

7.07 SELINEXOR, Tablet 20 mg, Xpovio[®], ANTENGENE (AUS) Pty. Ltd.

1 Purpose of submission

- 1.1 The resubmission requested a Section 100 (Highly Specialised Drug), Authority Required (telephone/online), listing for 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 approach (CMA) versus carfilzomib + dexamethasone (Cd).

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

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	Main comparator: carfilzomib + dexamethasone (Cd)
Outcomes	PFS; Safety
Clinical claim	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 1-1, p15 of the resubmission.

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

Blue shading indicates data previously seen by the PBAC.

2 Background

Registration status

- 2.1 SBd was TGA registered on 8 March 2022 for the treatment of adult patients with multiple myeloma who have received at least one prior therapy.
- 2.2 Selinexor is also TGA registered for use in combination with dexamethasone (Sd) for the treatment of adult patients with RRMM who have received at least three prior therapies and whose disease is refractory to at least one proteasome inhibitor, at least one immunomodulatory medicinal product (IMiD), and an anti-CD38 monoclonal antibody (mAb). The TGA indication is broader than the current PBS listing for Sd, which requires that the patient has progressive disease after at least four prior lines of therapy for RRMM, and has demonstrated refractory disease to at least two proteasome inhibitors, two immunomodulators, and one anti-CD38 monoclonal antibody.

Previous PBAC consideration

2.3 Summary of the key matters of concern from the previous PBAC consideration (March 2022) is presented in Table 2.

Table 2: Summary of key matters of concern

Component	Matter of concern	How the resubmission addresses it
Comparator	The PBAC noted that the resubmission nominated Cd as the primary comparator. The PBAC noted that international guidelines indicate a preference for triple combination therapies, and considered that triple combination therapies, such as ELd, may increasingly become relevant comparators (para 7.3, selinexor (RRMM) PSD, March 2022 PBAC meeting).	Consistent with the March 2022 resubmission, the resubmission nominated Cd as the primary comparator. The resubmission stated that as ELd and PBd were listed on a CMA basis versus Cd, based on non-inferiority claims, the use of Cd as the comparator was appropriate.
Clinical place in therapy	SBd was placed as a second, third or fourth line therapy, however the proposed listing would allow SBd in any line after first line. The PBAC also considered that SBd would likely be used as a third or later line treatment (para 7.4, selinexor (RRMM) PSD, March 2022 PBAC meeting).	The proposed listing remained unchanged from the March 2022 resubmission, allowing SBd use in any line after first line. However, the resubmission estimated that the majority of SBd use would be in third and fourth lines. The resubmission predicted minimal use of SBd in second line (due to the PBS restrictions for DBd being for second line use only) and minimal use in fifth and later lines (due to predicted pre-exposure and/or cumulative toxicities to one or more treatments in the regimen).
	There was an overlap between the proposed populations for SBd and Sd (TCR/PR MM), and there was a lack of clarity regarding reasons 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 (para 7.4, selinexor (RRMM) PSD, March 2022 PBAC meeting).	The resubmission stated that although the proposed listing of SBd overlaps with the restriction for Sd, due to high rates of attrition through lines of therapy it is estimated that less than 10% of patients would commence a fifth line treatment. The resubmission stated that by fifth line patients were likely to be more frail and less fit to tolerate triple therapies and are likely to be refractory to bortezomib, thus limiting the use of SBd in fifth or later lines.

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Component	Matter of concern	How the resubmission addresses it
Clinical effectiveness	<ul style="list-style-type: none"> The PBAC noted that four ITC models were presented in the March 2022 resubmission to assess PFS: (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 PBAC noted that 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) (para 7.8, selinexor (RRMM) PSD, March 2022 PBAC meeting). In regard to OS, the PBAC noted that the survival data presented in the March 2022 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). The PBAC also 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) (para 7.9, selinexor (RRMM) PSD, March 2022 PBAC meeting). 	<p>The resubmission re-presented the four ITC models for PFS previously considered by the PBAC in March 2022.</p>
Clinical claim	<p>The claim that SBd was non-inferior compared to Cd in terms of efficacy was not adequately supported by the resubmission. The PBAC noted that the OS data remained immature and did not demonstrate a significant benefit for SBd compared with Bd (para 7.1, selinexor (RRMM) PSD, March 2022 PBAC meeting).</p>	<p>The resubmission acknowledged that some uncertainty in the clinical claim remained as some differences between the datasets could not be accounted for in the adjusted ITCs, and the OS data remained immature. The resubmission maintained that the claim of non-inferiority between SBd and Cd was supported by the data presented.</p>
Economic evaluation (CMA)	<ul style="list-style-type: none"> The PBAC considered that the CMA was not informative given that the clinical claim was not supported (para 7.13, March 2022 PBAC PSD). The PBAC noted the following concerns with the CMA: (i) the assumption that Cd would always be used twice weekly was not justified and further consideration was required with respect to the carfilzomib dose assumed in the CMA; (ii) the cost associated with administration of bortezomib should be included; (iii) recommended concomitant drugs should be included (para 7.13, selinexor (RRMM) PSD, March 2022 PBAC meeting). 	<p>The resubmission presented a CMA based on the clinical claim of non-inferiority between SBd and Cd. The resubmission revised the CMA to address the PBAC concerns. The PSCR reiterated that uncertainty in the clinical claim was accommodated with a conservative CMA which reduced the proposed price of selinexor relative to the previous submission.</p>
Predicted use of the medicine in practice	<ul style="list-style-type: none"> The assumption of SBd replacing Cd may not be appropriate as SBd may displace Cd (and possibly other treatments such as Ld, Bd and Pd). The PBAC considered the place of therapy of SBd uncertain (para 7.14, selinexor (RRMM) PSD, March 2022 PBAC meeting). 	<p>An increase in net costs to PBS/RPBS was estimated due to the assumption that listing SBd will result in some patients receiving an additional line of therapy. The resubmission estimated that displacement would occur in 28% of patients. (see paragraph 6.53).</p>

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Source: Compiled during evaluation

Bd = bortezomib + dexamethasone; Cd = carfilzomib + dexamethasone; CI = confidence interval; CMA = cost minimisation approach; DBd = daratumumab + bortezomib + dexamethasone; ECOG = Eastern Cooperative Oncology Group; ELd = elotuzumab + lenalidomide + dexamethasone; HR = hazard rate; ITC = indirect treatment comparison; ITT = intention to treat; Ld = lenalidomide + dexamethasone; OS = overall survival; PBAC = Pharmaceutical Benefits Advisory Committee; PBd = pomalidomide + bortezomib + dexamethasone; Pd = pomalidomide + dexamethasone; PFS = progression free survival; PSD = Public Summary Document; RRMM = relapsed/refractory multiple myeloma; SBd = selinexor + bortezomib + dexamethasone; Sd = selinexor + dexamethasone; STC = simulated treatment comparison; TCR/PR = triple-class refractory/penta-refractory.

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

3 Requested listing

3.1 The submission requested the following new listing. Suggested additions are in italics and deletions are in strikethrough. An abridged version of the restriction is presented.

MEDICINAL PRODUCT medicinal product pack	Max. Qty	No. of Repeats	DPMQ	Proprietary Name
			Published price: (\$585 AEMP per tablet) \$9,360.00 (HSD Public) \$9,461.92 (HSD Private)	
SELINEXOR, selinexor 20 mg tablet, 16	16	2	Effective price (resubmission): (\$ [REDACTED] AEMP per tablet) \$ [REDACTED] (HSD Public) \$ [REDACTED] (HSD Private)	XPOVIO
			Effective price (Pre-PBAC response): (\$ [REDACTED] AEMP per tablet)	
			Published/ price: (\$585 AEMP per tablet) \$11,700.00 (HSD Public) \$11,801.92 (HSD Private)	
SELINEXOR, selinexor 20 mg tablet, 20	20	2	Effective price (resubmission): (\$ [REDACTED] AEMP per tablet) \$ [REDACTED] (HSD Public) \$ [REDACTED] (HSD Private)	XPOVIO
			Effective price (Pre-PBAC response): (\$ [REDACTED] AEMP per tablet)	

Proposed restriction (Initial)

Category/Program:	Section 100 (Highly Specialised Drugs Program)
Prescriber type	<input checked="" type="checkbox"/> Medical practitioner
Restriction type:	Authority Required – immediate/real-time assessment by Services Australia (telephone/online)
Episodicity	Relapsed and/or refractory
Condition:	Multiple myeloma
PBS Indication:	Relapsed and/or refractory multiple myeloma (RRMM)
Treatment Phase:	Initial treatment
Clinical criteria:	The condition must be confirmed by a histological diagnosis AND The patient must be undergoing triple combination therapy limited to: (i) this drug, (ii) bortezomib, (iii) dexamethasone treatment must be in combination with bortezomib and dexamethasone AND Patient must have progressive disease after at least one prior therapy

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	AND Patients must not have previously received this drug for this condition
Administrative advice:	No increase in the maximum quantity or number of units may be authorised.
	No increase in the maximum number of repeats may be authorised.
	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.

Proposed restriction (Continuing)

Category/Program:	Section 100 (Highly Specialised Drugs Program)
Prescriber type	<input checked="" type="checkbox"/> Medical practitioner
Restriction type:	Authority Required – immediate/real-time assessment by Services Australia (telephone/online)
Episodicity	Relapsed and/or refractory
Condition:	Multiple myeloma
PBS Indication:	Relapsed and/or refractory multiple myeloma (RRMM)
Treatment Phase:	Continuing treatment
Clinical criteria:	Patient must have previously received PBS-subsidised treatment with this drug for this condition AND <i>The patient must be undergoing triple combination therapy limited to: (i) this drug, (ii) bortezomib, (iii) dexamethasone;</i> AND Patient must not have developed disease progression while receiving treatment with this drug for this condition.
Administrative advice:	No increase in the maximum quantity or number of units may be authorised
	No increase in the maximum number of repeats may be authorised.
	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.

Proposed restriction (Grandfathering)

Category/Program:	Section 100 (Highly Specialised Drugs Program)
Prescriber type	<input checked="" type="checkbox"/> Medical practitioner
Restriction type:	Authority Required – immediate/real-time assessment by Services Australia (telephone/online)
Episodicity	Relapsed and/or refractory
Condition:	Multiple myeloma
PBS Indication:	Relapsed and/or refractory multiple myeloma (RRMM)
Treatment phase:	Grandfather treatment
Clinical criteria:	Patient must have received non-PBS-subsidised treatment with this drug for this condition prior to [date of selinexor PBS listing], AND <i>Patient must have met all initial treatment PBS-eligibility criteria applying to a non-grandfathered patient prior to having commenced treatment with this drug, which are: [to be confirmed]</i> The condition must be confirmed by a histological diagnosis AND The treatment must be in combination with bortezomib and dexamethasone AND Patient must have disease progression after at least one prior therapy for this condition AND 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 other than bortezomib, (ii) immunomodulators, (iii) anti-CD38 monoclonal

	antibody AND Patient must not have developed disease progression while receiving treatment with this drug for this condition.
Administrative advice:	No increase in the maximum quantity or number of units may be authorised.
	No increase in the maximum number of repeats may be authorised.
	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.

- 3.2 The submission sought listing for two pack sizes. 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 full recommended dose. The 16 tablet pack would provide 28 days treatment at a dose of 80 mg (4 x 20 mg), which is consistent with the median dose received in BOSTON. This differs from the recommended dose for selinexor in the Sd regimen, which is 160 mg per week at the full recommended dose, and between 60 and 100 mg per week for patients requiring dose reductions due to adverse reactions.
- 3.3 The resubmission proposed an effective price for selinexor of \$ [REDACTED] per 20 mg tablet (AEMP). The Pre-PBAC response offered a lower effective price, that was equal to the effective price for selinexor for its current PBS indication in RRMM (\$ [REDACTED] per tablet; AEMP)¹.
- 3.4 The resubmission’s requested restriction was for treatment following at least one prior line of therapy. This remained unchanged from the July 2021 submission and March 2022 resubmission.
- 3.5 The clinical criteria of the requested restriction were consistent with those applied to other RRMM therapies (including elotuzumab in combination with lenalidomide and dexamethasone (ELd), pomalidomide in combination with bortezomib and dexamethasone (PBd), daratumumab in combination with bortezomib and dexamethasone (DBd), Cd, lenalidomide + dexamethasone (Ld) and bortezomib + dexamethasone (Bd)).
- 3.6 The ESC considered that SBd would most likely be used in a relatively small proportion of the total RRMM population, however the SBd population was difficult to define. For example, SBd may be a useful option for a niche population of fit patients with high-risk disease, especially in patients unable to receive Cd. Also SBd is the only IMiD-free triplet and may therefore be useful in patients unsuitable for IMiDs.

¹ The current PBS indication is for use in combination with dexamethasone for the treatment of patients with RRMM, 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); also known as triple-class-refractory and penta-refractory multiple myeloma (TCR/PR MM).

