

7.09 SELINEXOR, Tablet 20 mg, Xpovio[®], Antengene Australia Pty Ltd.

1 Purpose of submission

- 1.1 The standard re-entry resubmission requested a Section 100 (Highly Specialised Drug), Authority Required (telephone/electronic) listing for selinexor in combination with dexamethasone (Sd) for the treatment of patients with relapsed and/or refractory multiple myeloma (RRMM), who had 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); referred in the resubmission as triple-class-refractory and penta-refractory multiple myeloma (TCR/PR MM).
- 1.2 Listing was requested on the basis of a cost-utility analysis (CUA) versus salvage chemotherapy, represented by dexamethasone + cyclophosphamide + etoposide + cisplatin (DCEP), as the main comparator. The components of the overall clinical issue addressed by the submission are summarised in Table 1.

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

Component	Description
Population	Adult patients with relapsed and/or refractory multiple myeloma, who have received at least four prior therapies and whose disease is refractory to at least two proteasome inhibitors, at least two immunomodulatory agents, and an anti-CD38 monoclonal antibody
Intervention	Selinexor 80 mg twice weekly, oral tablet ^a , in combination with low-dose dexamethasone (20 mg)
Comparator	Salvage chemotherapy ^b
Outcomes	Overall response rate, progression-free and overall survival, safety
Clinical claim	XPOVIO (selinexor) in combination with dexamethasone has superior efficacy and at least non-inferior safety relative to salvage chemotherapy ^c

Source: Table 1-2, p7 of the resubmission; Table 1, p1 Selinexor (TCR/PR), PBAC Minutes, July 2021 PBAC meeting

Abbreviations: mg = milligram.

Note: ^a Median dose in the trial was actually 115 mg/week ~60 mg twice weekly dose

^b the resubmission nominated salvage chemotherapy with DCEP (dexamethasone + cyclophosphamide + etoposide + cisplatin) as the main comparator consistent with the July 2021 submission

^c the clinical claim from the July 2021 submission was that 'selinexor in combination with dexamethasone provides clinical benefit for patients with TCR/PR MM and has a manageable safety/tolerability profile'

Blue shading denotes text remains unchanged from the July 2021 submission.

2 Background

Registration status

- 2.1 Selinexor was TGA registered on 8 March 2022 for the following indication:
- In combination with dexamethasone for the treatment of adult patients with relapsed or refractory multiple myeloma (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).
- 2.2 The submission was made under the TGA/PBAC Parallel Process. At the time of evaluation for PBAC consideration, the Clinical Evaluation Report, the Delegate's Overview and the Advisory Committee on Medicine (ACM) minutes were available.
- 2.3 The FDA in July 2019 and EMA in January 2021 approved the use of Sd for the treatment of adult patients with RRMM who have received at least four prior therapies and whose disease is refractory to at least two proteasome inhibitors, at least two immunomodulatory agents, and an anti-CD38 monoclonal antibody. The FDA and EMA indications are consistent with the requested PBS restriction.

Previous PBAC consideration

- 2.4 A summary of the key matters of concern from the previous PBAC consideration is presented in Table 2.

Table 2: Summary of key matters of concern

Component	Matter of concern	How the resubmission addresses it
Clinical Effectiveness	The PBAC considered that the naïve ITC between the TCR/PE MM subgroup of STORM and the MAMMOTH and FLATIRON were highly uncertain as: <ul style="list-style-type: none"> • there were differences between the patient populations • applicability issues included <ul style="list-style-type: none"> (i) the TCR/PE subgroup of STORM was not the PBS-proposed population, and (ii) MAMMOTH and FLATIRON did not represent the clinical outcomes of the proposed comparator (DCEP; Para. 7.7, July 2021 PBAC Meeting). 	The resubmission presented a naïve comparison between the TCR/PR MM sub-groups of STORM and MAMMOTH, consistent with the requested PBS population. Additional data from Goldsmith 2020 (previously presented in Section 3 of the July 2021 submission) was presented to represent patients who had received DCEP. However, this study included 74% of patients with PR MM. Assessment of baseline characteristics between the three studies was limited. Furthermore, the dosing regimen of DCEP within Goldsmith 2020 was different to that presented in the safety data and still different to that considered in the economic evaluation and financial estimates.
Safety	The PBAC noted that no comparative safety data were presented for DCEP. Therefore, the PBAC considered that the submission's claim that Sd was superior to DCEP in terms of safety was not supported. (Para. 7.10, July 2021 PBAC Meeting).	Comparative safety data was provided based on a comparison of STORM with studies of DCEP (Yuen 2018 and Griffin 2015). AE reporting between the three studies differed (e.g. STORM and Yuen 2018 presented Grade ≥ 3 AEs whilst Griffin presented clinically relevant AEs). Furthermore, the DCEP regimen between the two studies differed and a large proportion of patients in Yuen 2018 received either thalidomide (56%) or lenalidomide (18%) in addition to the DCEP backbone.
Economic evaluation	The PBAC considered the ICER unacceptably uncertain, and in this context, considered the ICER to be high (Para. 7.12, July 2021 PBAC Meeting).	The resubmission reduced the time horizon, increased prior assumption of duration and incidence of AEs and did not assume a treatment effect for Sd in terms of PFS as per PBAC's previous consideration. The price of selinexor was decreased by █% (effective DPMQ reduction from \$█ to \$█). The base case did not consider post progression costs, but this was applied as a sensitivity analysis.
Financial impact	The PBAC considered the estimates were overestimated due to the assumptions/inputs to the epidemiological approach and overestimation of selinexor uptake rates, duration of therapy and compliance rate (Para.6.55 and 7.13, July 2021 PBAC Meeting).	The resubmission applied a different epidemiological approach to that of the July 2021 submission. The resubmission estimated the eligible population as based on the PBS utilisation of Pd. The compliance rate and duration of therapy estimates were reduced. Although the selinexor uptake rate applied in the resubmission remained the same, the uptake rates were more conservatively applied given the approach to calculating the eligible population (i.e. █% of patients treated with Pd likely to receive subsequent therapy).

Source: Table E.1, pp110-111, pp159-61 of the resubmission.

Abbreviations: AE = adverse event; DCEP = dexamethasone + cyclophosphamide + etoposide + cisplatin; DPMQ = dispensed price for maximum quantity; ICER = incremental cost effectiveness ratio; ITC = indirect treatment comparison; MM = multiple myeloma; PBAC = Pharmaceutical Benefits Advisory Committee; PBS = Pharmaceutical Benefits Scheme; Pd = pomalidomide + dexamethasone; PR MM = penta-refractory multiple myeloma; Sd = selinexor + dexamethasone; TCR/PE = triple class refractory and penta-exposed multiple myeloma; TCR/PR MM = triple class refractory and penta-refractory multiple myeloma

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

3 Requested listing

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

Name, restriction, manner of administration, form	Max Qty (packs)	Max Qty (units)	No. of repeats	DPMQ	Proprietary name and manufacturer
Selinexor, 20 mg tablets	1	32	2	Published: \$23,050.88 (HSD Public) \$23,098.66 (HSD Private) Effective (after rebate): \$ (HSD Public) \$ (HSD Private)	XPOVIO, ANTENGENE Pty Ltd
	1	24	2	Published: \$17,288.16 (HSD Public) \$17,335.94 (HSD Private) Effective (after rebate): \$ (HSD Public) \$ (HSD Private)	
	1	20	2	Published: \$14,406.80 (HSD Public) \$14,454.58 (HSD Private) Effective (after rebate): \$ (HSD Public) \$ (HSD Private)	
	1	16	2	Published: \$11,525.44 (HSD Public) \$11,573.22 (HSD Private) Effective (after rebate): \$ (HSD Public) \$ (HSD Private)	

Restriction Summary [new] / Treatment of Concept: [new]	
	Category / Program: Section 100 – Highly Specialised Drugs Program
	Prescriber type: <input checked="" type="checkbox"/> Medical Practitioners
	Restriction type: <input checked="" type="checkbox"/> Authority Required – immediate/real-time assessment by Services Australia (telephone/electronic)
	Administrative Advice: <i>Special Pricing Arrangements apply.</i>
	Administrative Advice: <i>No increase in the maximum quantity or number of units may be authorised.</i>
	Administrative Advice: <i>No increase in the maximum number of repeats may be authorised.</i>
	Episodicity: <i>Relapsed and/or refractory</i>
	Severity: <i>[blank]</i>
	Condition: <i>Multiple myeloma</i>
	Indication: <i>Relapsed and/or refractory multiple myeloma</i>
	Treatment Phase: <i>Initial treatment</i>
	Clinical criteria:
	<i>The treatment must be in combination with dexamethasone</i>

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	AND
	Clinical criteria:
	Patient must have progressive disease after at least four prior <i>lines of therapy for this condition</i>
	AND
	Clinical criteria:
	<i>Patient must not have previously received this drug for this condition</i>
	AND
	Clinical criteria:
	Patient is must have demonstrated refractory disease to the following prior treatments for this condition, which must include: (i) a minimum of two proteasome inhibitors; and (ii) a minimum of two immunomodulatory agents; and (iii) an anti-CD38 monoclonal antibody
	AND
	Clinical criteria:
	Patient must not be receiving concomitant PBS-subsidised treatment with any of the following: (i) proteasome inhibitors, (ii) Immunomodulators, (iii) anti-CD38 monoclonal antibody bortezomib, carfilzomib, lenalidomide, thalidomide, pomalidomide or its analogues
	Prescribing Instructions: Progressive disease is defined as at least 1 of the following: (a) at least a 25% increase and an absolute increase of at least 5 g per L in serum M protein (monoclonal protein); or (b) at least a 25% increase in 24-hour urinary light chain M protein excretion, and an absolute increase of at least 200 mg per 24 hours; or (c) in oligo-secretory and non-secretory myeloma patients only, at least a 50% increase in the difference between involved free light chain and uninvolved free light chain; or (d) at least a 25% relative increase and at least a 10% absolute increase in plasma cells in a bone marrow aspirate or on biopsy; or (e) an increase in the size or number of lytic bone lesions (not including compression fractures); or (f) at least a 25% increase in the size of an existing or the development of a new soft tissue plasmacytoma (determined by clinical examination or diagnostic imaging); or (g) development of hypercalcaemia (corrected serum calcium greater than 2.65 mmol per L not attributable to any other cause).
	Prescribing Instructions: Oligo-secretory and non-secretory patients are defined as having active disease with less than 10 g per L serum M protein.
	Prescribing Instructions: Refractory disease is defined as $\leq 25\%$ response to therapy or progression during or within 60 days after completion of therapy
	Prescribing Instructions: 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.
	Administrative Advice: <i>Applications for authorisation under this restriction may be made in real time using the Online PBS Authorities system (see www.servicesaustralia.gov.au/HPOS) or by telephone by contacting Services Australia on 1800 888 333.</i>

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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.	
Restriction Summary [new] / Treatment of Concept: [new]	
Category / Program:	Section 100 – Highly Specialised Drugs Program
Prescriber type:	<input checked="" type="checkbox"/> Medical Practitioners
Restriction type:	<input checked="" type="checkbox"/> Authority Required – immediate/real-time assessment by Services Australia (telephone/electronic)
Episodicity:	Relapsed and/or refractory
Severity:	[blank]
Condition:	Multiple myeloma
Indication:	Relapsed and/or refractory multiple myeloma
Treatment Phase:	Continuing treatment
Clinical criteria:	Patient must have previously received PBS-subsidised treatment with been issued with an authority prescription for this drug for this condition
AND	
Clinical criteria:	The treatment must be in combination with dexamethasone
AND	
Clinical criteria:	Patient must not have progressive disease developed disease progression while receiving treatment with this drug for this condition
AND	
Clinical criteria:	Patient must not be receiving concomitant PBS-subsidised treatment with any of the following: (i) proteasome inhibitors , (ii) Immunomodulators, (iii) anti-CD38 monoclonal antibody bortezomib, carfilzomib, lenalidomide, thalidomide, pomalidomide or its analogues
Prescribing Instructions:	Progressive disease is defined as at least 1 of the following: (a) at least a 25% increase and an absolute increase of at least 5 g per L in serum M protein (monoclonal protein); or (b) at least a 25% increase in 24-hour urinary light chain M protein excretion, and an absolute increase of at least 200 mg per 24 hours; or (c) in oligo-secretory and non-secretory myeloma patients only, at least a 50% increase in the difference between involved free light chain and uninvolved free light chain; or (d) at least a 25% relative increase and at least a 10% absolute increase in plasma cells in a bone marrow aspirate or on biopsy; or (e) an increase in the size or number of lytic bone lesions (not including compression fractures); or (f) at least a 25% increase in the size of an existing or the development of a new soft tissue plasmacytoma (determined by clinical examination or diagnostic imaging); or (g) development of hypercalcaemia (corrected serum calcium greater than 2.65 mmol per L not attributable to any other cause).
Prescribing Instructions:	Oligo-secretory and non-secretory patients are defined as having active disease with less than 10 g per L serum M protein.
Administrative Advice:	Applications for authorisation under this restriction may be made in real time using the Online PBS Authorities system (see www.servicesaustralia.gov.au/HPOS) or by telephone by contacting Services Australia on 1800 888 333.

