5.09 SELINEXOR, Tablet 20 mg, Xpovio®, Antengene (Aus) Pty. Ltd.

1 Purpose of Application

1.1 The Category 1 submission requested Section 100 listing for selinexor for the treatment of adult patients with relapsed and/or refractory (RR) diffuse large B-cell lymphoma (DLBCL) after at least two lines of systemic therapy.

1.2 Listing was requested based on a cost-effectiveness analysis versus rituximab salvage therapy, specifically rituximab-gemcitabine-oxaliplatin (RGemOx).

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 diffuse large B-cell lymphoma (RR DLBCL), not otherwise specified, including DLBCL arising from follicular lymphoma, after at least two lines of systemic therapy
Intervention	Selinexor 60 mg twice weekly until progression
Comparator	Salvage chemotherapy, specifically rituximab-based (rituximab-gemcitabine-oxaliplatin (RGemOx)) which is the main comparator (current clinical practice) for RR DLBCL
Outcomes	Response rates, progression free survival and overall survival
Clinical claim	In adult patients with RR DLBCL after at least two lines of systemic therapy, treatment with selinexor is superior to salvage chemotherapy treatments in efficacy and safety outcomes in extending progression free survival

Source: Table 1-1, p16 of the submission.
DLBCL = diffuse large B-cell lymphoma; RGemOx = rituximab-gemcitabine-oxaliplatin; RR = relapsed/refractory

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 the treatment of:

'Adult patients with relapsed and/or refractory diffuse large B-cell lymphoma, not otherwise specified, including DLBCL arising from follicular lymphoma, after at least two lines of systemic therapy.'

2.3 Selinexor was approved by the US FDA for RR DLBCL in June 2020.

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

3 Requested listing

Name, Restriction, Manner of administration and form	Max. Qty	№.of Rpts	Dispensed Price for Max. Qty	Proprietary Name and Manufacturer
SELINEXOR Tablet 20 mg	20	2	Published: Public - $[redacted] Private - $[redacted] Effective: Public - $[redacted] Private - $[redacted]	XPOVIO®, Antengene
SELINEXOR Tablet 20 mg	24	2	Published: Public - $[redacted] Private - $[redacted] Effective: Public - $[redacted] Private - $[redacted]	

Category/Program:	Section 100 – Highly Specialised Drugs Program (Public/Private Hospital)
Prescriber type:	☐Dental ☒Medical Practitioners ☐Nurse practitioners ☐Optometrists ☐Midwives
Condition:	Diffuse large B-cell lymphoma
PBS indication:	Initial and continuing treatment following at least two lines of previous drug therapy for relapsed and/or refractory diffuse large B-cell lymphoma
Treatment phase:	Initial and continuing
Restriction:	☒ Authority Required – STREAMLINED
Clinical criteria:	Patient must have received an autologous haematopoietic stem cell transplant and experienced disease relapse OR Patient must not be eligible for stem cell transplantation AND The condition must be relapsed and/or refractory to at least two prior therapies. The condition must not be central nervous system lymphoma. The treatment must be used as monotherapy AND The treatment must be discontinued in patients who experience disease progression whilst on treatment.
Definitions:	Refractory disease is defined as progressive disease less than 6 months (if no previous autologous stem-cell transplantation) or less than 12 months (if previous autologous stem-cell transplantation) from end of treatment.

3.1 The submission proposed a special pricing arrangement. The proposed effective and published prices are shown in the in the table above.

3.2 The requested restrictions were consistent with the proposed TGA indication.

3.3 DUSC noted that the submission requested listing of two packs sizes of 20 mg tablets 20- and 24-packs, and that a 16- and 32-pack sizes were included in the TGA submission. The dose of selinexor, as per the draft Product Information, is 60 mg (3 x 20 mg tablets) on Days 1 and 3 of each week. Thus, the 24-tablet pack would allow for 4 weeks treatment. The 20-tablet pack is intended for use if dose reductions are required. In its pre-Sub-Committee Response (PSCR), the sponsor confirmed that all four pack sizes are intended to be listed on the PBS. DUSC considered it very likely that nearly all patients would be supplied the 24-pack size, self-modify the dose if necessary, and refill prescriptions less frequently.

3.4 The PBAC noted that the submission requested an Authority Required – Streamlined listing for initial, continuing and grandfather treatment. 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 its potential safety concerns.

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

4 Population and disease

4.1 The submission stated that non-Hodgkin's lymphoma (NHL) accounts for 90% of all types of lymphomas and that DLBCLs and follicular lymphoma (FL) are the most common subtypes of B-cell NHLs in adults. DLBCL is the most common, accounting for approximately 20-40% of all NHL cases and histologic transformation of FL to DLBCL (TFL) occurs in approximately 15% of patients and is generally associated with a poor clinical outcome. In Australia, NHL is diagnosed in approximately 6,000 individuals annually, with over 1,500 deaths each year. DLBCL may affect any age group, including adolescents and children, but primarily occurs in adults over the age of 60.

4.2 Currently the only potentially curative treatment options for patients with RR DLBCL are autologous stem cell transplant (ASCT) or treatment with anti-CD19-chimeric antigen receptor modified T cells (CAR-T). Accessibility to these treatments also presents additional burden for patients with both ASCT and CAR-T requiring hospitalisation at a limited number of specialist centres, with potentially prolonged stays.

4.3 Approximately 50% of patients fail these treatment modalities and require further therapy and a large proportion of patients who fail first-line treatment are not eligible for second-line curative therapy due to age, frailty and/or multiple comorbidities, and therefore are not 'fit' enough to tolerate such intensive treatment.

