

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

1 Purpose of submission

- 1.1 The Category 1 submission requested a Section 100 (Highly Specialised Drug), Authority Required (Streamlined) listing for selinexor in combination with dexamethasone (Sd) for the treatment of adult patients with relapsed and/or refractory multiple myeloma (RRMM), who have received at least four prior therapies 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). This has been described in the submission as triple class refractory and penta-refractory multiple myeloma (TCR/PR MM).
- 1.2 Listing was requested on the basis of a cost-utility (CUA) analysis versus salvage chemotherapy, represented by dexamethasone, cyclophosphamide, etoposide, and 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

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 (TCR/PR MM)
Intervention	Selinexor 80 mg twice weekly, oral tablet ^a , in combination with low dose dexamethasone (20 mg)
Comparator	Salvage chemotherapy
Outcomes	Overall response rate, progression free survival, overall survival and safety
Clinical claim	Selinexor in combination with dexamethasone provides clinical benefit for patients with TCR/PR MM and has a manageable safety/tolerability profile

Source: Table 1-1, p.18 of the submission.

TCR/PR MM = triple class refractory and penta-refractory multiple myeloma

^a Median dose in the study was 115 mg/week (~60 mg twice weekly dose)

2 Background

Registration status

- 2.1 The submission was made under the TGA/PBAC Parallel Process. At the time of PBAC consideration, only the Clinical Evaluation Report was available.
- 2.2 The proposed TGA indication is for use:
“In combination with dexamethasone for the treatment of adult patients with relapsed and/or refractory multiple myeloma, who have received at least three prior

therapies and whose disease is refractory to at least one proteasome inhibitor, at least one immunomodulatory agent, and an anti-CD38 monoclonal antibody”.

- 2.3 The FDA in July 2019 and EMA in January 2021 have 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.

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

3 Requested listing

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: \$ [REDACTED] (HSD Public)	XPOVIO, ANTENGENE Pty Ltd
				\$ [REDACTED] (HSD Private)	
				Effective: \$ [REDACTED] (HSD Public)	
				\$ [REDACTED] (HSD Private)	
	1	24	2	Published: \$ [REDACTED] (HSD Public)	
				\$ [REDACTED] (HSD Private)	
				Effective: \$ [REDACTED] (HSD Public)	
				\$ [REDACTED] (HSD Private)	
	1	20	2	Published: \$ [REDACTED] (HSD Public)	
				\$ [REDACTED] (HSD Private)	
				Effective: \$ [REDACTED] (HSD Public)	
				\$ [REDACTED] (HSD Private)	
	1	16	2	Published: \$ [REDACTED] (HSD Public)	
				\$ [REDACTED] (HSD Private)	
				Effective: \$ [REDACTED] (HSD Public)	
				\$ [REDACTED] (HSD Private)	

Category/Program	Section 100 (Highly Specialised Drugs Program)
Condition:	Multiple Myeloma
PBS Indication:	Relapsed and/or refractory multiple myeloma
Treatment phase:	Initial treatment
Restriction:	Authority Required – STREAMLINED
Treatment criteria:	Initial treatment
Clinical criteria	The treatment must be in combination with dexamethasone AND Patient must have progressive disease after at least four prior therapies AND Patient is refractory to prior treatments which must include at least two proteasome inhibitors, at least two immunomodulatory agents, and an anti-CD38 monoclonal antibody AND Patient must not be receiving concomitant PBS-subsidised daratumumab, bortezomib, carfilzomib, lenalidomide, thalidomide, pomalidomide or its analogues
Treatment phase:	Continuing treatment

Clinical criteria	Patient must have previously been issued with an authority prescription for this drug, AND The treatment must be in combination with dexamethasone AND Patient must not have progressive disease AND Patient must not be receiving concomitant PBS-subsidised daratumumab, bortezomib, carfilzomib, pomalidomide, lenalidomide, thalidomide or its analogues
Note	Authority applications for continuing treatment may be made by telephone to the Department of Human Services on 1800 700 270 (hours of operation 8 a.m. to 5 p.m. EST Monday to Friday).
Treatment phase:	Grandfather treatment - Transitioning from non-PBS to PBS-subsidised supply
Restriction:	Authority Required – STREAMLINED
Clinical criteria:	Patient must have received non-PBS-subsidised treatment with this drug for this condition prior to date of selinexor PBS listing, AND Patient must have met all initial treatment PBS-eligibility criteria applying to a non-grandfathered patient prior to having commenced treatment with this drug AND Patient must not have developed disease progression while receiving treatment with this drug for this condition.

Source: Table 1-11, p.39; Table 1-12, p.40-41; Table 1-13, p.41-42; Table 1-14, p.43 of the submission
DPMQ = dispensed price for maximum quantity; HSD = highly specialised drugs; PBS = Pharmaceutical Benefits Scheme

- 3.1 The requested restriction (i.e. being refractory to at least 2 PIs, at least 2 IMiDs, and at least 1 mAb) was narrower than the proposed TGA indication (i.e. at least 1 PI, at least 1 IMiD, and 1 mAb).
- 3.2 Given that daratumumab for use in combination with bortezomib and dexamethasone (DBd) is only available on the PBS for use in the second-line MM setting, a patient who is currently beyond that line of therapy for RRMM without previous experience of daratumumab would not qualify for Sd on the PBS unless: (1) they were to access daratumumab as combination therapy outside of the PBS; or (2) they were to access daratumumab as monotherapy via compassionate access. Although this may represent an issue of equity of access for current and future patients with respect to access for Sd for the proposed setting; the ESC noted that a number of RRMM patients have accessed daratumumab through clinical trials and compassionate access.
- 3.3 The ESC advised that a Streamlined listing would not be appropriate given the potential safety concerns and the novelty of the regimen. 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.

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

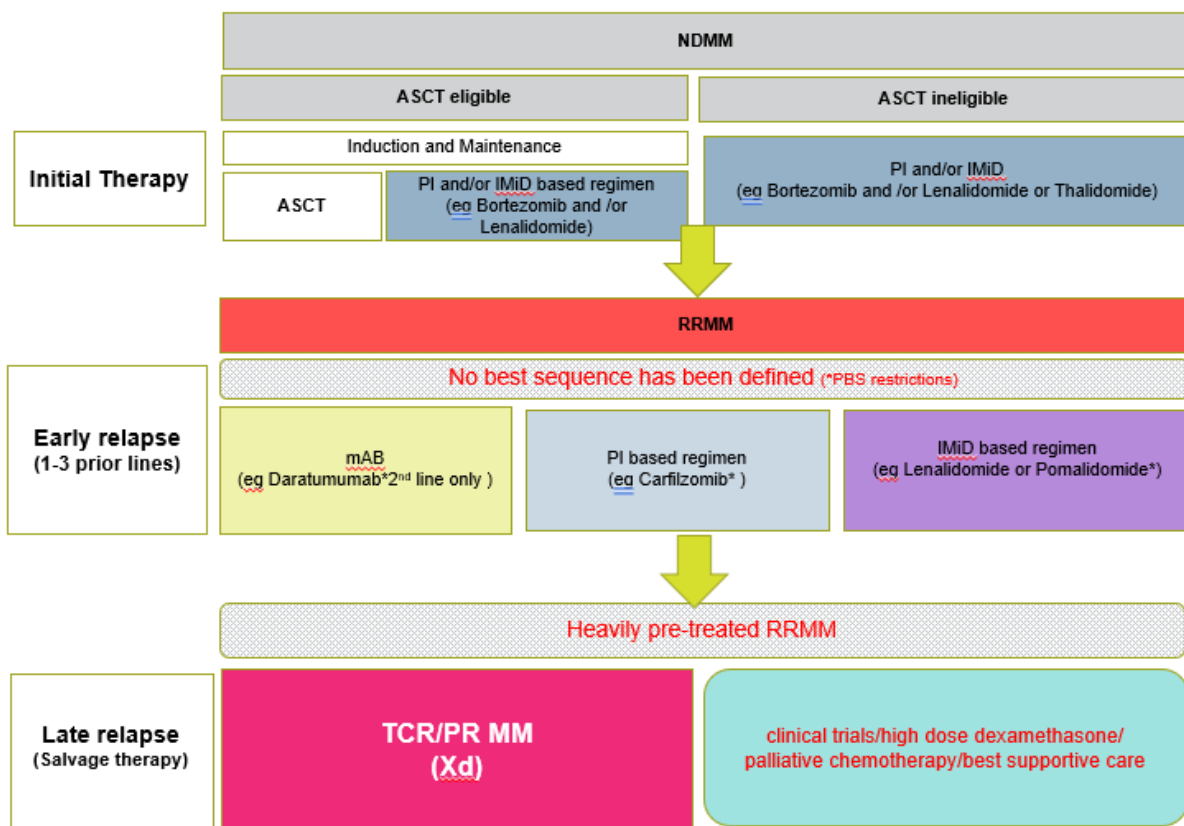
4 Population and disease

- 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. 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).