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	Administrative Advice: No increase in the maximum number of repeats may be authorised.
	Administrative Advice: Special Pricing Arrangements apply
	Caution: This drug is a category D drug and must not be given to pregnant women. If selinexor is taken during pregnancy, a teratogenic effect of selinexor in humans cannot be ruled out.
Restriction Summary [new] / Treatment of Concept: [new]	
	Category / Program: Section 100 – Highly Specialised Drugs Program
	Prescriber type: <input checked="" type="checkbox"/> Medical Practitioners
	Restriction type: <input checked="" type="checkbox"/> Authority Required – immediate/real-time assessment by Services Australia (telephone/electronic)
	Episodicity: Relapsed and/or refractory
	Severity: [blank]
	Condition: Multiple myeloma
	Indication: Relapsed and/or refractory multiple myeloma
	Treatment Phase: Grandfather treatment - Transitioning from non-PBS to PBS-subsidised supply
	Clinical criteria:
	Patient must have received non-PBS-subsidised treatment with this drug for this condition prior to [date of selinexor PBS listing]
	AND
	Clinical criteria:
	The treatment must be in combination with dexamethasone
	AND
	Clinical criteria
	AND
	Clinical criteria:
	Patient must have progressive disease after at least four prior lines of therapy, prior to initiating non-PBS subsidised therapy with this drug for this condition.
	AND
	Clinical criteria:
	Patient must have demonstrated refractory disease to prior treatments, prior to initiating non-PBS subsidised therapy with this drug for this condition, which must include: (i) a minimum of two proteasome inhibitors; and (ii) a minimum of two immunomodulatory agents; and (iii) an anti-CD38 monoclonal antibody
	AND
	Clinical criteria:
	Patient must not be receiving concomitant PBS-subsidised treatment with any of the following: (i) proteasome inhibitors, (ii) immunomodulators, (iii) anti-CD38 monoclonal antibody
	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
	Prescribing Instructions: Progressive disease is defined as at least 1 of the following: (a) at least a 25% increase and an absolute increase of at least 5 g per L in serum M protein (monoclonal protein); or (b) at least a 25% increase in 24-hour urinary light chain M protein excretion, and an absolute increase of at least 200 mg per 24 hours; or

	<p>(c) in oligo-secretory and non-secretory myeloma patients only, at least a 50% increase in the difference between involved free light chain and uninvolved free light chain; or</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>Prescribing Instructions: Oligo-secretory and non-secretory patients are defined as having active disease with less than 10 g per L serum M protein.</p>
	<p>Administrative Advice: Applications for authorisation under this restriction may be made in real time using the Online PBS Authorities system (see www.servicesaustralia.gov.au/HPOS) or by telephone by contacting Services Australia on 1800 888 333.</p>
	<p>Administrative Advice: No increase in the maximum number of repeats may be authorised.</p>
	<p>Administrative Advice: Special Pricing Arrangements apply</p>
	<p>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.</p>

- 3.2 The requested published prices presented in the resubmission were higher than in the July 2021 submission (7.1% for highly specialised drug [HSD] Public; 5.6% for HSD Private), whilst the effective price for selinexor in the resubmission was lower than the July 2021 submission (■% reduction). Consistent with the July 2021 submission, the resubmission proposed a special pricing arrangement (SPA) at a price approximately ■% lower than the published price.
- 3.3 No changes had been made to the wording of the requested restriction for Sd in the resubmission, noting that the restriction level had been changed from ‘streamlined’ (as per the July 2021 submission) to ‘authority required (telephone/electronic)’ as per the advice from the PBAC. In July 2021, the PBAC “considered that an Authority Required (telephone/electronic) listing would be more appropriate, given selinexor is a new chemical entity and a first-in-class medicine for which there is no prior experience on the PBS and given the potential safety concerns” (Para. 3.3, Selinexor (TCR/PR), PBAC Public Summary Document [PSD], July 2021 PBAC Meeting).

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

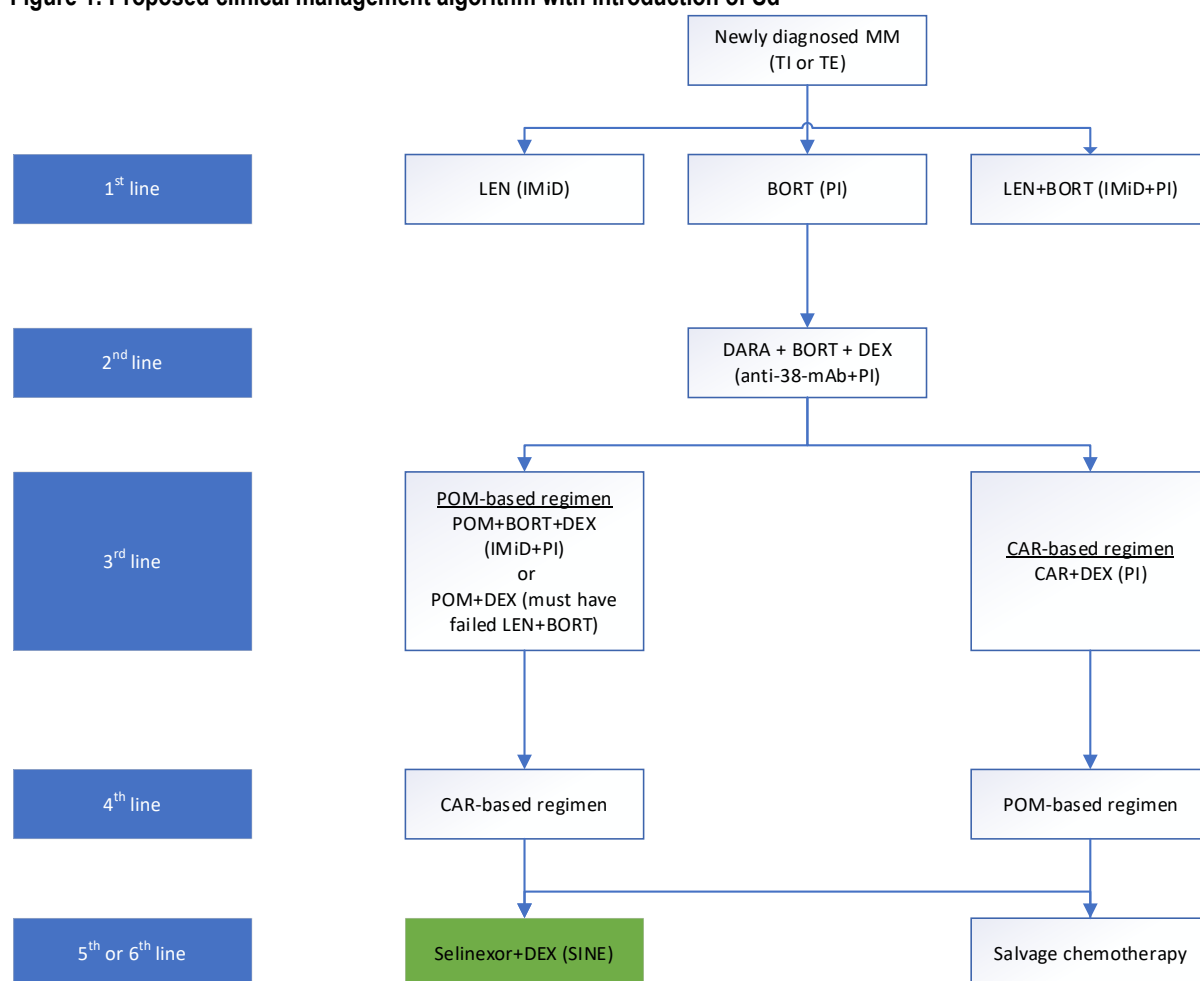
4 Population and disease

- 4.1 Multiple myeloma (MM) is a progressive, incurable haematologic cancer that undergoes genomic evolution over the course of the disease. It is a relatively uncommon cancer of plasma cells, accounting for approximately 1-2% of all cancers, and approximately 17% of haematological malignancies. MM patients diagnosed

between 2008 and 2012 showed a median overall survival (OS) of 6 years. For patients who have progressed to TCR/PR MM the median OS is only 5.6 months (Gandhi et al 2019). Most MM patients experience disease relapse and require further treatment options.

- 4.2 The clinical management algorithm for Sd as a treatment for TCR/PR MM was based on treatment guidelines including the US National Comprehensive Cancer Network (NCCN) clinical practice guidelines in oncology: MM, Version 3.2021 (Kumar et al., 2020), the European Hematology Association - the European Society Medical Oncology (EHA-ESMO) clinical practice guidelines (Dimopoulos et al., 2021), and the treatment guidelines from the Australian Medical Scientific Advisory Group (MSAG) (H. Quach et al., 2019).
- 4.3 The resubmission presented a proposed clinical management algorithm (Figure 1) which positioned selinexor as an alternative in the fifth or sixth line, consistent with the proposed restriction that to be eligible, a patient must have failed four prior lines of therapy.

Figure 1: Proposed clinical management algorithm with introduction of Sd



Source: Figure 1-5, p25 of the resubmission.

Abbreviations: BORT = bortezomib, CAR = carfilzomib, DARA = daratumumab, DEX = dexamethasone; IMiD = immunomodulators, LEN = lenalidomide; mAb = monoclonal antibodies; PI = proteasome inhibitors; POM = pomalidomide, Sd = selinexor + dexamethasone; SINE = selective inhibitor of nuclear export; TE = transplant eligible; TI = transplant ineligible.

Note: *carfilzomib and pomalidomide may not be available at first relapse

- 4.4 Selinexor is an oral, first-in-class, potent, selective inhibitor of nuclear export (SINE) compound that specifically blocks exportin 1 (XPO1). Inhibition of XPO1 leads, amongst other mechanisms, to the nuclear accumulation and activation of tumour suppressor proteins (TSP), which then initiate apoptosis in cancer cells. The resubmission stated that selinexor has demonstrated broad anti-tumour activities in patients with haematologic and solid tumour malignancies, many of which had previously been treated with all available standard anti-cancer agents, suggesting that XPO1 inhibition is a novel mechanism of action relevant to the treatment of diverse human cancers. The resubmission further claimed that this novel mechanism of action may provide significant benefit to patients who have already developed relapse or are refractory to currently available therapies.
- 4.5 The ESC noted that as an oral therapy, selinexor may offer benefits such as reduced need for clinic visits for drug administration, and that an oral therapy may be preferred, especially for end stage patients, compared with parenteral treatments.
- 4.6 The requested PBS listing for Sd was narrower than but consistent with the requested TGA indication and TGA approved selinexor product information, which states that selinexor should be used “In combination with dexamethasone for the treatment of adult patients with relapsed or refractory multiple myeloma (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)” (TGA approved selinexor product information).

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

5 Comparator

- 5.1 The resubmission nominated ‘salvage chemotherapy’ in the form of dexamethasone, cyclophosphamide, etoposide, and cisplatin (DCEP) as the main comparator. The nominated comparator was consistent with the July 2021 submission.
- 5.2 The PBAC previously considered that there was no standard therapy for patients with TCR/PR MM and considered that DCEP was representative of last-line care (Para. 7.4, Selinexor (TCR/PR), PBAC PSD, July 2021 PBAC Meeting). The clinical evidence presented in the resubmission compared Sd (TCR/PR population from STORM) to conventional chemotherapy from MAMMOTH. The PBAC, previously considered that there were applicability issues, where MAMMOTH did not represent the clinical outcomes of the proposed comparator (DCEP), but of conventional care (Para. 7.7,

Selinexor (TCR/PR), PBAC PSD, July 2021 PBAC Meeting). To address the applicability issue of the regimens used in MAMMOTH, the resubmission presented additional analyses comparing STORM with Goldsmith 2020 (previously presented in Section 3 of the July 2021 submission) in which 74% of PR MM participants were treated with DCEP. However, the dosing regimen of DCEP from Goldsmith 2020 was different to the regimen presented in the safety analysis and different again to that assumed for the economic and financial evaluations.

- 5.3 The ESC considered the nomination of DCEP as main comparator was reasonable and that variations in DCEP dosing across the trials were not likely to be clinically significant, especially at this line of therapy. The PBAC agreed with the ESC that the variations in DCEP dosing did not impact interpretation of the results.

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 TCR/PR MM as a critical area of unmet need in Australia, noting that the availability of more effective earlier lines of therapy is resulting in more patients surviving to a fourth relapse while maintaining good functional status. These patients require active therapy and palliation is not acceptable. The clinician described the benefits of Sd in patients with TCR/PR MM due to the novel mechanism of action of selinexor and described the GI side effects as manageable. The clinician had gained experience with selinexor through clinical trials and compassionate access programs, and spoke of the impact of even a minor response to these patients in terms of survival benefit. The clinician highlighted the importance of PBS access to improve equity of access, especially for patients unable to access clinical trials or compassionate access programs. The PBAC considered that the hearing was informative as it provided a clinical perspective on the potential use of Sd in Australian clinical practice.

Consumer comments

- 6.2 The PBAC noted and welcomed the input from individuals (6) and organisations (3) via the Consumer Comments facility on the PBS website. The comments from the individuals described the ongoing need for new treatment options for the management of RRMM and expressed concern about the cost of therapy if not PBS listed. Input from health professionals highlighted that selinexor is an oral therapy that can be administered away from hospital, and minimises COVID-19 infection risk associated with attendance at health care settings. Health professionals noted that adverse events such as nausea, anorexia, and thrombocytopenia are common, and may require dose modifications or treatment cessation. Individuals expressed a desire

to avoid heavy chemotherapy or stem cell transplant (SCT) at relapse. Input from individuals with personal experience taking selinexor described the gastrointestinal side-effects as less severe than those with chemotherapy.

- 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 the ongoing clinical need for new therapies for RRMM, and supported the proposed listing for Sd based on the efficacy and safety profile demonstrated in the STORM study. The MSAG described the adverse events as transient and reversible, and noted that Sd would be a therapeutic option for those who have exhausted all other options.