4.4 The PBAC considered a submission for this population in November 2019 (polatuzumab vedotin).

4.5 The algorithms suggest that selinexor can be used as either third- or fourth-line therapy which is consistent with the proposed listing.

4.6 Selinexor is an oral, first-in-class, potent, selective inhibitor of nuclear export (SINE) that specifically blocks exportin 1 (XPO1). Inhibition of XPO1 leads, amongst other mechanisms, to the nuclear accumulation and activation of tumour suppressor proteins (TSPs), which leads to apoptosis in cancer cells.

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

5 Comparator

5.1 The submission nominated RGemOx as the comparator regimen to represent all rituximab-based salvage chemotherapies. The main arguments provided in support of this nomination were that this population is unsuitable for CAR-T or ASCT and therefore the current guidelines used in Australia recommend rituximab salvage

regimens or participation in a clinical trial. The ESC considered that patients considered suitable for CAR-T or ASCT were unlikely to be considered for treatment with selinexor.

5.2 The ESC considered that RGemOx was a reasonable comparator in the third- or fourth-line settings, noting that the PBAC had previously considered it to be the appropriate comparator in the assessment of polatuzumab vedotin for RR DLBCL (paragraph 5.3, polatuzumab vedotin Public Summary Document (PSD), November 2019).

5.3 The ESC noted that there are multiple different chemotherapy regimens, most of which are rituximab based, which are used as salvage chemotherapy. The most common second- and third-line treatment appears to be rituximab, ifosfamide, carboplatin and etoposide (R-ICE). Other combinations include rituximab, dexamethasone, cytarabine, and cisplatin (R-DHAP) and rituximab, gemcitabine, dexamethasone and cisplatin (R-GDP). The ESC considered that RGemOx was reasonably representative of rituximab-based salvage chemotherapy.

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 provided information on the lack of current treatment options for patients with RR DLBCL and described the benefits that selinexor provides due to its alternate mode of action compared to chemotherapy, how it would be used in practice and management of the potential adverse events associated with treatment. The PBAC considered that the hearing was informative as it provided a clinical perspective on treating this uncommon disease.

Consumer comments

6.2 The PBAC noted and welcomed the input from health care professionals (1) and organisations (3) via the Consumer Comments facility on the PBS website. The comment from the health care professional described the lack of treatment options for patients with RR DLBCL and noted that an oral treatment option would be desirable, particularly for patients living in rural and remote locations.

6.3 The PBAC noted the advice received from (i) Rare Cancers Australia, (ii) Lymphoma Australia, and (iii) the Leukaemia Foundation which described the high clinical need for new therapies, such as selinexor, for patients with RR DLBCL. The organisations also noted the benefits of having an oral treatment available, particularly for elderly, rural and remote patients.

Clinical studies

6.4 The submission presented one open label single arm study for selinexor (SADAL). For the comparator, a published paper describing pooled patient data from four

databases (SCHOLAR-1, Crump 2017) and a cohort from an Australian registry database (LaRDR, unpublished) were presented. The PBAC noted that comparison of selinexor with rituximab salvage therapy was based on graphically overlaying the survival curves from these sources and digitising a survival estimate.

6.5 Details of the studies presented in the submission are provided in the table below.

Table 2: Studies and associated reports presented in the submission

Study ID	Protocol title/ Publication title	Publication citation
SADAL	KCP-330-009 A Phase 2b open-label study of selinexor (KPT-330) in patients with relapsed/refractory diffuse large B-cell lymphoma (DLBCL) Kalakonda N, Maerevoet M, Cavallo F, et al. Selinexor in patients with relapsed or refractory diffuse large B-cell lymphoma (SADAL): a single-arm, multinational, multicentre, open-label, phase 2 trial.	December 2019 *Lancet Haematol*. 2020; e511-e522.
SCHOLAR-1	Crump M, Neelapu SS, Farooq U, et al. Outcomes in refractory diffuse large B-cell lymphoma: Results from the international SCHOLAR-1 study.	*Blood* 2017; 130(16): 1800-1808.

Source: Table 2-3, p38-39; Table 2-23, p67-68 of the submission.

6.6 The key features of the evidence are summarised in the table below.

Table 3: Key features of the included evidence

Study	N	Design	Risk of bias	Patient population	Outcome(s)	Use in modelled evaluation
Selinexor						
SADAL	127	Single arm, open label	High	Third line relapsing	Complete and partial response, PFS, OS	Used
RGemOx						
SCHOLAR-1	658/851	Pooled databases	High	Mixed	Response, OS	Used
LaRDR	24	Patient registry	High	Mixed	Survival	Not used

Source: Section 2.3, p40-43; Section 2.6.1.1, p68; Section 2.6.1.2, p71-72 of the submission.
OS = overall survival; PFS = progression free survival; RGemOx = rituximab-gemcitabine-oxaliplatin

6.7 The SADAL is a Phase 2 dose finding study in patients with RR DLBCL with a randomisation step to select the dose patients received (100 or 60 mg of selinexor). The protocol for this study has 9 versions. Changes as the study proceeded included changes to the primary outcome of the study, inclusion of death as an outcome, the type of concomitant treatment, and dose and dosing frequency of selinexor. Version 6 of the protocol led to the exclusion of all patients included in versions 1-5 from the results and also modified the inclusion criteria to require at least 60 days between the last systemic therapy and first dose of selinexor. This requirement would not be reflective of the proposed usage of the drug on the PBS. Overall, 175 patients received selinexor 60 mg twice weekly (the proposed recommended dose) but data for only 127 patients were presented as the basis of the results in the submission. The clinical study report (CSR) included data on the 175 patients for safety. There were discrepancies between the data in the CSR and those in the publication that were not possible to resolve.