Figure 1: Proposed clinical management algorithm with introduction of Sd



Source: Figure 1-5, p.35 of the submission.

ASCT = autologous stem cell transplant; IMiD = an immunomodulatory agent; mAB = anti-CD38 monoclonal antibody; NDMM = newly diagnosed multiple myeloma; PI = proteasome inhibitors; PBS = Pharmaceutical Benefits Scheme; RRMM = relapsed and/or refractory multiple myeloma; TCR/PR MM = triple class refractory and penta-refractory multiple myeloma; Sd = selinexor plus dexamethasone; Xd = selinexor plus dexamethasone

*Carfilzomib and pomalidomide may not be available at first relapse

- 4.3 The proposed treatment algorithm proposed that Sd will be used in those with heavily pre-treated RRMM. The algorithm did not suggest the use of specific drugs (where there is more than one available drug per line of treatment) for each line of treatment. Given that DBd is listed for use in second-line treatment only, this could be more clearly specified in the algorithm, followed by later lines of therapy/drugs that would be required to qualify for treatment with Sd.

- 4.4 Most patients experience serial relapses and will be treated with a number of the agents available for RRMM. The duration and quality of response usually becomes progressively shorter and of lesser quality with each successive regimen. A preferred order has not been established. In general, patients are treated with a three-drug combination that incorporates at least two new drugs to which the patient has not been exposed. Retreatment with a regimen that includes a particular drug (or another drug in that class) is reasonable if the most recent duration of response was at least one year. The ESC noted that, given the currently available data and safety concerns, selinexor may be best placed for use by patients with penta-refractory multiple myeloma, which includes disease refractory to daratumumab, both lenalidomide and pomalidomide, bortezomib, and carfilzomib.
- 4.5 Selinexor is an oral, first-in-class, 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 Pre-Sub-Committee Response (PSCR) claimed there was a high unmet need for novel therapies, such as selinexor, that can help delay progressive disease and improve the OS of patients with this advanced stage of refractory disease. The PSCR also stated that selinexor would be a useful therapy in patients with advanced age, multiple comorbidities and concomitant medications. The ESC noted that there were various PBS listed treatment options available for patients with RRMM including thalidomide, bortezomib, lenalidomide, carfilzomib, daratumumab and pomalidomide. In addition, the ESC considered that the use of Sd in elderly patients with multiple comorbidities would be low considering the high incidence of adverse events, particularly haematological events.

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

5 Comparator

- 5.1 The submission nominated salvage chemotherapy, consisting of the combination of DCEP, as the main comparator. The clinical evidence relied upon for the clinical claim was based on a comparison of Sd with conventional care, that included salvage chemotherapy amongst other treatments.
- 5.2 The ESC noted that there was no standard of care for fifth- and later-line MM and that treatment can include single agent melphalan, cyclophosphamide or dexamethasone, radiotherapy, or an agent a patient has previously received and has had a reasonable response to. Overall, the ESC considered the proposed comparator was reasonable and likely representative of last-line care, but noted that the PBAC previously considered that dexamethasone was an appropriate comparator for plitidepsin as a last line (fourth) treatment for RRMM in March 2020 (paragraph 7.4, plitidepsin Public Summary Document (PSD), March 2020).

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 presented discussed the natural history of the disease. The clinician described the benefits of Sd therapy in patients with TCR/PR MM due to the novel mechanism of action of selinexor and described management of the potential adverse events associated with treatment. The PBAC considered that the hearing was informative as it provided a clinical perspective on the utilisation of Sd.

Consumer comments

- 6.2 The PBAC noted and welcomed the input from individuals (3) 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.
- 6.3 The PBAC noted the advice received from (i) Myeloma Australia, (ii) Rare Cancers Australia, and (iii) the Leukaemia Foundation which described the ongoing clinical need for new therapies, such as selinexor, for the treatment of RRMM.

Clinical studies

- 6.4 The submission was based on one single arm study, STORM Part 2 (hereafter referred to as STORM; N=122 for the modified intention to treat population) that included patients with penta-exposed (PE) MM, defined as patients who were previously treated with lenalidomide, pomalidomide, bortezomib, carfilzomib, and daratumumab (and an alkylating agent), and TCR, defined as patients whose disease is refractory to prior treatment with at least one IMiD, at least one PI, and the anti-CD38 mAb daratumumab and glucocorticoids (TCR/PE MM).
- 6.5 Clinical results relevant to the requested listing (TCR/PR MM) were based on a subgroup of patients in STORM (N = 83) who were treated and were refractory to lenalidomide, pomalidomide, bortezomib, carfilzomib and daratumumab (i.e. a subgroup of TCR/PE MM patients).
- 6.6 The submission also presented two naïve comparisons of OS and overall response rate (ORR) between Sd and conventional care, comparing the outcomes from STORM to two retrospective studies:
- Monoclonal Antibodies in Multiple Myeloma Outcomes after Therapy failure (MAMMOTH, N = 275) study. This study investigated outcomes of patients who had become refractory to daratumumab. Clinical outcomes used in the naive comparison with STORM were based on a subgroup of patients who were TCR/PE MM and who received subsequent therapy other than Sd (n = 128).

- The Flatiron Health Analytic Database (FLATIRON or FHAD, N = 36) study. This study investigated outcomes of patients who received at least one therapy after becoming TCR/PE MM and who received subsequent therapy other than Sd.

6.7 STORM patients included in the naïve comparison with MAMMOTH and FLATIRON were those who were TCR/PE MM, and received Sd as the subsequent treatment (TCR/PE MM with Sd as next subsequent treatment; n = 64). This subgroup used in the comparison was not consistent with the requested PBS restriction (TCR/PR MM).

6.8 A summary of the relevant populations from STORM presented by the submission is provided in Table 2.

Table 2: STORM populations referred to in the submission.

Population	TCR/PE MM	TCR/PR MM	TCR/PE MM with Sd as next subsequent treatment
Relevance in the submission	Whole population (Part 2; mITT)	Requested restriction	Used in the naïve comparison with MAMMOTH and FLATIRON
Number of patients	N = 122	N = 83	N = 64
Details	Exposed to BCLPD (and an alkylating agent)	Refractory to ≥ 2 IMiDs, ≥ 2 PIs and ≥ 1 mAbs (per the submission, i.e. those refractory to BCLPD in STORM)	Exposed to BCLPD (and an alkylating agent) and received Sd as next subsequent treatment.
Used for clinical claim	No	No	Yes
Used in economic model	No	Yes	No
Comments	Population is not consistent with the restriction requested population. Most patients were refractory to BCLPD.	No comparative evidence relating to this population was presented by the submission. Might receive other treatments prior to Sd after becoming penta-refractory.	Naive comparative evidence. Population is not consistent with the restriction requested population.

Source: Developed during the evaluation

BCLPD = bortezomib, carfilzomib, lenalidomide, pomalidomide, daratumumab; IMiD = immunomodulatory agent; mITT = modified intention to treat population; mAb = anti-CD38 monoclonal antibody; PI = proteasome inhibitor; TCR/PE MM = triple class refractory and penta-exposed multiple myeloma; TCR/PR MM = triple class refractory and penta-refractory multiple myeloma; Sd = selinexor plus dexamethasone

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

Table 3: Studies and associated reports presented in the submission

Study ID	Protocol title/ Publication title	Publication citation
STORM	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
NCT02336815		
EUCTR2016-003094-18-DE	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.
STORM vs MAMMOTH	Cornell R. Parameswaran H. Tang S. et a;. Real world vs. clinical trial outcomes of triple class refractory penta-exposed multiple myeloma (MM).	Clinical Lymphoma, Myeloma and Leukemia. Conference: 17th International Myeloma Workshop. United States. 19 (10 Supplement) (pp e115-e116), October 2019.
	Cornell R, Hari P, Tang S. et al. Overall survival of patients with triple-class refractory multiple myeloma treated with selinexor plus dexamethasone vs standard of care in MAMMOTH.	Am J Hematol. 2021 Jan;96(1):E5-E8. doi: 10.1002/ajh.26010. Epub 2020 Oct 21. PMID: 32974944.
STORM vs FLATIRON	Richardson P.G. Jagannath S. Chari A. et al., Overall survival (OS) with oral selinexor plus low dose dexamethasone (Xd) in patients with triple class refractory-multiple myeloma (TCR-MM).	Journal of Clinical Oncology. Conference: 2019 Annual Meeting of the American Society of Clinical Oncology, 37 (Supplement 15) (no pagination), May 2019.