Clinical studies

- 6.4 As for the July 2021 submission, the resubmission was based on one single arm study, STORM Part 2 (N = 122 for the modified intention to treat population). STORM Part 2 enrolled patients who had previously received ≥ 3 anti-MM regimens (lenalidomide, pomalidomide, bortezomib, carfilzomib, or daratumumab; penta-exposed) and had triple-class-refractory MM (refractory to glucocorticoids, at least 1 IMiD, at least 1 PI or anti-CD38 mAb daratumumab; pp26,78 STORM CSR).
- 6.5 Clinical results relevant to the requested listing (TCR/PR MM) were based on a subgroup of patients in STORM (N = 83). These patients represent the patients in the requested listing i.e., TCR/PR MM. This efficacy population (known as the BCLPD-ref population in STORM) was defined as “patients in the mITT population refractory to bortezomib, carfilzomib, lenalidomide, pomalidomide, and daratumumab” (Table 9, p54, STORM CSR). The PBAC previously considered that there were applicability issues in that the triple-class refractory penta-exposed (TCR/PE) population, which formed the basis of the clinical comparison in the July 2021 submission, was not consistent with the PBS-proposed population (Para. 7.7, Selinexor (TCR/PR), PBAC PSD, July 2021 PBAC Meeting). The resubmission provided an updated naïve comparison of Sd versus salvage chemotherapy using the TCR/PR population from STORM (n = 83). Unless otherwise stated all further references to STORM refer to the TCR/PR subgroup.
- 6.6 The resubmission provided naïve comparisons of STORM with two retrospective studies. These studies provided OS and progression free survival (PFS) data on the TCR/PR population in patients treated with DCEP and/or conventional care:
- Goldsmith 2020 (N = 58) was presented in the July 2021 submission as supportive evidence in Section 3. Data from Goldsmith 2020 was compared with the TCR/PR subgroup from STORM in the resubmission. Goldsmith 2020 was a single arm, single-centre study of patients who received DCEP (n = 31), of which 74% of the patients were TCR/PR.

- Results from MAMMOTH (N=275; TCR/PE) were utilised in the indirect comparison presented in the July 2021 submission. The resubmission stated that the analysis was criticised for using the TCR/PE cohort, and so to address the applicability of the population to the requested listing, data from Gandhi 2019 (previously presented in Section 3 of the July 2021 submission) based on the TCR/PR cohort (n = 70) of MAMMOTH formed the basis of the comparison with STORM. Unless otherwise specified all further references to MAMMOTH refer to the TCR/PR subgroup.

6.7 Details of the studies presented in the submission are provided in Table 3.

Table 3: Trials and associated reports presented in the submission

Trial ID	Protocol title/ Publication title	Publication citation
STORM NCT02336815 EUCTR2016-003094-18-DE	Clinical Study Report: Study KCP-330-012 (STORM study): Phase 2b study of selinexor plus low dose dexamethasone treatment in patients with penta-refractory RRMM [Phase 2b STORM study] – addresses patients with heavily pre-treated relapsed refractory multiple myeloma (RRMM)	The CSR. 2019 Nov.
	Chari A, Vogl DT, Gavriatopoulou M, et al. Oral Selinexor-Dexamethasone for Triple-Class Refractory Multiple Myeloma.	N Engl J Med. 2019 Aug 22;381(8):727-738.
	Vogl DT, Dingli D, Cornell RF, et al. Selective Inhibition of Nuclear Export With Oral Selinexor for Treatment of Relapsed or Refractory Multiple Myeloma.	J Clin Oncol. 2018 Mar 20;36(9):859-866.
Goldsmith 2020	Goldsmith, S. R., Fiala, M. A., Wang, B., et al. DCEP and bendamustine/prednisone as salvage therapy for quad- and penta-refractory multiple myeloma.	Annals of Hematology. 2020 Mar 99(5), 1041–1048.
Gandhi 2019 (MAMMOTH)	Gandhi, U. H., Cornell, R. F., Lakshman, A., et al. Outcomes of patients with multiple myeloma refractory to CD38-targeted monoclonal antibody therapy.	Leukemia, 2019 Mar 33(9), 2266–2275.

Source: Table 2-5, pp39-41 and pp42-43 of the resubmission, Blue shading denotes text remains unchanged from the July 2021 submission.

6.8 The key features of the studies are summarised in Table 4.

Table 4: Key features of the included evidence

Trial	N	Design/ duration	Risk of bias	Patient population	Outcomes	Use in modelled evaluation
Sd						
STORM	122 ^a	Single arm	High	TCR/PE MM	OS, PFS, ORR	Not used
	83 ^b			TCR/PR MM		OS
Conventional care						
Gandhi 2019 (MAMMOTH)	70	Retrospective	High	TCR/PR MM	OS, ORR	OS
Goldsmith 2020	31 ^c	Retrospective (single-centre)	High	QR and PR MM treated with DCEP ^d	ORR	Not used

Source: Developed during the evaluation (risk of bias in all studies was assessed using ROBINS I)

Abbreviations: BCLPD-ref = refractory to bortezomib, carfilzomib, lenalidomide, pomalidomide, and daratumumab; DCEP = dexamethasone + cyclophosphamide + etoposide + cisplatin; MM = multiple myeloma; ORR = overall response rate; OS = overall survival; PFS = progression-free survival; PR = penta-refractory; QR = quad refractory; Sd = selinexor + dexamethasone; TCR/PE MM = triple class refractory and penta-exposed multiple myeloma; TCR/PR MM = triple class refractory and penta-refractory multiple myeloma

Notes: ^a modified intent to treat population

^b TCR/PR population (known as the BCLPD-ref population in STORM)

^c total trial population = 58, but results of patients who had received DCEP (n = 31) formed the basis of the naïve comparison

^d QR MM were patients refractory to bortezomib, carfilzomib, lenalidomide, and pomalidomide, and PR MM patients had additional refractoriness to daratumumab

Blue shading denotes text remains unchanged from the July 2021 submission.

6.9 The overall risk of bias in STORM was high, given that it was an open-label, single arm non-randomised study. This includes a high probability of selection bias (exclusion of patients might favour clinical outcomes), performance bias (unblinded study), and potential measurement of outcome bias (unblinded study). The primary outcome of disease response was adjudicated by an independent review committee of four physicians and the outcome measures of response and disease progression were objective measures that were defined by pre-specified criteria (Para. 6.11, Selinexor (TCR/PR), PBAC PSD, July 2021 PBAC Meeting). The risk of bias in MAMMOTH and Goldsmith 2020 was also high given they were both retrospective single-arm studies. Limited information regarding methods and characteristics of patients were available for these studies.

6.10 Overall, a comparison of baseline characteristics of patients between the three studies was limited due to inadequate information from MAMMOTH and Goldsmith 2020. However, the following differences are of note:

- The median age of patients in STORM was higher (65.3 years) compared to MAMMOTH and Goldsmith (60 and 58.5 years respectively).
- Patients in STORM had a longer time since the initial diagnosis of the disease compared with MAMMOTH and Goldsmith 2020 (median = 7.0 years versus 5.7 years, 4.5 years respectively).
- A lower proportion of patients in STORM (12.0%) had an International Staging System (ISS) disease stage of I compared to MAMMOTH and Goldsmith 2020 (29% and 24.3% respectively; with a higher stage indicating more advanced disease), where STORM had a higher proportion of patients with stage II disease (67.5%) compared to MAMMOTH and Goldsmith 2020 (39% and 34.3%) whilst stage III disease was similar across the three studies. The resubmission considered that the ISS stage at baseline were comparable across the three studies however this was based on patients with known status where the number of unknowns were removed (16 patients; 22.8% from MAMMOTH and 5 patients; 16.1% from Goldsmith 2020 had unknown ISS staging).
- Patients in STORM and Goldsmith 2020 had a median of 8 prior therapies whilst patients in MAMMOTH had a median of 5 prior therapies.
- Patients in MAMMOTH and Goldsmith 2020 were required to have progressive disease (but not in STORM; STORM required patients to be refractory to previous therapy, defined as $\leq 25\%$ response to therapy or progression within 60 days after completion of therapy).
- Despite having late-stage MM, patients in STORM appeared to have a good Eastern Cooperative Oncology Group Performance status (ECOG-PS) score of 0 or

1 (32.5% and 56.6% respectively). There was no information about ECOG-PS score in MAMMOTH and Goldsmith 2020.

- For all three studies there were no details specifying which drug was used at each line of treatment and it is unclear whether the sequence of prior therapies may impact on response to subsequent therapies, especially in advanced MM where patients have been heavily pre-treated.

- 6.11 The ESC considered that STORM was conducted in a group of patients that had been relatively poorly studied to date, and noted that in clinical practice, younger patients were more likely to seek fifth line treatment compared with older patients. The ESC had previously considered that the longer time between initial diagnosis and enrolment into a study reflected a better disease prognosis in the STORM population compared with that in MAMMOTH (Para. 6.12 and 6.13 PSD, Selinexor, July 2021 PBAC Meeting). The ESC considered that additional characteristics including age, comorbidities and previous therapies were also relevant to the comparison of the populations.
- 6.12 In STORM, 50% (61/122) of mITT patients received subsequent treatments (Chari et al., 2019). The majority of patients (70.5%) received PIs, IMiDs, daratumumab or chemotherapy. Subsequent treatments received by patients in MAMMOTH and Goldsmith 2020 were not available to the PBAC in July 2021. The resubmission presented data on the proportion of patients receiving subsequent treatment following the index treatment in MAMMOTH showing that 63% (158/249) of patients received subsequent treatment. This was derived from the overall study population and not the TCR/PR subgroup (N=70) and no further detail was available on the subsequent therapies in MAMMOTH for comparison. The ESC considered that the role of subsequent treatments in STORM was uncertain and noted that comparisons across studies were limited by missing data for the comparator studies.
- 6.13 The resubmission did not define the dosing regimen for DCEP, and variations were seen across the trials presented in the resubmission (see Table 5).

Table 5: Dosing regimen for DCEP presented within the resubmission

Source		DCEP Dosing Regimen
Efficacy claim	Goldsmith 2020	dexamethasone 40 mg D1-4, cyclophosphamide 400 mg/m ² D1-4, cisplatin 10 mg/m ² D1-4 etoposide 40 mg/m ² D1-4 per 28-day cycle
Safety claim	Yuen 2018 ^a	dexamethasone 40 mg D1-4 cyclophosphamide 300 mg/m ² D1-4 cisplatin 15 mg/m ² D1-4 etoposide 30 mg/m ² D1-4 per 28-day cycle
	Griffin 2015	dexamethasone 40 mg D1-4 cyclophosphamide 400 mg/m ² D1-4 cisplatin 15 mg/m ² D1-4 etoposide 30 mg/m ² D1-4 per 28-day cycle
Resubmission	Section 3 – economic evaluation and Section 4 – financial estimates	dexamethasone 40 mg D1-4 cyclophosphamide 300 mg/m ² D1-4 cisplatin 15 mg/m ² D1-4 etoposide 30 mg/m ² D1-4 per 28-day cycle

Source: developed during the evaluation; TCRPR Section 3 November 2021 worksheet; p1042, Goldsmith et al 2020; p2843 Yuen et al 2018; p2623 Griffin et al 2015

Abbreviations: D = days; DCEP = dexamethasone + cyclophosphamide + etoposide + cisplatin; mg = milligrams; m = meters

Notes: ^a Yuen 2018 formed the basis of the clinical input into the economic evaluation and financial estimates

6.14 The resubmission presented results from two additional studies (presented in Section 3 of the July 2021 submission) to inform a naïve comparison of safety.

- Yuen 2018 (N = 62): consisted of a retrospective review of patients with RRMM who received DCEP chemotherapy between 2005 and 2017 at two tertiary hospitals in Melbourne, Australia. TRAEs were reported per cycle where the total number of cycles reported were 111 (pp2842-3, 5, Yuen et al 2018).
- Griffin 2015 (N = 107): was based on a single-centre retrospective analysis of 107 patients with RRMM who were treated with 3 salvage chemotherapy regimens including DCEP (n = 52), bortezomib + thalidomide + dexamethasone + cisplatin + doxorubicin + cyclophosphamide + etoposide (VTD-PACE; n = 22) and cyclophosphamide + vincristine + doxorubicin + dexamethasone (CVAD; n = 33; p3622, Griffin et al 2015). Griffin 2015 reported clinically relevant adverse events with no adverse event grading.

Comparative effectiveness

6.15 A summary of effectiveness results of Sd from STORM for the mITT population (TCR/PE MM) is presented in Table 6. Results from the TCR/PR subgroup of STORM are presented in Table 7.

Table 6: Summary of OS, PFS and ORR in STORM (TCR/PE population)

	mITT (N = 122)
OS	
Patients with event	76/122 (62.3%)
Median OS months (95% CI)	8.4 (6.2, 11.2)
PFS	
Patients with event	51/122 (41.8%)
Median PFS months (95% CI)	3.7 (2.8, 4.7)
ORR	
Patients with event	32/122
% (95% CI)	26.2 (18.7, 35.0)

Source: Table 2-19, 2-25, 2-26 pp62,68,70 of the resubmission

Abbreviations: CI = confidence interval; mITT = modified intention to treat population; PFS = progression free survival; ORR = overall response rate; OS = overall survival; TCR/PE = triple-class refractory/penta-exposed

Blue shading denotes text remains unchanged from the July 2021 submission.

6.16 In the mITT population of STORM (TCR/PE population), the ORR was 26.2%, median PFS was 3.7 months (95%CI; 2.8, 4.7) and median OS was 8.4 months (95%CI; 6.2, 11.2). While there appears to be a levelling out of the OS Kaplan-Meier curve after approximately 12 months (Figure 2), suggesting a low death rate beyond 12 months, the magnitude of the benefit should be interpreted with caution due to the small patient numbers and high rates of censoring.

6.17 A summary of the results from the TCR/PR subgroup of STORM and the naïve comparative results from the post-hoc analyses with MAMMOTH and Goldsmith 2020 are presented in Table 7. The submission did not provide any estimate of effects between the three studies and these were not able to be calculated by the evaluation given the available data.

