114.90 \$2,673.23	Carfilzomib twice weekly: 11229B, 11230C - AEMP Carfilzomib once weekly: 12219D, 12227M - AEMP	This was appropriately sourced and estimated. The PBAC agreed with this statement.
MBS costs	\$112.40	MBS item 13950	Attributed to the intravenous administration of carfilzomib. The resubmission applied 85% of the scheduled fee in their model. This was appropriate. The resubmission did not include the MBS costs associated with the treatment of haematological AEs associated with SBd. This was inconsistent with the CMA presented in Section 3.

Source: Table 4-1, p165; Table 4-4, p167; Table 4-5, p168; Text paragraph 3, p168; Table 4-8, p171; Table 4-9, p172 of the resubmission and Workbook 'RRMM Section 4_November 2021', work sheet '7. Net changes – MBS', of the resubmission.

Abbreviations: AEMP = approved ex-manufacturer price; AEs = adverse events; B = bortezomib; Bd = bortezomib + dexamethasone; Cd = carfilzomib + dexamethasone; CMA = cost minimisation analysis; DBd = daratumumab + bortezomib + dexamethasone; DPMQ = dispensed price for maximum quantity; MBS = Medical Benefits Scheme; RRMM = Relapsed and/or refractory multiple myeloma; SBd = selinexor + bortezomib + dexamethasone.

- 6.71 The resubmission assumed SBd will substitute the market described by the current and projected use of Cd. The resubmission's assumption that substitution will result in only replacement of SBd for Cd may not be appropriate as it is likely that it will result in displacement of Cd (and possibly Ld, Bd and Pd) to later line use. The resubmission noted inclusion of SBd on the PBS will not grow the RRMM market as it is already established. This was reasonable in terms of the number of patients accessing treatment, however, listing a new drug class might result in patients receiving an additional line of therapy, thereby increasing expenditure.
- 6.72 The July 2021 submission assumed SBd will substitute Bd, Cd and DBd. The resubmission assumed substitution of Cd only and stated that SBd was not expected to impact the remaining existing PBS reimbursed treatment regimens for RRMM (DBd, PBd, ELd, Ld, Bd and Pd). Given DBd is PBS listed for second-line therapy only and that ELd and PBd were only recently recommended by the PBAC, the exclusion of DBd, ELd and PBd from the market share analysis was reasonable. However, the exclusion of Pd, Ld and Bd was not sufficiently justified. The PBAC previously considered that SBd would most likely be used as third or later line and was most likely to replace and/or displace Cd, Ld, Pd and some bortezomib-based regimens including Bd (Para 7.3, Selinexor (RRMM), PBAC PSD, July 2021 PBAC meeting).
- 6.73 The resubmission provided detailed information in applying the market share approach. The Commentary noted the following issues of concern with the steps taken by the resubmission in applying the market share approach:
- The resubmission applied an assumed market share for once weekly (80%) and twice weekly (20%) carfilzomib scripts' respective equivalent script to get the estimated market share of each script type of carfilzomib over the six-year period). This was inconsistent with Section 3, which assumed 100% of Cd use was with the twice weekly regimen.

Public Summary Document – March 2022 PBAC Meeting

- The resubmission assumed a 20% substitution of carfilzomib use by SBd in year 1, increasing linearly to 50% in year 3, and remaining constant thereafter, noting the ultimate 50% market share of carfilzomib is consistent with the clinical claim of non-inferior effectiveness safety for SBd relative to Cd. The assumed substitution rate of carfilzomib use by SBd for the resubmission is lower than that presented for the July 2021 submission: 35% in Year 1, increasing to 60% in Year 6.
 - The resubmission excluded the grandfathered patients likely to receive selinexor via the proposed PBS listing from the selinexor utilisation and financial estimates. The sponsor justified this exclusion with the market share approach used and the small number of Australian patients in the KEAP (24 patients as of 21 October 2021). The July 2021 submission previously indicated that approximately 85 patients are likely to be grandfathered upon TGA approval of selinexor. Therefore, the exclusion of grandfathered patients is likely to result in an underestimation of projected utilisation and subsequent financial estimates of selinexor.
- 6.74 In estimating the utilisation of the two requested pack sizes, the resubmission assumed a lower proportion of selinexor scripts (48.4%) will be for the 20-tablet formulation which on a per tablet basis is equivalent to 53.94% of the substituted carfilzomib. This does not align with DUSC previous consideration on the likely use of 20- and 16- tablet formulation (see paragraph 3.6).
- 6.75 No cost was assumed for subcutaneous administration of bortezomib, as part of SBd. The PBAC considered that MBS Item 13950 (parenteral administration) should have also been applied in the estimates for bortezomib injections (administered subcutaneously).
- 6.76 A summary of the estimated use and financial implications for listing SBd on the PBS is presented in Table 23. The estimates are based on an assumed effective price for selinexor as described in paragraph 6.69.

