

**7.08 DAUNORUBICIN WITH CYTARABINE,  
Powder for I.V. infusion containing daunorubicin  
44 mg and cytarabine 100 mg,  
Vyxeos<sup>®</sup>,  
Jazz Pharmaceuticals ANZ Pty Ltd.**

**1 Purpose**

- 1.1 The early re-entry resubmission requested a Section 100 (Efficient Funding of Chemotherapy Program) listing for liposomal daunorubicin and cytarabine for the treatment of therapy-related acute myeloid leukaemia (t-AML) or acute myeloid leukaemia with myelodysplasia-related changes (AML-MRC).
- 1.2 The resubmission was based on the PBAC decision to not recommend liposomal daunorubicin and cytarabine for this indication at the July 2023 PBAC meeting (refer to e-agenda for full minutes). Table 1 presents how this resubmission addressed the issues raised by PBAC.

**Table 1: Summary of key matters from the July 2023 minutes to be addressed**

Matter of concern	Response	Addressed?
Present a revised restriction which: - Included a criterion that prevents treatment in patients with favourable risk cytogenetics; - Excluded patients who are FLT3 mutation positive; - Was age agnostic (paragraph 7.15)	Restriction amended as requested	Yes
Present a revised economic model in which: - The OS curves converged within the 25-year time horizon (paragraph 7.11); - The costs of HSCT were increased by 50%, as indicative of increasing the costs associated with liposomal daunorubicin and cytarabine treatment (paragraph 7.12); - The AEMP of liposomal daunorubicin and cytarabine was decreased to result in an ICER of no more than \$60,000 per QALY (paragraph 7.13).	- Not addressed  - Costs of HSCT were increased by 25%  - The AEMP of liposomal daunorubicin and cytarabine was reduced from \$████ per vial to \$████ per vial to result in an ICER of \$████ <sup>1</sup> per QALY	No  Partially  Partially
Present revised financial impact estimates in which: - The uptake rates were amended (increased for first induction and reduced for second induction); - Potential midostaurin patients were removed from the estimates; - Use in the public and private inpatient setting was increased, as use in an outpatient setting, particularly during consolidation, was uncertain due to prolonged time of recovery; - Use in the private and public hospital settings aligned with that previously accepted for gemtuzumab (i.e. 17% and 83% respectively) (paragraph 7.14).	- Uptake rates were amended  - Patients with a FLT3 mutation were removed from the estimates - Accepted (see below)  - Accepted. The resubmission assumed 17% of use would be PBS supply (i.e. private in/out patients and public outpatients) and 83% of use would be non-PBS supply (i.e. public inpatients)	Yes  Yes Yes  Yes

Source: Compiled during preparation of the submission overview

AEMP = approved ex-manufacturer price; HSCT = haematopoietic stem cell transplant; ICER = incremental cost effectiveness ratio; OS = overall survival; QALY = quality adjusted life year

The redacted values correspond to the following ranges:

<sup>1</sup> \$55,000 to < \$75,000

1.3 For the scenario presented in the early re-entry submission, the base case incremental cost-effectiveness ratio (ICER) was \$55,000 to < \$75,000 per quality adjusted life year (QALY) gained.

1.4 The resubmission estimated a net cost to the PBS/RPBS of \$0 to < \$10 million in Year 6 of listing, with a total net cost to the PBS/RPBS of \$0 to < \$10 million over the first 6 years of listing.

## 2 Background

2.1 Liposomal daunorubicin and cytarabine was TGA registered on 3 June 2022 for the treatment of adults with newly diagnosed, therapy-related acute myeloid leukaemia (t-AML) or AML with myelodysplasia-related changes (AML-MRC).