Table 7: Summary of OS, PFS and ORR for Sd versus salvage chemotherapy for the TCR/PR population

	Sd STORM (N = 83)	Salvage Chemotherapy	
		DCEP Goldsmith 2020 (N = 31) ^a	Conventional care MAMMOTH (N = 70)
OS			
Median OS (months)	8.4	6.2	5.6
95% CI	5.9, 11.2	4.4, 7.8	3.5, 7.8
PFS			
Median PFS (months)	2.8	2.7	NR
95% CI	1.9, 4.3	1.5, 3.8	NR
ORR			
ORR	25.3%	35%	30%

Source: Table 2-39,2-40,2-41 p98-100 of the resubmission

Abbreviations: CI = confidence interval; HR = hazard ratio; DCEP = dexamethasone + cyclophosphamide + etoposide + cisplatin; NR = not reported; ORR = overall response rate; OS = overall survival; PFS = progression free survival; Sd = selinexor + dexamethasone; TCR/PR = triple class refractory and penta-refractory

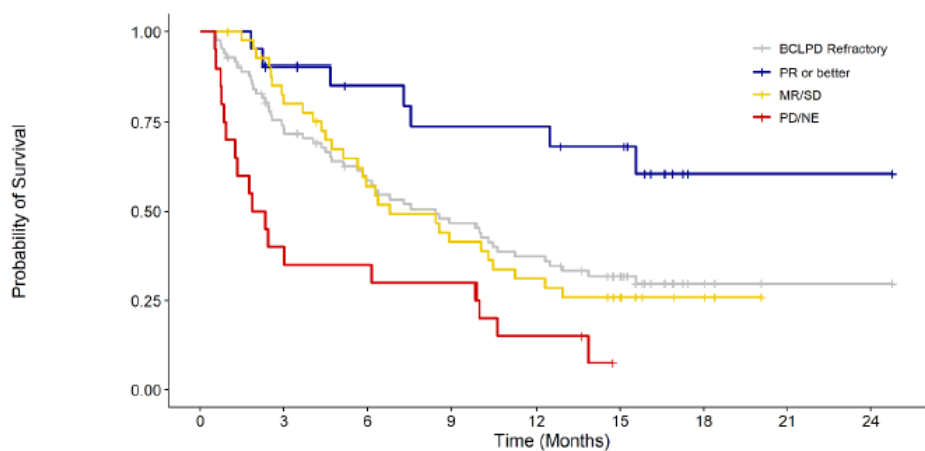
Note: ^a 23/31 (74%) of patients receiving DCEP were penta-refractory

Blue shading denotes text remains unchanged from the July 2021 submission.

6.18 The Kaplan-Meier (KM) plot for OS for Sd by level of response and PFS for the TCR/PR population in STORM is shown in Figure 2.

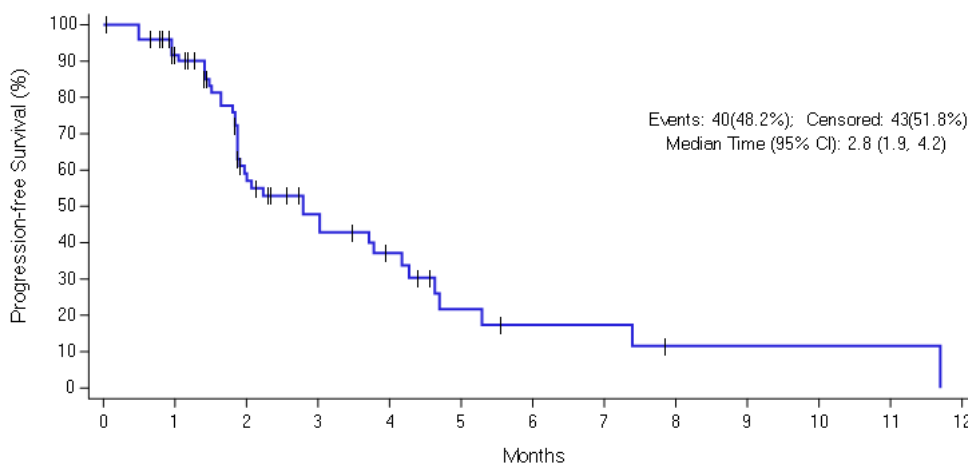
Figure 2: KM estimates of OS by response (A) and PFS (B) of the TCR/PR population in STORM

(A) OS by response



Number at risk		0	3	6	9	12	15	18	21	24
BCLPD Refractory	83	58	44	35	28	19	4	1	1	1
PR or better	21	18	15	13	13	11	1	1	1	1
MR/SD	42	32	22	16	12	8	3	0	0	0
PD/NE	20	8	7	6	3	0	0	0	0	0

(B) PFS



Subjects at Risk		0	1	2	3	4	5	6	7	8	9	10	11	12
Total	83	58	29	19	11	5	3	3	1	1	1	1	1	0

Source: Figure 2-10, p71 of the resubmission; Figure 2-8, p69 of the resubmission.

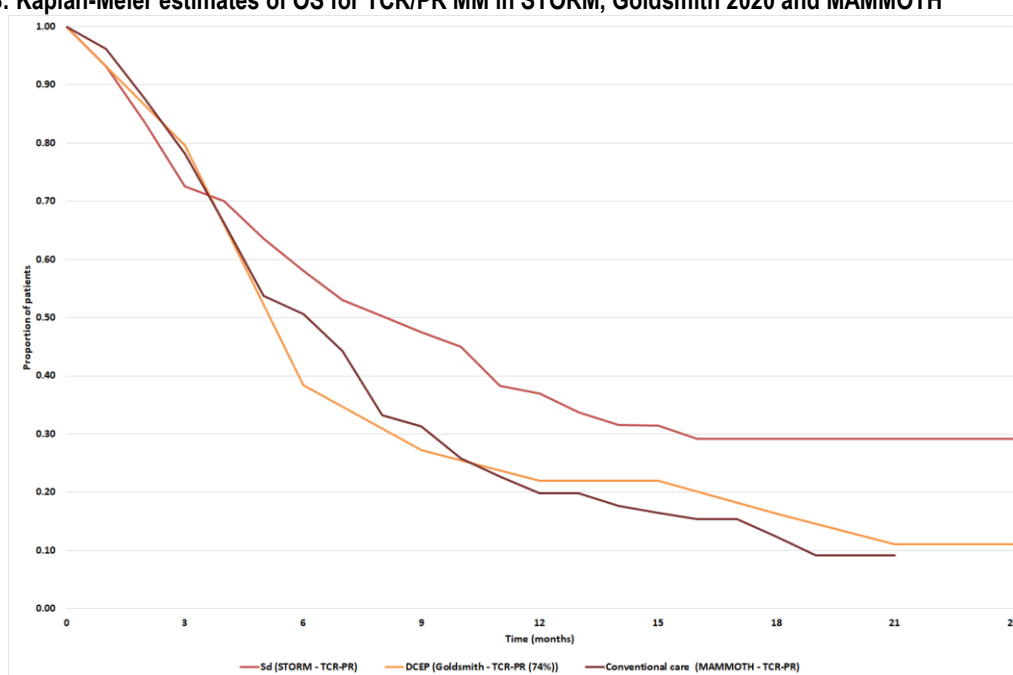
Abbreviations: BCLPD refractory = TCR/PR refractory; MR = minimal response; NE = not estimable/evaluable; OS = overall survival; PD = progressive disease; PFS = progression free survival; PR = partial response; SD = stable disease.; TCR/PR = triple class refractory and penta-refractory.

6.19 The median OS for TCR/PR patients treated with Sd from STORM was 8.4 months (95% CI: 5.9, 11.2) compared to 6.2 months (95% CI: 4.4, 7.8) for patients treated with DCEP (Goldsmith 2020) and 5.6 months (95% CI: 3.5, 7.8) for conventional care (MAMMOTH). The confidence interval was broader in STORM compared to Goldsmith

2020 and MAMMOTH and overlapped with these studies. The ESC noted that the data suggested longer OS with Sd compared with DCEP in the TCR/PR population, however the role of subsequent lines of therapy in STORM was unclear (see paragraph 6.9).

- 6.20 The median PFS for TCR/PR patients treated with Sd (STORM) was 2.8 months (95% CI: 1.9, 4.3) compared to 2.7 months (95% CI: 1.5, 3.8) for DCEP (Goldsmith 2020). The comparison between STORM and Goldsmith 2020 does not suggest any benefit in PFS of Sd compared to DCEP. The median PFS for the TCR/PR population from MAMMOTH was not available. The ESC noted that the median PFS appeared similar for selinexor and DCEP in the TCR/PR population based on the evidence presented.
- 6.21 The resubmission stated that as approximately 74% of patients in Goldsmith 2020 were TCR/PR (i.e., 26% of patients were quad-refractory i.e., not refractory to daratumumab) the median OS and PFS may be overestimated. Furthermore, the resubmission stated that as the median follow-up in the MAMMOTH TCR/PR subset and in Goldsmith 2020 was not reported, thus compromising the comparison of ORR.
- 6.22 The KM plot for OS for the TCR/PR population in STORM, Goldsmith 2020 and MAMMOTH is presented in Figure 3 and the KM plot for PFS for the TCR/PR population in STORM and Goldsmith 2020 in Figure 4.

Figure 3: Kaplan-Meier estimates of OS for TCR/PR MM in STORM, Goldsmith 2020 and MAMMOTH

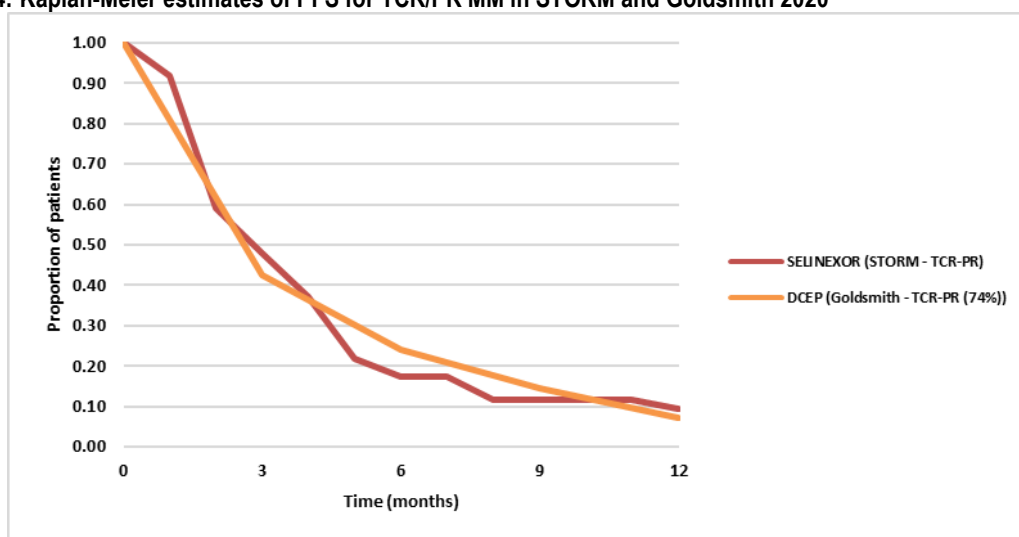


Source: Figure 21, p98 of the resubmission.

Abbreviations: DCEP = dexamethasone + cyclophosphamide + etoposide + cisplatin; OS = overall survival; Sd = selinexor + dexamethasone; TCR/PR MM = triple class refractory and penta-refractory multiple myeloma

Note: 23/31 (74%) of patients receiving DCEP were penta-refractory

Figure 4: Kaplan-Meier estimates of PFS for TCR/PR MM in STORM and Goldsmith 2020



Source: Figure 22, p99 of the resubmission.

Abbreviations: DCEP = dexamethasone + cyclophosphamide + etoposide + cisplatin; PFS = progression free survival; TCR/PR MM = triple class refractory and penta-refractory multiple myeloma

Note: 23/31 (74%) of patients receiving DCEP were penta-refractory

6.23 A naïve comparison of OS estimates and visual comparison of the OS KM curves in STORM compared to both Goldsmith 2020 and MAMMOTH suggest that patients that received Sd had longer OS than patients that received DCEP. However, the ability to draw any conclusions from the comparison of STORM with Goldsmith 2020 and MAMMOTH was limited for the following reasons:

- The number of patients with events were not available for estimate of effects to be calculated during the evaluation. This along with the retrospective and observational study design of Goldsmith 2020 and MAMMOTH make the results difficult to interpret.
- The patient population in Goldsmith 2020 were slightly different from the STORM patient population, i.e., 74% of patients were penta-refractory (consistent with the PBS population) whilst the remainder of patients were quad-refractory (i.e., not refractory to daratumumab and therefore inconsistent with the requested PBS population). Whilst patients in STORM appeared to be healthier and/or had less advanced disease than MAMMOTH.
- Conventional care in MAMMOTH appeared to consist of therapies not available in Australia for this MM population, such as daratumumab (19.5%).
- Goldsmith 2020 was based on a single-centre retrospective analysis with small patient numbers. Furthermore, the dosing regimen of DCEP used in this study was different to that considered in the economic evaluation and financial estimates of the resubmission (see Table 5) and thus it is unclear what the impact of variation

in DCEP dosing would have on the clinical outcomes. The ESC considered that differences in DCEP dosing were not clinically meaningful.

- 6.24 The Pre-Sub-Committee Response (PSCR) stated that the naïve ITC provided in the resubmission represented an improvement on the ITC presented in the original submission with data specific to the proposed PBS population compared. The PSCR maintained that the visual comparison of survival curves (Figure 3) adequately supports a conclusion of superiority of Sd vs salvage chemotherapy in the context of a naïve comparison. The ESC considered that the comparison was hampered by small patient numbers in the trials, noting that this group of patients has been relatively poorly studied to date compared with other lines of MM. The ESC also considered that patients corresponding to the proposed PBS listing, those seeking fifth line treatment, are uncommon in clinical practice.

Comparative harms

- 6.25 A summary of treatment-emergent adverse event (TEAEs) in the safety analysis population (TCR/PE MM) of STORM is presented in Table 8. Three deaths occurred that were as a result of adverse events that were treatment related.