Source: Table 2-3, p48-50 of the submission

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

Table 4: Key features of the included evidence

Study	N	Design/ duration	Risk of bias	Patient population	Outcomes	Use in modelled evaluation
Sd						
STORM	122 (mITT)	Single arm	High	TCR/PE MM	OS, PFS, ORR	Not used
	83			TCR/PR MM		OS, PFS
	64 ^a			TCR/PE MM (Sd as next subsequent treatment) ^b		Not used
Conventional care						
MAMMOTH	128 ^c	Retrospective	High	TCR/PE MM	OS, ORR	Not used
FLATIRON	36	Retrospective	High	TCR/PE MM	OS	Not used
Naïve comparison						
STORM vs MAMMOTH	192 ^d	Naïve comparison	High	TCR/PE MM (Sd as next subsequent treatment) ^b	OS, ORR	Not used
STORM vs FLATIRON	100 ^e	Naïve comparison	High	TCR/PE MM (Sd as next subsequent treatment) ^b	OS	Not used

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

mITT = modified intention to treat population; ORR = overall response rate; OS = overall survival; PFS = progression-free survival; Sd = selinexor plus dexamethasone; TCR/PE MM = triple class refractory and penta-exposed multiple myeloma; TCR/PR MM = triple class refractory and penta-refractory multiple myeloma

^a Used in the naïve comparison with MAMMOTH and FLATIRON.

^b Patients that were TCR/PE and received Sd as the subsequent treatment after this status.

^c Used in the naïve comparison with STORM. Subgroup of the MAMMOTH study (128/275 patients) included TCR/PE patients that received subsequent therapy other than Sd. MAMMOTH included all patients that had become refractory to MM.

^d 64 patients from STORM and 128 patients from MAMMOTH

^e 64 patients from STORM and 36 patients from MAMMOTH

6.11 The overall risk of bias in STORM was high, given that it is 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 measurement of outcome bias (unblinded study). The PSCR stated that 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 used were objective measures that were defined by pre-specified criteria. The risk of bias in MAMMOTH and FLATIRON was high given they are both retrospective single-arm studies. Limited information regarding methods and characteristics of patients from both studies was available. The PSCR provided a comparison of the baseline characteristics of the TCR/PR MM subgroups from STORM and MAMMOTH.

6.12 The ESC noted that patients in STORM appeared to be healthier and/or had less advanced disease than MAMMOTH and FLATIRON given that:

- Patients with limited life expectancy (less than four months) were excluded in STORM.
- Patients in STORM had longer time between initial diagnosis of the disease and date receiving the studied intervention (median = 6.4 years) compared with MAMMOTH (median = 5.0 years) and FLATIRON (median = 3.4 years).

- A high proportion of patients in STORM previously received stem cell transplantation (ASCT; 53/64; 82.8%) compared with FLATIRON (22/36; 61.1%). There was no information regarding the proportion of patients receiving ASCT in MAMMOTH.
- The majority of patients in STORM had an ECOG performance status (PS) score of 0 or 1 (74/83; 89.1% of TCR/PR MM) despite having late-stage MM. There was no information about ECOG score in MAMMOTH. In FLATIRON, a high proportion of patients had an unknown ECOG PS (15/36; 41.7% was reported as 0 or missing).
- In STORM, a high proportion of patients (61/122; 50%) received subsequent treatments after Sd (Chari et al., 2019). Most patients received PIs, IMiDs, daratumumab or chemotherapy (41/122; 34%) and autologous stem cell transplant (ASCT; 10/122; 8%). The use of subsequent treatments might bias OS in favour of Sd. No details for subsequent treatments in MAMMOTH and FLATIRON were presented in the submission.

6.13 The PSCR claimed that while STORM and MAMMOTH were well matched for gender and race, the STORM population had a higher proportion of high-risk chromosomal abnormalities, were more heavily pre-treated and had more advanced disease (STORM = 6.4 years from diagnosis; MAMMOTH = 5.0 years) when compared with the MAMMOTH TCR/PR cohort. The ESC considered that the longer time between initial diagnosis and enrolment into a study reflected a better disease prognosis.

6.14 The most common therapies administered to patients after becoming TCR/PE MM in MAMMOTH were pomalidomide-based treatments (36.8%), traditional chemotherapy (33.6%) and daratumumab-based treatments (19.5%). No detail was provided regarding the conventional treatments provided to patients after becoming TCR/PE MM in FLATIRON. Therefore, the outcomes observed in both MAMMOTH and FLATIRON may not represent outcomes of salvage chemotherapy.

Comparative effectiveness

6.15 A summary of effectiveness results of Sd from STORM for the mITT population (TCR/PE MM) and TCR/PR MM is presented in Table 5.

Table 5: Summary of OS, PFS and ORR in STORM

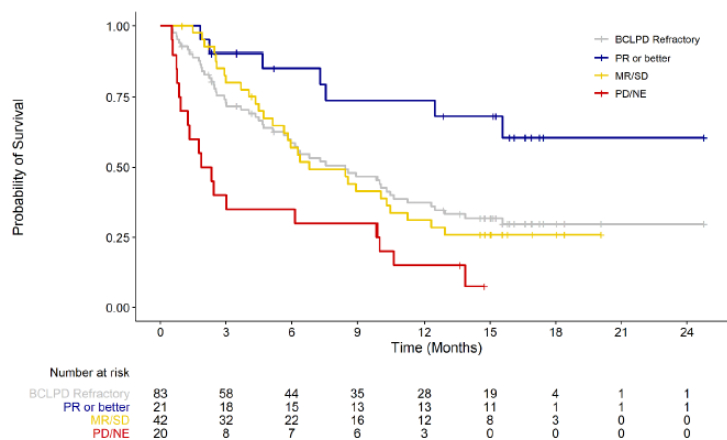
	mITT (N=122)	TCR/PR MM (N=83)
OS		
Patients with event	76/122 (62.3%)	54/83 (65.1%)
Median OS months (95% CI)	8.4 (6.2, 11.2)	8.4 (6.2, 11.2)
PFS		
Patients with event	51/122 (41.8%)	40/83 (48.2%)
Median PFS months (95% CI)	3.7 (2.8, 4.7)	2.8 (1.9, 4.3)
ORR		
Patients with event	32/122	21/83
% (95% CI)	26.2% (18.7, 35.0)	25.3% (16.4, 36.0)

Source: Table 2-14, p66; Table 2-21, p73; Table 2-22, p75 of the submission

CI = confident interval; mITT = modified intention to treat population; ORR = overall response rate; OS = overall survival; PFS = progression free survival

- 6.16 In the modified intention to treat (mITT) population of STORM, median OS was 8.4 months (95% CI: 6.2, 11.2), median progression free survival (PFS) was 3.7 months (95% CI: 2.8, 4.7), and ORR was 26.2% (95% CI: 18.7%, 35.0%). In the STORM TCR/PR MM subgroup, the median OS was 8.4 months (95% CI: 6.2, 11.2), and the median PFS was 2.8 months (95% CI: 1.9, 4.3). The median OS for the TCR/PR MM group appeared to be consistent with the mITT population while the median PFS was numerically shorter (3.7; 95% CI: 2.8, 4.7 in mITT).
- 6.17 The Kaplan Meier plot for OS for Sd by level of response for the TCR/PR MM subgroup in STORM is shown in Figure 2.

Figure 2: Kaplan-Meier estimates of OS for TCR/PR MM in STORM by response

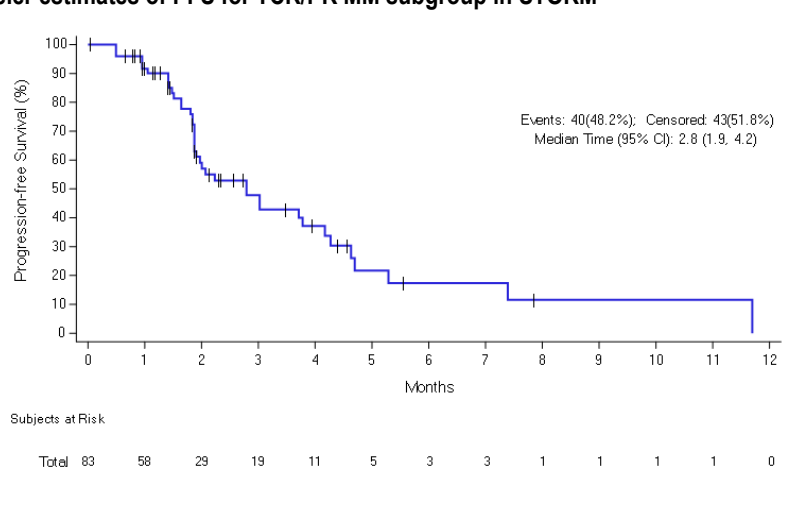


Source: Figure 2-8, p76 of the submission.