6.8 The submission stated that the SCHOLAR-1 publication (Crump 2017), described as 'a patient-level, retrospective pooled analysis of response rates in patients with DLBCL from several sources', was included to provide a rigorous assessment of response to

rituximab-based salvage chemotherapy among the patient population studied in SADAL. SCHOLAR-1 pooled data from two trials and two observational cohorts.

6.9 The data from LaRDR, which included only < 500 patients, were not provided as a report that could be evaluated.

6.10 The ESC noted that both the SADAL and SCHOLAR-1 studies had a high risk of bias. The SADAL study was a non-randomised, single arm study and assessment of response was not blinded, although external review of data was added in a late version of the protocol. Although two of the trials included in SCHOLAR-1 were randomised, the two observational cohorts were not randomised and data from these groups were pooled together. In addition, no information was provided as to whether assessment was blinded. The LaRDR was a patient registry with a small number of patients (N= < 500). No information was provided on the methodology used for assessment of registry data, indicating a high risk of bias for LaRDR.

6.11 The ESC considered that the patient populations in SADAL and SCHOLAR-1 were not comparable as SADAL patients were older, more heavily treated, had worse prognostic indicators but better Eastern Cooperative Oncology Group (ECOG) status, were ineligible for ASCT (which was not representative of a portion of the proposed PBS population) and were required to have had at least 60 days since the last chemotherapy. Half of the patients included in the SCHOLAR-1 database were not refractory to second-line therapy.

6.12 There was also a lack of information provided by the submission on the definitions of outcomes used in the SCHOLAR-1 study and LaRDR, and it could not be determined if the outcomes were sufficiently comparable across SADAL, SCHOLAR-1 and LaRDR to infer any difference in effects of interventions. The PSCR provided definitions for response and overall survival in the SADAL and SCHOLAR-1 studies; however, the definitions for progression free survival were not provided.

Comparative effectiveness

6.13 The results for the SADAL study are presented below (median follow-up = 14.7 months).

Table 4: Outcomes from SADAL

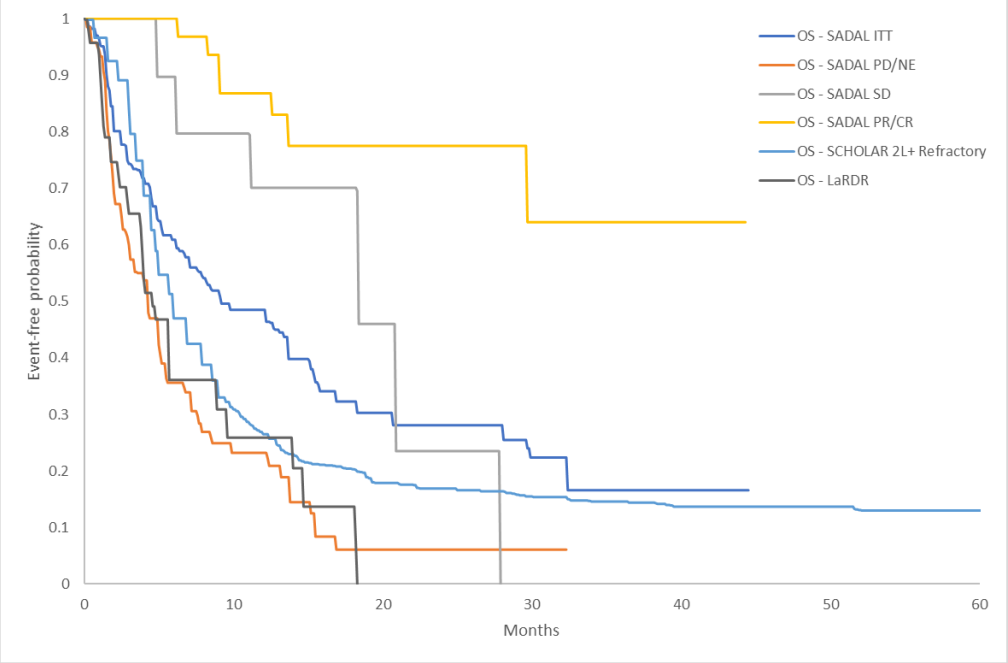
Outcome	Result
Overall response	36/127 (28.3%)
Complete response	15/127 (11.8%)
Median duration of complete response (months)	23
Partial response	21/127 (16.5%)
Median duration of partial response (months)	4.4
Median overall survival (months; 95% CI)	9.1 (6.6, 15.1)
Median progression-free survival (months; 95% CI)	2.6 (1.9, 4.0)
Grade 3 or 4 adverse event	102/127 (80.3%)
Worst on-study ECOG status = 0-1[a]	72/127 (56.7%)
Worst on-study ECOG status = 2-4	50/127 (39.4%)

Source: CSR Table 13, p63; Table 16, p69; Table 14.3.18.1.1
CI = confidence interval; ECOG = Eastern Cooperative Oncology Group
[a] ECOG = 0-1 was 89.0% at baseline.

6.14 Given the high risk of bias of the study, the most appropriate interpretation of the data may be that the study shows that selinexor has some activity in RR DLBCL but it is not possible to determine the extent of any effect.

6.15 As noted above in paragraph 6.4, the submission did not provide an assessment of comparative effectiveness with rituximab-based therapies other than a graphical overlay of survival curves – see Figure 1.