2.2 The PICO from the July 2023 submission is presented in Table 2 below.

**Table 2: Key components of the clinical issue addressed in the July 2023 submission**

Component	Description
Population	Adults with newly diagnosed therapy-related acute myeloid leukaemia or acute myeloid leukaemia with myelodysplasia-related changes.
Intervention	First induction: liposomal daunorubicin 44 mg/m <sup>2</sup> and cytarabine 100 mg/m <sup>2</sup> via intravenous infusion on Days 1, 3 and 5. Second induction, as required: liposomal daunorubicin 44 mg/m <sup>2</sup> and cytarabine 100 mg/m <sup>2</sup> via intravenous infusion on Days 1 and 3. Up to 2 consolidation cycles, as required: liposomal daunorubicin 29 mg/m <sup>2</sup> and cytarabine 65 mg/m <sup>2</sup> via intravenous infusion on Days 1 and 3.
Comparator	First induction: idarubicin 12 mg/m <sup>2</sup> via intravenous infusion on Days 1 to 3 + cytarabine 100 mg/m <sup>2</sup> via continuous intravenous infusion on Days 1 to 7 (7+3 regimen). Second induction, as required: idarubicin 12 mg/m <sup>2</sup> on Days 1 and 2 + cytarabine 100 mg/m <sup>2</sup> via on Days 1 to 5 (5+2 regimen). Up to 2 consolidation cycles, as required: idarubicin 12 mg/m <sup>2</sup> via intravenous infusion on Days 1 and 2 + cytarabine 100 mg/m <sup>2</sup> via continuous intravenous infusion on Days 1 to 5 (5+2 regimen).
Outcomes	Higher rates of complete remission, event-free survival and bridging to haematopoietic stem cell transplantation leading to improved overall survival
Clinical claim	Liposomal daunorubicin + cytarabine is superior in terms of efficacy and non-inferior in terms of safety compared to idarubicin + cytarabine.

Source: Table 1-1, p4 of the July 2023 submission

For more detail on PBAC's view, see section 5 PBAC outcome.

### 3 Requested listing

3.1 The resubmission accepted the proposed amendments to the previously considered PBS restriction and now:

- prevents treatment in patients with favourable risk cytogenetics;
- excludes patients who are FLT3 mutation positive; and
- is age agnostic.

MEDICINAL PRODUCT, Form	DPMA	Max. Amount	No. of Rpts
DAUNORUBICIN + CYTARABINE Injection	Published: Public - \$20,132.73 Private - \$20,455.00 Effective: Public - \$█ Private - \$█	132mg/300mg (i.e. 3 vials)	4
<b>Available brands</b>			
Vyxeos (daunorubicin hydrochloride 44 mg + cytarabine 100 mg injection, 1 vial)			
<b>Restriction Summary [new] / Treatment of Concept: [new]</b>			
<b>Category / Program:</b> Section 100 – Efficient Funding of Chemotherapy Public/Private hospitals			
<b>Prescriber type:</b> <input checked="" type="checkbox"/> Medical Practitioners			
<b>Restriction type:</b> <input checked="" type="checkbox"/> Authority Required (telephone/online PBS Authorities system)			
<b>Indication:</b> Acute myeloid leukaemia			
<b>Treatment phase:</b> Induction			
<b>Clinical criteria:</b>			
Patient must not have received prior chemotherapy as induction therapy for this condition			