BCLPD = bortezomib, carfilzomib, lenalidomide, pomalidomide, daratumumab; MR = minimal response; NE = not estimable/evaluable; OS = overall survival; PD = progressive disease; PR = partial response; SD = stable disease; TCR/PR MM = triple class refractory and penta-refractory multiple myeloma

- 6.18 The Kaplan Meier plot for PFS for Sd for TCR/PR MM subgroup in STORM is shown in Figure 3.

Figure 3: Kaplan-Meier estimates of PFS for TCR/PR MM subgroup in STORM



Source: Figure 2-6, p74 of the submission.

CI = confident interval; PFS = progression free survival; TCR/PR MM = triple class refractory and penta-refractory multiple myeloma

6.19 A summary of the naïve comparative results for TCR/PE MM patients receiving Sd as next subsequent treatment (based on STORM) compared with TCR/PE MM patients receiving conventional care (based on MAMMOTH and FLATIRON) is presented in Table 6.

Table 6: Summary of results from the naïve comparisons in TCR/PE MM subpopulations

	Sd TCR/PE MM with Sd as next subsequent treatment (N = 64) ^a	Conventional care	Naïve comparison (Sd as next subsequent treatment vs. conventional care)
OS			
		MAMMOTH (N=128)	HR (95% CI)
Patients with event	NR	NR	0.64 (0.41, 0.98) ^c p = 0.043
Median OS months (95% CI)	10.4 (7.2, 13.7) ^b	6.9 (5.4, 8.3)	
		FLATIRON (N=36)	HR (95% CI)
Patients with event	NR	NR	0.52 (0.29, 0.95) ^d p = NR
Median OS months (95% CI)	10.4 (7.9, NE) ^b	5.8 (2.8, 12.6)	
ORR			
		MAMMOTH (N=128)	ORR treatment difference (95% CI)
Patients with event	21/64	32/128	NR p = 0.078
% (95% CI)	32.8 (NR, NR)	25.0 (NR, NR)	

Source: Table 2-14, p66; Table 2-21, p73; Table 2-22, p75; Table 2-31, p91; Figure 2-10, p92; Table 2-33, p95 of the submission.

CI = confidence interval; HR = hazard ratio; NA = not applicable; NE = not estimable/evaluable; NR = not reported; ORR = overall response rate; OS = overall survival; Sd = selinexor plus dexamethasone; TCR/PE MM = triple class refractory and penta-exposed multiple myeloma
^a Sd as next subsequent treatment in STORM;

^b Differences in the 95% CIs as reported in the submission. The reason for the difference was unclear;

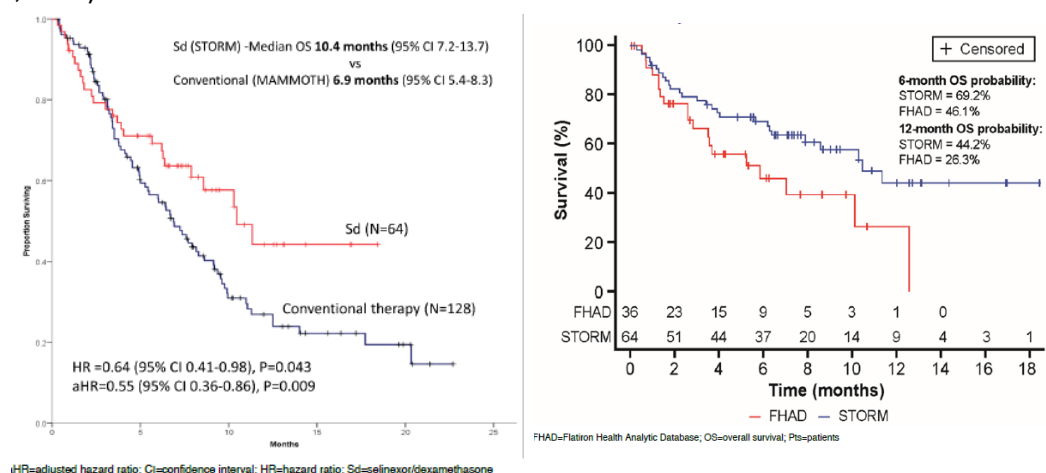
^c Adjusted HR based on multivariate analysis (using study group age, sex, time from diagnosis to study entry, refractoriness to carfilzomib, refractoriness to pomalidomide, and cytogenetic risk) was 0.55 (95% CI: 0.36, 0.86; p=0.009);

^d Adjusted HR using lactate dehydrogenase at baseline, prior number of treatment regimens, and time since initial diagnosis was 0.33 (95% CI: 0.09, 1.15).

6.20 The median OS was 10.4 months (95% CI: 7.2, 13.7) in the STORM TCR/PE MM with Sd as next subsequent treatment versus 6.9 months (95% CI: 5.4, 8.3) in MAMMOTH TCR/PE MM with conventional care; with a hazard ratio (HR) of 0.64 (95% CI: 0.41, 0.98). The median OS in FLATIRON with conventional care was 5.8 months (95% CI: 2.8, 12.6); with a HR (STORM versus FLATIRON) of 0.52 (95% CI; 0.29, 0.95).

6.21 The Kaplan Meier plots for OS for TCR/PE MM subgroup in STORM (TCR/PE MM with Sd as next subsequent treatment) versus MAMMOTH and FLATIRON are shown in Figure 4.

Figure 4: OS in STORM TCR/PE MM with Sd as next subsequent treatment versus MAMMOTH (left) and FLATIRON (right; FHAD)



Source: Figure 2-10, p92, Figure 2-11, p95 of the submission.

CI = confident interval; HR = hazard ratio; OS = overall survival; Sd = selinexor plus dexamethasone; TCR/PE MM = triple class refractory and penta-exposed multiple myeloma

- 6.22 No PFS results were compared in the naïve comparison.
- 6.23 The estimated magnitude of improvement in outcomes in STORM compared with MAMMOTH and FLATIRON, although statistically significant, was uncertain. Patient characteristics differed across the studies whereby patients in STORM appeared to be healthier and/or had less advanced disease than those in MAMMOTH and FLATIRON. This may have biased the outcome in favour of Sd.
- 6.24 The ESC noted that the naïve comparison was subject to applicability issues as (i) it was not based on the requested population for the listing, TCR/PR MM, but a subgroup of patients with TCR/PE MM (and who received Sd as next subsequent treatment); and (ii) MAMMOTH and FLATIRON did not represent the clinical outcomes of the proposed comparator (DCEP) but of conventional care. The direction of bias in the comparison is unclear.

Comparative harms

- 6.25 A summary of treatment-emergent adverse event (TEAEs) in STORM is presented in Table 7.

Table 7: Overall summary of TEAEs 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 2-25, p80 of the submission.

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

^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.

6.26 A summary of TEAEs that occurred in $\geq 10\%$ of patients treated with Sd is presented in Table 8.

Table 8: TEAEs occurring in ≥ 10% patients overall treated with Sd

System organ class preferred term	SAP (N=123); n (%)	TCR/PR MM (N=83) n (%)
Patients with ≥ 1 TEAE	123 (100)	83 (100)
Blood and lymphatic system disorders	105 (85.4)	72 (86.7)
Thrombocytopenia	92 (74.8)	63 (75.9)
Anaemia	82 (66.7)	55 (66.3)
Neutropenia	49 (39.8)	35 (42.2)
Leukopenia	41 (33.3)	30 (36.1)
Lymphopenia	20 (16.3)	12 (14.5)
Eye disorders	29 (23.6)	17 (20.5)
Vision blurred	13 (10.6)	10 (12.0)
Gastrointestinal disorders	113 (91.9)	76 (91.6)
Nausea	88 (71.5)	56 (67.5)
Diarrhoea	58 (47.2)	42 (50.6)
Vomiting	48 (39.0)	32 (38.6)
Constipation	27 (22.0)	19 (22.9)
General disorders and administration site conditions	102 (82.9)	65 (78.3)
Fatigue	77 (62.6)	50 (60.2)
Pyrexia	20 (16.3)	15 (18.1)
Asthenia	22 (17.9)	13 (15.7)
Infections and infestations	71 (57.7)	47 (56.6)
Upper respiratory tract infection	17 (13.8)	11 (13.3)
Pneumonia	21 (17.1)	10 (12.0)
Investigations	75 (61.0)	50 (60.2)
Weight decreased	62 (50.4)	38 (45.8)
Metabolism and nutrition disorders	99 (80.5)	67 (80.7)
Decreased appetite	70 (56.9)	46 (55.4)
Hyponatraemia	46 (37.4)	32 (38.6)
Hyperglycaemia	15 (12.2)	9 (10.8)
Dehydration	13 (10.6)	7 (8.4)
Hypokalaemia	24 (19.5)	18 (21.7)
Hypercreatininaemia	6 (4.9)	4 (4.8)
Nervous system disorders	63 (51.2)	43 (51.8)
Dizziness	19 (15.4)	15 (18.1)
Dysgeusia	10 (8.1)	8 (9.6)
Psychiatric disorders	52 (42.3)	36 (43.4)
Insomnia	22 (17.9)	17 (20.5)
Confusional state	15 (12.2)	13 (15.7)
Respiratory, thoracic, and mediastinal disorders	61 (49.6)	38 (45.8)
Dyspnoea	28 (22.8)	13 (15.7)
Cough	18 (14.6)	9 (10.8)
Epistaxis	15 (12.2)	8 (9.6)