Figure 1: Kaplan-Meier curves for OS from SADAL, SCHOLAR-1 (2L+ refractory) and LaRDR



Source: Figure 2-20, p79 of the submission
CR = complete response; ITT = intention to treat; NE = not evaluable; OS = overall survival; PD = progressive disease; PR = partial response; SD = stable disease; 2L+ = second and later line

6.16 The submission stated that the median overall survival (OS) for SADAL – ITT was 9.1 months compared to 6.1 months in SCHOLAR-1 and 4.6 months in LaRDR.

Table 5: Median OS across the studies

Population	Median OS
SADAL – ITT	9.1 months
SADAL – SD (8.7%)	18.3 months
SADAL – PR/CR (28.3%)	NR
SADAL – PD/NR	4.3 months
SCHOLAR-2 – 2L+ refractory	6.1 months
LaRDR	4.6 months

Source: Table 2-27, p79 of the submission
CR = complete response; ITT = intention to treat; NE = not evaluable; NR = not reported; OS = overall survival; PD = progressive disease; PR = partial response; SD = stable disease; 2L+ = second and later line

Comparative harms

6.17 The safety data as reported in the SADAL study is summarised in Table 6 below. The submission also provided an extended assessment of safety based on its use in other indications.

Table 6: Summary of key adverse events in the SADAL study

Event	n (%); N=127		
Deaths	9 (7.6%)		
Withdrawal due to disease progression	80 (67.8%)		
Withdrawal by patient	13 (11.0%)		
Treatment-emergent AE	125 (98.4%)		
Grade 3 or 4 AE	102 (80.3%)		
AE with outcome of death	5 (3.9%)		
AE leading to withdrawal	22 (17.3%)		
	Grade 1-2	**Grade 3-4**	**Leading to withdrawal**
Thrombocytopenia	10 (7.9%)	58 (45.7%)	. 3 (2.4%)
Neutropenia	7 (5.5%)	31 (24.4%)	0 (0%)
Nausea	66 (52.0%)	8 (6.3%)	3 (2.4%)
Fatigue + asthenia	67 (52.8%)	20 (15.7%)	4 (3.1%)
Anaemia	26 (20.5%)	28 (22.0%)	1 (0.8%)
Diarrhoea	41 (32.3%)	4 (3.1%)	1 (0.8%)
Decreased appetite	42 (33.1%)	5 (3.9%)	1 (0.8%)

Source: CSR Table 7, p52; Table 26, pp87-8, Table 14.3.7.1.3.
AE = adverse event

6.18 The main adverse events were nausea and vomiting, diarrhoea, thrombocytopenia, neutropenia, hyponatremia, fatigue and weight loss. The adverse events appear to occur with similar frequency across all indications. In the SADAL study a significant proportion of patients (35/127) required dose reduction to enable them to continue treatment, which suggests there may be toxicity concerns with selinexor. The ESC noted the high incidence of Grade 3 or 4 adverse events, particularly noting the high rate of Grade 3 or 4 haematological events and the rate of adverse events resulting in death. The ESC also noted that adverse events associated with dose modifications (i.e. dose reductions, interruptions and discontinuations) were not reported.

6.19 The ESC noted that the submission did not provide any information about the safety of the comparator.

6.20 The pre-PBAC response noted that as selinexor is an oral treatment it offers quality of life advantages in terms of reduced hospital visits for chemotherapy infusions and a reduced risk of infusion site infections.

Benefits/harms

6.21 The naïve comparison presented in the submission did not allow for a quantitative comparison of the benefits and harms of selinexor and rituximab salvage therapy. Accordingly, a benefits/harms table has not been presented.

Clinical claim

6.22 The submission described selinexor as superior in terms of effectiveness compared to RGemOx. The PBAC considered that this claim was highly uncertain and could not be supported due to the absence of comparative data presented. The key issues were: the very high risk of bias in the single arm clinical study provided; the absence of any comparative effectiveness data allowing for an indirect comparison; and the likelihood that PBS patients would be sicker and less likely to 'respond' to selinexor treatment than patients in the SADAL study as the SADAL study required that patients have at least 60 days between their last chemotherapy and starting treatment with selinexor.

6.23 The submission described selinexor as superior in terms of safety compared to rituximab salvage therapy. The PBAC considered that this claim could not be supported as no comparative safety data were provided.

Economic analysis

6.24 The submission presented a cost-utility analysis comparing selinexor and RGemOx. As noted above, the absence of comparative effectiveness and safety data indicated that there was no support for a modelled economic evaluation. Nonetheless, for reference a description of the submission's model has been provided.

6.25 The table below outlines the model structure and key inputs.

Table 7: Summary of model structure, key inputs and rationale

Component	Summary
Treatments	Selinexor versus RGemOx
Time horizon	7 years in the model base case versus median follow-up of 14.7 months in SADAL
Outcomes	QALYs; LYs
Methods used to generate results	Partitioned survival model
Health states	3 health states: progression-free, progressive disease, death.
Cycle length	14 days
Allocation to health states	Determined by PFS and OS survival curves, which were based on SADAL and SCHOLAR-1 data with extrapolation.
Extrapolation method	Parametric models were fitted to each treatment arm and the following were selected for use in the base case based on goodness of fit and visual inspection: OS selinexor: Generalised F; OS RGemOx: Generalised F PFS selinexor: Generalised gamma; PFS RGemOx: time-varying hazard ratios for selinexor OS-PFS Convergence was applied from Year 5 (60 months) to Year 7 (84 months) so the selinexor and RGemOx OS curves converged at the end of the modelled time horizon.
Health related quality of life	Literature-based (NICE TA559) Progression-free: 0.72; progressive disease: 0.65 for selinexor and RGemOx
Dose intensity	The submission applied dose intensity of 83.33% for selinexor, although this value could not be validated. It differed considerably from the rate of compliance of 99.5% used in the financial estimates.