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

4 Population and disease

- 4.1 Multiple myeloma (MM) is a 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 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 resubmission presented a revised clinical management algorithm, primarily based on advice from six Australian haematologists with expertise in myeloma. The resubmission stated that the consensus among clinicians was that newly diagnosed patients typically receive first line treatment with lenalidomide, bortezomib, or a combination of both with dexamethasone, or a combination of bortezomib with cyclophosphamide and dexamethasone. The resubmission noted the likely preferential use of DBd in the second line, as its PBS restriction is specific to second line use. The resubmission stated that not all patients are suitable for DBd and therefore it is still important to have access to alternative triple therapies options, particularly those with a unique mode of action, in this setting, and that treatment options that are not lenalidomide based may be preferred for patients who are refractory to lenalidomide.
- 4.3 The resubmission stated that according to the clinical experts, after the second line setting there is no clear preference for regimens in the third- and fourth line settings rather the decision would be based on patient and disease characteristics.
- 4.4 The MM Clinical Expert Consultation Meeting (June 2022) noted that selinexor (as SBd or Sd) was difficult to administer due to adverse events and it was generally used in a small, niche population of relatively fit patients with high-risk disease. The resubmission did not describe the characteristics of the patient population that is likely to be prescribed SBd.
- 4.5 The proposed clinical algorithm depicts the majority of SBd use as third or fourth line of therapy. The clinical evidence presented in the resubmission was for the use of SBd after 1-3 prior therapies (second, third and fourth lines of therapy). The resubmission also re-presented the subgroup analyses of patients who received SBd after two or more prior lines of therapy. The PBAC has previously considered that that SBd would likely be used as a third or later line treatment (para 7.4, selinexor (RRMM) PSD, March 2022 PBAC meeting).
- 4.6 During the March 2022 PBAC meeting a sponsor hearing was presented for selinexor where a clinician described the role of SBd therapy for patients who are refractory to lenalidomide, have high risk cytogenetics (including 17p deletion) or extramedullary disease, and those who cannot receive Cd due to cardiac comorbidities.

- 4.7 The resubmission indicated that there is a potential overlap between the SBd and Sd regimens in the fifth or later lines, however indicated that the overlap is minimal as patients at later lines are more frail and are unfit to receive triple therapies. Further, by the fifth line, patients are likely to be refractory or have experienced cumulative toxicity to bortezomib. The ESC considered that the number of patients receiving Sd under the current listing may be reduced if SBd is listed as proposed because a patient is unlikely to receive selinexor in two different lines of therapy.
- 4.8 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.
- 4.9 The recommended dosing schedule of SBd proposed by the resubmission was consistent with the selinexor product information and clinical evidence obtained from BOSTON. Prophylactic concomitant treatment with a 5-HT3 antagonist and/or other antiemetics is recommended prior to and during treatment with selinexor; these concomitant treatments were included in the economic evaluation in the resubmission, however were not included in the estimates of financial impact presented in the resubmission.

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

5 Comparator

- 5.1 The comparator remains unchanged from the March 2022 resubmission. 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 comparator informing the recommendations for the listing of new regimens (ELd and PBd) in the proposed patient population (elotuzumab PSD, July 2021 PBAC meeting; pomalidomide PSD, November 2019 PBAC meeting). Based on the proposed clinical algorithm, second, third and fourth line SBd use may replace: ELd, PBd, CLd, Bd, Cd and Pd. The PBAC previously noted that the international guidelines indicate a preference for triple combination therapies, and considered that PBS listed triple therapies, such as ELd, may increasingly become relevant comparators (para 7.3, selinexor (RRMM) PSD, March 2022 PBAC meeting).
- 5.2 The Pre-Sub-Committee Response (PSCR) reiterated that the nominated comparator is consistent with the PBAC's three most recent decisions in this population, elotuzumab, pomalidomide and carfilzomib triplet combinations, for which Cd was accepted as the comparator. The PSCR claimed that given elotuzumab, pomalidomide and carfilzomib amongst other drugs, were PBS listed for the same population on a cost-minimisation basis versus Cd, it can be inferred that if SBd is non-inferior to Cd, it would also be non-inferior to these other drugs. The ESC noted the claim of non-inferior efficacy versus Cd, and by extension versus the elotuzumab and pomalidomide regimens, was uncertain. Given the safety profile of each regimen differed, it was also

uncertain whether SBd would be non-inferior in terms of safety to other comparators such as elotuzumab and pomalidomide.

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 described the clinical place of SBd within the Australian treatment landscape, stating it will be most applicable to patients who have high risk disease or specific circumstances (such as IMiD refractory, cardiac disease or CNS involvement). The clinician emphasised that SBd would address important unmet clinical needs for these patients. The clinician expressed the importance of treatment options and the ability for patients to switch drug classes. The clinician described subgroup analyses demonstrating that SBd is effective irrespective of age, frailty and renal function. The clinician stated that adverse events with selinexor are manageable, and that prescribers will become more proficient in managing selinexor-related adverse events with increasing experience with the drug. The PBAC considered that the hearing was informative as it provided an expert perspective on the proposed use of SBd in Australian clinical practice.

Consumer comments

- 6.2 The PBAC noted and welcomed the input from individuals (64) and organisations (3) via the Consumer Comments facility on the PBS website. It was noted that several medicines are available, but not all work for each patient, and eventually these must be discontinued because they are no longer effective or because of side-effects. The comments from individuals supported the proposed listing on the basis of it providing an additional treatment option, prolonging quality of life and also noted that selinexor is a tablet that may be taken at home. The PBAC considered that these comments added to the contributions of consumers supporting the proposed listing which were considered during PBAC's previous considerations in July 2021 and March 2022.
- 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 noted that the new class of drug in an effective combination would make significant impact on patients. The Leukemia Foundation reiterated the ongoing need for therapies in patients with relapsed and or refractory multiple myeloma to extend progression-free survival with a lower toxicity profile than existing treatments. 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 As in the March 2022 resubmission, the current resubmission presented anchored, adjusted 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. The BOSTON trial is an active trial with expected completion in September 2023 (clinicaltrials.gov).
- 6.5 Details of the two trials presented in the resubmission are provided in Table 3. Two new publications were located during the evaluation that presented post hoc subgroup analyses of the BOSTON trial efficacy and safety outcomes according to patients' renal insufficiency (based on the creatine clearance volume) (Delimpasi et al., 2022) and age and frailty status (<65 and ≥65 years, non-frail and frail) (Auner et al., 2021). Based on the data in the publications, it appears that the analyses were based on the February 2021 data cut-off. Additionally, two publications were presented in the March 2022 resubmission exploring the efficacy and safety of SBd based on cytogenetic risk (Richard et al., 2021) and the impact of prior lines of treatment (Mateos et al., 2021). The findings of these studies appear to be aligned with the feedback from the Australian clinicians expressed at the MM Clinical Expert Consultation Meeting (June 2022) in that they reported subgroup analyses and findings supportive of the potential role of SBd in certain patients in clinical practice.
- 6.6 The PSCR stated that the additional post-hoc analyses of renal insufficiency demonstrated that SBd is effective and safe in patients <65 and ≥65 years of age, and in both frail and non-frail patients (Auner et al., 2021²) and that the regimen induced deep and durable responses in patients with renal insufficiency, despite the fact that these patients were older and had more high-risk cytogenetics than those with normal renal function. The PSCR stated these results are supportive of the proposed listing of SBd, allowing for treatment decisions to be tailored to individual patients on the basis of prior treatment history, comorbidities, disease and patient characteristics.

² Auner, H.W., Gavriatopoulou, M., Delimpasi, S., Simonova, M., Spicka, I., Pour, L., Dimopoulos, M.A., Kriachok, I., Pylypenko, H., Leleu, X. and Doronin, V., 2021. Effect of age and frailty on the efficacy and tolerability of once-weekly selinexor, bortezomib, and dexamethasone in previously treated multiple myeloma.

Table 3: Trials and associated reports presented in the resubmission

Trial ID	Protocol title/ Publication title	Publication citation
Direct trials (SBd versus Bd)		
BOSTON NCT 03110562	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).	May 2020
	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.	Lancet 2020 Nov; 14;396(10262):1563-1573.
	Mateos MV, Gavriatopoulou M, Facon T, et al. Effect of prior treatments on selinexor, bortezomib, and dexamethasone in previously treated multiple myeloma.	Journal of hematology & oncology; 2021;14(1).
	Richard S, Chari A, Delimpasi S, et al. Selinexor, bortezomib, and dexamethasone versus bortezomib and dexamethasone in previously treated multiple myeloma: Outcomes by cytogenetic risk.	American Journal of Hematology; 2021;96(9):1120-30.
	Auner, H.W., Gavriatopoulou, M., Delimpasi, S., Simonova, M., Spicka, I., Pour, L., Dimopoulos, M.A., Kriachok, I., Pylypenko, H., Leleu, X. and Doronin, V., 2021. Effect of age and frailty on the efficacy and tolerability of once-weekly selinexor, bortezomib, and dexamethasone in previously treated multiple myeloma.	Am J Hematology 2021 Jun; 96(6): 708-18.
	Delimpasi, S., Mateos, M.V., Auner, H.W., Gavriatopoulou, M., Dimopoulos, M.A., Quach, H., Pylypenko, H., Hájek, R., Leleu, X., Dolai, T.K. and Sinha, D.K., 2022. Efficacy and tolerability of once-weekly selinexor, bortezomib, and dexamethasone in comparison with standard twice-weekly bortezomib and dexamethasone in previously treated multiple myeloma with renal impairment: subgroup analysis from the BOSTON study.	Am J Hematology 2022 Mar 1; 97(3): E83-E86.
Direct trials (Cd versus Bd)		
ENDEAVOR NCT 01568866	Dimopoulos MA, Moreau P, Palumbo A, et al. Carfilzomib and dexamethasone versus bortezomib and dexamethasone for patients with relapsed or refractory multiple myeloma (ENDEAVOR): A randomised, phase 3, open-label, multicentre study.	The Lancet Oncology 2016; 17(1): 27-38.
	Dimopoulos MA, 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.	The Lancet Oncology 2017; 18(10): 1327-1337. The Lancet Oncology. 18(10): e562.
	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.	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 March 2022 resubmission.

Bd = bortezomib + dexamethasone; Cd = carfilzomib + dexamethasone; N/A = not applicable; NCT = National Clinical Trial (number); OS = overall survival; PFS = progression free survival; SBd = selinexor + bortezomib + dexamethasone.

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/ duration	Risk of bias	Patient population	Outcomes	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 March 2022 resubmission.

BIW = twice weekly; Bd = bortezomib + dexamethasone; Cd = carfilzomib + dexamethasone; CMA = cost minimisation approach; CUA = cost utility analysis; IV = intravenous; IRC = Independent Review Committee; IMWG = International Myeloma Working Group; OL = open-label; ORR = overall response rate; OS = overall survival; PFS = progression free survival; PN = peripheral neuropathy; QW = once weekly; R = randomised; SC = subcutaneous; SBd = selinexor + bortezomib + dexamethasone; TTNT = time to next treatment; VGPR = very good partial response.

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, and 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);
- that the bortezomib dosing regimen in the Bd arm 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;
- As of the updated data cut-off (February 2021), the median follow-up for overall survival (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. Patients who did not experience a PFS event were censored at the date of their last assessment. The median follow-up for PFS 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; see Table 5). The main reason for censoring was treatment discontinuation³.

- 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 (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). The median follow-up time for PFS in BOSTON was longer than ENDEAVOR, whilst the median follow-up time for OS in BOSTON was shorter than ENDEAVOR.

Comparative effectiveness

BOSTON (SBd versus Bd)

6.10 As of the data cut-off date of February 2021, the median PFS was 13.2 months in the SBd arm and 9.5 months in the Bd arm (HR = 0.71; 95% CI: 0.54, 0.93; p=0.006; see Table 5 and Figure 1).

6.11 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 (data cut-off Feb 2021)	
	SBd arm (N=195)	Bd arm (N=207)
Median follow-up (months)	13.5	24.5
Progression-free survival (months), Median	13.2	9.5
Difference in median PFS (months)	3.7	
95% CI	(11.73, 23.43)	(8.11, 10.78)
Stratified log-rank test ^a One sided P-value	0.0064	
Hazard ratio ^{a,b} (95% CI)	0.71 (0.54, 0.93)	
Patients with events, n (%)	92 (47.2)	137 (66.2)
PD	79 (40.5)	122 (58.9)
Death	13 (6.7)	15 (7.2)
Patients censored, n (%)	103 (52.8)	70 (33.8)

Source: Table 2-19, p92 of the March 2022 resubmission.

Bd = bortezomib + dexamethasone; CI = confidence interval; ITT = intent to treat; PD = progressive disease; PFS = progression free survival; SBd = selinexor + bortezomib + dexamethasone.

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.

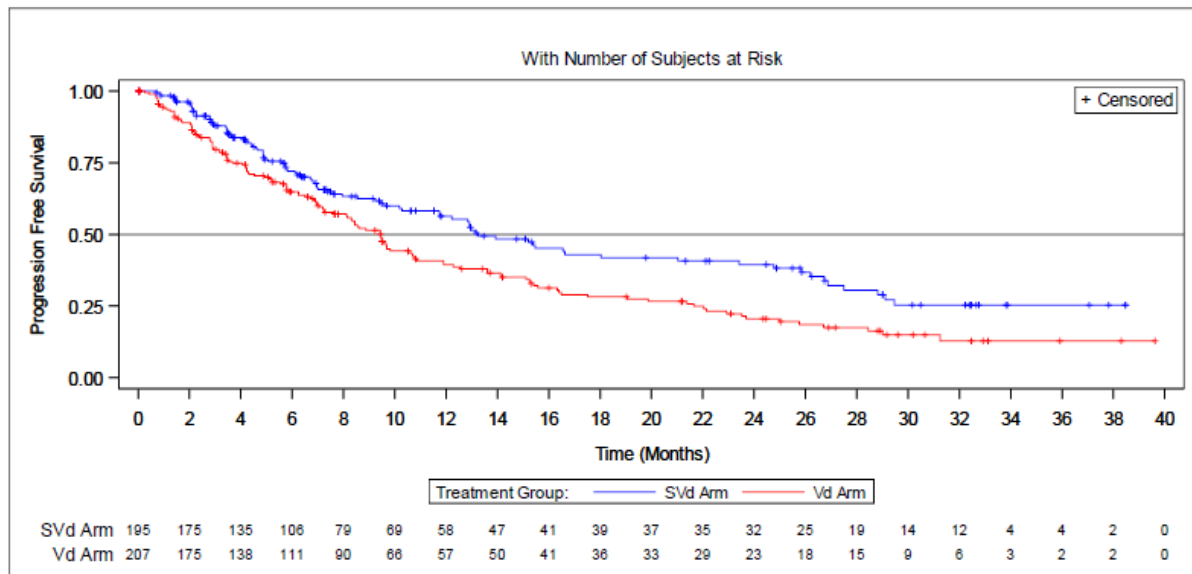
Blue shading indicates data previously seen by the PBAC.