Source: Table 2-26, p81 of the submission

SAP = safety analysis population; TCR/PR MM = triple class refractory and penta-refractory multiple myeloma; TEAE = treatment-emergent adverse event; Sd = selinexor plus dexamethasone

Note: Adverse Events are coded using MedDRA version 22.0. Patients are counted once within each system organ class and preferred term. Percentages are based on the number of all-treated patients in each treatment group. A TEAE is defined as an adverse event that emerged or worsened in the period from date of first dose to 30 days after the date of last dose. The date of onset of the adverse event was used to determine treatment emergence.

6.27 The majority of the mITT population in STORM had a ≥ Grade 3 TEAE (93.5%). The submission provided details on any grade TEAE (Table 8). Based on the Clinical Study

Report of STORM, the ESC noted that the most frequently occurring (>10% of patients) \geq Grade 3 severe hematologic adverse events included thrombocytopenia (61.8%), anaemia (44.7%), neutropenia (22.0%), leukopenia (13.8%), and lymphopenia (11.4%). The most frequently occurring (> 10% of patients) \geq Grade 3 severe non-hematologic adverse events included hyponatremia (22.0%) and fatigue (21.1%). Further, 89.4% of patients were assessed to have \geq Grade 3 adverse events that related to Sd. Other TEAEs with potentially serious implications included pneumonia (14/123; 11.4%) and sepsis (12/123; 9.8%). Of the mITT population, 61.8% had any dose reduction of selinexor and 31.7% discontinued treatment due to an adverse event.

- 6.28 The safety profile of the TCR/PR MM subgroup appears to be similar to the STORM mITT population. For TCR/PR MM, nearly all patients treated on study (94.0%) had a \geq Grade 3 TEAE. The most frequently occurring (>10% of patients) severe hematologic adverse events included thrombocytopenia (62.7%), anaemia (48.2%), neutropenia (24.1%), leukopenia (18.1%), and lymphopenia (10.8%). The most frequently occurring (> 10% of patients) severe non-hematologic severe adverse events included hyponatremia (22.9%) and fatigue (20.5%). Of the TCR/PR MM patients, 59.0% had any dose reduction. No data were reported for the number of patients who discontinued treatment due to an adverse event in this subgroup.
- 6.29 The ESC noted that there were no comparative safety data between Sd and the proposed comparator presented in the submission. The PSCR and the pre-PBAC response stated that there was limited comparative safety assessment given safety data was not reported in MAMMOTH; however, the adverse events associated with Sd were generally manageable.
- 6.30 The ESC noted that a high proportion of Sd patients experienced adverse events, particularly haematological, and dose reduction or discontinuation of treatment.

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 submission described Sd as superior in terms of effectiveness when compared to current standard care, with the PSCR stating that the effectiveness claim was supported by the clinical evidence presented in the STORM study including a 25.3% ORR and a rapid time to response (4 weeks for the responders). The ESC considered that this claim was not adequately supported. The key transitivity and applicability issues were: (i) the high risk of bias in STORM given it is a non-randomised, single arm, open-label study; (ii) the naïve comparison appeared to be based on patients with characteristics which differed across studies which may favour Sd (in particular, patients were more likely to be healthier and/or had less advanced disease and a high proportion of patients received subsequent treatment after Sd in STORM); (iii)

the naïve comparison was based on populations that were not applicable to the requested listing; and (iv) no comparative PFS data were provided.

- 6.33 The PBAC considered that the claim of superior comparative effectiveness was not adequately supported by the data.
- 6.34 The submission described Sd as superior in terms of safety compared to salvage chemotherapy. The ESC considered that this claim was not adequately supported as there were no comparative safety data between Sd and the proposed comparator presented in the submission. The ESC noted that a high proportion of Sd patients experienced adverse events, particularly haematological, and dose reduction or treatment discontinuation when receiving Sd. Overall, the ESC considered the comparative benefit of Sd compared to conventional therapy was uncertain and Sd was associated with significant toxicity.
- 6.35 The PBAC considered that the claim of superior comparative safety was not adequately supported by the data.

Economic analysis

- 6.36 The submission 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. Given that the evidence presented in the clinical section did not support the claim of superior clinical efficacy the use of a CUA was not appropriate. A summary of key components of the economic evaluation is presented in Table 9.

Table 9: Key components of the economic evaluation

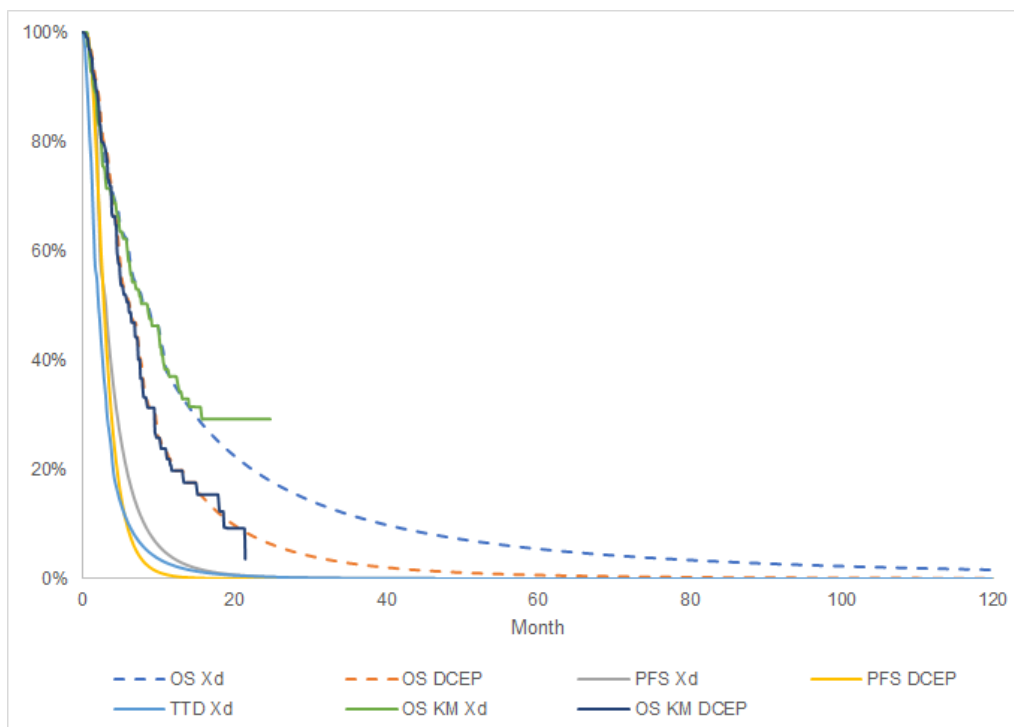
Component	Description	Justification/comments
Type of model	Cost-utility analysis	Not appropriate; claim of clinical superiority was not supported by the clinical evidence.
Outcomes	QALYs gained	Appropriate
Time horizon	7 years	Inadequately justified. Shorter time horizon (5 years) was previously suggested by the PBAC for RRMM patients (6.46, plitidepsin, PSD, July 2019 PBAC meeting).
Method used to generate results	PSA incorporating a cohort expected value analysis	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. The PSCR stated that based on the baseline characteristics of patients in the TCR/PR subgroups of STORM and MAMMOTH, the overall direction of bias of clinical outcomes used in the economic model was against Sd. The PSCR stated that this suggested that the use of a PSA would be conservative. The ESC considered that it was likely that the patients in STORM were fitter and had a better disease prognosis and that the direction of bias likely favoured Sd.
Health states	Progression free, progressive disease, and death	Appropriate
Cycle length	1 week	Appropriate
Allocation to health states	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 use of KM curves appears appropriate. Approaches for the extrapolation were inadequately justified and the proportion of patients alive at the end of time horizon appears to be overestimated.
Health utility values	Derived using an existing regression equation estimating utility values of RRMM patients based on the NIMBUS trial. Data from STORM and MAMMOTH (and an external study Yuen et al., 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 which requires at least four prior treatment regimens. This equation has been considered by the PBAC before (July 2019 plitidepsin submission).
Software	Excel 2010	-

Source: Table 3-1, p108-109 of the submission.