Source: Section 3.2.2, p103-108 of the submission.
LY = life year; OS = overall survival; PFS = progression-free survival; QALY = quality adjusted life year; RGemOx = rituximab-gemcitabine-oxaliplatin

6.26 The ESC considered that the primary issue with the modelled evaluation was the lack of comparative effectiveness and safety data upon which to base the model. The ESC also noted that partitioned survival analyses 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 progression free survival (PFS) curves for the selinexor and RGemOx arms meant that the relationship between the OS and PFS curves may be due to the differences between the different studies. Thus, the ESC considered the use of this model structure to be inherently uncertain. The pre-PBAC response stated that as PFS was not reported for the SCHOLAR-1 cohort, this was derived within the model base case by assuming that the relationship between OS and PFS were equivalent between the treatment arms. The pre-PBAC response stated that as the impact of the assumed PFS benefits was negligible in sensitivity analyses, the uncertainty associated with the use of the partitioned survival analysis was minimal.

6.27 As noted above, the cohorts in SADAL and SCHOLAR-1 were not comparable and could not be used as the basis of inferring any treatment effect. While the submission digitised survival curves for a relapsed/refractory group in SCHOLAR-1, there was no detailed information available for this patient group and thus, little support for the comparison made by the submission.

6.28 The ESC noted that the submission selected the generalised F distribution to extrapolate overall survival for both the selinexor and RGemOx arms of the model.

The ESC noted the high variability in the OS estimates across the parametric extrapolations.

6.29 The NICE TA559 report indicated that the utility values were based on 87 observations from 34 patients in the ZUMA-1 study. This is a reasonably small sample of patients, some of which had other forms of B-cell NHL. The submission claimed that the populations in SADAL, SCHOLAR-1 and ZUMA-1 are generally well-matched. As discussed above, the populations in SADAL and SCHOLAR-1 are not comparable.

6.30 Adverse event data for the comparator, RGemOx, were sourced from six studies which the submission noted generally had limited applicability, due to patients either being in earlier lines of therapy or not DLBCL patients. For the model presented, adverse events had little impact on the results.

6.31 For the economic model the submission applied a dose intensity of 83.33% for selinexor, and dose intensities of 91.6%, 93.6% and 92.5% were used for rituximab, gemcitabine and oxaliplatin, respectively. The submission did not provide a source for the selinexor dose intensity that could be validated, nor did the submission explain why varying methods for drug usage were applied across the economic model and financial estimates, where for the latter a compliance rate of 99.5% was used for both selinexor and RGemOx. The PSCR stated that the dose intensity applied in the economic model was based on the median weekly dose of 100 mg relative to the protocol dose of 60 mg twice weekly (i.e. 100/120 = 83.33%). The PSCR added that it was similar to the mean weekly dose of 96.5 mg, which resulted in a dose intensity of 80.42%. The ESC considered that the lower dose intensity for selinexor compared to the components of RGemOx reflected the high rate of adverse events associated with selinexor and the likely required dose modifications (i.e. dose reductions and interruptions).

6.32 Given that the model does not have a valid comparative basis, key drivers of the model have not been identified.

6.33 The submission did not provide a stepped economic evaluation. Results of the economic evaluation are in the table below.

Table 8: Results of the economic evaluation

Component	Selinexor	RGemOx	Increment
Modelled evaluation – 7-year time horizon (discounted)			
Costs	$[redacted]	$80,839	$[redacted]
LY	1.71	1.19	0.523
Incremental cost/extra LY gained (base case)			$[redacted][1]
QALY	1.15	0.81	0.342
Incremental cost/extra QALY gained (base case)			**$**[redacted][2]

Source: Table 3-27, p143 of the submission.

LY = life year; QALY = quality adjusted life year; RGemOx = rituximab-gemcitabine-oxaliplatin

The redacted values correspond to the following ranges:

[1] *$45,000 to < $55,000*

[2] *$55,000 to < $75,000*

6.34 The ESC considered that the estimated incremental cost effectiveness ratio (ICER) of $55,000 to < $75,000 per quality adjusted life year (QALY) was not reliable for decision making, given there was no comparative data upon which to base the purported comparison.

6.35 The sensitivity analyses presented by the submission showed considerable variation in model results. For example, altering the extrapolation start point from when 20% of patients remained at risk to when 10% of patients were at risk changed the ICER per QALY by 66%. Extrapolating from the start of the model increased the ICER per QALY by 186%. Changing the parametric function used for OS extrapolation for selinexor (generalised F) altered the ICER per QALY by 2% (generalised gamma) to 41% (log-normal), while changing the parametric function used for RGemOx extrapolation (generalised F) showed a decrease of 0.7% (generalised gamma) to 7.9% (log normal). Altering the source of the utility values decreased the ICER per QALY by 3% to 9%. The model also showed some sensitivity to time horizon, with the ICER increasing by 30% to close to $95,000 to < $115,000 per QALY when the time horizon was shortened to 3 years and decreasing by 10% when the time horizon was lengthened to 10 years. This level of variation in model results, using reasonable changes in the model parameters, suggests a degree of unreliability in the model.

6.36 Given the differences in the SADAL and SCHOLAR-1 patient cohorts the ESC considered that any extrapolation of benefit over time should be more conservative. For example, assuming convergence of the OS curves at 48 months, which was the point at which the Kaplan-Meier curve for the SCHOLAR-1 study began to plateau, and using the log-normal extrapolation for both the SADAL and SCHOLAR-1 studies, which generated the lowest AIC and BIC values for the selinexor arm, resulted in an ICER of $95,000 to < $115,000 per QALY.