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.

³ It was reported that 77 of 195 (39.5%) of patients in the SBd arm and 48 of 207 (23.2%) patients in the Bd arm were censored due to documented treatment discontinuation. Source: Table 2-19, March 2022 PBAC submission.

Figure 1: Kaplan-Meier curve of PFS by treatment arm (ITT population, data cut-off Feb 2021)



Source: Figure 2-9, p93 of the March 2022 resubmission.

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

The abbreviation of SVd was referred to as SBd (selinexor, bortezomib plus dexamethasone) in this ESC Advice.

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

- 6.12 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). The PBAC previously noted that the OS data remained immature with an event rate of 35% and 39% for SBd and Bd, respectively. The difference in OS was not statistically significant between the two trial arms (HR = 0.88; 95% CI: 0.63, 1.22). The PBAC previously considered that 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 (para 7.9, selinexor (RRMM) PSD, March 2022 PBAC meeting).
- 6.13 As for the March 2022 resubmission, the current resubmission did not provide updated crossover data corresponding to the February 2021 data cut-off. At the February 2020 data cut-off, the resubmission 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.

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

Patients with events, n (%)	BOSTON (data cut-off Feb 2021)	
	SBd arm (N=195)	Bd arm (N=207)
Death	68 (34.9)	80 (38.6)
Patients Censored, n (%)	127 (65.1)	127 (61.4)
Median Follow-up Time (Months), 95% CI	28.71 (27.24, 29.90)	28.65 (27.63, 29.67)
Overall Survival (Months)		
Median, 95% CI	36.7 (30.19, NE)	32.7 (27.83, NE)
Stratified log-rank test ^a		
One Sided P-value	0.2152	
Hazard Ratio ^{a,b}	0.88	
95% CI	(0.63, 1.22)	

Source: Table 2-22, pp95-96 of the March 2022 resubmission.

Bd = bortezomib + dexamethasone; CI = confidence interval; ITT = intention to treat; NE = not evaluable; SBd= selinexor + bortezomib + dexamethasone. Overall survival is calculated from date of randomisation to date of death.

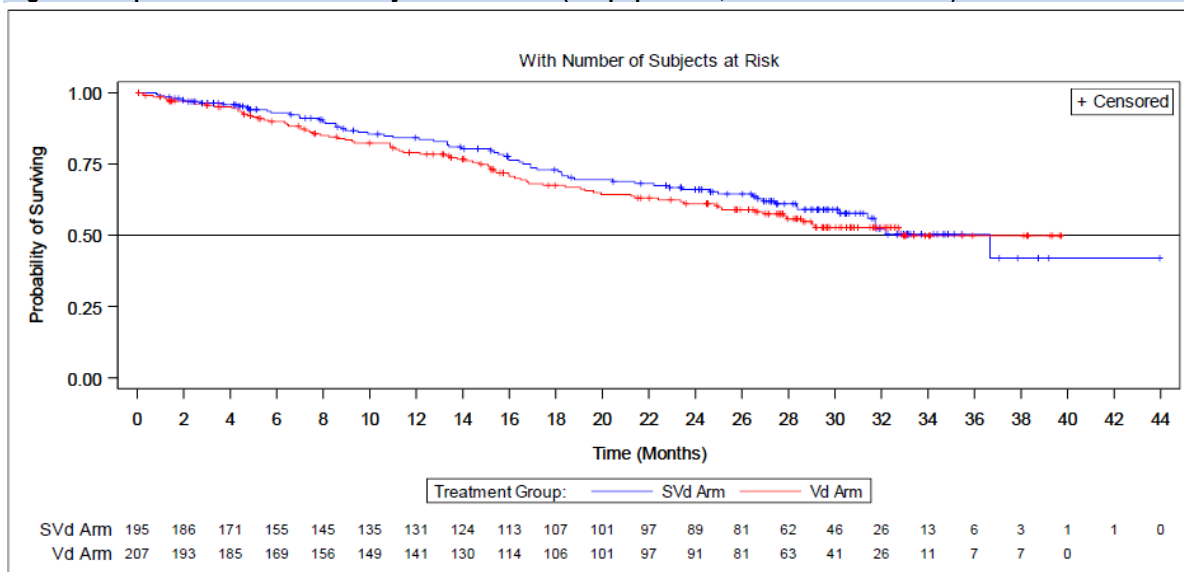
Patients without events were censored at the date of study discontinuation or date of last participating visit, whichever occurred first.

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, data cut-off Feb 2021)



Source: Figure 2-10, p96 of the March 2022 resubmission.

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

The abbreviation of SVd was referred to as SBd (selinexor, bortezomib plus dexamethasone) in this ESC Advice.

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

6.14 Results for ORR from BOSTON (data cut-off February 2021) showed a significantly higher ORR 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) of 1.94 (95% CI: 1.25, 3.03); p=0.0016 (see Table 7).

Table 7: ORR by treatment arm (ITT population)

	BOSTON (data cut-off Feb 2021)	
	SBd arm (N=195)	Bd arm (N=207)
ORR, n (%) ^a	150 (76.9)	131 (63.3)
Exact 95% CI	(70.4, 82.6)	(56.3, 69.9)
Cochran-Mantel-Haenszel Test (SBd vs. Bd) ^b		
OR (95% CI)	1.94 (1.25, 3.03)	
One Sided P-value	0.0016	

Source: Table 2-21, p94 of the March 2022 resubmission.

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

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)

6.15 As of the data cut-off date of November 2014, median PFS was 18.7 months in the Cd arm versus 9.4 months in Bd arm with a HR of 0.53 (95% CI: 0.44, 0.65); $p < 0.0001$ (see Table 8, Figure 3). Results from a later data cut-off (3 March 2016) 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 7.5 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 (data cut-off November 2014)

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)			

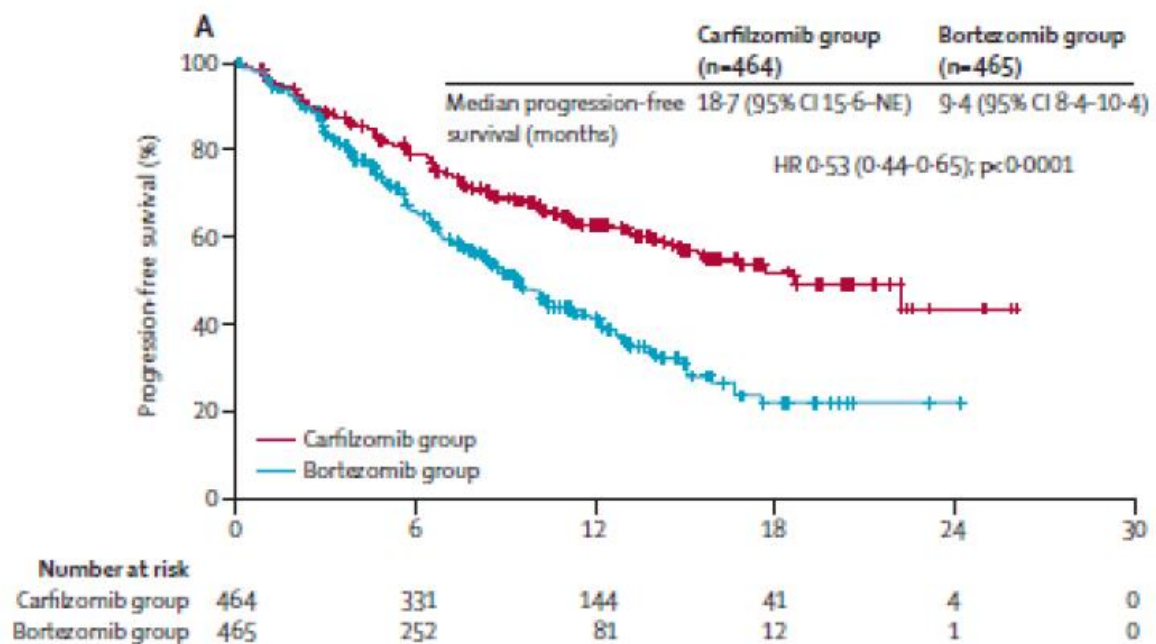
Source: Table 2-25, p103 of the March 2022 resubmission.

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.

Bold indicates statistically significant results.

Blue shading indicates data previously seen by the PBAC.

Figure 3: Kaplan Meier curve PFS (ITT), ENDEAVOR



Source: Figure 2, Dimopoulos, Moreau et al., (2016).

CI = confidence interval; Cd56 = carfilzomib + dexamethasone; HR = hazard ratio; n= number of patients; OS = overall survival.

Kd56 was referred to using the abbreviation Cd (carfilzomib plus dexamethasone) in this ESC Advice.

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

ENDEAVOR data cut-off November 2014.

6.16 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. 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 of 0.76 (95% CI: 0.63, 0.92); 1-sided $p = 0.0017$). The PBAC previously noted that for Cd, the clinical evidence demonstrated a significant improvement in OS for Cd compared to Bd (para 7.9, selinexor (RRMM) PSD, March 2022 PBAC meeting).

Efficacy ITC (SBd versus Cd)

6.17 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 resubmission presented four different ITC models to assess PFS (see paragraph 6.19). In March 2022, the PBAC noted that although there were no statistically significant differences between SBd and Cd, 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 (para 7.8, selinexor (RRMM) PSD, March 2022 PBAC meeting).

- 6.18 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 as the OS data were immature in BOSTON and PFS was not influenced by cross over.
- 6.19 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 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). 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, 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, for the reasons described in paragraph 6.21).
- 6.20 The ITC models described above were performed on the 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.
- 6.21 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, and with the other countries. The March 2022 resubmission stated 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.

6.22 The key results of the adjusted ITC of SBd versus Cd via Bd for PFS (ITT population) 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) ^a HR (95% CI)	Cd vs Bd (ENDEAVOR) ^b 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	NA	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 March 2022 resubmission.

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

Blue shading indicates data previously seen by the PBAC.

a: BOSTON data cut-off as of February 2021

b: ENDEAVOR data cut-off as of November 2014.

6.23 The ESC noted that 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 confidence intervals (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).-The ESC noted there was a large difference in median PFS between SBd and Cd (13.2 vs 18.7 months) whereas results in Bd common comparator arms very similar (9.5 vs 9.4 months; see Table 5 (BOSTON) and Table 8 (ENDEAVOR)).

6.24 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 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 point estimate for 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 proposed positioning of SBd in the clinical management algorithm which indicated that while use could

occur from the 2nd line, the majority of use would occur in patients that had received ≥ 2 prior lines of therapy. This subgroup analysis was also consistent with previous PBAC consideration that SBd would likely be used as a third or later line treatment (para 7.4, Selinexor (RRMM) PSD, March 2022 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) ^a HR (95% CI)	Cd vs Bd (ENDEAVOR) ^b 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	NA	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 2-1, p29 of the resubmission.

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.

Blue shading indicates data previously seen by the PBAC.

a: BOSTON data cut-off as of February 2021

b: ENDEAVOR data cut-off as of November 2014.

- 6.25 The evaluation considered the 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.
- 6.26 The ESC maintained its previous view (February 2022), that the analyses provided (see Table 9 and Table 10) possibly supported a conclusion of non-inferiority of SBd compared with Cd in terms of PFS, however this was uncertain due to the limitations of the evidence available.

Comparative harms

SBd versus Bd

Treatment emergent adverse events (TEAEs)

- 6.27 The resubmission presented a summary of TEAEs in the safety population of BOSTON (N= 399) based on the February 2020 (see Table 11) and February 2021 data cut-offs (data not shown). The difference between the treatment arms for overall TEAEs was not statistically significant in terms of relative risk (RR), 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 for RR, OR and RD in favour of the Bd arm. This is to be anticipated given that SBd is adding a third therapy to the existing Bd regimen.

Table 11: Summary of TEAEs (safety population)

Patients with at least one n (%)	BOSTON (data cut-off Feb 2020)				
	SBd arm (N=195) ^a	Bd arm (N=204) ^b	OR (95% CI)	RR (95% CI) ^c	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)
Grade 3/4 TEAE ^d	154 (79.0)	114 (55.9)	2.97 (1.91, 4.61)	1.41 (1.23, 1.63)	0.23 (0.14, 0.32)
Grade 4 TEAE ^d	34 (17.4)	22 (10.8)	1.75 (0.98, 3.11)	1.62 (0.98, 2.66)	N/A
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)
TEAE Leading to Dose Modification ^e	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	141 (72.3)	104 (51.0)	2.51 (1.65, 3.81)	1.42 (1.21, 1.66)	0.21 (0.12, 0.31)
TEAE Leading to Dose Interruption	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)
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)

Source: Table 2-2, p31 of the resubmission and Table 2-27, p108, Table 2-28, p109 of the March 2022 resubmission.