Table 8: Overall summary of treatment-emergent adverse events in STORM

Patients with at least 1 event by category	SAP (N = 123) n (%)
All causality^a	
TEAE	123 (100)
Grade 3 or 4 TEAE	115 (93.5)
TESAE	78 (63.4)
TEAE leading to dose modification	97 (78.9)
TEAE leading to dose hold	80 (65.0)
TEAE leading to dose reduction	72 (58.5)
TEAE leading to treatment discontinuation	39 (31.7)
TEAE with an outcome of death	12 (9.8)
Treatment related^b	
TEAE	121 (98.4)
Grade 3 or 4 TEAE	110 (89.4)
TESAE	38 (30.9)
TEAE leading to dose modification	88 (71.5)
TEAE leading to dose hold	64 (52.0)
TEAE leading to dose reduction	70 (56.9)
TEAE leading to treatment discontinuation	24 (19.5)
TEAE with an outcome of death	3 (2.4)

Source: Table 2-29, p75 of the resubmission.

Abbreviations: SAP = safety analysis population; TEAE = treatment-emergent adverse event; TESAE = serious TEAE

Note: ^a 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.

^b TEAEs with a relationship of Possible, Probable, or Definite to either selinexor or dexamethasone per Investigator are considered related to study treatment.

Note: Percentages are based on the number of all-treated patients in each treatment group. A TEAE is defined as an AE that emerged or worsened from first dose to 30 days after last dose.

Blue shading denotes text remains unchanged from the July 2021 submission.

6.26 A summary of the safety results from the TCR/PR subgroup of STORM and results from Yuen 2018 and Griffin 2015 are presented in Table 9. The ESC agreed with the resubmission, that data from Yuen 2018 and Griffin 2015 populations were not necessarily directly applicable to the TCR/PR population, yet nevertheless provided safety data for the comparator regimen DCEP, in heavily pre-treated MM patients. Yuen 2018 (two-centres) and Griffin 2015 (single-centre) were both retrospective studies of patients with RRMM who had received DCEP.

Table 9: Summary of naïve safety comparison of Grade ≥ 3 TEAE for Sd versus DCEP

Adverse event	Sd STORM TCR/PR n/N (%)	DCEP Yuen 2018 Events/cycles (%)	DCEP Griffin 2015 n/N (%)
N	83	62 ^c (Cycles = 111)	52
Asthenia	6/83 (7.2)	NR	NR
Diarrhoea	6/83 (7.2)	NR	NR
Fatigue	17/83 (20.5)	NR	NR
Febrile neutropenia	1/83 (1.2)	32/111 (28.8)	15/52 (28.8) ^e
Neutropenia	20/83 (24.1)	78/111 (70.3)	NR
Hyponatraemia	19/83 (22.9)	NR	NR
Leukopenia	15/83 (18.1)	NR	NR
Nausea	9/83 (10.8)	NR	NR
Pneumonia	5/83 (6.0)	NR	NR
Sepsis	7/83 (8.4)	NR	NR
Thrombocytopenia	52/83 (62.7)	48/111 (43.2)	NR
Venous thromboembolism	NR	NR	3/52 (5.8) ^e
Anaemia	40/83 (48.2) ^a	50/111 (45.0)	NR
Mortality due to treatment	3/123 (2.4) ^b	6/62 (9.7) ^d	3/52 (5.8)

Source: Table 2-29,2-42, pp75,101 of the resubmission; Yuen et al 2018

Abbreviations: AE = adverse event; DCEP = dexamethasone + cyclophosphamide + etoposide + cisplatin; FN = febrile neutropenia; N = number of participants; n = number of participants with event; NR = not reported; SAP = safety analysis population; Sd = selinexor + dexamethasone; TCR/PR MM = triple class refractory and penta-refractory multiple myeloma; TEAE = treatment emergent adverse event
Note: ^a the resubmission reported anaemia as 55 (44.7%) however this was corrected in the table as per Table 6.2.1a from the reference provided by the resubmission

^b the resubmission reported the number of mortalities due to treatment for STORM as 2/123 (1.6%) indicative of the SAP population, however this was inconsistent with the results presented in Table 2-29 p75 of the resubmission

^c the resubmission reported the total number of patients as 58, Yuen 2018 stated that 62 patients were included in the study of which 58 patients (93.5%) had refractory disease to prior treatment.

^d the resubmission stated that the number of mortalities due to treatment for Yuen 2018 as 5/58 (8.6%) however, according to Yuen 2018, 5 deaths were associated with FN and one patient died from pneumonia without sepsis, and that rate of treatment related mortality was 9.7% (i.e. 6/62 deaths).

^e Griffin 2015 did not report Grade ≥ 3 TEAE, rather refers to clinically relevant AEs.

Blue shading denotes text remains unchanged from the July 2021 submission.

6.27 The safety comparison was limited to febrile neutropenia, neutropenia, thrombocytopenia, anaemia and death due to treatment given the lack of data reported in the studies by Yuen 2018 and Griffin 2015. Yuen 2018 reports event rates per cycles, whereas STORM and Griffin 2015 report the proportion of patients experiencing an AE. A lower proportion of patients on Sd experienced febrile neutropenia (1.2% vs 28.8% in both studies), and neutropenia (24.1% vs 70.3% in Yuen 2018). Conversely, the rate of thrombocytopenia per cycle with DCEP was lower than

the proportion of patients with Sd that experienced thrombocytopenia (43.2% in Yuen 2018 vs 62.7% in STORM).

- 6.28 Overall, the Commentary stated that the safety claim made by the resubmission was inconclusive based on the following issues:
- AEs in STORM and Griffin 2015 were reported as number of patients experiencing an AE event, whilst results from Yuen 2018 were reported as AE events arising per cycle of DCEP. It is unclear from Yuen 2018 as to the number of cycles each patient received and whether reported AEs were experienced several times by the one patient or by multiple patients. Whilst the former would have only been counted once by STORM and Griffin 2015, these would have been counted per incidence in Yuen 2018 thus potentially biasing results against Yuen 2018.
 - STORM and Yuen 2018 presented the number of Grade ≥ 3 treatment emergent AEs, whilst Griffin 2015 referred to clinically relevant AEs, potentially biasing results against Griffin 2015 where all clinically relevant AEs (irrespective of severity) may have been reported.
 - The majority of patients from Yuen 2018 received DCEP with the addition of thalidomide (56%) or lenalidomide (18%; p2843, Yuen et al 2018) and two patients received bortezomib and thalidomide with DCEP; whilst four of the 52 patients from Griffin 2015 receiving DCEP were treated with additional thalidomide (p3625, Griffin 2015).
 - The resubmission stated that data from the DCEP studies were not necessarily directly applicable to the TCR/PR population but provided safety data from the comparator regimen in a heavily pre-treated MM population. Differences in baseline disease characteristics may have potentially impacted the incidence and severity of AEs. For example, patients who were more heavily pre-treated and more advanced in disease are more likely to experience AEs in general compared to healthier patients.
- 6.29 The ESC noted that the majority of Grade ≥ 3 adverse events with Sd were thrombocytopenia (which the ESC considered are usually manageable for patients in the care of a haematologist), and there were relatively few febrile neutropenia complications (Table 9). The ESC considered that thrombocytopenia is less resource intensive and more easily managed compared with febrile neutropenia.
- 6.30 The PBAC noted that STORM measured QoL using the FACT-MM instrument. Data from the supplementary appendix indicated a numerical decline in QoL scores during STORM. The PBAC considered it was common for QoL to not improve in RRMM studies as patients are often treated at biochemical rather than symptomatic relapse, although a decline in QoL may be associated with treatment-related adverse events.

Further discussion on this topic has been published by Chakraborty & Efficace (2020)¹, and Tremblay et al. (2021)².

Benefits/harms

- 6.31 The naïve comparisons presented in the submission did not allow for a quantitative comparison of the benefits and harms of Sd and DCEP. Accordingly, a benefits/harms table has not been presented.

Clinical claim

- 6.32 The resubmission described Sd as superior in terms of effectiveness compared to salvage chemotherapy in (represented by DCEP) in terms of OS. This was based on the naïve comparison of Sd versus salvage chemotherapy from the TCR/PR population of STORM, Goldsmith 2020 and MAMMOTH. The ESC considered that the resubmission's claim that Sd was superior to DCEP in terms of OS was likely reasonable, based on the point estimates in the naïve comparison (Table 7), however uncertainties remained due to limitations of the naïve comparison (see paragraphs 6.23 and 6.24).
- 6.33 The submission described Sd as at least non-inferior in terms of safety compared to DCEP. The ESC considered that Sd may be safer than cytotoxic chemotherapy regimens including DCEP, noting there were few febrile neutropenia events reported with Sd, however a claim of superior safety was not supported by the data presented in the resubmission, noting there was no direct evidence to support this. The ESC considered that the claim that Sd is at least non-inferior to DCEP in terms of safety was reasonable.
- 6.34 The PBAC considered that the magnitude of the effect on overall survival was uncertain and difficult to determine due to the limitations of the available clinical evidence, however the claim of superior comparative effectiveness of Sd compared with DCEP was reasonable in the context of significant unmet need in a small patient population. The PBAC noted that the proposed PBS listing of Sd for TCR/PR MM includes some patients who have exhausted all available treatment options.
- 6.35 The PBAC noted that additional evidence regarding the use of selinexor was provided in Item 7.10 (March 2022 PBAC meeting). Item 7.10 referred to a request for PBS listing of selinexor in combination with bortezomib and dexamethasone (SBd) for the treatment of adult patients with relapsed and/or refractory multiple myeloma (RRMM) who have received at least one prior therapy. The PBAC noted that the SBd submission reported the results of the BOSTON trial³, a randomised phase 3 trial

¹ Chakraborty R, Efficace F. Importance of quality of life in early phase clinical trials: A case study of selinexor in multiple myeloma. *Br J Haematol*. 2020 May;189(3):e112-e113.

² Tremblay G, et al. Quality of life analyses in patients with multiple myeloma: results from the Selinexor (KPT-330) Treatment of Refractory Myeloma (STORM) phase 2b study. *BMC Cancer*. 2021 Sep 6;21(1):993.

³ Grosicki S, et al. Once-per-week selinexor, bortezomib, and dexamethasone 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.

comparing SBd with bortezomib and dexamethasone (Bd) for the treatment of patients with RRMM who had previously been treated with one to three lines of therapy (n=402).

- 6.36 The PBAC considered that the claim of non-inferior safety was reasonable, but noted the uncertainty associated with single-arm data and the unanchored naïve indirect comparison.

Economic analysis

- 6.37 The resubmission presented a modelled economic evaluation based on a naïve comparison of two non-randomised studies (STORM vs MAMMOTH). The type of economic evaluation presented was a CUA. The PSCR acknowledged the uncontrolled nature of the clinical evidence upon which the model is based and stated that the resubmission had sought to address all of PBAC’s concerns as outlined in the July 2021 PBAC PSD, including provision of a revised economic model which was conservative in its assumptions, together with a reduced ICER.
- 6.38 A summary of key components of the economic evaluation is presented in Table 10.

Table 10: Key components of the economic evaluation

Component	Description	Justification/comments
Type of model	Cost-utility analysis	The ESC considered that the cost-utility analysis was difficult to interpret due to the unadjusted clinical data used to populate the model.
Outcomes	QALY gained	Appropriate
Time horizon	5 years	Appropriate. The PBAC previously considered a 5-year time horizon would be more appropriate than 7 years (Para. 6.38, Selinexor (TCR/PR), PBAC PSD, July 2021 meeting).
Method used to generate results	Partitioned survival model incorporating a cohort expected value analysis	The PBAC previously considered that the use of PSA model structure was inherently uncertain (Table 9, Selinexor (TCR/PR), PBAC PSD, July 2021 PBAC meeting).
Health states	Progression free, progressive disease, and death	Appropriate
Cycle length	1 week	Appropriate
Transitional probabilities (area under the curve)	Based on KM curves from STORM and MAMMOTH and extrapolation. Data from KM curves were used up to the time point at which 20% of patients remained at risk. After that the results from extrapolation were applied. Log-normal distribution was chosen for OS of Sd and DCEP, PFS of Sd and TTD of Sd. DCEP was fixed for 2 cycles of treatment. The model assumed convergence of the OS curves after 48-months.	The use of KM curves appears appropriate. Approaches for the extrapolation were inadequately justified.
Health utility values	Derived using existing regression equation estimating utility values of RRMM patients based on NIMBUS trial. Data from STORM, MAMMOTH and Yuen 2018 were applied to obtain treatment-specific utility values.	The equation was developed based on patients that had less advanced disease (have had at least two prior treatment regimens in NIMBUS) compared to the proposed population. This equation has been considered by the PBAC before (July 2019 plitidepsin submission and July 2021 selinexor submission).
Software	Excel 2010	Appropriate

Source: Table 3-1, pp112-113 of the resubmission.

Abbreviations: DCEP = dexamethasone, cyclophosphamide, etoposide, and cisplatin; HR = hazard ratio; KM = Kaplan-Meier; OS = overall survival; PBAC = Pharmaceutical Benefits Advisory Committee; PFS = progression free survival; PSA = partitioned survival analysis; PSD = public document summary; QALY = quality-adjusted life years; RRMM = relapsed/refractory multiple myeloma; TCR/PR = triple-class refractory and penta-refractory; TTD = time to treatment discontinuation; Sd = selinexor + dexamethasone

Blue shading denotes text remains unchanged from the July 2021 submission and/or Commentary.

6.39 The resubmission stated that the economic model of Sd relative to salvage chemotherapy presented in the resubmission was the same as presented in the July 2021 submission with some minor technical updates and revised data inputs as advised by the PBAC. The PBAC previously considered that the revised model should result in a base case incremental cost effectiveness ratio (ICER) which appropriately accounted for the uncertainties in the clinical data (Para. 7.15, Selinexor (TCR/PR), PBAC PSD, July 2021 PBAC Meeting). Input changes to the revised economic model included:

- time horizon of 5 years (previously 7 years). The PBAC consideration that a 5-year time horizon would be more appropriate given STORM had limited follow-up and

there were no long-term data for OS outcomes (Para. 7.11 Selinexor (TCR/PR), PBAC PSD, July 2021 PBAC Meeting).