6.37 The pre-PBAC response presented a revised base case which applied a five-year time horizon, OS convergence from 36 to 48 months and the assumption of no PFS benefit. This resulted in an ICER of $95,000 to < $115,000 per QALY. The pre-PBAC response also proposed a reduced DPMQ for selinexor ($[redacted] for 20 mg x 24), which resulted in an ICER for the revised base case of $75,000 to < $95,000 per QALY.

Drug cost/patient/course and month

Table 9: Intervention costs per patient across one month and model duration

	Selinexor	RGemOx
Treatment duration in model	6.02 months	1.79 months
Cost of treatment for model duration	$[redacted]	$7,253
Cost per month	$[redacted]	$4,054.42

Source: Table 3-26, p143 of the submission.
RGemOx = rituximab-gemcitabine-oxaliplatin

6.38 The estimated costs should be interpreted with caution, given they were based on values sourced from a model with minimal support. In addition, for RGemOx the treatment duration was based on the submission's assumption that patients would receive four fixed cycles of treatment, consistent with the median number of cycles

received in the published literature. The submission cited Dhanapal 2017, Franch-Sarto 2019 and Lopez 2007 as the literature supporting this assumption; however, these were small studies (N=44 for Dhanapal 2017; N=32 for Lopez 2007; Franch-Sarto was a letter to the editor discussing Dhanapal 2017) which were acknowledged by the submission as having limited applicability.

Estimated PBS usage & financial implications

6.39 DUSC considered this submission. The submission applied an incidence-based epidemiological approach to estimate the number of patients eligible for treatment with selinexor. The table below summarises the inputs used for the financial estimates.

Table 10: Key inputs for financial estimates

Parameter	Value applied and source	Comment
Incidence population	AIHW data (2020): Number of patients with NHL, age-adjusted for ≥18 years; assume 35% have DLBCL. Sponsor assumption that 95% would receive active treatment. Incidence count from 2016 was applied to Year 1 (2021), 2017 to Year 2 (2022) and so on - this was based on the estimation of 5 years from diagnosis to time to third-line treatment. DLBCL patients that are RR after first-line therapy: 40% RR DLBCL patients that are eligible for ASCT: 50% DLBCL patients that are RR after ASCT and second-line therapy: 45% DLBCL patients that are ineligible for ASCT and are RR after second-line therapy: 90%	Reasonable, although there was limited support for the assumption that the time from diagnosis to third-line treatment is 5 years. Also, the assumption that 50% of patients are eligible for ASCT did not correspond to SADAL, where all patients were ineligible for ASCT at baseline, although 30% of patients had a previous ASCT.
Uptake rate	[redacted]% in Year 1, [redacted]% in Year 2, [redacted]% in Year 3 to Year 6. Based on sponsor assumption.	Likely overestimated as clinical evidence supporting selinexor was not strong.
Compliance rate	99.5% for selinexor and RGemOx. Based on the SADAL study.	Likely overestimated as usage of selinexor in SADAL did not reflect 99.5% compliance.
Grandfathered patients	[redacted][1]	-
Dose/duration	Selinexor: 60 mg twice weekly for 6.02 months (based on economic model) RGemOx: 4 cycles of treatment, literature-based	Consistent with economic model.
Offsets for comparator	Cost offsets for RGemOx were estimated.	Agents considered were consistent with the economic model, although offsets were likely overestimated.
MBS item	MBS item 13950 (infusion for RGemOx) MBS item 13706 (transfusion blood or bone marrow) MBS item 13750 (therapeutic haemapheresis) MBS item 23 (GP consult)	Appropriate.

Source: Table 4-3, p155; Table 4-6, p158; Table 4-17, p164-165; Section 4.2.1.3, p155-157 of the submission.
ASCT = autologous stem cell transplant; chemo = chemotherapy; DLBCL = diffuse large B-cell lymphoma; NHL = non-Hodgkin's lymphoma; RGemOx = rituximab-gemcitabine-oxaliplatin; RR = relapsed/refractory
The redacted values correspond to the following ranges:
[1] *< 500*

6.40 The estimated patient numbers, prescription numbers and costs for the PBS listing of selinexor for RR DLBCL are provided below.

Table 11: Estimated use and financial implications

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
Estimated extent of use						
Number of patients treated	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]
Number of prescriptions[a]	[redacted][2]	[redacted][2]	[redacted][2]	[redacted][2]	[redacted][2]	[redacted][2]
Estimated financial implications of selinexor						
Cost to PBS/RPBS less copayments	$[redacted][3]	$[redacted][3]	$[redacted][3]	$[redacted][3]	$[redacted][3]	$[redacted][3]
Cost offsets for substituted RGemOx (less copayments)	-$[redacted][4]	-$[redacted][4]	-$[redacted][3]	-$[redacted][3]	-$[redacted][3]	-$[redacted][3]
Net financial implications						
Net cost to PBS/RPBS	$[redacted][4]	$[redacted][4]	$[redacted][4]	$[redacted][4]	$[redacted][4]	$[redacted][4]
Net cost to MBS	-$[redacted][4]	-$[redacted][4]	-$[redacted][4]	-$[redacted][4]	-$[redacted][4]	-$[redacted][4]
Net cost to PBS/RPBS/MBS	**$**[redacted][4]	**$**[redacted][4]	**$**[redacted][4]	**$**[redacted][4]	**$**[redacted][4]	**$**[redacted][4]

Source: Table 4-6, p158; Table 4-7, p158; Table 4-10, p160; Table 4-13, p162; Table 4-15, p163; Table 4-18, p165; Table 4-19, p165 of the submission; Excel workbook 'PBAC submission March 2021_Section 4 Workbook_XPOVIO_DLBCL_Final'

MBS = Medicare Benefits Schedule; PBS = Pharmaceutical Benefits Scheme; RGemOx = rituximab-gemcitabine-oxaliplatin; RPBS = Repatriation Pharmaceutical Benefits Scheme

[a] Assuming 6.51 scripts/year for the 20-tablet pack and 5.43 scripts/year for the 24-tablet pack as estimated by the submission.