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.

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

Blue shading indicates statistically significant results.

Blue shading indicates data previously seen by the PBAC.

a: Median duration of study treatment in SBd arm was 30.0 weeks.

b: Median duration of study treatment in Bd arm was 32.0 weeks.

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

d. Based on maximum severity grade of each patient.

e. 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

6.28 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 selinexor 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 (once weekly bortezomib in the SBd arm compared with twice weekly bortezomib in 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.

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.

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 March 2022 evaluation.

Grade ≥ 3 TEAEs

6.29 The occurrence of Grade ≥ 3 TEAEs is presented in Table 13. The PBAC previously 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 (para 7.10, selinexor (RRMM) PSD, March 2022 PBAC meeting).

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)
Anaemia	31 (15.9)	21 (10.3)	1.65 (0.91, 2.98)^b	1.54 (0.92, 2.59)^b	0.06 (-0.01, 0.12)^b
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 2-3, p32 of the resubmission and Table 2-31, p112 of the March 2022 resubmission.

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.

Bold indicates statistically significant results.

Blue shading indicates data previously seen by the PBAC.

a. RD and RR was calculated during the March 2022 evaluation.

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

Cd versus Bd

6.30 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 the PBAC considered that the overall safety profile of carfilzomib was inferior to bortezomib (para 7.5, carfilzomib PSD, July 2017 PBAC meeting).

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 AE 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 March 2022 resubmission.

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.

Bold indicates statistically significant results.

Blue shading indicates data previously seen by the PBAC.

RR was calculated during the March 2022 evaluation.

The AEs are presented for ENDEAVOR data cut-off from July 2017. Median treatment exposure for an earlier data cut-off (January 2017) was 48 weeks in Cd arm and 27 weeks in Bd arm.

a: Median duration of study treatment in Cd arm was not reported.

b: Median duration of study treatment in Bd arm was not reported.

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

6.31 The most commonly experienced Grade ≥ 3 AEs 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 2-3, p32 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 March 2022 evaluation.

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

Safety ITC (SBd versus Cd)

- 6.32 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). The PBAC previously considered that the claim of non-inferior comparative safety was reasonable, noting that SBd is associated with a different safety profile compared with Cd (para 7.12, selinexor (RRMM) PSD, March 2022 PBAC meeting). The unadjusted ITC presented by the resubmission was still confounded by the underlying transitivity issues between the studies.
- 6.33 The PBAC previously 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 16). Results of safety ITCs with respect to individual Grade ≥ 3 TEAEs for SBd vs Cd are shown in Table 17. Significantly lower rates of hypertension (OR= 0.27; 95% CI: 0.08, 0.93) and dyspnoea (OR= 0.07; 95% CI: 0.01, 0.74) were observed for SBd compared with Cd. Conversely, significantly higher rates of 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) were observed for SBd compared with Cd. The PBAC previously considered that the results were broadly consistent with the known safety profile of SBd and Cd (para 7.11, selinexor (RRMM) PSD, March 2022 PBAC meeting).

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

Adverse event, 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 March 2022 resubmission.

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

Blue shading indicates data previously seen by the PBAC.

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

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)	0 (-0.02, 0.01)	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 ^b	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 2-3, p32 of the resubmission.

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.

Blue shading indicates data previously seen by the PBAC.

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

b. Referred to as 'myocardial ischaemia'.

Clinical claim

- 6.34 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. All data relied upon for the clinical claim were previously considered by the PBAC in March 2022.
- 6.35 In regard to PFS, the PBAC previously considered that given the submission did not include a stated non-inferiority margin, the indirect nature of the comparison and the potential transitivity issues, the lack of a statistically significant difference between SBd and Cd did not adequately establish non-inferiority. Secondly, the PBAC previously noted that a statistically significant improvement in OS was demonstrated for Cd versus Bd (in ENDEAVOR), but not for SBd versus Bd (in BOSTON) (para 6.50 and para 7.12, selinexor (RRMM) PSD, March 2022 PBAC meeting).

6.36 The PBAC considered that the analyses provided (see Table 9 and Table 10) possibly supported a conclusion of non-inferiority of SBd compared with Cd in terms of PFS, however uncertainty remained due to the limitations of the evidence available. The PBAC noted there were no direct randomised trials comparing SBd with Cd, and therefore the clinical evaluation was informed by ITCs. The PBAC noted that limitations of the evidence included differences between the pivotal trials (see paragraph 6.9), and modest patient numbers in the pivotal trials which resulted in wide confidence intervals in the ITCs (see paragraph 6.23).

6.37 In regard to safety, the PBAC previously considered that the claim of non-inferior comparative safety was reasonable, noting that SBd is associated with a different safety profile compared with Cd (para 7.12, selinexor (RRMM) PSD, March 2022 PBAC meeting). The PBAC reaffirmed its previous view that the claim of non-inferior comparative safety was reasonable for SBd compared with Cd.

Economic analysis

6.38 The resubmission presented an updated CMA comparing SBd and Cd, that was a more conservative CMA compared with that provided in the March 2022 resubmission. The key revisions included once weekly and twice weekly carfilzomib doses, inclusion of bortezomib administration costs, exclusion of carfilzomib administration costs (conservative assumption which reduces the proposed price of selinexor; see paragraph 6.44) and inclusion of concomitant therapies during treatment with SBd.

6.39 The key components and assumptions of the CMA are presented in Table 18.

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

Component	March 2022 resubmission claim or assumption	November 2022 resubmission claim or assumption	PBAC concern (March 2022)	Comment
Equi-effective doses	<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) Bortezomib (once weekly dosing): 116 milligrams (inclusive of wastage)^a 	<p><u>Cd (100% dose intensity):</u></p> <ul style="list-style-type: none"> Carfilzomib (twice weekly dosing): 7278 milligrams over 74 infusions and carfilzomib (once weekly): 4969 milligrams over 40 infusions (carfilzomib, July 2020 PSD) <p><u>SBd (100% dose intensity):</u></p> <ul style="list-style-type: none"> Selinexor (once weekly dosing): 5333 milligrams (266.75 x 20 mg tablets) Bortezomib (once weekly dosing): 125 milligrams (inclusive of wastage)^a 	The PBAC noted that the assumption of use of only twice weekly Cd was not justified.	The resubmission included twice weekly and once weekly Cd use in the updated CMA.

Component	March 2022 resubmission claim or assumption	November 2022 resubmission claim or assumption	PBAC concern (March 2022)	Comment
Duration of treatment	The treatment duration of SBd was made equivalent to that of Cd (49.3 weeks).	The treatment duration of SBd was made equivalent to the treatment duration of Cd (once weekly) at 53.3 weeks.	The ESC noted that the duration of treatment of SBd and Cd being the same was consistent with a non-inferiority claim but that the relative treatment durations were uncertain.	The duration of SBd treatment applied in the CMA was higher than that observed in BOSTON (47.8 weeks based on February 21 data cut), which results in a lower price for SBd determined in the CMA.
Other costs or cost offsets	<ul style="list-style-type: none"> • Infusion administration costs with carfilzomib. • Costs of haematological AEs that are 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. • The costs of diarrhoea and fatigue events were not incorporated. • The costs of concomitant treatments were not considered. 	<ul style="list-style-type: none"> • Infusion administration costs for carfilzomib were not included. • Cost associated with subcutaneous administration of bortezomib included. • Costs of haematological AEs that are 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. • The costs of diarrhoea and fatigue events were not incorporated. • Cost of recommended concomitant drugs during treatment with selinexor included. 	<p>The PBAC considered that adverse event costs should be incorporated, particularly haematological events related to SBd use.</p> <p>The PBAC considered that the cost associated with administration of bortezomib should be included.</p> <p>The PBAC considered that recommended concomitant treatments should have been included.</p>	Costs of haematological AEs, administration costs associated with bortezomib and concomitant treatments were included in the CMA.

Source: Table 3-1, p156 of the March 2022 resubmission and compiled during evaluation.

AEs = adverse events; Bd = bortezomib + dexamethasone; Cd = carfilzomib + dexamethasone; CMA = cost minimisation approach; mg = milligram; ITC = indirect treatment comparison; ITT = intention to treat; OS = overall survival; PFS = progression free survival; PSD = public summary document; SBd = selinexor + bortezomib + dexamethasone.

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.

6.40 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 resubmission assumed use of both the Cd twice and once weekly regimens. The resubmission assumed a 50:50 utilisation weighting between the two dose regimens, but did not justify this weighting. The PBAC considered that the calculation should assume 60%

once weekly Cd dosing and 40% twice weekly Cd dosing, consistent with a recent consideration in this indication (Paragraph 6.62, Carfilzomib PSD, March 2022 meeting).

- 6.41 The cost of dexamethasone was not included in the CMA. This was reasonable given the low cost associated with dexamethasone treatment and similar dosage regimen (20 mg twice weekly) for both SBd and Cd.
- 6.42 The duration of treatment with SBd and Cd (twice weekly) was made equivalent to that of Cd (once weekly regimen) (53.3 weeks) within the CMA. The resubmission stated that the use of the longer duration of treatment in the CMA was conservative, and therefore biased against SBd. The ESC noted this approach results in a lower price for SBd than if a shorter treatment duration was assumed for SBd versus Cd. The ESC previously considered the application of an equivalent treatment duration was consistent with a non-inferiority claim, but that the relative treatment durations were uncertain (para 6.59, selinexor (RRMM) PSD, March 2022 PBAC meeting).
- 6.43 The SBd 5-week treatment cycle consists of selinexor 100 mg orally every week and bortezomib 1.3 mg/m² administered intravenously once weekly for 4 weeks, with a break in the fifth week. At the assumed treatment duration of 53.3 weeks, this is equivalent to 10.67 treatment cycles at full compliance (53.3/5) and 266.67 x 20 mg selinexor tablets (10.67 cycles x 5 tablets per dose x 5 doses per cycle) and 42.67 doses of bortezomib (10.67 cycles x 4 doses per cycle). The resubmission stated that based on a mean BSA of 1.8 m² and after incorporating wastage, each dose of bortezomib is 2.93 mg.
- 6.44 The resubmission included the administration cost associated with bortezomib in the SBd regimen, and excluded the cost of administration associated with carfilzomib. The resubmission stated that these assumptions were conservative, and would bias against SBd. The ESC noted this was a conservative approach and sensitivity analyses showed that the inclusion of a cost associated with administration of carfilzomib increased the price of selinexor to \$| per 20 mg tablet compared to \$| per 20 mg tablet as estimated by the base case CMA.
- 6.45 The CMA included haematological TEAEs of Grade ≥3. The resubmission estimated the cost of AEs by assuming all Grade 3 AEs require hospital care with the inputs sourced from the NHDC Non-admitted care summary (2018-19; see Table 19). The analysis did not include AEs which are more prevalent with Cd and therefore biased against SBd. The ESC noted that given not all Grade ≥3 AEs are likely to receive hospital care, the costs applied were possibly conservative, decreasing the cost-minimised price of selinexor, although the assumed cost of additional SBd adverse events was minimal in the CMA (\$126.34, see Table 19).
- 6.46 The resubmission included the concomitant administration of a 5-HT3 antagonist for the entire duration of treatment with selinexor. This was consistent with the PBAC's previous consideration that concomitant treatments should have been included in the CMA (para 6.63, selinexor (RRMM) PSD, March 2022 PBAC meeting).

- 6.47 The resubmission presented a CMA based on the assumed effective AEMP of Cd with a % SPA rebate. The equi-effective dosing of Cd (twice weekly) was 7,278 mg and Cd (once weekly) was 4,969 mg per patients assuming a 50:50 weighting of the two dose regimens. The total cost per course of Cd (weighted for twice and once weekly dose regimens) was estimated to be \$ per patient, while the cost per patient of selinexor was estimated to be \$ (after removing the costs of additional haematological AEs with SBd, concomitant drugs for SBd and the costs of bortezomib and its administration). The equi-effective dosing of selinexor was 5,333 milligrams per patient resulting in a cost-minimising price of selinexor of \$ per 20 mg tablet (see Table 19).

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

Row	Parameter	Cd 56 - BIW	Cd 70 - QW	Cd – Weighted	Reference
A	Equi-effective dosing per patient	7,278	4,969	N/A	Carfilzomib July 2020 PSD, Table 4
B	Carfilzomib cost/mg (published)	\$21.1490	\$21.1490	N/A	PBS items 11229B, 11230C, 12243J, 12244K
C	Carfilzomib cost/mg (effective)	\$█	\$█	N/A	BIW = B x (1-0.3) ^a QW = BIW x 1.465 ^b
D	Cd cost per patient (excluding administration costs)	\$█	\$█	\$█	A x C BIW x 50% + QW x 50% ^c
E	Bortezomib equi effective dose (mg)	125	125	125	10.67 ^d cycles X 4 doses per cycle X 2.9281 ^e mg per dose
F	Bortezomib cost per milligram	\$172.91	\$172.91	\$172.91	AEMP based on PBS items 12219D, 12227M
G	Bortezomib drug costs ^f	\$21,601.93	\$21,601.93	\$21,601.93	=E*F
H	Bortezomib admin costs	\$4,872.53	\$4,872.53	\$4,872.53	10.67d cycles *4 doses per cycle * \$114.2g (MBS item 12950)
I	Additional SBd AE costs ^h	\$126.34	\$126.34	\$126.34	See Error! Reference source not found.
J	5-HT3 costs ⁱ	\$1,591.15	\$1,591.15	\$1,591.15	See Table 21
K	Cost-minimising drug costs for selinexor component of SBd – per patient	\$█	\$█	\$█	D – SUM(G:J)
L	Selinexor equi-effective dose (mg) ^j	5,333	5,333	5,333	See Table 20
M	Selinexor tablets per patient ^k	266.67	266.67	266.67	=L / 20 mg (1 tablet)
N	Cost per selinexor tablet	\$█	\$█	\$█	=K/M

Source: Table 3-1, pp35-36, Table 3-5, p39 of the resubmission.