- OS benefit is assumed to converge over the last year of the model (i.e. from 48 months to 60 months; previously no convergence was assumed).
- assumption of no treatment benefit of Sd compared to DCEP in terms of PFS (hazard ratio; HR; of 1 for MAMMOTH compared to Sd).
- assumption of two AEs per patient and two treatment cycles per event (previously assumed AE only once and resolution within once treatment cycle).
- reduction in the proposed effective price of selinexor by ■■■%.

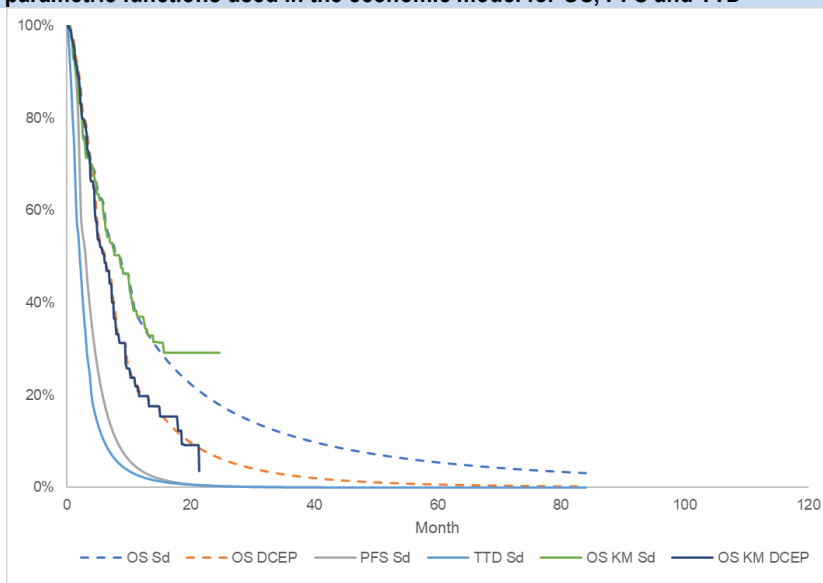
6.40 The ESC considered that the changes to the model (paragraph 6.38) were consistent with the July 2021 PBAC advice, with the exception of PBAC's advice concerning inclusion of post-progression costs which was not adopted in the resubmission's base case. The ESC noted that post-progression costs were considered in a sensitivity analysis (see paragraph 6.47).

6.41 The economic model included three mutually exclusive health states (progression-free, progressive disease and death) that were modelled using the PFS and OS outcomes from STORM and MAMMOTH. The July 2021 PBAC Meeting PSD stated that "PSAs rely on the within-trial relationship between non-mutually exclusive survival curves to determine health state membership. The use of different sources to derive the OS and PFS curves for the Sd and DCEP arms means that the relationship between the OS and PFS curves may be due to differences between the different studies. Thus, the use of this model structure was inherently uncertain."

6.42 The results of the KM outcomes and the parametric functions used in the economic model for OS (Sd and DCEP), PFS (Sd) and time to treatment discontinuation (TTD; Sd) are presented in Figure 5. These results of the KM outcomes and the parametric functions remained unchanged from the July 2021 submission as they were based on the same clinical data (i.e. TCR/PR population of STORM and MAMMOTH). In contrast to the July 2021 submission, the resubmission assumed no treatment benefit of Sd compared to DCEP in terms of PFS (hazard ratio; HR; of 1 for MAMMOTH compared to Sd).

6.43 There were no changes to the way in which parametric survival curves were selected for the extrapolation of the various survival curves, compared with the July 2021 submission. However, OS convergence was assumed from 48 to 60 months which was applied over these extrapolation methods. The convergence of the OS curves was introduced in the resubmission to address the PBAC's previous consideration that the modelled survival benefits was optimistic and not reasonable (Para. 7.11, Selinexor (TCR/PR), PBAC PSD, July 2021 PBAC Meeting).

Figure 5: KM and parametric functions used in the economic model for OS, PFS and TTD



Source: Developed during the evaluation based on the economic Excel model.

Abbreviations: DCEP = dexamethasone + cyclophosphamide + etoposide + cisplatin; KM = Kaplan-Meier; OS = overall survival; PFS = progression free survival; TTD = time to treatment discontinuation; Sd = selinexor + dexamethasone

Note: KM curve of PFS and TTD were excluded in this chart due to visibility reason.

Blue shading denotes figure inputs remain unchanged from the PBAC Minutes, July 2021 PBAC Meeting

6.44 A summary of the key drivers of the model is presented in Table 11.

Table 11: Key drivers of the model

Description	Method/Value	Impact Base case: \$ ¹ per QALY
Extrapolation of OS (Sd)	Log-normal distribution (appropriate based on AIC and BIC criteria; however, data were immature)	High, favours DCEP Use of generalized gamma decreased the ICER to \$ ² per QALY.
Dose intensity of Sd	Dose intensity of 65.4% for selinexor and 80% for dexamethasone, calculated based on the median average dose received per week	Moderate, favours Sd Use of the mean average dose received per week increased the ICER to \$ ¹ per QALY
Convergence for OS of Sd	OS convergence was assumed from 48 to 60 months	Moderate, favours DCEP Applying no convergence decreased the ICER to \$ ² per QALY
Extrapolation of TTD (Sd)	Log-normal distribution (choice justified based on alignment with the choice of the log-normal distribution for OS and PFS)	Moderate, favours DCEP Used of gamma (best fit) decreased the ICER to \$ ² per QALY
Point of extrapolation	20% patients remain at risk for OS/PFS/TTD	Moderate, favours DCEP Extrapolation from 10% patient at risk decreased the ICER to \$ ² per QALY

Source: compiled during the evaluation

Abbreviations: AIC = Akaike Information Criterion; BIC = Bayesian information criterion; DCEP = dexamethasone + cyclophosphamide + etoposide + cisplatin; ICER = incremental cost effectiveness ratio; OS = overall survival; PFS = progression free survival; QALY = quality adjusted life year; Sd = selinexor + dexamethasone; TTD = time to treatment discontinuation

The redacted values correspond to the following ranges:

¹ \$55,000 to < \$75,000

² \$45,000 to < \$55,000

6.45 A summary of the results of the economic evaluation is presented in Table 12.

Table 12: Results of the economic evaluation

Component	Sd	DCEP	Incremental
Total costs (\$)			
Life-years	1.0883	0.7137	0.3747
QALYs	0.6376	0.4169	0.2207
Incremental cost per LY gained (\$)			1
Incremental cost per QALY gained (\$)			2

Source: Table 3-25, p156 of the resubmission.

Abbreviations: DCEP = dexamethasone + cyclophosphamide + etoposide + cisplatin; ICER = incremental cost effectiveness ratio; LY = life years; QALYs = quality adjusted life years; Sd = selinexor + dexamethasone

The redacted values correspond to the following ranges:

¹ \$35,000 to < \$45,000

² \$55,000 to < \$75,000

6.46 Treatment with Sd resulted in estimated incremental cost of \$ [redacted], incremental life years (LYs) of 0.3747 and incremental QALYs of 0.2207, compared with treatment with DCEP, resulting in an ICER per LY of \$35,000 to < \$45,000 (updated \$35,000 to < \$45,000; based on Round 23 data (2018-19), with a national efficient price of \$ [redacted] per national weighted activity unit 2021-22) and an ICER per QALY of \$55,000 to < \$75,000 (updated \$55,000 to < \$75,000). The results of key sensitivity analyses are summarised in Table 13.

Table 13: Results of sensitivity analyses conducted by the resubmission and during the evaluation

Scenario	Base-case value	Scenario analysis value	Incremental costs (\$)	Incremental outcomes	ICER (\$)	Change in ICER from base case
Base-case ^a				0.2207	[redacted] ¹	-
OS extrapolation	Sd: Log-normal SoC: Log-normal	Sd: Gen. gamma		0.2867	[redacted] ²	-23.3%
OS Converge	48 to 60 months	Off		0.2308	[redacted] ²	-13.5%
TTD extrapolation	Sd: Log-normal	Sd: Gamma		0.2207	[redacted] ²	-14.6%
Point to initiate extrapolation from KM data	Where 20% patients remain at risk for OS/PFS/TTD	From start 10% patients remain at risk		0.2516	[redacted] ²	-13.3%
				0.2535	[redacted] ²	-13.5%
Revised base case (updated costs) ^b				0.2207	[redacted] ¹	-
Dose intensity ^c	median; 65.4% for selinexor and 80% for dexamethasone	Mean (71.5% for selinexor and 77.8% for dexamethasone)		0.2207	[redacted] ¹	11.3%

Source: Table 3-27, pp158 of the resubmission and developed during the evaluation

Abbreviations: DCEP = dexamethasone + cyclophosphamide + etoposide + cisplatin; ICER = incremental cost effectiveness ratio; KM = Kaplan Meier; OS = overall survival; PFS = progression free survival; Sd = selinexor + dexamethasone; SoC = standard of care (denoting DCEP); TTD = time to discontinuation

Note: ^a base case as per the resubmission (i.e., without the updated costs referring to costs based on Round 23 data (2018-19), with a national effective price (NEP) of \$ [redacted] per national weighted activity unit (NWAU) 2021-22)

^b updated based on NHCDC Round 22 (2018-19) and national effective price (NEP) of \$ [redacted] per national weighted activity unit (NWAU) 2020-21

^c The resubmission applied a dose intensity of 65.4% for selinexor and 80% for dexamethasone calculated from the median dose per week for selinexor and dexamethasone (104.6 mg and 32.0 mg, respectively) from the STORM TCR/PR subgroup. The mean dose intensities (selinexor 114.4 mg and dexamethasone 31.1 mg per week) correspond to inputs of 71.5% for selinexor and 77.8% for dexamethasone.

The redacted values correspond to the following ranges:

¹ \$55,000 to < \$75,000

² \$45,000 to < \$55,000

- 6.47 The PSCR noted that four of the five drivers of the model favoured the comparator treatment (Table 11). The ESC noted that the use of median dose intensity for selinexor (65.4%) as compared with mean dose intensity (71.5%) was not conservative as it favoured selinexor. The ESC considered that mean dose intensity should be used and would result in an ICER of \$55,000 to < \$75,000 per QALY as shown in Table 13 above.
- 6.48 The PSCR noted that the resubmission had followed all but one of the PBAC’s recommendations for a re-specified base case. The time horizon, increased adverse events, convergence of OS and removal of a PFS treatment effect all followed the PBAC’s recommendation. The resubmission’s base case did not consider post progression costs, but this was applied as a sensitivity analysis. The ESC considered the sensitivity analysis (Table 14) and considered that exclusion of post-progression costs from the base case analysis may be reasonable as there was no information to suggest that the subsequent treatments would be different between the arms. The PBAC considered that exclusion of post-progression costs from the base case analysis was reasonable as described by the ESC.

Table 14: Sensitivity analysis of subsequent treatment costs

Sensitivity analysis	Proportion of patients with and expected cost of subsequent treatment ^a	Incremental cost (\$)	Incremental QALYs	ICER (\$)	Change in ICER from base case
Base-case	Sd: 0%, \$0 SoC: 0%, \$0		0.2207	■ ¹	-
As per the respective trials	Sd: 50%, \$2560 SoC: 63%, \$3226		0.2207	■ ¹	-4.9%
Only applied to Sd patients	Sd: 50%, \$2560 SoC: 0%, \$0		0.2207	■ ¹	19.0%

Source: Table 3-26, p157 of the resubmission

Abbreviations: DCEP = dexamethasone + cyclophosphamide + etoposide + cisplatin; PFS = progression free survival; Sd = selinexor + dexamethasone; SoC = standard of care (denoting DCEP); QALY = quality adjusted life years

The redacted values correspond to the following ranges:

¹ \$55,000 to < \$75,000

Drug cost/patient/course

- 6.49 A summary of the drug cost per patient for Sd and DCEP is presented in Table 15. The average time on treatment of Sd estimated from the model was 12.35 weeks, and the proposed drug cost/patient/course was estimated to be \$|. The duration of therapy based on observed data in STORM was lower for Sd than the modelled durations in the economic and financial estimates.

Table 15: Drug cost per patient for proposed and comparator drugs

	Sd			DCEP		
	Study dose and duration	Model	Financial estimates	Study dose and duration	Model	Financial estimates
Dose intensity	S: 65.4% D: 80.0%	S: 65.4% D: 80.0%	S: 65.4% D: 80.0%	NA	100%	100%
Mean duration ^a	9	12.35	12.35	NA	7.6	7.6
Cost/patient/dose/week ^{b,c}	S: █ D: █	S: █ D: █	S: █ D: █	NA	D: █ E: █ C: █ P: █	D: █ C: █ E: █ P: █
Cost/patient ^b	█			NA	█	

Source: Developed during the evaluation

Abbreviations: C = cyclophosphamide; D = dexamethasone; DCEP = dexamethasone + cyclophosphamide + etoposide + cisplatin; E = etoposide; NA = not applicable; P = cisplatin; S = selinexor; Sd = selinexor + dexamethasone

Note: ^a in weeks

^b drug costs were weighted (private/private) as per the economic evaluation

^c costs for DCEP were calculated based on a BSA of 1.89 as per the economic evaluation

Estimated PBS usage & financial implications

6.50 This resubmission was not considered by DUSC. The resubmission used an epidemiological approach to estimate the financial implications. A summary of key inputs used in the estimation is presented in Table 16.