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	<b>AND</b>		
	<b>Clinical criteria:</b>		
	The condition must be either (i) newly-diagnosed therapy-related acute myeloid leukaemia (AML), (ii) newly-diagnosed AML with myelodysplasia-related changes (MRC) (prior myelodysplastic syndromes (MDS) or MDS-related cytogenetic or molecular abnormality),		
	<b>AND</b>		
	<b>Clinical criteria:</b>		
	<del>Patient must not be suitable for treatment with midostaurin</del> The condition must not be either (i) internal tandem duplication (ITD), or (ii) tyrosine kinase domain (TKD) FMS tyrosine kinase 3 (FLT3), mutation positive		
	<b>AND</b>		
	<b>Clinical criteria:</b>		
	Patient must not have favourable cytogenetic risk AML		
	<b>AND</b>		
	<b>Clinical criteria:</b>		
	Patient must have a World Health Organization (WHO) performance status score of 2 or less.		
	<b>Treatment criteria:</b>		
	The treatment must not exceed two cycles of induction therapy under this restriction.		
	<b>Population criteria:</b>		
	Patient must be at least 18 years of age.		
	<b>Prescribing Instructions:</b> This product is not PBS-subsidised if it is administered to an in-patient in a public hospital setting.		
	<b>Administrative advice:</b> No increase in the maximum number of repeats may be authorised.		
	<b>Administrative advice:</b> Special Pricing Arrangements apply.		
	<b>Administrative advice:</b> Applications for authorisation under this restriction may be made in real time using the Online PBS Authorities system (see <a href="http://www.servicesaustralia.gov.au/HPOS">www.servicesaustralia.gov.au/HPOS</a> ) or by telephone by contacting Services Australia on 1800 700 270 (hours of operation 8 a.m. to 5 p.m. Monday to Friday).		
<b>MEDICINAL PRODUCT, Form</b>	<b>DPMA</b>	<b>Max. Amount</b>	<b>No. of Rpts</b>
DAUNORUBICIN + CYTARABINE Injection	Published: Public - \$16,277.80 Private - \$16,546.10 Effective: Public - \$█ Private - \$█	88mg/200mg (i.e. 2 vials)	3
<b>Available brands</b>			
Vyxeos (daunorubicin hydrochloride 44 mg + cytarabine 100 mg injection, 1 vial)			
<b>Restriction Summary [new] / Treatment of Concept: [new]</b>			
<b>Category / Program:</b> Section 100 – Efficient Funding of Chemotherapy Public/Private hospitals			
<b>Prescriber type:</b> <input checked="" type="checkbox"/> Medical Practitioners			
<b>Restriction type:</b> <input checked="" type="checkbox"/> Authority Required (telephone/online PBS Authorities system)			

	<b>Indication:</b> Acute myeloid leukaemia
	<b>Treatment phase:</b> Consolidation
	<b>Clinical criteria:</b>
	The treatment must be for consolidation treatment following induction treatment with this product,
	<b>AND</b>
	<b>Clinical criteria:</b>
	The condition must be either (i) newly-diagnosed therapy-related acute myeloid leukaemia (AML), (ii) newly-diagnosed AML with myelodysplasia-related changes (MRC) (prior myelodysplastic syndromes (MDS) or MDS-related cytogenetic or molecular abnormality),
	<b>AND</b>
	<b>Clinical criteria:</b>
	Patient must have had either: (i) a complete response, (ii) complete response with incomplete platelet or neutrophil recovery, to induction treatment.
	<b>Treatment criteria:</b>
	The treatment must not exceed two cycles of consolidation therapy under this restriction.
	<b>Population criteria:</b>
	Patient must be at least 18 years of age.
	<b>Prescribing Instructions:</b> This product is not PBS-subsidised if it is administered to an in-patient in a public hospital setting.
	<b>Administrative advice:</b> No increase in the maximum number of repeats may be authorised.
	<b>Administrative advice:</b> Special Pricing Arrangements apply.
	<b>Administrative advice:</b> Applications for authorisation under this restriction may be made in real time using the Online PBS Authorities system (see <a href="http://www.servicesaustralia.gov.au/HPOS">www.servicesaustralia.gov.au/HPOS</a> ) or by telephone by contacting Services Australia on 1800 700 270 (hours of operation 8 a.m. to 5 p.m. Monday to Friday).

For more detail on PBAC's view, see section 5 PBAC outcome.

## 4 Consideration of the evidence

### **Sponsor hearing**

4.1 There was no hearing for this item.

### **Consumer comments**

4.2 The PBAC noted and welcomed the input from one health care professional (in addition to the 13 health care professionals and 2 organisations who provided advice in July 2023) via the Consumer Comments facility on the PBS website. The comment described the benefits of treatment with liposomal daunorubicin with cytarabine, including improved progression free and overall survival, in patients who received induction and consolidation.