AE = adverse event; BIW= twice a week; Cd= carfilzomib + dexamethasone; mg = milligrams; N/A = not applicable; QW= once a week; SBd= selinexor + bortezomib + dexamethasone.

a: Assumed rebate for carfilzomib (twice weekly dose) of █%

b: Assumed carfilzomib dose relativity between BIW and QW (based on therapeutic relativity value 1:1.465 (Table 4, carfilzomib PSD, July 2020 PBAC meeting).

c: Weighting assumes 50% Cd 56 – BIW and 50% Cd 70 QW

d: cycles per patient estimated from treatment duration 53.3 weeks over 5 cycles per week.

e: estimated dispensed amount of bortezomib per dose based on the available dose (1,2,3,3,3, and 4 mg), dose mg/m² per protocol of BOSTON, and assumed body surface area mean and standard deviation parameters sourced from Carfilzomib PSD and Sacco (2010), respectively.

f: estimated as \$172.91 per mg x 2.9281 mg/dose x 4 doses/cycle x 10.67 cycles per patient. Increased from \$19,981.79 per patient in March 2022 due to increase in the number of cycles per patient (from 9.87 to 10.67)

g: MBS cost updated during the evaluation to reflect July 2022 values.

h: \$2.36908 per week (updated during evaluation) x 5 weeks per cycle x 10.67 cycles. Increased from \$111.14 per patient due to increase in the number of cycles per patient (from 9.87 to 10.67)

i: Updated during the evaluation, using the updated cost of 5-HT3 of \$126.34.

j: equi-effective dose was estimated based on 10.67 cycles per patients, doses per cycle and mg per dose.

k: 10.67 cycles x 5 tablets per dose x 5 doses per cycle. Increased from █ tablets per patient due to increase in the number of cycles per patient (from 9.87 to 10.67).

Table 20: Cost of AEs included in the CMA

Event ^a	Cost per event	Source ^b	Additional events with SBd	Expected AE costs per week
Anaemia	\$571	Tier2 code: 2010	0.000373	\$0.21
Thrombocytopenia	\$571	Tier2 code: 2010	0.003092	\$1.77
Neutropenia	\$571	Tier2 code: 2010	0.000684	\$0.39
Total additional haematological AE costs with SBd over Cd – per week				\$2.369
Total additional haematological AE costs with SBd over Cd – per patient (53.3 weeks)				\$126.34

Source: Excel workbook SBd RRMM Section 3_July 2022.xlsx; worksheet 'AECosts' of the resubmission; Attachment ES.3 of the commentary.

AE = adverse event; Cd = carfilzomib + dexamethasone; CMA = cost-minimisation approach; SBd = selinexor + bortezomib + dexamethasone.

Blue shading indicates data previously seen by the PBAC.

a. (haem) and (different) suffixes signify events included on the basis they are haematological (haem) or showed statistically significant differences (different) in the indirect comparison.

b. Sources: Tier2 codes, NHDC Non-admitted care summary (2018-19); ARDRG codes, NHDC Round 24 (2019-20).

Table 21: Cost of 5-HT3 antagonists applied to the SBd arm of the CMA

Cost item	Value	Reference
Daily dose of 5-HT3 antagonist	8 mg daily	BOSTON trial (costs as 4 mg twice daily)
Daily cost of 5-HT3 antagonist (Ondansetron)	\$4.26	DPMQ \$21.31 / 10 x 2 (PBS items 5472B ^a)
Duration of SBd treatment	53.3 weeks	Aligned with Cd treatment duration
5-HT3 costs per patient	\$1,591.15	53.3 x 7 x \$4.26

Source: Table 3-4, p38 of the resubmission; Attachment ES.3 of the commentary.

5-HT3 = 5-hydroxytryptamine receptor; Cd = carfilzomib + dexamethasone; DPMQ = dispensed price per maximum quantity; mg = milligrams; SBd = selinexor + bortezomib + dexamethasone.

a: The cost of ondansetron was based on the PBS item 5472B (4 mg tablet, 10). The cost was updated during evaluation to the current DPMQ of \$21.31.

6.48 The ESC considered the CMA may provide a relevant frame of reference to determine a cost-effective price for SBd. In this context, in view of the remaining uncertainty in the comparative efficacy claim, it may be appropriate for the cost of SBd to be less than for Cd (whether administered QW or BIW), ELd and PBd.

6.49 The PBAC considered that SBd would be considered acceptably cost-effective if the selinexor effective price was determined on the basis of the CMA of SBd vs Cd presented in the resubmission, updated with 1) the confidential carfilzomib effective price; and 2) an assumption that 60% of carfilzomib use will be the once weekly regimen, and the remaining 40% will be the twice weekly regimen.

Drug cost/patient/course

6.50 A summary of the drug cost per patient for SBd and Cd is presented in Table 22.

Table 22: Drug cost per patient for proposed and comparator drugs (assumed effective prices)

	SBd			Cd		
	Trial dose and duration	CMA	Financial estimates	Trial dose and duration	CMA	Financial estimates
Mean dose	78.89 mg per week ^a Total dose: 3559.4 mg	5333 mg (100 mg per week for 53.3 weeks)	5333 mg	NR	7278 mg BIW and 4969 QW	7278 mg BIW and 4969 QW
Duration of treatment/Script per course of treatment	47.8 weeks ^b	53.3 weeks	Selinexor: 20-pack: 6.45 ^c scripts 16-pack: 8.60 ^c scripts Bortezomib: estimated ratio of bortezomib: 43.19 scripts ^e	39.9 weeks ^f	53.3 weeks (40 scripts for QW) 49.33 weeks (40 scripts for BIW), not applied in base case The resubmission base case assumed a duration of 53.3 weeks for both Cd regimens (and SBd).	BIW 74 scripts; QW 40 scripts with 80:20 split, resulting in BIW 14.8 scripts, QW 32 scripts
Cost/patient/course	NE	Selinexor: \$ ^g Bortezomib: \$ ^g	Selinexor: \$ ^h Bortezomib: \$ ^h	NE	\$ ^j	\$ ^j

Source: Table 3-1, pp35-36, Table 3-5, p39 and Excel workbook SBd RRMM Section 3_July 2022.xlsx; worksheet 'CMA_July2022', workbook SBd_RRMM Section 4_July2022 worksheets '1. Overview', '3a. Scripts-proposed', '4b. Impact-affected' of the resubmission.

BIW = twice weekly; Cd = carfilzomib + dexamethasone; CMA = cost-minimisation approach; mg = milligram; SBd = selinexor + bortezomib + dexamethasone; NE = not estimated; NR = not reported by the resubmission; QW = once weekly.

a. BOSTON CSR Table 14.1.8.1.1, also note that selinexor median dose was 80 mg once weekly.

b. Mean duration of study treatment based on BOSTON February 2021 data cut-off.

c. Estimated for selinexor 20-pack 13.33 scripts per treatment = 5,333mg/400mg, and for selinexor 16-pack 16.67 scripts per treatment = 5,333mg /320mg. Based on assumed distribution of pack sizes the estimated selinexor 20-pack of 6.45 scripts (13.33*48.4%) and 16-pack of 8.60 scripts (51.6% *16.67 scripts)

e. Based on total selinexor scripts 897 and total bortezomib scripts 2,575 estimated in Year 1 (financial utilisation) a ratio of 2.87 bortezomib scripts for every selinexor script was estimated. 2.87*6.45 scripts + 2.87*8.60 scripts = 43.19 scripts.

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

g. AEMP of \$^g per tablet.

h. Assumed effective DPMQ 20-pack \$^h 16-pack: \$^h weighted Public/Private DPMQs.

i. weighted DPMQ for bortezomib of \$^h (Private DPMQ \$^h*68.2% + Public DPMQ \$^h*31.8%). Percent utilisation assumed in the resubmission.

j. weighted DPMQ of carfilzomib of \$^j BIW and \$^j QW. Based on assumed effective price of carfilzomib BIW and QW in the resubmission, a Public/Private split of 40:60 for Cd BIW and 28/72 for Cd QW.

Estimated PBS usage & financial implications

6.51 This resubmission was not considered by DUSC.

6.52 As per the March 2022 resubmission a market share approach was used in the updated financial estimates.

6.53 The resubmission stated that the revised financial estimates included the following updates:

- Revised effective price of selinexor (as per the estimates of the revised CMA);

- Assumed effective price of carfilzomib, with 10% rebate on a twice weekly dose regimen and a 1.465 therapeutic dose relativity (weekly 70mg Cd: twice weekly 56mg Cd) (Table 4, carfilzomib PSD, July 2020 PBAC meeting) with the carfilzomib once weekly dose regimen. This was consistent with the assumptions applied in the revised CMA.
- Assumption that SBd would displace rather than replace other RRMM treatment regimens in a proportion of patients, based on treatment attrition rates through sequential lines of RRMM therapy.
 - For simplicity the estimation of the displaced therapies used the Cd regimen as a proxy for other regimens.
 - The resubmission used attrition data based on an analysis of treatment rates through subsequent lines of RRMM therapy in over 22,000 transplant ineligible patients with MM based in the United States (Fonseca, 2020). US based data may not be reflective of the clinical use of RRMM therapies in Australia. Additionally, in BOSTON 39% of patients in the SBd arm received stem cell transplant, which may indicate a different population from the US based sample (Fonseca, 2020).
 - In the estimation of the proportion of carfilzomib scripts that will be displaced by SBd, the resubmission assumed that 10% of SBd use would occur in second line; 40% would be in third and fourth lines, and 10% would receive SBd in fifth line. The resubmission stated that a total of 27.8% of all SBd patients would displace Cd (Table 23). The ESC considered the displacement was difficult to estimate but the estimate of 28% was possibly reasonable.
 - The resubmission presented a figure showing the rates of treatment attrition through lines of therapy in an Australian myeloma population (sourced from confidential information provided by the Myeloma and Related Disease Registry (MRDR)). No cross verification of the MRDR figure and the data from Fonseca (2020) was presented by the resubmission. The MRDR figure is a graphical representation of the attrition to the lines of therapy and while it does not provide numeric values, it appeared to be approximately consistent.

Table 23: Expected extent of treatment displacement of Cd with listing of SBd on PBS

Line where SBd can be used	Expected utilisation of SBd in each line [A]	Proportion of use which is displaced (as opposed to replaced) [B]	Total displacement [C]=[A]x[B]
Source	Assumptions based on clinical algorithm in Section 1	Fonseca (2020)	Calculated
2 nd line	10%	10.4%	1.0%
3 rd line	40%	19.1%	7.6%
4 th line	40%	33.3%	13.3%
5 th line	10%	58.0%	5.8%
Total	100%	-	27.8%

Source: Table 4-2, p44 of the resubmission.

Cd = carfilzomib + dexamethasone; PBS = Pharmaceutical Benefits Scheme; SBd= selinexor in combination with bortezomib and dexamethasone.

6.54 The resubmission did not address the previous concern of the PBAC regarding the potential overlap in the populations for SBd and Sd (selinexor (TCR/PR) PSD, March 2022 PBAC meeting). The use of SBd in the third or fourth line will impact use of Sd in later lines, as the PBS listing of Sd indicates that ‘patients must not have previously received this drug for this condition’.