Table 16: Key inputs for financial estimates

Parameter	Value applied and source	Comment
Patients treated in the TCR/PR setting	Yr 1-6 (2022-2027): 221 per year Assumption based on: - Constant number of patients treated with Pd: <500 - Constant proportion of Pd patients moving on to subsequent therapy: █%	This estimate was not well justified.
Uptake rate	50% in Year 1 increasing to 90% in Year 6. Based on assumption.	Likely overestimated. Despite the resubmission's consideration that the uptake rates were more conservatively applied (i.e. █% of patients treated with Pd likely to receive subsequent therapy), this does not fully account for DUSC's previous consideration that the uptake rate (90%) was substantially overestimated in the July 2021 submission and would likely be approximately █-█% given the unclear benefit and high toxicity of selinexor (Selinexor (TCR/PR), DUSC Minutes, July 2021 PBAC Meeting).
Duration of Sd treatment	2.84 months (12.35 weeks)	Appropriate, consistent with the duration of treatment applied in the economic model.
Grandfathered patients	Nil	Inconsistent with Section 1 which assumed at least 13 RRMM patients on the expanded access registry. The resubmission stated that the revised approach would implicitly capture grandfathered patients.
MBS costs	13950 (IV infusion for DCEP; █% rebate)	Only IV infusion costs were included. Costs associated with routine care and the management of AEs for Sd and DCEP were not considered in the net impact on the MBS.

Source: Table 4-5 p166, Table 4-7 p167, Table 4-8 p168, Table 4-9 168, Table 4-13 p170 of the resubmission.

Abbreviations: AE = adverse event; DCEP = dexamethasone + cyclophosphamide + etoposide + cisplatin; DUSC = Drug Utilisation Subcommittee; IV = intravenous; MBS = Medicare Benefits Schedule; RR MM = replaced and/or refractory multiple myeloma; Pd = pomalidomide + dexamethasone; Sd = selinexor + dexamethasone; TCR/PR = triple class refractory and penta-refractory; Yr = year

- 6.51 The resubmission determined the eligible population by estimating the number of patients failing treatment with PBS listed pomalidomide. This was justified on the basis that failing pomalidomide was a necessary precursor to the TCR/PR requirement of failing two IMiDs. The resubmission also acknowledged that failing pomalidomide was not sufficient for TCR/PR eligibility as failure of a second PI and a mAb are not requirements for access to pomalidomide, however considered it likely that patients treated with pomalidomide would have met the TCR/PR criteria given the eligibility criteria for daratumumab and carfilzomib on the PBS. The July 2021 submission estimated the number of patients in the TCR/PR setting by quantifying the proportion of patients failing each of up to four previous lines of therapy.
- 6.52 Consistent with the discussion provided in the resubmission (paragraph 6.52), the PSCR acknowledged that failing Pd, is a necessary but not sufficient condition for defining penta-refractory MM, however maintained that the approach taken by the resubmission was more certain than attempting to follow patients through multiple lines of therapy. The ESC considered that the approach in the resubmission may overestimate the potential number of Sd patients, however the proportion of patients taking up later lines of therapy is difficult to predict due to lack of data in this population.
- 6.53 The following issues with the approach adopted by the resubmission were noted during the evaluation:
- Pd (pomalidomide + dexamethasone) and PBd (pomalidomide + bortezomib + dexamethasone) require prior treatment with lenalidomide (i.e., failure of two IMiDs) and patients eligible for Pd must have also experienced treatment failure with bortezomib, whilst this is not necessary for PBd. Thus, pomalidomide can be accessed on the PBS as third line therapy. Hence, failure with pomalidomide could be indicative of quad-refractory rather than penta-refractory MM, therefore overestimating the number of patients eligible for selinexor.
 - The resubmission considered that a small number of patients would use thalidomide for MM and that the current approach may underestimate patients becoming eligible for Sd via thalidomide rather than Pd. The PBAC considered that thalidomide has largely been superseded in clinical practice, and it was reasonable to assume most patients would be treated with pomalidomide-based therapies before selinexor.
 - The approach taken does not directly consider patients prior therapy with mAbs, as their prior use is not a criterion for pomalidomide access.
- 6.54 The resubmission estimated that a █% uptake rate would be reached by Year 4. This final uptake rate was consistent with the July 2021 submission. The resubmission however, considered that these uptake rates were more conservative as it was applied to █% of patients failing therapy with Pd and moving to subsequent therapy. DUSC previously considered that the uptake rate was substantially overestimated given the

toxicity profile of selinexor (Table 15, Selinexor (TCR/PR), PBAC PSD, July 2021 PBAC Meeting). DUSC noted that the 10% rate of death could be higher in practice and the uptake rate would be much lower at approximately 11% (Selinexor (TCR/PR), DUSC Minutes, July 2021 PBAC Meeting). The PBAC previously considered that uptake rates of 81.9% and 45% for third-line treatment and fourth-line treatment respectively of plitidepsin were overestimated (Para. 6.52, Selinexor (TCR/PR), PBAC PSD, July 2021 PBAC Meeting).

6.55 A summary of the estimated use and financial implications of selinexor is presented in Table 17.

Table 17: Estimated use and financial implications (effective)

	2022 (Year 1)	2023	2024	2025	2026	2027
Estimated extent of use						
Number of patients treated with Sd	1	1	1	1	1	1
Number of scripts dispensed	1	1	1	3	2	3
Estimated financial implications of selinexor						
Cost to PBS/RPBS less copayments (\$)	2	2	2	2	2	2
Estimated financial implications for other medicines						
Cost to PBS/RPBS less copayments (\$)	-2	-2	-2	-2	-2	-2
Net financial implications						
Net cost to PBS/RPBS (\$)	2	2	2	2	2	2
Net cost to MBS ^a (\$)	-2	-2	-2	-2	-2	-2
Net cost to PBS/RPBS/MBS (\$)	2	2	2	2	2	2

Source: Table 4-7, p167; Table 4-8, p168; Table 4-10, p169; Table 4-14, p161; Table 4-18, p173; Table 4-19, p174 of the resubmission
 Abbreviations: MBS = Medicare Benefits Schedule; PBS = Pharmaceutical Benefits Scheme; RPBS = Repatriation Schedule of Pharmaceutical Benefits; Sd = selinexor + dexamethasone

^a MBS item 13950.

The redacted values correspond to the following ranges:

¹ < 500

² \$0 to < \$10 million

³ 500 to < 5,000

6.56 The total cost to the PBS/RPBS of listing selinexor was estimated to be \$0 to < \$10 million in Year 6, and a total of \$10 to < \$20 million in the first 6 years of listing. This was significantly reduced from the estimates in the July 2021 submission, in which the total cost to the PBS/RPBS of listing selinexor was estimated to be \$30 to < \$40 million in the first 6 years of listing. The results of key sensitivity analyses are summarised in Table 18.

Table 18: Results of sensitivity analyses on net cost to PBS/RPBS (effective)

Sensitivity analysis (base case)	Values	2022 (Yr 1) (\$)	2023 (\$)	2024 (\$)	2025 (\$)	2026 (\$)	2027 (\$)	Change ^c
Base-case	-	█ ¹	█ ¹	█ ¹	█ ¹	█ ¹	█ ¹	-
Probability becoming eligible for Sd after Pd (60%)	50%	█ ¹	█ ¹	█ ¹	█ ¹	█ ¹	█ ¹	-17%
	70%	█ ¹	█ ¹	█ ¹	█ ¹	█ ¹	█ ¹	17%
Selinexor treatment duration (2.84 months)	2.50 months	█ ¹	█ ¹	█ ¹	█ ¹	█ ¹	█ ¹	-15%
	3.30 months	█ ¹	█ ¹	█ ¹	█ ¹	█ ¹	█ ¹	20%
Uptake of Sd (50%-90%)	10-20% ^a	█ ¹	█ ¹	█ ¹	█ ¹	█ ¹	█ ¹	-79% ^d
Sd treatment duration (2.84 months)	2.07 months ^b	█ ¹	█ ¹	█ ¹	█ ¹	█ ¹	█ ¹	-33%
Median dose intensity selinexor 65.4%	Mean dose intensity selinexor 71.5%	█ ¹	█ ¹	█ ¹	█ ¹	█ ¹	█ ¹	11%

Source: Table 4-20, p176 of the resubmission and developed during the evaluation

Abbreviations: Pd = pomalidomide + dexamethasone; Sd = selinexor + dexamethasone; TCR/PR = triple class refractory and penta-refractory

Notes: ^a Based on DUSC's previous consideration that an uptake rate was substantially overestimated and that the uptake rate would be much lower at approximately 10-20% (p5, Selinexor (TCR/PR), DUSC Minutes, July 2021 PBAC Meeting). The sensitivity analysis applied an uptake rate of 10% (Yr 1 and 2) and 20% thereafter.

^b Based on the duration of Sd treatment in the TCR/PR subgroup of STORM (i.e. 9 weeks)

^c average change per year

^d -80% in Year 1, -86% in Year 2, -75% in Year 3 and -78% in Years 4-6

The redacted values correspond to the following ranges:

¹ \$0 to < \$10 million

6.57 Based on the results of the sensitivity analyses, the financial estimates were sensitive to the duration of treatment with Sd and the probability of becoming eligible for Sd following Pd failure. Assuming a lower uptake rate (as per DUSC's previous consideration (i.e., █%; Selinexor (TCR/PR), DUSC Minutes, July 2021 PBAC Meeting) resulted in a █% lower financial impact to the PBS/RPBS (from \$0 to < \$10 million to \$0 to < \$10 million in Year 6). Reducing the duration of Sd treatment from 2.84 months (based on the economic model) to 2.07 months (TCR/PR subgroup in STORM) resulted in a █% lower financial impact to the PBS/RPBS (from \$0 to < \$10 million to \$0 to < \$10 million in Year 6). Applying the mean average dose received per week (rather than the median dose) of selinexor increased the financial impact of selinexor to the PBS/RPBS by 11% (from \$0 to < \$10 million to \$0 to < \$10 million in Year 6).

Quality Use of Medicines

6.58 The resubmission committed to supporting the education of health professionals, patients and caregivers to ensure the safe and appropriate use of selinexor through a multi-stakeholder quality use of medicines approach for haematologists, nurse, pharmacist and patients. The sponsor is working with MSAG to create suitable guidelines and education, with Myeloma Australia on nurse education and with the Haematology Society of Australia and New Zealand (HSANZ) on Australian practical

management treatment recommendations for selinexor. The resubmission also stated it would also establish a patient support program to help monitor and support patients treated with selinexor.

- 6.59 Only the 32-pack of selinexor is sufficient for a month's supply of treatment whilst the other pack sizes (24-pack, 20-pack and 16-pack) would only be required in the case of a dose reduction. Thus, this could potentially lead to prescriber and patient confusion with the dosing regimen, in the context of multiple pack-sizes being available and the high rate of dose reductions in STORM.

Financial Management – Risk Sharing Arrangements

- 6.60 The resubmission did not present a risk sharing arrangement (RSA) for selinexor.

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 dexamethasone (Sd), for the treatment of triple class refractory and penta-refractory multiple myeloma (TCR/PR MM). The PBAC considered that the clinical evidence for Sd was adequate to support listing in a small patient population with significant unmet need, and on this basis was satisfied that Sd provides, for some patients, a significant improvement in efficacy over salvage chemotherapy, represented by dexamethasone + cyclophosphamide + etoposide + cisplatin (DCEP). The PBAC noted that the resubmission had addressed a number of its previous concerns with the economic model. The PBAC's recommendation for listing was based on, among other matters, its assessment that selinexor would be cost-effective if its price was reduced such that the incremental cost-effectiveness ratio (ICER) was less than \$60,000 per quality adjusted life year (QALY) for the scenario using the mean doses of Sd.
- 7.2 The PBAC considered there was a high clinical need for effective therapies for patients with TCR/PR MM. The PBAC noted the consumer comments which described the ongoing need for new therapies and supported the proposed PBS listing of Sd. The PBAC noted that selinexor is the first of a new class of anti-myeloma medicines known as selective inhibitors of nuclear export (SINE), and it is administered orally.
- 7.3 The PBAC noted that the proposed place in therapy for Sd was in patients who have received at least four prior lines of therapy and whose disease is refractory to at least two proteasome inhibitors, at least two immunomodulatory agents and at least one anti-CD38 monoclonal antibody. The PBAC, noted that the requested restriction was narrower than the proposed TGA indication, and considered this was appropriate.
- 7.4 The PBAC considered that the nomination of salvage chemotherapy, represented by DCEP, as primary comparator was appropriate, consistent with its previous advice at the July 2021 PBAC meeting.

- 7.5 As for the July 2021 consideration, the primary clinical evidence presented to support the proposed listing was drawn from STORM, an open label, single arm study of Sd in patients with heavily pre-treated RRMM. The PBAC noted that consistent with its previous advice, the resubmission presented clinical evidence from a subgroup of patients in STORM reflecting the proposed PBS population (TCR/PR MM subgroup). The resubmission provided an updated naïve comparison of Sd versus salvage chemotherapy based on the TCR/PR population of STORM (N=83) and two single arm comparator studies (MAMMOTH, N=70; and Goldsmith 2020, N=31). The PBAC noted the differences across the populations in the three studies (see paragraph 6.10), and that the comparisons remained difficult and uncertain due to the limited data available.
- 7.6 The PBAC noted that for the TCR/PR MM subgroup treated with Sd, the median OS was 8.4 months (95% CI: 5.9, 11.2), median progression free survival (PFS) was 2.8 months (95% CI: 1.9, 4.3) and the overall response rate (ORR) was 25.3% (Table 7). The PBAC noted that OS was longer in patients achieving a response (see Figure 2).
- 7.7 In terms of comparative benefits, the PBAC noted the naïve comparison suggested an improvement in OS, although a corresponding improvement in PFS was not demonstrated. The PBAC noted that the efficacy of selinexor had been assessed in a randomised trial, although in combination with bortezomib and in an earlier line of treatment (paragraph 6.35). Overall, the PBAC considered that the clinical evidence for Sd was adequate to support listing in a small patient population with significant unmet need, and on this basis was satisfied that Sd provides, for some patients, a significant improvement in efficacy over salvage chemotherapy. The PBAC accepted the resubmission's claim of superior comparative effectiveness, in the context of significant unmet need in a small population.
- 7.8 To assess comparative harms, the resubmission presented a naïve comparison of adverse events reported in STORM with those reported in two retrospective studies of patients with heavily pre-treated MM patients receiving DCEP (Yuen 2018, Griffin 2015). The PBAC noted the limitations of the naïve safety comparison and the uncertainties arising from differences between the trials, however considered the comparison informative. The PBAC noted that the majority of patients in STORM reported Grade 3 or greater treatment related adverse events (93.5%; Table 8) and that the majority of patients had a dose reduction (61.8%; 7.09.COM.72). The PBAC noted that the majority of Grade ≥ 3 AEs with Sd were thrombocytopenia, and that there were relatively few febrile neutropenia complications with selinexor compared with DCEP (see paragraph 6.27). The PBAC considered thrombocytopenia is generally more easily managed than febrile neutropenia which often requires hospitalisation. Overall, the PBAC noted the resubmission's claim of non-inferior comparative safety was based on limited evidence, however accepted this claim in the context of significant unmet need in a small population.