The redacted values correspond to the following ranges:

[1] < 500

[2] 500 to < 5,000

[3] $10 million to < $20 million

[4] $0 to < $10 million

6.41 The total cost to the PBS/RPBS/MBS of listing selinexor for the treatment of RR DLBCL was estimated to be $0 to < $10 million in Year 6, and a total of $0 to < $10 million in the first 6 years of listing.

6.42 The estimated net cost was likely to be inaccurate, given the submission's assumption that compliance for selinexor and RGemOx would be 99.5%. The submission provided no evidence to support this level of compliance for selinexor or RGemOx and it unlikely to occur in clinical practice. The SADAL study confirmed this assertion as:

- close to 50% of patients had a dose reduction;
- 64% had a dose interruption or a withheld dose;
- 44% of patients had > 2 weeks duration for dose interruption, and;
- 45.7% had a mean dose of < 100 mg per week.

6.43 In addition, by Week 9, which was the median duration of treatment, the mean dose received was 74.5 mg per week (the recommended dose is 60 mg twice weekly). These numbers and proportions do not concur with a compliance of 99.5%, and it is likely that compliance as reported by the submission and in the CSR refers to compliance to reduced doses. It would have improved the accuracy of the estimates if an alternate measure, such as dose intensity was used.

6.44 Given the points above regarding usage of selinexor, it was likely that the assumed 99.5% compliance for RGemOx contributed to the considerable cost offsets that were estimated ($0 to < $10 million in Year 1, up to $10 million to < $20 million in Year 6). As this level of compliance was not likely to be observed in clinical practice, it was

probable that the cost offsets for RGemOx were overestimated. If the dose intensities of RGemOx that were used in the economic model were applied (91.6%, 93.6%, 92.5%, respectively), the estimated net cost to Government increased to $10 million to < $20 million over the first 6 years of listing. If the dose intensity of selinexor that was used in the economic model (83.33%) was applied as the compliance level for both selinexor and RGemOx, corresponding to the submission's assumption of the same compliance for selinexor and RGemOx, the estimated net cost to Government increased to $10 million to < $20 million over the first 6 years of listing.

6.45 The financial estimates are also likely to be underestimated given the lack of inclusion of PBS items such as romiplostim or granulocyte colony-stimulating factor (GCSF) to treat thrombocytopenia and ondansetron for nausea and vomiting. The inconsistent application of costs for adverse event treatment (MBS items only in the financial estimates, PBS and MBS items in the economic model) indicated that estimated cost to Government was likely to be inaccurate.

6.46 The DUSC considered that the estimate of eligible patients presented in the submission was underestimated and the estimate of treated patients was overestimated. The DUSC noted that the main issues were:

- basing the estimates only on an incident population underestimated the number of eligible patients and was not appropriate. DUSC advised that would be more appropriate to use a prevalence approach. The sponsor, in the pre-PBAC response agreed that inclusion of the prevalent DLBCL population would be appropriate;
- the incidence of DLBCL was based on a rate of 35% of NHL patients; however, the reference provided by the submission to support this states that DLBCL accounts for around 30% of all lymphoma cases. The pre-PBAC response noted that a range of rates were identified in the literature, ranging from 18% (Van Leewan, 2014) to 47.8% (Smith, 2015), and that 35% was reasonable given the variation of published incidence rates;
- given the adverse event profile, DUSC considered the uptake of selinexor would be much lower than that estimated by the submission. DUSC suggested a treatment uptake rate of [redacted]% in Year 1 increasing to [redacted]% in Year 6 may be more reasonable. The pre-PBAC response stated that the uptake rate applied was reasonable and reflected the superior efficacy of selinexor over salvage chemotherapy;
- the estimated net cost was not likely to be accurate due to an overestimate of cost offsets for RGemOx ($0 to < $10 million in Year 1 increasing to $10 million to < $20 million in Year 6) given the submission's assumption that compliance for selinexor and RGemOx would be 99.5%;
- it would have been more reasonable to apply separate rates for compliance and dose intensity. The submission did not provide any evidence that the level of compliance for selinexor and RGemOx would be 99.5%. This level of compliance

was unlikely as, by Week 9 (the median duration of treatment) of the SADAL study, the mean dose of selinexor received was 74.5 mg per week (draft Product Information recommended dose is 60 mg twice weekly; and

- the costs associated with PBS items used to treat adverse events were not included in the financial model. The pre-PBAC response noted that the inclusion of these costs in the financial estimates would be appropriate.

Quality use of medicines

6.47 The submission did not provide discussion of quality use of medicines. DUSC noted the dose of selinexor, as per the draft Product Information, is 60 mg (3 x 20 mg tablets) on Days 1 and 3 of each week. DUSC considered twice weekly dosing could make it challenging for patients to adhere to the dosing schedule without assistance and considered the sponsor should consider planning activities to improve and encourage compliance to the dosing schedule.