Public Summary Document – March 2022 PBAC Meeting

Table 23: Estimated use and financial implications

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
Estimated extent of use						
Number of scripts dispensed ^a	1	1	1	1	1	1
Estimated financial implications of Selinexor (assumed effective price)						
Cost to PBS/RPBS less copayments (\$)	2	2	4	4	4	4
Estimated financial implications for other medicines						
Cost to PBS/RPBS less copayments – bortezomib (\$)	2	2	2	2	2	2
Cost to PBS/RPBS less copayments – carfilzomib (\$)	- 2	- 4	- 4	- 4	- 4	- 4
Net financial implications						
Net cost to PBS/RPBS (\$)	2	2	2	2	2	2
Net cost to MBS (\$)	- 2	- 2	- 2	- 2	- 2	- 2
Net cost to PBS/RPBS/MBS (\$)	2	2	2	2	2	2
Previous submission (July 2021, based on effective prices)						
Number of scripts dispensed	1	1	1	1	6	6
Estimated financial implications of Selinexor (assumed effective price)						
Cost to PBS/RPBS less copayments (\$)	3	3	5	5	5	7
Estimated financial implications for other medicines						
Cost to PBS/RPBS less copayments – daratumumab (\$)	- 2	- 4	- 4	- 3	- 5	- 5
Cost to PBS/RPBS less copayments – carfilzomib ^b (\$)	- 2	- 2	- 2	- 2	- 2	- 4
Cost to PBS/RPBS less copayments – bortezomib (\$)	2	2	2	2	2	2
Cost to PBS/RPBS less copayments – dexamethasone (\$)	- 2	- 2	2	2	2	2
Cost to PBS/RPBS less copayments – filgrastim (\$)	2	2	2	2	2	2
Cost to PBS/RPBS less copayments – Total (\$)	- 2	- 4	- 3	- 3	- 5	- 3
Net financial implications						
Net cost to PBS/RPBS (\$)	4	4	4	2	- 2	2
Net cost to PBS/RPBS/MBS (\$)	4	4	2	2	- 2	2

Source: Table 4-13, p175, Tables 4-17 and 4-18, p180 and Workbook 'RRMM Section 4_November 2021', work sheet '5. Impact - net', of the resubmission.

Abbreviations: PBS = Pharmaceutical Benefit Scheme; MBS = Medical Benefit Scheme; RPBS = Repatriation Pharmaceutical Benefit Scheme

Note: ^a Assuming number of scripts per year as estimated by the submission.

^b The July 2021 submission base case assumed 100% patients received the twice-weekly dosing
Italicised compiled during the current evaluation and the previous evaluation for the July 2021 submission.

The redacted values correspond to the following ranges:

¹ 500 to < 5,000

² \$0 to < \$10 million

³ \$20 to < \$30 million

⁴ \$10 to < \$20 million

⁵ \$30 to < \$40 million

⁶ 5,000 to < 10,000

⁷ \$50 to < \$60 million

⁸ \$40 to < \$50 million

Public Summary Document – March 2022 PBAC Meeting

- 6.77 The total cost to the PBS/RPBS/MBS of listing SBd was estimated to be \$0 to < \$10 million per year in Year 6, and a total of approximately \$0 to < \$10 million in the first 6 years of listing. During the evaluation, the values presented for the net financial implications to the PBS/RPBS could not be reconciled with the estimations in the financial model workbook for the resubmission. Therefore, the commentary reported the values presented in the financial model workbook after verifying the calculations.
- 6.78 Unlike the July 2021 submission, the resubmission excluded the use and cost of dexamethasone (as part of the SBd regimen) and filgrastim used in the treatment of Grade 3-4 neutropenia associated with SBd from the financial impact analysis. The resubmission justified the exclusion of dexamethasone by arguing a slight difference in its use between SBd and Cd regimens, and its low cost, resulting in an inconsequential impact on the PBS budget. No justification was provided for the exclusion of filgrastim from the analysis. The exclusion of the cost of filgrastim used in the treatment of Grade 3-4 neutropenia associated with SBd and that of dexamethasone may have resulted in underestimation of the financial impacts, however, the impact of this cost is negligible. The costs associated with treating the haematological AEs due to SBd was not included in the financial estimates, which was inconsistent with the CMA. Concomitant treatment costs for SBd and Cd were not included in the financial estimates.
- 6.79 Sensitivity analyses were conducted during the evaluation (Table 24) to test the:
- Assumed proportions of once- and twice weekly carfilzomib scripts; the lower the proportion attributable to once weekly carfilzomib scripts, the lower the net financial impact on the health budget.
 - Treatment duration of Cd from ENDEAVOR; minimal impact on the health budget.

Table 24: Results of sensitivity analysis (Net Impact on PBS/RPBS/MBS), Assumed Effective Prices

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
Base case (\$)	█ ¹	█ ¹	█ ¹	█ ¹	█ ¹	█ ¹
Assumed proportions of once- and twice weekly carfilzomib scripts (base case 80%/20%)						
70%/30% (\$)	█ ¹	█ ¹	█ ¹	█ ¹	█ ¹	█ ¹
60%/40% (\$)	█ ¹	█ ¹	█ ¹	█ ¹	█ ¹	█ ¹
50%/50% (\$)	█ ¹	█ ¹	█ ¹	█ ¹	█ ¹	█ ¹
44%/66% (\$)	█ ¹	█ ¹	█ ¹	█ ¹	█ ¹	█ ¹
Treatment duration of Cd from ENDEAVOR (base case 49.3 weeks)						
48 weeks (\$)	█ ¹	█ ¹	█ ¹	█ ¹	█ ¹	█ ¹

Source: calculated during the evaluation using the Workbook 'RRMM Section 4_November 2021

The redacted values correspond to the following ranges:

¹ \$0 to < \$10 million

- 6.80 The ESC considered that use of a market share approach was appropriate and noted that the overall budget impact of the proposed listing was negligible, based on assumed effective prices for selinexor and carfilzomib. However, the ESC considered that the place in therapy for SBd was unclear (paragraphs 4.5), which may have implications for the financial estimates.

Quality Use of Medicines

- 6.81 The resubmission provided a summary of ongoing work on a multi-stakeholder quality use of medicine approach for haematologists, nurses, pharmacists, patients and their caregivers to minimise AEs and optimise treatment for all patients.

Financial Management – Risk Sharing Arrangements

- 6.82 The resubmission proposed SBd would join the PBS expenditure cap that applies for carfilzomib.

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

7 PBAC Outcome

- 7.1 The PBAC did not recommend selinexor, in combination with bortezomib and dexamethasone (SBd), for the treatment of relapsed and/or refractory multiple myeloma (RRMM). The PBAC noted that additional analyses of progression free survival (PFS) were provided by the resubmission however, considered that the claim of non-inferior effectiveness of SBd compared with the nominated main comparator, Cd, was not adequately supported by the data. The PBAC also noted that the data for overall survival (OS) remained immature and did not demonstrate a significant benefit for SBd compared with bortezomib plus dexamethasone (Bd). In contrast, a significant improvement in OS has been demonstrated for Cd compared with Bd. As non-inferiority was not demonstrated the PBAC considered the cost minimisation analysis (CMA) between SBd and Cd was not informative.
- 7.2 The PBAC noted the consumer comments from individuals which described the debilitating impact of relapsed myeloma. The PBAC noted that advice was received from organisations including Myeloma Australia, the Leukaemia Foundation, and Myeloma Australia's Medical and Scientific Advisory Group (MSAG), which described an ongoing need for new treatment options and supported the proposed listing for SBd on the basis of results from the BOSTON trial.
- 7.3 The PBAC noted that the multiple treatment options for RRMM, and the changing treatment algorithm, complicated the selection of a main comparator(s). The PBAC recalled the July 2021 submission nominated Bd as the primary comparator and Cd a secondary comparator and, at that time, the Committee considered that SBd was most likely to replace and/or displace Cd, Ld, Pd and some bortezomib-based regimens including Bd. The PBAC noted that the resubmission nominated Cd as the primary comparator. Noting international guidelines indicate a preference for triple combination therapies, the PBAC considered that PBS listed triple therapies, such as ELd, may increasingly become relevant comparators.