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; PSCR = pre-Subcommittee Response; PSD = public document summary; QALY = quality-adjusted life year; RRMM = relapsed and/or refractory multiple myeloma; Sd = selinexor plus dexamethasone; TCR/PR MM = triple class refractory and penta-refractory multiple myeloma; TTD = time to treatment discontinuation

- 6.37 The clinical outcomes used in the economic model were based on TCR/PR MM from STORM (PFS, OS and time-to-treatment discontinuation; TTD) and MAMMOTH (OS). This was consistent with the proposed population. However, these clinical data were not the same data used in the naïve comparison (that were based on TCR/PE MM) but were based on different subgroups of STORM and MAMMOTH (STORM TCR/PR MM for Sd, n = 83 and MAMMOTH TCR/PR MM; n = 70, Gandhi et al., 2019; see Table 2 for a detailed comparison of the different subgroups from STORM).
- 6.38 The submission used a 7-year time horizon in the base case. The PBAC had previously considered that a 7-year time horizon for plitidepsin when used as a fourth line MM treatment was not appropriate and suggested that a 5-year time horizon might be more reasonable (paragraph 6.46, plitidepsin PSD, July 2019). In addition, the proposed patients in this submission appeared to be more heavily pre-treated than those requested for plitidepsin. The PSCR argued that a 7-year time horizon was appropriate given the median OS had not yet been reached. The ESC considered this was not justified given the study had limited follow-up time and no long-term data for OS outcomes. Decreasing the time horizon from 7 years to 5 years increased the incremental cost effectiveness ratio (ICER) from \$55,000 to < \$75,000 per quality-adjusted life year (QALY) gained in the base case to \$75,000 to < \$95,000 per QALY gained.
- 6.39 The log-normal distribution for OS of Sd was chosen for the base case analysis of the model. The choice of the log-normal distribution was supported by the goodness-of-fit statistics (as it had the lowest Akaike information criteria (AIC) and Bayesian information criteria (BIC)); see Figure 5. The log-normal distribution had a slow death rate at the later time points in the model, such that a small proportion of patients (3.2%) remained alive at the end of the time horizon (7 years). The ESC considered that a modelled survival benefit was not reasonable given the clinical claim of superior efficacy was not adequately supported. In STORM, only 4 patients remained at risk at Month 18 and 1 patient remained at risk at Month 24. The ESC noted that the magnitude of OS gain estimated by the economic model was a significant driver of the model with 81% of the life years gained in the progressive disease state.
- 6.40 The Weibull and Gamma distributions did not result in a survival advantage for Sd. Applying a Weibull distribution to both arms increased the ICER from \$55,000 to < \$75,000 per QALY in the base case to \$95,000 to < \$115,000 per QALY.

Figure 5: Base case OS, PFS, and TTD estimated in the economic model



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

DCEP = dexamethasone, cyclophosphamide, etoposide, and cisplatin; KM = Kaplan Meier; OS = overall survival; PFS = progression free survival; TTD = time to treatment discontinuation; Xd = selinexor plus dexamethasone

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

- 6.41 The ESC noted that the modelled benefit in PFS was not supported by the presented clinical evidence. The pre-PBAC response noted that although PFS was not reported for the MAMMOTH population, it was derived in the base case by assuming that the relationship between OS and PFS was equivalent between the treatment arms. The pre-PBAC response stated that as the impact of the assumed PFS benefit was minimal in sensitivity analyses the uncertainty associated with the use of a partitioned survival analysis was also minimal.
- 6.42 The submission did not account for post-progression costs in the economic model. This was inappropriate given that half of the patients in STORM (61/122; 50%) received subsequent treatments following Sd. The pre-PBAC response explored the impact of the inclusion of post-progression treatment costs (see paragraph 6.48).
- 6.43 The submission calculated treatment specific utility values using a regression equation from the submission of pomalidomide for RRMM previously treated with lenalidomide and bortezomib submitted to NICE in 2016 (TA427; pomalidomide with dexamethasone versus high-dose dexamethasone for treatment of RRMM). The PBAC has previously considered the use of this regression equation in calculating utility values for RRMM to be appropriate in its consideration of plitidepsin (paragraph 6.42, plitidepsin PSD, July 2019). The submission provided a comparison of the utility values used in this submission with the plitidepsin submission from July 2019 as presented in

Table 10. The utility values used in this submission are slightly lower than those used in the plitidepsin submission. This may be reasonable given that Sd patients had more previous treatments than patients in the plitidepsin submission (3 to 4 previous treatments).

Table 10: Comparison of utility values calculated for STORM, MAMMOTH and ADMYRE

Calculated utility sources	Progression-free survival	Progressive disease	Decrement
Plitidepsin (ADMYRE) PBAC evaluation (PBAC, 2019)	0.7051	0.6241	0.081
Sd: STORM	0.677	0.588	0.089
DCEP: MAMMOTH and Yuen et al., 2018	0.651	0.569	0.082

Source: Table 3-14, p149-150 of the submission.

DCEP = dexamethasone, cyclophosphamide, etoposide, and cisplatin; PBAC = Pharmaceutical Benefits Advisory Committee; Sd = selinexor plus dexamethasone

6.44 A summary of the key drivers of the model as per the Table 11.

Table 11: Key drivers of the model

Description	Method/Value	Impact
		Base case: \$ [redacted] 1 per QALY
Extrapolation of OS (Sd)	Log-normal distribution (appropriate based on AIC and BIC criteria; however, data were immature)	High; favours Sd Use of the Weibull distribution increased the ICER to \$ [redacted] 2 per QALY.
Convergence for OS of Sd	No convergence applied for OS of Sd	Moderate, favours Sd Convergence applied from month 48 increased the ICER to \$ [redacted] 3 per QALY
Time horizon	7 years	Moderate, favours Sd Use of 5 years for time horizon increased the ICER to \$ [redacted] 3 per QALY

Source: Developed during the evaluation

AIC = Akaike information criterion; BIC Bayesian information criterion; ICER = incremental cost effectiveness ratio; OS = overall survival; QALY = quality-adjusted life year; Sd = selinexor plus dexamethasone

The redacted values correspond to the following ranges:

¹ \$55,000 to < \$75,000

² \$115,000 to < \$135,000

³ \$75,000 to < \$95,000

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
Life years	1.17	0.72	0.45 ^a
QALYs	0.68	0.41	0.27
Total Costs	\$ [redacted]	\$40,819	\$ [redacted]
ICER (cost per life year gained)			\$ [redacted] ¹
ICER (cost per QALY gained)			\$ [redacted] ²

Source: Table 3-21, p155 of the submission.

DCEP = dexamethasone, cyclophosphamide, etoposide, and cisplatin; ICER= incremental cost effectiveness ratio; QALY= quality adjusted life year; Sd = selinexor plus dexamethasone

^a undiscounted value was 0.51 life years.

The redacted values correspond to the following ranges:

¹ \$35,000 to < \$45,000

² \$55,000 to < \$75,000

6.46 The results of key sensitivity analyses are summarised in Table 13.

Table 13: Key results of sensitivity analyses

Scenario	Base-case value	Scenario analysis value	Inc. QALY	Inc. costs	ICER	Change
Base case			0.270	\$ [REDACTED]	\$ [REDACTED] ¹	-
Time horizon	7 years	3 years	0.180	\$ [REDACTED]	\$ [REDACTED] ²	+33%
		5 years	0.239	\$ [REDACTED]	\$ [REDACTED] ³	+9%
Application of disutility for AE	As per NICE TA427 utility regression model (covariates for progressed status, best overall response and AE)	Rate of DCEP AEs equal to Sd	0.256	\$ [REDACTED]	\$ [REDACTED] ³	+5%
Convergence of OS for Sd	No convergence	Convergence begins at month 72 (12 months prior the end of time horizon) ^a	0.264	\$ [REDACTED]	\$ [REDACTED] ³	+8%
		7 years and convergence beginning at month 48 ^a	0.257	\$ [REDACTED]	\$ [REDACTED] ³	+11%
Discontinuation due to AE for DCEP	60.5%	30.1% (same as Sd)	0.256	\$ [REDACTED]	\$ [REDACTED] ³	+5%
OS extrapolation: Sd	Log-normal	Weibull	0.156	\$ [REDACTED]	\$ [REDACTED] ⁴	+77%
Time horizon and convergence of OS for Sd	7 years and no convergence	5 years and convergence beginning at month 48 (12 months prior the end of time horizon) ^a	0.228	\$ [REDACTED]	\$ [REDACTED] ³	+25%