6.48 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 AEs 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 the treatment of adult patients with relapsed and/or refractory (RR) diffuse large B-cell lymphoma (DLBCL) after at least two lines of systemic therapy. The PBAC, noting the lack of comparative data between selinexor and the nominated comparator, rituximab in combination with gemcitabine and oxaliplatin (RGemOx), 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 estimates were highly uncertain.

7.2 The PBAC noted the consumer comments and agreed that there was a high clinical need for effective treatments for patients with RR DLBCL.

7.3 The PBAC noted that the submission nominated RGemOx to represent all rituximab-based salvage chemotherapies as the primary comparator. The PBAC, recalling that it had considered RGemOx to be the appropriate comparator in the assessment of polatuzumab vedotin for RR DLBCL in November 2019, considered that RGemOx was a reasonable comparator in the third- or fourth-line settings.

7.4 The PBAC noted that the submission was primarily based on the results of one open label, single arm, Phase 2 dose-finding study of selinexor, SADAL. For the comparator, the submission relied on a published paper describing response to rituximab-based salvage chemotherapy from pooled patient data from four databases (SCHOLAR-1), and a cohort from an Australian registry database (LaRDR). The PBAC considered that the risk of bias was high in each of the three studies.

7.5 The PBAC considered that the efficacy results from the SADAL study were difficult to interpret, given its single arm nature.

7.6 The PBAC considered that the patient populations in SADAL and SCHOLAR-1 were not comparable as SADAL patients were older, more heavily treated, had worse prognostic indicators and were ineligible for autologous stem cell transplant. In addition, the PBAC noted that the populations in SADAL was not representative of the proposed PBS population as patients were required to have had at least 60 days between last receiving chemotherapy and starting treatment with selinexor, which is not what would occur in clinical practice. The PBAC also noted that approximately half of the patients included in SCHOLAR-1 were not refractory to second-line therapy. The PBAC noted that the submission did not provide information on the patients in the LaRDR study.

7.7 The PBAC noted that the submission did not present any comparative data, instead it presented a graphical overlay of the survival curves from the SADAL, SCHOLAR-1 and LaRDR studies and digitised an overall survival (OS) estimate. The PBAC considered that the results were difficult to interpret given that the populations were not comparable. The PBAC also noted that no progression free survival (PFS) data were presented for the comparator.

7.8 The PBAC considered that the submissions claim that selinexor was superior compared to RGemOx in terms of comparative effectiveness could not be supported based on the data presented.

7.9 The PBAC noted that the results from the SADAL study indicated that selinexor was associated with a high incidence of treatment emergent adverse events. The PBAC particularly noted the high incidence of Grade 3 or 4 adverse events (80.3%) associated with selinexor treatment and the high proportion of patients (27.5%) that required a dose reduction.

7.10 The PBAC, noting that the submission did not present any comparative safety data, considered that the claim that selinexor was superior compared to RGemOx in terms of safety was not reasonable.

7.11 Noting that the patient cohorts in SADAL and SCHOLAR-1 were not comparable and could not be used to infer a treatment effect, the PBAC considered that the cost utility analysis presented in the submission was highly unreliable. In addition, the PBAC noted uncertainties related to:

- the lack of patient characteristic data to inform the comparator arm of the model;
- the lack of PFS data for the comparator arm,
- the application of utility values which were based on a very small sample size of patients (N = 37), some who had other forms of B-cell non-Hodgkin lymphoma,
- the use of the generalised F distribution, which was not the best fit in terms of AIC and BIC values, for extrapolation of the selinexor OS curve; and

- concerns regarding the dose intensity of selinexor applied.

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 applied (i) a five-year time horizon (reduced from 7 years); (ii) OS convergence from 36 to 48 months (revised from 60 to 84 months); and (iii) the assumption of no PFS benefit, and resulted in an ICER of \$95,000 to < \$115,000 per QALY. The PBAC noted that the pre-PBAC response also proposed a reduced price for selinexor, which resulted in an ICER for the revised base case 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 The PBAC noted that the majority of the incremental gains in health outcomes attributed to selinexor were due to modelled differences in post-progression outcomes. The PBAC considered that, given the differences between the patient cohorts in SADAL and SCHOLAR-1 and the lack of clinical certainty in terms of efficacy of selinexor over RGemOx, any benefit attributed to selinexor should be conservative.

7.14 In terms of the utilisation estimates, the PBAC agreed with the DUSC and considered that the eligible population was underestimated, and the treated population was overestimated for the reasons outlined in paragraph 6.45. The PBAC noted that uptake of selinexor ([redacted]% in Year 1, increasing to [redacted]% in Years 3 to 6) was overestimated, particularly considering the lack of comparative efficacy data and the high incidence of adverse events, and that separate rates for compliance rate and dose intensity should have been applied.

7.15 The PBAC noted that the submission did not propose a Risk Sharing Arrangement (RSA).

7.16 The PBAC considered that any future resubmission for selinexor should present:

- efficacy data for selinexor that is more relevant to the proposed PBS population. The PBAC suggested that it might be possible to adjust the efficacy data from the SADAL study by estimating the impact of removing the study criteria that required a break of 60 days between chemotherapy and selinexor;
- more comparative data, possibly by presenting data for a basket of rituximab-containing therapies in the proposed population;
- a revised economic model which addressed the uncertainties outlined in paragraph 7.11 and was conservative in its assumptions. The PBAC considered that the revised model should result in a base case ICER which appropriately accounts for the uncertainties in the clinical data;
- revised utilisation and financial estimates which incorporate the advice provided by DUSC (paragraph 6.45); and
- a RSA to help mitigate the financial risks given the uncertainties associated with

the clinical data and hence cost effectiveness.

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

7.18 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 relapsed/refractory diffuse large B-Cell lymphoma. 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.