6.55 A summary of key inputs for the financial estimates is provided in Table 24.

Table 24: 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 March 2022 resubmission	Remained unchanged from the March 2022 resubmission which assumed a constant numbers of twice weekly regimen scripts across the six-year analysis period by reasoning carfilzomib has achieved its optimal market share. Due to the high attrition rate in subsequent lines of therapy, approximately 50% of these scripts were written for second-line patients (PBS 10% dataset, and Figure 4-1, p 43 of the resubmission). Given DBd is expected to become the dominant second line treatment choice the uptake rates for SBd may be more accurately applied to the third line and later market of Cd scripts in 2020 (e.g. 23,753 * 50% = 11,877).
Treatment utilisation			
Assumed market share of twice and once weekly carfilzomib	20% for twice weekly script and 80% for once weekly script	Unchanged from the March 2022 resubmission which 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, this assumption was made from data for only the first six months of the once weekly script listing. The March 2022 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. The assumed market share was inconsistent with the revised CMA presented in the resubmission which used a 50:50 weighting for the two carfilzomib dose regimens, which if applied would impact the estimated number of SBd scripts

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Parameter	Value applied	Source	Comment
			from ██████ ¹ to ██████ ¹ (Year 1) and from ██████ ¹ to ██████ ¹ (Year 6). The ESC noted a different split for the QW and BIW regimens in the CMA versus that in clinical practice may result in additional PBS/RPBS expenditure or savings depending on the relative cost of the regimens.
Uptake (substitution) rate of selinexor	Yr 1: 20% Yr 2: 35% Yr 3: 50% Yr 4: 50% Yr 5: 50% Yr 6: 50%	Unchanged from the March 2022 resubmission. Assumption.	The proposed uptake rates were unsupported. The uptake rates provided by the March 2022 resubmission may be overestimated, given the toxicity associated with SBd. The resubmission stated that for simplicity Cd was used as proxy for other regimens that would be replaced by SBd. The ESC noted replacement for regimens which are less expensive than Cd will increase PBS/RPBS expenditure.
Proposed scripts per course of treatment	13.33 for the 20-pack and 16.67 for the 16-pack	Based on the equivalent effective dose of selinexor and 400 mg in a 20-pack and 320 mg in a 16-pack tablets.	The resubmission did not correct the proposed scripts for selinexor based on the updated CMA, where the equivalent effective dose of selinexor changed to 5,333 mg from 4,933 mg (March 2022 resubmission). This has a moderate impact on the estimated number of scripts for selinexor, with an increase of SBd scripts from ██████ ¹ to ██████ ¹ (Year 1) and from ██████ ¹ to ██████ ¹ (Year 6).
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 March 2022 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 (effective) 20 X 20 mg = \$ ██████ ² 16 X 20 mg = \$ ██████ ²	Selinexor 20 X 20 mg tablets and 16 X 20 mg tablets Requested price, weighted AEMP for Public and Private	The resubmission proposed an effective AEMP based on the results of the updated CMA.
Other medicine included in therapy	Bortezomib (1,3 and 3.5 mg) Dispensed price - \$593.36, \$642.08 (below current published DPMA: \$605.79, \$654.689)	Bortezomib 12219D, 12227M – AEMP of \$518.72. A mean dose of 2,928 mcg was applied to estimate the public and private AEMP per dose.	Bortezomib as part of SBd. The resubmission did not include the costs attributable to dexamethasone as part of the SBd regimen, by arguing a slight difference in the use of dexamethasone between Cd and SBd and a low cost per patient hence costs would be inconsequential to the PBS budget. This was reasonable. The DPMQ of bortezomib was updated to reflect the increase in AHI mark-ups.
Comparator	Carfilzomib twice and once weekly (10, 30, 60 mg) Assumed effective - \$ ██████ ² (private), \$ ██████ ² (public)	Carfilzomib twice weekly: 11230C at AEMP \$1,268.94 and DPMA at \$2,700.71	The resubmission assumed a ██████% rebate for carfilzomib twice weekly dose and a 1.465 dose relativity between twice-weekly and once-weekly dose regimens. This was aligned with the assumption applied in the updated CMA.
MBS costs	\$114.20	MBS item 13950	Attributed to the intravenous administration of carfilzomib and bortezomib. The resubmission applied 85% of the scheduled fee.

Parameter	Value applied	Source	Comment
			The recently updated cost of MBS item 13950 (\$114.20) was incorporated during evaluation. The resubmission did not include the MBS costs associated with the treatment of haematological AEs associated with SBd or the cost of 5-HT3 antagonist (concomitant to SBd) in the financial estimates. 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.

5-HT3 = 5-hydroxytryptamine; AEMP = approved ex-manufacturer price; AEs = adverse events; B = bortezomib; Bd = bortezomib + dexamethasone; Cd = carfilzomib + dexamethasone; CMA = cost minimisation approach; DBd = daratumumab + bortezomib + dexamethasone; DPMA = dispensed price for maximum amount; MBS = Medical Benefits Scheme; mcg = micrograms; RRMM = Relapsed and/or refractory multiple myeloma; SBd = selinexor + bortezomib + dexamethasone.

Blue shading indicates data previously seen by the PBAC.

The redacted values correspond to the following ranges:

¹ 500 to < 5,000

² \$0 to < \$10 million

6.56 The resubmission based its estimated number of scripts on the market share approach presented in March 2022 resubmission. Concerns with the approach included:

- The resubmission used the total number of Cd scripts in 2020 (23,753) to describe the target market of the Australian RRMM second line and later treatment setting. Due to the high attrition rate in subsequent lines of therapy, approximately 50% of these scripts were written for second-line patients (PBS 10% dataset, and Figure 4-1, p 43 of the resubmission). Since its PBS listing in January 2021, DBd is expected to become the dominant second line treatment choice, as acknowledged by the resubmission, which proposed 90% of SBd use would be in the third line or later, noting that 90% of second line treatments (i.e. DBd) would be replacements, not displacements. As such, the uptake rates for SBd may be more accurately applied to the third line and later market of Cd scripts in 2020 (e.g. 23,753 * 50% = 11,877). Uptake of SBd from third line and later was applied by the evaluation in a sensitivity analysis.
- Consistent with the March 2022 resubmission, the uptake rate of carfilzomib assumed by the resubmission of 20% 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 uptake rates provided by the resubmission may be overestimated, given the uncertain efficacy of SBd, and recent PBS-listing of three other triple therapies which will also be used in the third line or later. Furthermore, the MM Clinical Expert Consultation Meeting (June 2022) noted that selinexor is difficult to administer due to adverse events and it that it is generally used in a small, niche population of relatively fit patients with high-risk disease. The ESC considered the uptake rates were overestimated.
- The resubmission did not update the equi-effective dose of selinexor that was estimated in the CMA of the resubmission from 4,696 mg to 5,333 mg. This resulted in an underestimation of the number of selinexor scripts. The estimated

utilisation of SBd presented in Table 25 is based on the revised number of scripts for selinexor using the updated equi-effective dose of selinexor from Section 3 of the resubmission.

- The resubmission assumed a 20:80 split in the financial estimates for the twice-weekly and once weekly carfilzomib dosing respectively, which was inconsistent with the weighting applied in the CMA in Section 3 of the resubmission of 50:50 split between the two carfilzomib dose regimens (see paragraph 6.40).
- As per the March 2022 resubmission, the resubmission did not include additional grandfathered patients in the selinexor utilisation and financial estimates. The PSCR estimated that up to 40 patients may require grandfathering, however stated these patients are already captured in the estimates of patients treated.

6.57 In estimating the utilisation of the two requested pack sizes, the resubmission assumed 48.4% of selinexor scripts will be for the 20-tablet formulation.

6.58 A summary of the estimated use and financial implications for listing SBd on the PBS is presented in Table 25. The estimates are based on an assumed effective price for selinexor as described in paragraph 6.53.

Table 25: 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	█ ²	█ ²	█ ²	█ ²
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 ^b (\$)	█ ²	█ ²	█ ³	█ ³	█ ³	█ ³
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
March 2022 resubmission	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	█ ³	█ ³	█ ³	█ ³
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 ^c (\$)	█ ²	█ ³	█ ³	█ ³	█ ³	█ ³
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

Source: Table 4-4-1, p42, Table4-5, p47 Workbook 'RRMM Section 4_July 2022, work sheets '3a.Scripts -proposed', '3c. Impact-proposed', '4c. Impact – effected', '5. Impact - net', of the resubmission.

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

Blue shading indicates data previously seen by the PBAC. Italicised compiled during the current evaluation of the resubmission.

^a Assuming number of scripts per year as re-estimated during evaluation.

During evaluation the following values were updated and reflect the estimates provided in table above: the equi-effective dose of selinexor was updated to 5,333mg (as per Section 3 of the resubmission); the PBS AHI mark-up fees for bortezomib were updated to reflect July 2022 values; the MBS fee for Item 13950 was updated to reflect current value; the co-payment values were updated to reflect July 2022 values.

^b: Resubmission assumed █% rebate for carfilzomib.

^c: March 2022 resubmission assumed a █% rebate for carfilzomib.

The redacted values correspond to the following ranges:

¹ 500 to < 5,000

² \$0 to < \$10 million

³ \$10 million to < \$20 million

6.59 The total cost to the PBS/RPBS/MBS of listing SBd was estimated to be \$█ in Year 6 compared to the \$█ in the March 2022 resubmission, and a total of approximately \$█ in the first six years of listing compared to \$█ in the March 2022 resubmission. This increase in the cost of listing SBd is due to the assumption of approximately 28% displacement rate of Cd due to listing of SBd in comparison with an assumption of 0%

displacement in the previous resubmission⁴. A variation in the assumed displacement rate will directly impact the estimated net costs to PBS/RPBS (the net costs are increased if higher rates of displacement are assumed).

- 6.60 As per March 2022, 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 on the basis of similar use between the 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 however the impact of this cost is negligible. The costs associated with treating the haematological AEs due to SBd were not included in the financial estimates. Concomitant treatment costs for SBd and pre- and post- infusions for Cd regimen were also not included in the financial estimates.
- 6.61 A sensitivity analysis was conducted during evaluation, assuming zero uptake of SBd in the second line and applying the third line and later market of Cd scripts in 2020 (23,753 * 50% = 11,877). The impact was high, resulting in a decrease of PBS/RPBS cost in Year 6 to \$0 to < \$10 million and an overall cost to the Government of \$0 to < \$10 million over six years. The results are presented in Table 26.

Table 26: Estimated use and financial implications, sensitivity analysis; assuming third line or later use of SBd

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
Estimated extent of use						
Number of scripts dispensed ^a	■ ¹	■ ²	■ ²	■ ²	■ ²	■ ²
Estimated financial implications of selinexor (assumed effective price)						
Cost to PBS/RPBS less copay (\$)	■ ³	■ ³	■ ³	■ ³	■ ³	■ ³
Estimated financial implications for other medicines						
Cost to PBS/RPBS less copay - bortezomib(\$)	■ ³	■ ³	■ ³	■ ³	■ ³	■ ³
Cost to PBS/RPBS less copay - carfilzomib(\$)	-■ ³	-■ ³	-■ ³	-■ ³	-■ ³	-■ ³
Net financial implications						
Net cost to PBS/RPBS(\$)	■ ³	■ ³	■ ³	■ ³	■ ³	■ ³
Net cost to MBS(\$)	-■ ³	-■ ³	-■ ³	-■ ³	-■ ³	-■ ³
Net cost to PBS/RPBS/MBS(\$)	■ ³	■ ³	■ ³	■ ³	■ ³	■ ³

Source: Conducted by the evaluation

PBS = Pharmaceutical Benefit Scheme; MBS = Medical Benefit Scheme; RPBS = Repatriation Pharmaceutical Benefit Scheme; SBd = selinexor + bortezomib + dexamethasone.

^a Assuming number of scripts per year based on 11,877 Cd scripts (assuming 50% of 2020 scripts were for second line)

During evaluation the following values were updated and reflect the estimates provided in table above: the equi-effective dose of selinexor was updated to 5,333mg (as per Section 3 of the resubmission); the PBS AHI mark-up fees for bortezomib were updated to reflect July 2022 values; the MBS fee for Item 13950 was updated to reflect current value; the co-payment values were updated to reflect July 2022 values.

The redacted values correspond to the following ranges:

¹ < 500

² 500 to < 5,000

³ \$0 to < \$10 million

⁴ The March 2022 resubmission assumed that SBd would result in replacement of Cd only.

- 6.62 The ESC considered that the uptake rate for SBd remained highly uncertain, but that it would most likely be used in a relatively small niche population. The ESC agreed with the evaluation, that the resubmission had overestimated the script numbers for SBd, by applying Cd script numbers from 2020 to describe the target market of the Australian RRMM second line or later treatments, such that approximately 50% of these scripts represented second line therapy. The resubmission proposed 90% of SBd use would be third line or later, but did not adjust for this when applying anticipated uptake rates to the 2020 Cd script numbers. A sensitivity analysis conducted during the evaluation, assuming zero uptake of SBd in the second line resulted in a decrease of PBS/RPBS cost by 50% percent (see Table 26). The ESC considered this sensitivity analysis was informative as it could be assumed that daratumumab would be used in the second line position for most patients.
- 6.63 The ESC noted that the resubmission had estimated an increase in net cost to PBS/RPBS despite the cost-minimisation approach, which amounted to \$10 million to <\$20 million over six years in the base case (Table 25) and \$0 to <\$10 million over six years in the sensitivity analysis assuming third line or later use of SBd (Table 26). An increase in net cost to PBS/RPBS was consistent with the resubmission's acknowledgement that a proportion of patients may receive an additional line of therapy after PBS listing of SBd. The ESC considered it was difficult to predict the proportion of existing therapies that would be displaced by SBd rather than replaced, but the estimate of 28% was possibly reasonable (see paragraph 6.53).
- 6.64 With reference to Table 26, the Pre-PBAC Response noted that utilisation is estimated to be approximately 500 to < 5,000 units per annum by Year 6. This is 500 to < 5,000 cycles of treatment or, at ten cycles per patient on average (as per the cost-minimisation analysis), approximately <500 patients which can reasonably be considered a relatively small, niche population.

Quality Use of Medicines

- 6.65 The PSCR noted that the sponsor is committed to ensuring the safe and appropriate use of selinexor through a comprehensive education and patient support program on this new drug class for health care professionals, patients and caregivers. It was noted that the sponsor is working with the MSAG to create educational case studies, and working with Myeloma Australia on nurse education and a patient support program. The PSCR also described support for the publication of Australian practical management consensus recommendations by the Myeloma Specialist Practice Network (M-SPN) of the Haematology Society of Australia and New Zealand (HSANZ), and EviQ treatment protocols that are currently under review and due to be published in October 2022.