- 7.9 With regard to the economic analysis, the PBAC noted the resubmission had revised the economic model consistent with its advice with respect to the time horizon, convergence of the survival curves, assumption of no PFS benefit, and impact of adverse events (see paragraph 6.38). However, the PBAC noted that the use of median dose intensities favoured Sd in the analysis, and applying the mean dose received per week increased the ICER from \$55,000 to < \$75,000 per QALY gained in the revised base case to \$55,000 to < \$75,000 per QALY gained (Table 13). The PBAC considered that the mean dose better reflects the extent of dose modifications and time spent at each dose level, and overall provide a more accurate basis for estimating the drug costs and thus should be used in the economic evaluation. The PBAC considered that selinexor would be considered cost-effective if the mean dose intensities were applied to the revised base case, and the price of selinexor was reduced such that the ICER was less than \$60,000/QALY.
- 7.10 The PBAC noted that the resubmission estimated the size of the eligible patient population based on the PBS utilisation of pomalidomide plus dexamethasone (Pd). The PBAC considered this may overestimate the potential number of Sd patients, although it was reasonable to assume most patients would be treated with pomalidomide-based therapies before selinexor. The PBAC noted the financial estimates were appropriately substantially reduced compared with those in the July 2021 submission (paragraph 6.55). The PBAC noted the sensitivity analyses prepared during the evaluation (Table 18) which indicated that net cost to PBS/RPBS over six years may be less than proposed by the resubmission, although assuming utilisation based on mean doses rather than median doses would increase the estimates.
- 7.11 The PBAC made the following comments with regard to the restriction:
- The PBAC considered that an ‘authority required (telephone/electronic)’ was appropriate as requested by the resubmission, consistent with previous advice (paragraph 3.3, Selinexor (TCR/PR), PSD, July 2021 PBAC Meeting).
 - The PBAC confirmed that the restriction should refer to previous lines of therapy consistent with the algorithm proposed by the submission (i.e. “at least four prior lines of therapy” as compared with “at least four prior therapies”).
 - The submission sought listings for the 16, 20, 24 and 32 tablet pack sizes. The dose of selinexor, as per the TGA-approved Product Information is 80 mg (4 x 20 mg tablets) on Days 1 and 3 of each week. Thus, the 32 tablet pack would allow for 4 weeks treatment. The PBAC recommended a maximum quantity of up to 32 tablets.
 - The requested maximum quantity of one pack and two repeats was appropriate.
 - The PBAC considered it appropriate for clinicians to determine at their discretion whether their patient has trialled the pre-requisite drugs and experienced

progression (as per the standard criteria) and that it would not be necessary to capture proof for each previous drug in the application process.

- The PBAC considered it was appropriate to include a criterion stating that ‘Patient must not have previously received this drug for this condition’ to prevent patients being retreated with selinexor.
- The TGA-approved Product Information states that selinexor is a Category D medicine in terms of use during pregnancy. A caution stating that selinexor should not be given to pregnant women was added to the proposed restrictions.
- The PBAC considered that the grandfather restriction was appropriate to allow continuing supply of selinexor to patients commencing treatment prior to PBS listing, noting that the resubmission had reported 13 such patients were receiving treatment as of October 2021.

7.12 The PBAC recommended that selinexor should not be treated as interchangeable on an individual patient basis with any other drugs.

7.13 The PBAC advised that selinexor is not suitable for prescribing by nurse practitioners.

7.14 The PBAC recommended that the Early Supply Rule should not apply.

7.15 The PBAC found that the criteria prescribed by the *National Health (Pharmaceuticals and Vaccines – Cost Recovery) Regulations 2009* for Pricing Pathway A were not met. Specifically the PBAC found that in the circumstances of its recommendation for selinexor:

- a) The treatment is not expected to provide a substantial and clinically relevant improvement in efficacy over alternative therapies. The PBAC considered this criteria was not met as the available evidence showed a clinically relevant but modest improvement in OS for some patients;
- b) The treatment is not expected to address a high and urgent unmet clinical need. The PBAC considered this criteria was not met as other PBS-subsidised therapies were available;
- c) It was not necessary to make a finding in relation to whether it would be in the public interest for the subsequent pricing application to be progressed under Pricing Pathway A because one or more of the preceding tests had failed.

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

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

Outcome:

Recommended

8 Recommended listing

8.1 Add new medicinal product as follows:

MEDICINAL PRODUCT medicinal product pack	PBS item code	Max. qty packs	Max. qty units	No. of Rpts	Available brands
SELINEXOR					
selinexor 20 mg tablet, TBA	NEW (Public) / NEW (Private)	TBA	32	2	Xpovio
Restriction Summary [new] / Treatment of Concept: [new]					
Category / Program: Section 100 – Highly Specialised Drugs Program					
Prescriber type: <input checked="" type="checkbox"/> Medical Practitioners					
Restriction type: <input checked="" type="checkbox"/> Authority Required – immediate/real-time assessment by Services Australia (telephone/electronic)					
Administrative Advice: Special Pricing Arrangements apply.					
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.					
Episodicity: Relapsed and/or refractory					
Severity: [blank]					
Condition: Multiple myeloma					
Indication: Relapsed and/or refractory multiple myeloma					
Treatment Phase: Initial treatment					
Clinical criteria:					
The treatment must be in combination with dexamethasone					
AND					
Clinical criteria:					
Patient must have progressive disease after at least four prior lines of therapy for this condition					
AND					
Clinical criteria:					
Patient must not have previously received this drug for this condition					
AND					
Clinical criteria:					
Patient must have demonstrated refractory disease to the following prior treatments for this condition, which must include: (i) a minimum of two proteasome inhibitors; and (ii) a minimum of two immunomodulators; and (iii) an anti-CD38 monoclonal antibody					
AND					
Clinical criteria:					
Patient must not be receiving concomitant PBS-subsidised treatment with any of the following: (i) proteasome inhibitors, (ii) Immunomodulators, (iii) anti-CD38 monoclonal antibody					
Prescribing Instructions:					
Progressive disease is defined as at least 1 of the following: (a) at least a 25% increase and an absolute increase of at least 5 g per L in serum M protein (monoclonal protein); or					

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	(b) at least a 25% increase in 24-hour urinary light chain M protein excretion, and an absolute increase of at least 200 mg per 24 hours; or (c) in oligo-secretory and non-secretory myeloma patients only, at least a 50% increase in the difference between involved free light chain and uninvolved free light chain; or (d) at least a 25% relative increase and at least a 10% absolute increase in plasma cells in a bone marrow aspirate or on biopsy; or (e) an increase in the size or number of lytic bone lesions (not including compression fractures); or (f) at least a 25% increase in the size of an existing or the development of a new soft tissue plasmacytoma (determined by clinical examination or diagnostic imaging); or (g) development of hypercalcaemia (corrected serum calcium greater than 2.65 mmol per L not attributable to any other cause).
	Prescribing Instructions: Oligo-secretory and non-secretory patients are defined as having active disease with less than 10 g per L serum M protein.
	Prescribing Instructions: Refractory disease is defined as $\leq 25\%$ response to therapy or progression during or within 60 days after completion of therapy
	Prescribing Instructions: 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.
	Administrative Advice: Applications for authorisation under this restriction may be made in real time using the Online PBS Authorities system (see www.servicesaustralia.gov.au/HPOS) or by telephone by contacting Services Australia on 1800 888 333.
	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.
Restriction Summary [new] / Treatment of Concept: [new]	
	Category / Program: Section 100 – Highly Specialised Drugs Program
	Prescriber type: <input checked="" type="checkbox"/> Medical Practitioners
	Restriction type: <input checked="" type="checkbox"/> Authority Required – immediate/real-time assessment by Services Australia (telephone/electronic)
	Episodicity: Relapsed and/or refractory
	Severity: [blank]
	Condition: Multiple myeloma
	Indication: Relapsed and/or refractory multiple myeloma
	Treatment Phase: Continuing treatment
	Clinical criteria: Patient must have previously received PBS-subsidised treatment with this drug for this condition
	AND
	Clinical criteria: The treatment must be in combination with dexamethasone
	AND

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	Clinical criteria:
	Patient must not have developed disease progression while receiving treatment with this drug for this condition
	AND
	Clinical criteria:
	Patient must not be receiving concomitant PBS-subsidised treatment with any of the following: (i) proteasome inhibitors , (ii) Immunomodulators, (iii) anti-CD38 monoclonal antibody
	Prescribing Instructions: Progressive disease is defined as at least 1 of the following: (a) at least a 25% increase and an absolute increase of at least 5 g per L in serum M protein (monoclonal protein); or (b) at least a 25% increase in 24-hour urinary light chain M protein excretion, and an absolute increase of at least 200 mg per 24 hours; or (c) in oligo-secretory and non-secretory myeloma patients only, at least a 50% increase in the difference between involved free light chain and uninvolved free light chain; or (d) at least a 25% relative increase and at least a 10% absolute increase in plasma cells in a bone marrow aspirate or on biopsy; or (e) an increase in the size or number of lytic bone lesions (not including compression fractures); or (f) at least a 25% increase in the size of an existing or the development of a new soft tissue plasmacytoma (determined by clinical examination or diagnostic imaging); or (g) development of hypercalcaemia (corrected serum calcium greater than 2.65 mmol per L not attributable to any other cause).
	Prescribing Instructions: Oligo-secretory and non-secretory patients are defined as having active disease with less than 10 g per L serum M protein.
	Administrative Advice: Applications for authorisation under this restriction may be made in real time using the Online PBS Authorities system (see www.servicesaustralia.gov.au/HPOS) or by telephone by contacting Services Australia on 1800 888 333.
	Administrative Advice: No increase in the maximum number of repeats may be authorised.
	Administrative Advice: Special Pricing Arrangements apply
	Caution: This drug is a category D drug and must not be given to pregnant women. If selinexor is taken during pregnancy, a teratogenic effect of selinexor in humans cannot be ruled out.
Restriction Summary [new] / Treatment of Concept: [new]	
Concept ID	Category / Program: Section 100 – Highly Specialised Drugs Program
(for internal Dept. use)	Prescriber type: <input checked="" type="checkbox"/> Medical Practitioners
	Restriction type: <input checked="" type="checkbox"/> Authority Required – immediate/real-time assessment by Services Australia (telephone/electronic)
	Episodicity: Relapsed and/or refractory
	Severity: [blank]
	Condition: Multiple myeloma
	Indication: Relapsed and/or refractory multiple myeloma
	Treatment Phase: Grandfather treatment - Transitioning from non-PBS to PBS-subsidised supply
	Clinical criteria:
	Patient must have received non-PBS-subsidised treatment with this drug for this condition prior to [date of selinexor PBS listing]
	AND
	Clinical criteria:

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	The treatment must be in combination with dexamethasone
	AND
	Clinical criteria
	AND
	Clinical criteria:
	Patient must have progressive disease after at least four prior lines of therapy, prior to initiating non-PBS subsidised therapy with this drug for this condition.
	AND
	Clinical criteria:
	Patient must have demonstrated refractory disease to prior treatments, prior to initiating non-PBS subsidised therapy with this drug for this condition, which must include: (i) a minimum of two proteasome inhibitors; and (ii) a minimum of two immunomodulators; and (iii) an anti-CD38 monoclonal antibody
	AND
	Clinical criteria:
	Patient must not be receiving concomitant PBS-subsidised treatment with any of the following: (i) proteasome inhibitors, (ii) immunomodulators, (iii) anti-CD38 monoclonal antibody
	Prescribing Instructions: Progressive disease is defined as at least 1 of the following: (a) at least a 25% increase and an absolute increase of at least 5 g per L in serum M protein (monoclonal protein); or (b) at least a 25% increase in 24-hour urinary light chain M protein excretion, and an absolute increase of at least 200 mg per 24 hours; or (c) in oligo-secretory and non-secretory myeloma patients only, at least a 50% increase in the difference between involved free light chain and uninvolved free light chain; or (d) at least a 25% relative increase and at least a 10% absolute increase in plasma cells in a bone marrow aspirate or on biopsy; or (e) an increase in the size or number of lytic bone lesions (not including compression fractures); or (f) at least a 25% increase in the size of an existing or the development of a new soft tissue plasmacytoma (determined by clinical examination or diagnostic imaging); or (g) development of hypercalcaemia (corrected serum calcium greater than 2.65 mmol per L not attributable to any other cause).
	Prescribing Instructions: Oligo-secretory and non-secretory patients are defined as having active disease with less than 10 g per L serum M protein.
	Administrative Advice: Applications for authorisation under this restriction may be made in real time using the Online PBS Authorities system (see www.servicesaustralia.gov.au/HPOS) or by telephone by contacting Services Australia on 1800 888 333.
	Administrative Advice: No increase in the maximum number of repeats may be authorised.
	Administrative Advice: Special Pricing Arrangements apply
	Caution: This drug is a category D drug and must not be given to pregnant women. If selinexor is taken during pregnancy, a teratogenic effect of selinexor in humans cannot be ruled out.

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 wishes to thank all of the patients, patient organisations and health care professionals for their support of this submission and we are very proud to provide the first indication of XPOVIO access to patients in Australia.