Source: Table 3-26, p163-164 of the submission; Conducted during the evaluation

AE = adverse event; DCEP = dexamethasone, cyclophosphamide, etoposide, and cisplatin; ICER = incremental cost effectiveness ratio; Inc = incremental; NICE TA = National Institute for Health and Care Excellence technology appraisal; OS = overall survival; QALY = quality-adjusted life year; Sd = selinexor plus dexamethasone; TTD = time to treatment discontinuation

^a Arbitrarily chosen by the evaluator

The redacted values correspond to the following ranges:

¹ \$55,000 to < \$75,000

² \$95,000 to < \$115,000

³ \$75,000 to < \$95,000

⁴ \$115,000 to < \$135,000

6.47 Given the uncertainty surrounding the clinical claim, the differences in the STORM and MAMMOTH patient cohorts and the high risk of bias associated with the clinical data, the ESC considered that a revised model should be conservative and incorporate: (i) a 5-year time horizon; (ii) the fitting of independent survival curves for OS that predicted more realistic survival effects; and (iii) no PFS advantage for Sd. Additional revisions would be required to include post-progression and adverse event costs.

6.48 The pre-PBAC response presented a multivariate analysis which applied a 5-year time horizon, incorporated post progression treatment costs and assumed no PFS benefit. This resulted in an ICER of \$75,000 to < \$95,000 per QALY. The pre-PBAC response included a multivariate analysis that also applied convergence of OS from years 4 to 5, resulting in an ICER of \$95,000 to < \$115,000 per QALY. The pre-PBAC response then proposed a reduced DPMQ for selinexor (\$ [REDACTED] for 20 mg x 32) which resulted in an ICER of \$75,000 to < \$95,000 per QALY.

Drug cost/patient/course

6.49 A summary of the drug cost per patient for Sd and DCEP is presented in Table 14. The average time on treatment of Sd estimated from the model was 13.35 weeks, and the proposed drug cost/patient/course was estimated to be \$ [REDACTED]. The estimated cost/patient/course for DCEP in the economic model (\$3,645.68) was higher than in the financial analysis (\$915.63). This discrepancy was due to wastage being taken into account in the economic model, but not in the financial estimates and inconsistent application between the model and the financial estimates in the cost/pack of etoposide. The overall impact of these inconsistencies is small due to the low price of DCEP.

Table 14: 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: 71.5% d: 80.0%	S: 65.4% d: 80.0%	S: 65.4% d: 80.0%	NA	100%	100%
Mean duration	11.2 weeks	13.35 weeks	13.35 weeks	NA	Mean duration: 7.73 weeks ^a Mean number of doses: 7.73	Mean duration: 7.61 weeks Mean number of doses: 7.61
Compliance	NA	NA	98.4%	NA	Not applied	98.4%
Cost/patient/dose/week	S: \$ [REDACTED]/w d: \$ [REDACTED]/w	S: \$ [REDACTED]/w d: \$ [REDACTED]/w	S: \$ [REDACTED]/w d: \$ [REDACTED]/w	NA	Cost/dose D: \$5.76 C: \$157.48 E: \$158.90 P: \$149.61	Cost/dose D: \$5.76 C: \$66.33 E: \$14.06 P: \$36.13
Cost/patient	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	NA	\$3,645.68	\$915.63

Source: Developed during the evaluation

C = cyclophosphamide; d/D = dexamethasone; DCEP = dexamethasone, cyclophosphamide, etoposide, cisplatin; E = etoposide; NA = not applicable; P = cisplatin; S = selinexor; Sd = selinexor plus dexamethasone; w = week

^a based on fixed 2 cycles of (4-week treatment-cycle) assumed in the economic model and adjusted by death of patients in the second-cycle of treatment = 1.93 treatment-cycles.

Estimated PBS usage & financial implications

6.50 This submission was considered by DUSC. The submission used an epidemiological approach to estimate the financial implications. A summary of key inputs used in the estimation is presented in Table 15.

Table 15: Key inputs for financial estimates

Parameter	Value applied and source	Comment
Prevalent patients	23.9 per 100,000 (AIHW 2017)	-
Receive active treatment	94.64% (AIHW 2017, PBS 10% Dataset, Yong et al., 2016)	-
On 2L treatment	31.96% (PBS 10%)	Number of patients on 2L treatment was overestimated. The PBAC previously acknowledged the results of 2018 PBS data analysis suggesting the total number of patients accessing 2L treatments to be 1,127 (paragraph 7.14, daratumumab PSD, November 2019).
On 2L treatment with DBd	50% in Year 1 increasing to 90% in Year 6 (daratumumab, PSD, July 2020 PBAC meeting)	DUSC considered that this was overestimated
Time on 2L to 4L treatment	45.3 months (sum of median TTNT of 33.3 of 2L; DBd in CASTOR 2L population, median time to progression of 7 months in 3L; Yong et al., 2016, and median TTNT of 5 months in 4L; Yong et al., 2016)	These data could not be verified. All patients were assumed to have time on 2L to 4L treatment of 45.3 months. Likely underestimated number of patients at early period of the estimate.
Proportion of 2L to 4L refractory and become Sd eligible	20.9%: 85% (2L; assumption based on CASTOR) x 62.3% (3L; Yong et al., 2016) x 39.5% (4L; Yong et al., 2016)	These data could not be verified. Likely overestimated.
Sd eligible patients based on clinical trials or Janssen's compassionate / early access program (CAP/EAP)	█ ¹ in Year 1 increasing to █ ¹ in Year 6 (observed and forecasted daratumumab initiations in the MRDR report)	Could not be verified. DUSC considered that this was overestimated and the number would be closer to █ ¹ patients in Year 1.
Grandfather patients	█ ¹	Inconsistent with Section 1 of the submission which stated that approximately █ ¹ patients will be grandfathered.
Uptake rate	█%	DUSC considered that the uptake rate was substantially overestimated given the toxicity profile of selinexor.
Duration of Sd treatment	3.07 months	DUSC considered that this was overestimated given the toxicity profile of selinexor.
Compliance rate	98.4% (STORM)	DUSC considered that this was overestimated given the toxicity profile of selinexor.

Source: Table 4-1, p166, Table 4-2, p167; Table 4-3, p168; Table 4-4, p170; Table 4-5, p170; Table 4-7, p172 of the submission.

2L = second-line treatment, 3L = third-line treatment; 4L = fourth-line treatment; AIHW = Australian Institute of Health and Welfare; DBd = daratumumab plus bortezomib and dexamethasone; DUSC = Drug Utilisation Sub-Committee; MRDR = Myeloma and Related Diseases Registry; PBAC = Pharmaceutical Benefits Advisory Committee; PBS = Pharmaceutical Benefits Scheme; PSD = public summary document; Sd = selinexor plus dexamethasone; TTNT = time to next treatment

The redacted values correspond to the following ranges:

¹ < 500

6.51 The submission estimated the number of patients on second-line treatment to be 500 to < 5,000 patients in Year 1; whereas, the PBS data considered by the PBAC for the daratumumab submission indicated that the total number of patients accessing

second-line treatment was 1,127 in 2018 (paragraph 6.63. daratumumab PSD, November 2019).

6.52 The uptake of █% appeared to be overestimated given that Sd appeared to have high toxicity. The PBAC previously considered that an uptake rate of 81.9% and 45% for third-line treatment and fourth-line treatment respectively of plitidepsin were overestimated (Table 22, plitidepsin, PSD, March 2020 PBAC meeting).

6.53 A summary of the estimated use and financial implications of selinexor is presented in Table 16.

Table 16: Estimated use and financial implications (effective)

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
Estimated extent of use						
Number of patients treated	█ ¹	█ ¹	█ ¹	█ ¹	█ ¹	█ ¹
Number of scripts dispensed	█ ¹	█ ¹	█ ¹	█ ²	█ ²	█ ²
Estimated financial implications of selinexor						
Cost to PBS/RPBS less copayments	\$█ ³	\$█ ³	\$█ ³	\$█ ³	\$█ ³	\$█ ³
Estimated financial implications for other medicines						
Cost to PBS/RPBS less copayments	-\$█ ³	-\$█ ³	-\$█ ³	-\$█ ³	-\$█ ³	-\$█ ³
Net financial implications						
Net cost to PBS/RPBS	\$█ ³	\$█ ³	\$█ ³	\$█ ³	\$█ ³	\$█ ³
Net cost to MBS	-\$█ ³	-\$█ ³	-\$█ ³	-\$█ ³	-\$█ ³	-\$█ ³
Net cost to PBS/RPBS/MBS	\$█ ³	\$█ ³	\$█ ³	\$█ ³	\$█ ³	\$█ ³

Source: financial worksheet; Table 4-6, p17; Table 4-8, p172; Table 4-11, p173; Table 4-21, p180 of the submission.
MBS = Medicare Benefits Schedule; PBS = Pharmaceutical Benefits Scheme; RPBS = Repatriation Pharmaceutical Benefits Scheme
The redacted values correspond to the following ranges:
¹ < 500
² 500 to < 5,000
³ \$0 to < \$10 million

6.54 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 \$30 million to < \$40 million in the first 6 years of listing.