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

7 PBAC Outcome

- 7.1 The PBAC recommended the listing of selinexor, for use in combination with bortezomib and dexamethasone (SBd), for the treatment of patients with relapsed and/or refractory multiple myeloma (RRMM) who have received at least one prior therapy. The PBAC noted that MM is heterogeneous disease and that there is a clinical need for multiple treatment options, including different drug classes. The PBAC considered that there should be a single listing for selinexor which allows use in patients as a second or later line treatment either with or without bortezomib to enable clinicians to utilise the appropriate regimen for their patient (either SBd or Sd) based on clinical judgement. The PBAC considered that the claim of non-inferior effectiveness versus Cd was uncertain due to the transitivity issues across the trials and the wide confidence intervals for the indirect estimates. However, the PBAC accepted the effectiveness claim on the basis that further data are unlikely to be available to increase the certainty for the non-inferiority claim and that SBd will be used in a relatively small niche population. The PBAC noted that the revised CMA was sufficiently conservative to address the uncertainty regarding the non-inferiority claim versus Cd and considered that SBd could be considered cost-effective if the selinexor price was determined on the basis of the CMA of SBd vs Cd presented in the resubmission, after inclusion of the confidential effective price for carfilzomib and an adjusted weighting for the use of carfilzomib once weekly and twice-weekly regimens.
- 7.2 The PBAC recommended the listing of selinexor as part of SBd, on the basis that it should be available only under special arrangements under Section 100, through the Highly Specialised Drugs program.
- 7.3 The PBAC noted that the proposed listing for SBd for use as a second or later line treatment is broader than, although also overlaps with, the current listing for Sd for use as a fifth or later line treatment. The PBAC considered that there should be a single listing for selinexor which allows use in patients as a second or later line treatment either with or without bortezomib to enable clinicians to utilise the appropriate regimen for their patient (either SBd or Sd) based on clinical judgement. The PBAC noted that the TGA approved product information for selinexor recommends a starting dose of 100 mg once weekly when used in combination with bortezomib and dexamethasone, with lower doses (between 40 mg weekly and 80 mg weekly) for patients requiring dose reductions for adverse reactions. For the Sd regimen, the recommended starting dose for selinexor is 160 mg weekly, and between 60 mg and 100 mg weekly for patients requiring dose reductions. The PBAC noted as for the current PBS listing, the prescriber will need to identify the dose requirement for the individual patient and select the appropriate pack size according to the expected weekly dose of selinexor. The PBAC estimated that in clinical practice the majority of selinexor use would occur in the third- and fourth-line settings, and a minority of use would be in the fifth line or beyond (permitted under current Sd listing).
- 7.4 The PBAC considered that the nomination of Cd as primary comparator was

reasonable, although also noted that international guidelines indicate a preference for triple combination therapies, and therefore PBS listed triple therapies, such as ELd, PBd (and CLd if it proceeds to PBS listing) are also relevant alternative therapies, consistent with its previous advice at the March 2022 PBAC meeting.

- 7.5 The PBAC considered that SBd would be used in a relatively small proportion of the total RRMM population, however the SBd population was difficult to define. The PBAC considered that SBd may be a useful option for a niche population of fit patients with high-risk disease, especially in patients unsuitable for IMiDs, as it would be the only IMiD-free triplet available on the PBS. The PBAC also noted the advice provided by the clinical expert in the sponsor hearing concerning specific circumstances in which SBd may be most applicable (paragraph 6.1).
- 7.6 The PBAC noted there were no direct randomised trials comparing SBd with Cd, and therefore the clinical evaluation was informed by indirect treatment comparisons (ITCs). The resubmission was based on one head-to-head randomised controlled trial comparing SBd to Bd (BOSTON) and ITCs between SBd and Cd using the ENDEAVOR trial (comparing Cd with Bd) with Bd as the common reference. 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 The PBAC considered that the claim of non-inferior effectiveness versus Cd was uncertain due to the transitivity issues across the trials and the wide confidence intervals for the indirect estimates. However, the PBAC acknowledged that further data are unlikely to be available to increase the certainty for the non-inferiority claim and that SBd will be used in a relatively small niche population, and in this context the PBAC accepted the effectiveness claim on the basis that conservative assumptions informed the economic evaluation (paragraph 7.9) and that the price for selinexor (per 20 mg tablet) determined from the CMA of SBd vs Cd would be applied to all patients treated under the proposed single listing for selinexor (paragraph 7.3).
- 7.8 In regard to safety, the PBAC reaffirmed its previous view that the claim of non-inferior comparative safety was reasonable for SBd compared with Cd.
- 7.9 The PBAC considered the revised CMA sufficiently conservative to address the uncertainty regarding the non-inferiority claim versus Cd, noting that the administration costs for carfilzomib were excluded which decreased the price of selinexor derived from the CMA (see paragraph 6.44). The PBAC considered that SBd would be considered acceptably cost-effective if the selinexor effective price was determined on the basis of the CMA of SBd vs Cd presented in the resubmission, updated with 1) the confidential carfilzomib effective price; and 2) an assumption that 60% of carfilzomib use will be the once weekly regimen, and the remaining 40% will be the twice weekly regimen. The PBAC also considered the price of SBd should be no higher than the price of ELd or PBd for this population.

- 7.10 The PBAC considered that the equi-effective doses are selinexor 5,333 mg plus bortezomib 125 mg per patient being equivalent to 7,278 mg of carfilzomib per patient when Cd is administered twice weekly and 4,969 mg per patient when Cd is administered once weekly (Table 19), and assuming that 60% of carfilzomib use will be the once weekly regimen, and the remaining 40% will be the twice weekly regimen.
- 7.11 In regard to the utilisation and financial estimates, the PBAC considered that the resubmission had overestimated the script numbers for SBd. A sensitivity analysis conducted during the evaluation, assuming zero uptake of SBd in the second line resulted in a decrease of PBS/RPBS cost by 50%. In addition, the uptake rates proposed by the resubmission may be overestimated due to the uncertain efficacy of SBd, the recent PBS-listing of three other triple therapies which will also be used in the third line or later and overall PBAC considered that SBd would be used in a small, niche population. The PBAC considered the sensitivity analysis conducted during the evaluation (see Table 26) that assumed third line or later use of SBd to better reflect the likely utilisation of SBd if listed.
- 7.12 The PBAC noted that the proposed listing of selinexor aligns with the 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:
- There should be a single listing for selinexor which allows use in patients as a second or later line treatment either with or without bortezomib to enable clinicians to utilise the appropriate regimen for their patient (either SBd or Sd) based on clinical judgement (i.e. the current listing for Sd would be replaced).
 - The price for selinexor (per 20 mg tablet) determined from the CMA of SBd vs Cd (see paragraph 7.9) should apply to all patients treated under the recommended single listing for selinexor (with or without bortezomib), i.e., a single price would apply for selinexor per 20 mg tablet, from the effective date of the recommended single listing.
 - The submission sought listings for the 16 and 20 tablet pack sizes (see paragraph 3.2). The requested maximum quantity of one pack and two repeats was appropriate.
 - The recommended dosing for selinexor when used as part of either SBd or Sd regimens is described in Table 1 of the TGA approved product information, including dose reductions for management of adverse reactions.
 - The grandfather restriction was appropriate to allow continuing supply of selinexor to patients commencing treatment prior to PBS listing, noting that the PSCR had estimated 40 such patients.
 - As there are several PBS listed medicines for the treatment of RRMM, it will be necessary to review the current listings for potential flow-on changes.

- 7.13 The PBAC considered there is a low risk of utilisation outside of the recommended restriction or above that predicted and therefore that it is not necessary to implement a financial cap for selinexor.
- 7.14 The PBAC advised that selinexor is not suitable for prescribing by nurse practitioners.
- 7.15 The PBAC recommended that the Early Supply Rule should not apply.
- 7.16 The PBAC noted that its recommendation was on a cost-minimisation basis and advised that, because selinexor is not expected to provide a substantial and clinically relevant improvement in efficacy, or reduction of toxicity, over Cd or other medicines listed on the PBS for RRMM, or not expected to address a high and urgent unmet clinical need given the presence of an alternative therapy, the criteria prescribed by the National Health (Pharmaceuticals and Vaccines – Cost Recovery) Regulations 2022 for Pricing Pathway A were not met.
- 7.17 The PBAC noted that this submission is not eligible for an Independent Review as it received a positive recommendation.
- 7.18 The restriction is considered to be complex, due to the potential for flow-on changes.

Outcome:

Recommended

8 Recommended listing

8.1 Apply the listing for the three pack sizes as follows:

- Pack of 16 tablets- Dose requirement of 80 mg, 60 mg or 40 mg per week
- Pack of 20 tablets- Dose requirement of 100 mg per week
- Pack of 32 tablets- Dose requirement of 160 mg per week (Sd regimen only)

8.2 Impacted item numbers to be replaced by recommended listing:

- selinexor 20 mg tablet, 16: 13099K (Private); 13085Q (Public)
- selinexor 20 mg tablet, 20: 13103P (Private); 13086R (Public)
- selinexor 20 mg tablet, 32: 13105R (Private); 13104Q (Public)

8.3 Amend existing listing as follows:

MEDICINAL PRODUCT medicinal product pack	PBS item code	Max. qty packs	Max. qty units	№.of Rpts	Available brands
SELINEXOR					
selinexor 20 mg tablet, 16	13099K / Private 13085Q / Public	1	16	2	Xpovio
Amend Restriction Summary [13227] / Treatment of Concept: [13115]					
Category / Program: S100 Highly Specialised Drugs Program (HSD)					
Prescriber type: <input checked="" type="checkbox"/> Medical Practitioners					
Restriction type: <input checked="" type="checkbox"/> Authority Required (telephone/electronic):					
Administrative advice: No increase in the maximum quantity or number of units may be authorised					
Administrative advice: No increase in the maximum number of repeats may be authorised.					
Administrative advice: Special Pricing Arrangements apply					
Administrative advice: Applications for authorisation under this restriction may be made in real time using the Online PBS Authorities system (see www.servicesaustralia.gov.au/HPOS) or by telephone by contacting Services Australia on 1800 700 270 (hours of operation 8 a.m. to 5 p.m. Monday to Friday).					
Caution: This drug is a Category D drug and must not be given to pregnant women. If this drug is taken during pregnancy, a teratogenic effect in humans cannot be ruled out.					
Indication: Relapsed and/or refractory multiple myeloma (RRMM)					
Treatment Phase: Initial treatment – Dose requirement of 80mg, 60mg or 40mg per week					
Clinical criteria: The condition must be confirmed by a histological diagnosis					
AND					
Clinical criteria:					

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	Patient must be undergoing triple combination therapy limited to: (i) this drug, (ii) bortezomib, (iii) dexamethasone; or
	Patient must be undergoing dual combination therapy limited to: (i) this drug, (ii) dexamethasone.
	AND
	Clinical criteria:
	Patient must have progressive disease after at least one prior therapy
	AND
	Clinical criteria:
	Patient must not have previously received this drug for this condition
	Prescriber instruction: Refractory disease is defined as less than or equal to a 25% response to therapy, or progression during or within 60 days after completion of therapy
	<p>Prescriber instruction: Progressive disease is defined as at least one of the following:</p> <ul style="list-style-type: none"> (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). <p>Oligo-secretory and non-secretory patients are defined as having active disease with less than 10 g per L serum M-protein.</p>
	<p>Prescriber instruction: 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.</p> <p>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:</p> <ul style="list-style-type: none"> (a) the level of serum monoclonal protein; or (b) Bence-Jones proteinuria - the results of 24-hour urinary light chain M-protein excretion; or (c) the serum level of free kappa and lambda light chains; or (d) bone marrow aspirate or trephine; or (e) if present, the size and location of lytic bone lesions (not including compression fractures); or (f) if present, the size and location of all soft tissue plasmacytomas by clinical or radiographic examination (i.e. MRI or CT scan); or (g) if present, the level of hypercalcaemia, corrected for albumin concentration. <p>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 non-secretory nature of the multiple myeloma (current serum M-protein less than 10 g per L) must be documented in the patient's medical records.</p>

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	<p>Prescriber instruction: A line of therapy is defined as 1 or more cycles of a planned treatment program. This may consist of 1 or more planned cycles of single-agent therapy or combination therapy, as well as a sequence of treatments administered in a planned manner. A new line of therapy starts when a planned course of therapy is modified to include other treatment agents (alone or in combination) as a result of disease progression, relapse, or toxicity, with the exception to this being the need to attain a sufficient response for stem cell transplantation to proceed. A new line of therapy also starts when a planned period of observation off therapy is interrupted by a need for additional treatment for the disease.</p>
Amend Restriction Summary [13157] / Treatment of Concept: [13229]	
	<p>Treatment Phase: Continuing treatment – Dose requirement of 80mg, 60mg or 40mg per week</p>
	<p>Clinical criteria: Patient must have previously received PBS-subsidised treatment this drug for this condition</p>
AND	
	<p>Clinical criteria: Patient must be undergoing triple combination therapy limited to: (i) this drug, (ii) bortezomib, (iii) dexamethasone; or</p>
	<p>Patient must be undergoing dual combination therapy limited to: (i) this drug, (ii) dexamethasone.</p>
AND	
	<p>Clinical criteria: Patient must not have developed disease progression while receiving treatment with this drug for this condition</p>
	<p>Prescriber instruction: Progressive disease is defined as at least one of the following: (a) at least a 25% increase and an absolute increase of at least 5 g per L in serum M-protein (monoclonal protein); or (b) at least a 25% increase in 24-hour urinary light chain M-protein excretion, and an absolute increase of at least 200 mg per 24 hours; or (c) in oligo-secretory and non-secretory myeloma patients only, at least a 50% increase of the difference between involved free light chain and uninvolved free light chain; or (d) at least a 25% relative increase and at least a 10% absolute increase in plasma cells in a bone marrow aspirate or on biopsy; or (e) an increase in the size or number of lytic bone lesions (not including compression fractures); or (f) at least a 25% increase in the size of an existing or the development of a new soft tissue plasmacytoma (determined by clinical examination or diagnostic imaging); or (g) development of hypercalcaemia (corrected serum calcium greater than 2.65 mmol per L not attributable to any other cause). Oligo-secretory and non-secretory patients are defined as having active disease with less than 10 g per L serum M-protein.</p>
Amend Restriction Summary [13162] / Treatment of Concept: [13256]	
	<p>Treatment Phase: Grandfather treatment – Transitioning from non-PBS to PBS-subsidised supply – Dose requirement of 80mg, 60mg or 40mg per week</p>