- 7.4 The PBAC noted that the clinical algorithm presented in the pre-PBAC response placed SBd as a second, third or fourth line therapy; however this was not consistent with the proposed listing which would allow use of SBd in any line after first line. The PBAC considered that it is not yet clear where SBd would fit in the treatment algorithm given that several drug classes are currently PBS listed for use as double or triple combination therapies including immunomodulators (IMiD), protease inhibitors (PI), anti-CD38 monoclonal antibodies and corticosteroids. Consistent with previous advice, the PBAC considered that SBd would likely be used as a third or later line treatment, however there appears to be overlap between the proposed populations for SBd and that for Sd (which was the subject of a separate consideration at the March 2022 PBAC meeting). The resubmission did not discuss reasons for a clinician to prescribe SBd rather than Sd, or vice versa, for patients eligible for both. The PBAC considered this information was needed to understand the place in therapy for SBd and may have implications for comparator selection as well as the financial estimates.
- 7.5 The PBAC noted that the resubmission was based on one head-to-head randomised controlled trial comparing SBd to Bd (BOSTON) and ITCs between SBd and Cd that were informed by the BOSTON and ENDEAVOR (comparing Cd with Bd) trials. The resubmission presented efficacy data with a longer follow-up duration from BOSTON, with a data-cut of February 2021 compared to February 2020 presented in the July 2021 submission. Both efficacy and safety data from ENDEAVOR remained unchanged from July 2021 submission.
- 7.6 The key outcomes presented by the resubmission in the ITCs were PFS and safety. The resubmission justified that the ITCs were not performed for OS as the data were immature in BOSTON and it was impacted by cross-over.
- 7.7 In regard to PFS, the PBAC recalled that in the July 2021 submission a statistically significant improvement in PFS was demonstrated in the BOSTON trial (ITT population) for SBd compared to Bd (HR = 0.70; 95% CI: 0.53, 0.93). The PBAC noted that the resubmission presented similar results for SBd compared to Bd based on the updated data cut (HR = 0.71; 95% CI: 0.54, 0.93).
- 7.8 The PBAC noted that four different ITC models were presented in the resubmission to assess PFS, which included (i) Unadjusted ITCs; (ii) Unadjusted ITCs with matching of statistical methods; (iii) Adjusted ITCs (multivariate) based on age and ECOG status; and (iv) STC (multivariate) based on age and ECOG status. The results were presented for three subgroups (ITT – excluding India, Subgroup ≥ 2 prior lines, and Subgroup ≥ 2 prior lines and excluding India). The PBAC noted although there were no statistically significant differences, the ITCs using the ITT population did not exclude the possibility of SBd being less effective than Cd (the point estimate [upper 95% CI] for the ITC HRs ranged from 1.08 [1.63] for the STC analysis to 1.32 [1.86] for the unadjusted analysis; Table 9). The results from the subgroup analyses were generally consistent with the results for the ITT population although for some of the analyses the point estimate for the indirect estimates of effect favoured SBd (Table 10).