6.55 The DUSC considered that the net financial implications were likely overestimated, as:

- the number of patients receiving second-line daratumumab treatment was overestimated;
- it was unclear how many of the < 500 patients from the Myeloma and Related Diseases Registry (MRDR) who received daratumumab would be considered second-line use or compassionate use of third-line or subsequent lines of therapy. DUSC considered that < 500 patients in Year 1 was an overestimate and suggested that the number would be closer to < 500 patients in the first year. The pre-PBAC response noted that < 500 patients had accessed daratumumab via the compassionate/early access program or via clinical trials since 2016;

- the uptake rate was substantially overestimated. DUSC commented that there was an unclear benefit and a high toxicity associated with selinexor. DUSC noted that the estimates were sensitive to the uptake rates applied;
- patients would be frailer in real world practice and the treatment duration of 3.1 months proposed in the submission was likely overestimated;
- the compliance rate of 98.4% was likely overestimated. DUSC considered that given the toxicity profile of selinexor, patients were likely to omit doses or elect to stop treatment. DUSC considered that a compliance rate of 80% would be more appropriate.

Quality Use of Medicines

- 6.56 The submission did not provide discussion of quality use of medicines. DUSC expressed concern that the quality use of medicines issues for this first in class medication with significant toxicities was not addressed in the submission. DUSC considered that as the sponsor has knowledge of both study data and overseas use, this should form a comprehensive training and education program such that practitioners are well-equipped to handle selinexor's adverse event profile.
- 6.57 The pre-PBAC response indicated that the sponsor was preparing a multi-stakeholder quality use of medicines approach for haematologists, nurses, pharmacists and patients to ensure minimisation of adverse events and optimised treatment.

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

7 PBAC Outcome

- 7.1 The PBAC did not recommend 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, noting the lack of comparative data between Sd and the nominated comparator, salvage chemotherapy consisting of dexamethasone, cyclophosphamide, etoposide and cisplatin (DCEP), considered that the clinical claims of superior efficacy and safety were not supported. The PBAC considered that the economic model was unreliable for decision making and that the financial impact estimates were likely overestimated.
- 7.2 The PBAC noted the consumer comments describing the ongoing need for new therapies for the treatment of MM.
- 7.3 The PBAC noted that the proposed place in therapy of Sd was as a salvage therapy following late relapse in patients 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 at least one anti-CD38 monoclonal antibody. The PBAC, noting that the requested restriction was narrower than the proposed TGA indication, considered that this was reasonable.
- 7.4 The PBAC noted that the submission nominated salvage chemotherapy, represented

by DCEP, as the primary comparator. The PBAC, noting that there was no standard therapy for patients with TCR/PR MM, considered that DCEP was representative of last-line care.

- 7.5 The PBAC noted the submission was based on data from a non-randomised, single arm, open-label study, STORM, that included patients with penta-exposed (PE) MM who received Sd. The PBAC noted that data were presented for a subgroup of patients who had TCR/PR MM. In addition, the PBAC noted that the submission presented naïve indirect treatment comparisons (ITCs) for overall survival (OS) and overall response rate (ORR) between another subgroup of STORM, those with TCR/PE MM receiving Sd as the next subsequent treatment, and patients from two retrospective studies, MAMMOTH and FLATIRON. The PBAC noted that the TCR/PE subgroup from STORM was used to align with patients from MAMMOTH who had TCR/PE MM and received at least one further line of conventional therapy.
- 7.6 The PBAC noted that for the TCR/PR MM subgroup treated with Sd, the median OS was 8.4 months (95% CI: 6.2, 11.2), median progression free survival (PFS) was 2.8 months (95% CI: 1.9, 4.3) and the ORR was 25.3% (95% CI: 16.4%, 36.0%). For the TCR/PE MM subgroup who received Sd as the next subsequent treatment, the PBAC noted that median OS was 10.4 months (95% CI: 7.2, 13.7) and the ORR was 32.8% (95% CI: NR, NR).
- 7.7 The PBAC considered that the naïve ITCs between the TCR/PE subgroup of STORM and the MAMMOTH and FLATIRON retrospective studies were highly uncertain as:
- no comparative PFS data were presented;
 - there were differences between the patient populations that indicated that STORM patients were healthier and had less advanced disease than those in MAMMOTH and FLATIRON (see paragraph 6.12); and
 - there were applicability issues including that (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), but of conventional care (see paragraph 6.14).
- 7.8 In addition, the PBAC noted that the results for the TCR/PE subgroup from STORM were improved compared to the TCR/PR subgroup. The PBAC considered that it would be informative to see a comparison using data from the TRC/PR subgroup, as this was the proposed PBS population.
- 7.9 Overall, the PBAC considered that the submission's claim that Sd was superior compared to DCEP in terms of efficacy was not supported.
- 7.10 The PBAC noted that the majority of patients in the STORM study experienced a Grade ≥ 3 adverse event (93.5%), with patients experiencing high rates of Grade ≥ 3 haematological and gastrointestinal adverse events and events resulting in dose modifications or discontinuation. 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.

7.11 The PBAC considered that as the clinical data presented in the submission did not support the claims that Sd was superior in terms of efficacy and safety compared to DCEP, the cost utility analysis was not justified. In addition, the PBAC noted that the clinical outcomes used in the economic model, although consistent with the proposed PBS population, were based on the TCR/PR MM subgroup from STORM whereas the naïve ITC was based on the TCR/PE MM subgroup. The PBAC noted other uncertainties, including the:

- time horizon of 7 years. The PBAC considered 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;
- modelled survival benefit that resulted in 3.2% of Sd patients alive at the end of the 7-year time horizon. The PBAC, noting that 81% of the life years gained were in the progressed disease state, considered that the modelled survival benefit was optimistic and not reasonable;
- modelled benefit in PFS was not supported by the evidence presented, as PFS was not reported for the MAMMOTH population;
- model did not account for post progression treatment costs despite 50% of patients in STORM receiving subsequent treatment following Sd; and
- underestimation of adverse events costs associated with Sd as the model assumed patients experienced an event only once and that events were resolved within one treatment cycle.

7.12 The PBAC considered that the resultant incremental cost effectiveness ratio (ICER) of \$55,000 to < \$75,000 per quality adjusted life year (QALY) was highly uncertain and likely underestimated. The PBAC noted that the pre-PBAC response presented a revised base case which (i) applied a 5 year time horizon, (ii) incorporated post progression treatment costs, (iii) assumed no PFS benefit, (iv) applied OS convergence from years 4 to 5, and (v) applied a reduced price for selinexor. The PBAC noted that the revised base case resulted an ICER of \$75,000 to < \$95,000 per QALY. The PBAC considered that the revised base case ICER remained unacceptably uncertain and, in this context, considered the ICER to be high.

7.13 In terms of the utilisation and financial impact estimates, the PBAC agreed with the DUSC and considered that these were overestimated for the reasons outlined in paragraph 6.55.

7.14 The PBAC noted that the submission did not propose a Risk Sharing Arrangement.

7.15 The PBAC considered that any future resubmission for Sd should present:

- efficacy data for the proposed PBS population in the ITC;

- comparative safety data;
- a revised economic model which addressed the uncertainties outlined in paragraph 7.11 and that was conservative in its assumptions. The PBAC considered that the revised model should result in a base case ICER which appropriately accounted for the uncertainties in the clinical data; and
- revised utilisation and financial impact estimates which incorporate the advice provided by DUSC (paragraph 6.55).

7.16 The resubmission may be lodged at any future standard due date for PBAC submission using the standard re-entry pathway.

7.17 The PBAC advised that this submission is eligible for an Independent Review.

Outcome:

Not recommended

8 Context for Decision

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

9 Sponsor's Comment

Antengene is committed to working with the PBAC to secure equitable access to selinexor for patients and physicians in penta-refractory multiple myeloma. Patients at this late stage have very limited options and it is important for them to have access to novel agents with a new mechanism of action. We wish to thank and acknowledge the contribution of clinicians, patients, and advocacy groups in supporting this submission.