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	Clinical criteria:
	Patient must have received non-PBS-subsidised treatment with this drug for this condition prior to [listing date],
	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, which are: (a) the condition was confirmed by histological diagnosis, (b) the treatment is/was being used as part of combination therapy limited to this drug in combination with either: (i) dexamethasone, (ii) dexamethasone plus bortezomib, (c) the condition progressed (see definition of progressive disease below) after at least one prior therapy, (d) the patient had never been treated with this drug.
	AND
	Clinical criteria:
	Patient must not have developed disease progression while receiving treatment with this drug for this condition
	Prescriber instruction: Refractory disease is defined as less than or equal to a 25% response to therapy, or progression during or within 60 days after completion of therapy
	Prescriber instruction: Progressive disease is defined as at least one of the following: (a) at least a 25% increase and an absolute increase of at least 5 g per L in serum M-protein (monoclonal protein); or (b) at least a 25% increase in 24-hour urinary light chain M-protein excretion, and an absolute increase of at least 200 mg per 24 hours; or (c) in oligo-secretory and non-secretory myeloma patients only, at least a 50% increase of the difference between involved free light chain and uninvolved free light chain; or (d) at least a 25% relative increase and at least a 10% absolute increase in plasma cells in a bone marrow aspirate or on biopsy; or (e) an increase in the size or number of lytic bone lesions (not including compression fractures); or (f) at least a 25% increase in the size of an existing or the development of a new soft tissue plasmacytoma (determined by clinical examination or diagnostic imaging); or (g) development of hypercalcaemia (corrected serum calcium greater than 2.65 mmol per L not attributable to any other cause). Oligo-secretory and non-secretory patients are defined as having active disease with less than 10 g per L serum M-protein.
	Prescriber instruction: A line of therapy is defined as 1 or more cycles of a planned treatment program. This may consist of 1 or more planned cycles of single-agent therapy or combination therapy, as well as a sequence of treatments administered in a planned manner. A new line of therapy starts when a planned course of therapy is modified to include other treatment agents (alone or in combination) as a result of disease progression, relapse, or toxicity, with the exception to this being the need to attain a sufficient response for stem cell transplantation to proceed. A new line of therapy also starts when a planned period of observation off therapy is interrupted by a need for additional treatment for the disease.

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MEDICINAL PRODUCT medicinal product pack	PBS item code	Max. qty packs	Max. qty units	№.of Rpts	Available brands
SELINEXOR					
selinexor 20 mg tablet, 20	13103P / Private 13086R / Public	1	20	2	Xpovio
Amend Restriction Summary [13265] / Treatment of Concept: [13116]					
Category / Program: S100 Highly Specialised Drugs Program (HSD)					
Prescriber type: <input checked="" type="checkbox"/> Medical Practitioners					
Restriction type: <input checked="" type="checkbox"/> Authority Required (telephone/electronic):					
Administrative advice: No increase in the maximum quantity or number of units may be authorised					
Administrative advice: No increase in the maximum number of repeats may be authorised.					
Administrative advice: Special Pricing Arrangements apply					
Administrative advice: Applications for authorisation under this restriction may be made in real time using the Online PBS Authorities system (see www.servicesaustralia.gov.au/HPOS) or by telephone by contacting Services Australia on 1800 700 270 (hours of operation 8 a.m. to 5 p.m. Monday to Friday).					
Caution: This drug is a Category D drug and must not be given to pregnant women. If this drug is taken during pregnancy, a teratogenic effect in humans cannot be ruled out.					
Indication: Relapsed and/or refractory multiple myeloma (RRMM)					
Treatment Phase: Initial treatment – Dose requirement of 100 mg per week					
Clinical criteria: The condition must be confirmed by a histological diagnosis					
AND					
Clinical criteria: Patient must be undergoing triple combination therapy limited to: (i) this drug, (ii) bortezomib, (iii) dexamethasone; or					
Patient must be undergoing dual combination therapy limited to: (i) this drug, (ii) dexamethasone.					
AND					
Clinical criteria: Patient must have progressive disease after at least one prior therapy					
AND					
Clinical criteria: Patient must not have previously received this drug for this condition					
Prescriber instruction: Refractory disease is defined as less than or equal to a 25% response to therapy, or progression during or within 60 days after completion of therapy					
Prescriber instruction: Progressive disease is defined as at least one of the following:					

	<p>(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).</p> <p>Oligo-secretory and non-secretory patients are defined as having active disease with less than 10 g per L serum M-protein.</p>
	<p>Prescriber instruction: A line of therapy is defined as 1 or more cycles of a planned treatment program. This may consist of 1 or more planned cycles of single-agent therapy or combination therapy, as well as a sequence of treatments administered in a planned manner.</p> <p>A new line of therapy starts when a planned course of therapy is modified to include other treatment agents (alone or in combination) as a result of disease progression, relapse, or toxicity, with the exception to this being the need to attain a sufficient response for stem cell transplantation to proceed. A new line of therapy also starts when a planned period of observation off therapy is interrupted by a need for additional treatment for the disease.</p>
<p>Amend Restriction Summary [13266] / Treatment of Concept: [13228]</p>	
	<p>Treatment Phase: Continuing treatment – Dose requirement of 100mg per week</p>
	<p>Clinical criteria:</p>
	<p>Patient must have previously received PBS-subsidised treatment this drug for this condition</p>
	<p>AND</p>
	<p>Clinical criteria:</p>
	<p>Patient must be undergoing triple combination therapy limited to: (i) this drug, (ii) bortezomib, (iii) dexamethasone; or</p>
	<p>Patient must be undergoing dual combination therapy limited to: (i) this drug, (ii) dexamethasone.</p>
	<p>AND</p>
	<p>Clinical criteria:</p>
	<p>Patient must not have developed disease progression while receiving treatment with this drug for this condition</p>
	<p>Prescriber instruction: Progressive disease is defined as at least one 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</p>

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	<p>(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).</p> <p>Oligo-secretory and non-secretory patients are defined as having active disease with less than 10 g per L serum M-protein.</p>
Amend Restriction Summary [13266] / Treatment of Concept: [13228]	
	<p>Treatment Phase: Grandfather treatment – Transitioning from non-PBS to PBS-subsidised supply – Dose requirement of 100mg per week</p>
	<p>Clinical criteria: Patient must have received non-PBS-subsidised treatment with this drug for this condition prior to [listing date],</p>
	AND
	<p>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, which are: (a) the condition was confirmed by histological diagnosis, (b) the treatment is/was being used as part of combination therapy limited to this drug in combination with either: (i) dexamethasone, (ii) dexamethasone plus bortezomib, (c) the condition progressed (see definition of progressive disease below) after at least one prior therapy, (d) the patient had never been treated with this drug.</p>
	AND
	<p>Clinical criteria: Patient must not have developed disease progression while receiving treatment with this drug for this condition</p>
	<p>Prescriber instruction: Refractory disease is defined as less than or equal to a 25% response to therapy, or progression during or within 60 days after completion of therapy</p>
	<p>Prescriber instruction: Progressive disease is defined as at least one 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).</p> <p>Oligo-secretory and non-secretory patients are defined as having active disease with less than 10 g per L serum M-protein.</p>

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<p>Prescriber instruction: A line of therapy is defined as 1 or more cycles of a planned treatment program. This may consist of 1 or more planned cycles of single-agent therapy or combination therapy, as well as a sequence of treatments administered in a planned manner. A new line of therapy starts when a planned course of therapy is modified to include other treatment agents (alone or in combination) as a result of disease progression, relapse, or toxicity, with the exception to this being the need to attain a sufficient response for stem cell transplantation to proceed. A new line of therapy also starts when a planned period of observation off therapy is interrupted by a need for additional treatment for the disease.</p>

MEDICINAL PRODUCT medicinal product pack	PBS item code	Max. qty packs	Max. qty units	№.of Rpts	Available brands
SELINEXOR					
selinexor 20 mg tablet, 32	13105R / Private 13104Q / Public	1	32	2	Xpovio

Amend Restriction Summary [13158] / Treatment of Concept: [13159]

Category / Program: S100 Highly Specialised Drugs Program (HSD)	
Prescriber type: <input checked="" type="checkbox"/> Medical Practitioners	
Restriction type: <input checked="" type="checkbox"/> Authority Required (telephone/electronic):	
Administrative advice:	No increase in the maximum quantity or number of units may be authorised
Administrative advice:	No increase in the maximum number of repeats may be authorised.
Administrative advice:	Special Pricing Arrangements apply
Administrative advice:	Applications for authorisation under this restriction may be made in real time using the Online PBS Authorities system (see www.servicesaustralia.gov.au/HPOS) or by telephone by contacting Services Australia on 1800 700 270 (hours of operation 8 a.m. to 5 p.m. Monday to Friday).
Caution:	This drug is a Category D drug and must not be given to pregnant women. If this drug is taken during pregnancy, a teratogenic effect in humans cannot be ruled out.
Indication: Relapsed and/or refractory multiple myeloma (RRMM)	
Treatment Phase: Initial treatment - Dose requirement of 160mg per week	
Clinical criteria: The condition must be confirmed by a histological diagnosis	
AND	
Clinical criteria: Patient must be undergoing dual combination therapy limited to: (i) this drug, (ii) dexamethasone	
AND	
Clinical criteria: Patient must have progressive disease after at least one prior therapy	
AND	
Clinical criteria:	

	Patient must not have previously received this drug for this condition
	Prescriber instruction: Refractory disease is defined as less than or equal to a 25% response to therapy, or progression during or within 60 days after completion of therapy
	Prescriber instruction: Progressive disease is defined as at least one of the following: (a) at least a 25% increase and an absolute increase of at least 5 g per L in serum M-protein (monoclonal protein); or (b) at least a 25% increase in 24-hour urinary light chain M-protein excretion, and an absolute increase of at least 200 mg per 24 hours; or (c) in oligo-secretory and non-secretory myeloma patients only, at least a 50% increase of the difference between involved free light chain and uninvolved free light chain; or (d) at least a 25% relative increase and at least a 10% absolute increase in plasma cells in a bone marrow aspirate or on biopsy; or (e) an increase in the size or number of lytic bone lesions (not including compression fractures); or (f) at least a 25% increase in the size of an existing or the development of a new soft tissue plasmacytoma (determined by clinical examination or diagnostic imaging); or (g) development of hypercalcaemia (corrected serum calcium greater than 2.65 mmol per L not attributable to any other cause). Oligo-secretory and non-secretory patients are defined as having active disease with less than 10 g per L serum M-protein.
	Prescriber instruction: A line of therapy is defined as 1 or more cycles of a planned treatment program. This may consist of 1 or more planned cycles of single-agent therapy or combination therapy, as well as a sequence of treatments administered in a planned manner. A new line of therapy starts when a planned course of therapy is modified to include other treatment agents (alone or in combination) as a result of disease progression, relapse, or toxicity, with the exception to this being the need to attain a sufficient response for stem cell transplantation to proceed. A new line of therapy also starts when a planned period of observation off therapy is interrupted by a need for additional treatment for the disease.
Amend Restriction Summary [13117] / Treatment of Concept: [13160]	
	Treatment Phase: Continuing treatment - Dose requirement of 160mg per week
	Clinical criteria: Patient must have previously received PBS-subsidised treatment this drug for this condition
	AND
	Clinical criteria: Patient must be undergoing dual combination therapy limited to: (i) this drug, (ii) dexamethasone
	AND
	Clinical criteria: Patient must not have developed disease progression while receiving treatment with this drug for this condition
	Prescriber instruction: Progressive disease is defined as at least one 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

<p>(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</p> <p>(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</p> <p>(d) at least a 25% relative increase and at least a 10% absolute increase in plasma cells in a bone marrow aspirate or on biopsy; or</p> <p>(e) an increase in the size or number of lytic bone lesions (not including compression fractures); or</p> <p>(f) at least a 25% increase in the size of an existing or the development of a new soft tissue plasmacytoma (determined by clinical examination or diagnostic imaging); or</p> <p>(g) development of hypercalcaemia (corrected serum calcium greater than 2.65 mmol per L not attributable to any other cause).</p> <p>Oligo-secretory and non-secretory patients are defined as having active disease with less than 10 g per L serum M-protein.</p>
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This restriction may be subject to further review. Should there be any changes made to the restriction the sponsor will be informed

9 Context for Decision

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

10 Sponsor's Comment

Antengene (AUS) Pty Ltd wishes to thank the health care professionals, healthcare and patient organisations and patients for their support. We are very pleased with this positive recommendation and we look forward to working with the department to ensure early access for multiple myeloma patients to benefit.