- 7.9 In regard to OS, the PBAC noted that despite the longer follow-up, the survival data presented in the resubmission remained immature with an event rate of 35% and 39% for SBd and Bd arms, respectively. The difference in OS based on the updated data cut-off was not statistically significant between the two trial arms (HR = 0.88; 95% CI: 0.63, 1.22), a result that was consistent with the February 2020 data cut-off as presented in the July 2021 submission (HR = 0.84; 95% CI: 0.57, 1.23). The PBAC considered although this result may be in part due to the impact of crossover within the Bd treatment arm to SBd treatment, the impact of SBd on OS remained uncertain. In contrast, the PBAC noted that for Cd, the clinical evidence (ENDEAVOR) demonstrated a significant improvement in OS for Cd compared with Bd (HR = 0.76; 95% CI: 0.63, 0.92).
- 7.10 In regard to adverse events, the PBAC noted the occurrence of Grade ≥ 3 TEAEs in BOSTON which indicated statistically significantly more thrombocytopenia (39.5% versus 17.2%), fatigue (13.3% versus 1.0%), neutropenia (8.7% versus 3.4%), nausea (7.7% versus 0.0%), cataract (8.7% versus 1.5%), and diarrhoea (6.2% versus 0.5%) for SBd compared with Bd.
- 7.11 The PBAC noted that results of safety ITCs with respect to overall AEs showed no statistically significant differences were observed between SBd and Cd with respect to any AE, any SAE, AEs leading to discontinuation and AEs resulting in death (Table 17). Results of safety ITCs with respect to individual Grade ≥ 3 TEAEs for SBd vs Cd showed statistically significant differences in favour of SBd with respect to hypertension (OR= 0.27; 95% CI: 0.08, 0.93) and dyspnoea (OR= 0.07; 95% CI: 0.01, 0.74). Conversely, statistically significant differences in favour of Cd were observed for fatigue (OR= 17.46; 95% CI: 3.76, 81.12), diarrhoea (OR= 29.58; 95% CI: 3.52, 248.49) and thrombocytopenia (OR= 3.80; 95% CI: 2.09, 6.9) (Table 18). The PBAC considered that the results were broadly consistent with the known safety profile of SBd and Cd. The PBAC also noted that the resubmission included the cost of the AEs that were more prevalent with SBd in the CMA, but not those more prevalent with Cd, in acknowledgement of the uncertainty within the safety ITCs.
- 7.12 Overall the PBAC considered that the claim of non-inferior comparative effectiveness was not adequately supported by the data. The PBAC noted the additional analyses of PFS provided by the resubmission, however considered that a lack of a statistically significant difference between SBd and Cd did not adequately establish non-inferiority. Secondly, the PBAC noted that a statistically significant improvement in OS was demonstrated for Cd versus Bd (in ENDEAVOR), but not for SBd versus Bd (in BOSTON). The PBAC considered that the claim of non-inferior comparative safety was reasonable, noting that SBd is associated with a different safety profile compared with Cd.
- 7.13 As the claim of non-inferiority between SBd and Cd was not supported, the PBAC considered that the CMA was not informative. The PBAC did note however, the following concerns with the CMA presented in the resubmission: (i) the assumption that Cd would always be used twice weekly was not justified and that further

consideration was required with respect to the carfilzomib dose assumed in the CMA (paragraph 6.56); (ii) the costs associated with subcutaneous administration of bortezomib (paragraph 6.61) should have been included; and (iii) recommended concomitant drugs should have been included (paragraph 6.63).

- 7.14 In regard to the utilisation estimates, the PBAC considered the resubmission's assumption that substitution will result in only replacement of Cd may not be appropriate as SBd, being a new drug class, may displace Cd (and possibly other treatments such as Ld, Bd and Pd) to later line use. Overall, the PBAC considered that the utilisation estimates for SBd were uncertain, noting that the place in therapy for SBd and the impact on other RRMM regimens was unclear. In addition, the resubmission did not quantify the potential overlap in the populations for SBd and Sd (proposed in the separate submission considered at the March 2022 meeting).
- 7.15 The PBAC noted that the proposed listing of selinexor aligns with the proposed TGA indication, which would allow use in combination with bortezomib plus dexamethasone for the treatment of patients with relapsed and/or refractory MM who have received at least one prior line of therapy. The PBAC provided the following comments on the proposed restriction:
- The requested maximum quantity of one pack and two repeats are considered appropriate.
 - A criterion should be added stating that 'Patient must not have previously received this drug for this condition' to prevent patients being retreated with selinexor.
 - A caution stating that selinexor should not be given to pregnant women should be added to the proposed restrictions.
 - Prescriber instructions for the histological diagnosis of MM in the grandfather restriction should be added.
- 7.16 The resubmission may be lodged at any future standard due date for PBAC submission using the standard re-entry pathway.
- 7.17 The PBAC noted that this submission is eligible for an Independent Review.

Outcome:

Not recommended

8 Context for Decision

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

in which it should be made available through the PBS. The PBAC welcomes applications containing new information at any time.

9 Sponsor's Comment

Antengene wishes to thank the patients, patient organisations and health care professionals for supporting this submission. Antengene will continue to work with the Myeloma community and the PBAC to provide access for XPOVIO in this patient population.