### **Clinical claim**

4.3 In July 2023, the PBAC:

- accepted that daunorubicin was an acceptable proxy for idarubicin when given at the recommended dose for the 7+3 regimen in the induction setting;

- considered that liposomal daunorubicin and cytarabine was superior compared to daunorubicin/idarubicin plus cytarabine in the first induction setting;
- considered that the claim that liposomal daunorubicin and cytarabine was non-inferior in terms of safety compared to daunorubicin/idarubicin and cytarabine was not supported in the first induction setting; and
- considered that the claim that liposomal daunorubicin and cytarabine was superior in terms of efficacy and non-inferior in terms of safety compared to daunorubicin/idarubicin and cytarabine (5+2 regimen) in the second induction and consolidation therapy settings was not supported as the 5+2 regimen was not standard clinical practice in Australia.

### **Economic analysis**

- 4.4 As an early re-entry resubmission, the economic analysis has not been independently evaluated.
- 4.5 In July 2023, the PBAC advised that a revised economic model should:
- Apply convergence so that the OS curves converged within the 25-year time horizon. This was not applied in the revised economic model;
  - Increase the costs associated with HSCT by 50% to be indicative of the increased costs associated with liposomal daunorubicin and cytarabine treatments. The revised economic model increased the costs associated with HSCT by 25%; and
  - Result in an ICER of no more than \$60,000 per QALY.
- 4.6 The resubmission also applied a 17%/83% private/public hospital split to align with the revised financial estimates.
- 4.7 The resubmission stated that if the costs associated with HSCT were increased by 50%, then the ICER increased from \$75,000 to < \$95,000 per QALY in the July 2023 submission to \$75,000 to < \$95,000 per QALY. To achieve an ICER of \$60,000 per QALY, the effective AEMP of liposomal daunorubicin and cytarabine would need to be reduced from \$█ per vial to \$█ per vial. This price reduction (█%) █.
- 4.8 Increasing the costs associated with HSCT by 25% resulted in an ICER of \$75,000 to < \$95,000 per QALY. The resubmission reduced the effective AEMP of liposomal daunorubicin and cytarabine by █% (from \$█ per vial to \$█ per vial) so that the ICER was \$55,000 to < \$75,000 per QALY.

**Table 3: Results of the economic analyses**

	Liposomal daunorubicin and cytarabine	Idarubicin and cytarabine	Increment	Effective AEMP of LDC to achieve an ICER of \$60,000 per QALY
<b>July 2023 submission base case</b>				
Costs (\$)	█	\$96,591	█	
QALYs	1.837	0.904	0.933	
Incremental cost/extra QALY gained			█ <sup>1</sup>	█
<b>July 2023 PBAC requested change: 50% higher HSCT cost</b>				
Costs(\$)	█	\$112,393	█	
QALYs	1.837	0.904	0.933	
Incremental cost/extra QALY gained			█ <sup>1</sup>	█
<b>July 2023 PBAC requested change: 50% higher HSCT cost and convergence from 10 to 25 years</b>				
Costs(\$)	█	\$112,393	█	
QALYs	1.794	0.904	0.890	
Incremental cost/extra QALY gained			█ <sup>2</sup>	█
<b>November 2023 resubmission: 25% higher HSCT cost</b>				
Costs(\$)	█	\$104,492	█	
QALYs	1.837	0.904	0.933	
Incremental cost/extra QALY gained			█ <sup>1</sup>	█

Source: Vyxeos – t-AML & AML-MRC – economic analysis – July 2023 PBAC.xlsx

AEMP = approved ex-manufacturer price; HSCT = haematopoietic stem cell transplant; ICER = incremental cost effectiveness ratio; LDC = liposomal daunorubicin and cytarabine; QALY = quality adjusted life year

The redacted values correspond to the following ranges:

<sup>1</sup> \$75,000 to < \$95,000

<sup>2</sup> \$95,000 to < \$115,000

**Table 4: Sensitivity analyses**

	Liposomal daunorubicin and cytarabine	Idarubicin and cytarabine	Increment
<b>50% higher HSCT cost, convergence from 10 to 25 years and LDC AEMP = \$█</b>			
Costs(\$)	█	\$112,393	█
QALYs	1.794	0.904	0.890
Incremental cost/extra QALY gained			█ <sup>1</sup>
<b>25% higher HSCT cost, convergence from 10 to 25 years and LDC AEMP = \$█</b>			
Costs(\$)	█	\$104,492	█
QALYs	1.794	0.904	0.933
Incremental cost/extra QALY gained			█ <sup>1</sup>

AEMP = approved ex-manufacturer price; HSCT = haematopoietic stem cell transplant; LDC = liposomal daunorubicin and cytarabine; QALY = quality adjusted life year

The redacted values correspond to the following ranges:

<sup>1</sup> \$55,000 to < \$75,000

### **Estimated PBS usage & financial implications**

4.9 In July 2023, the PBAC recommended that revised utilisation and financial estimates be presented which addressed the issues identified by DUSC by:

- Revising the uptake rates (which were considered underestimated for first induction and overestimated for second induction);
- Removing patients with a FLT3 mutation;
- Providing more accurate estimates of use in the private and public inpatient settings. Use in the outpatient setting was considered to be overestimated,

particularly during consolidation, due to the prolonged time to recovery of neutrophils and platelets; and

- Applying a private to public hospital split of 17% to 83%. This aligned with that previously accepted in the gemtuzumab ozogamicin submission (paragraph 6.102, gemtuzumab ozogamicin Public Summary Document, November 2021).

4.10 Table 5 presents a comparison of the inputs and patient numbers in the July 2023 and November 2023 submissions and Table 6 presents the cost to the PBS/RPBS.

**Table 5: Comparison of inputs and patient numbers across the July 2023 and November 2023 submissions**

Input	July 2023 value	November 2023 value	Sources
Patients with AML	2024: 1,259 2025: 1,288 2026: 1,317 2027: 1,347 2028: 1,377 2029: 1,406	2024: 1,259 2025: 1,288 2026: 1,317 2027: 1,347 2028: 1,377 2029: 1,406	Average age-specific incidence of AML reported in AIHW Cancer Data in Australia (2022). Fixed incidence over 6 years, applied to Australian population ≥18 years
% with t-AML or AML-MRC	33.76%	33.76%	Based on an Australian registry cohort of patients with t-AML (5.4%) and AML-MRC (28.3%) (ALLG NBCR 2020 report).
Patients with t-AML or AML-MRC	2024: 425 2025: 435 2026: 444 2027: 455 2028: 465 2029: 475	2024: 425 2025: 435 2026: 444 2027: 455 2028: 465 2029: 475	-
% eligible for intensive chemotherapy	50%	62%	July 2023: Based on the average of responses received in the KOL 2021 survey. November 2023: previously accepted for gemtuzumab ozogamicin (Nov 2021)
% of patients with FLT3 mutation	-	13.9% (i.e. proportion of patients without FLT3 mutation = 100% - 13.9% = 86.1%)	% of patients in Study 301 who had AML that was FLT3 mutation positive.
Patients eligible for liposomal daunorubicin and cytarabine	2024: 1 2025: 1 2026: 1 2027: 1 2028: 1 2029: 1	2024: 1 2025: 1 2026: 1 2027: 1 2028: 1 2029: 1	-
% of patients eligible for each cycle of therapy	Induction 1: 100% Induction 2: 31% Consolidation 1: 32% Consolidation 2: 15%	Induction 1: 100% Induction 2: 31% Consolidation 1: 32% Consolidation 2: 15%	Based on results of Study 301.

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Input	July 2023 value					November 2023 value					Sources
		Ind 1	Ind 2	Con 1	Con 2		Ind 1	Ind 2	Con 1	Con 2	
Patients eligible for each cycle of therapy	2024	1	1	1	1	2024	1	1	1	1	-
	2025	1	1	1	1	2025	1	1	1	1	
	2026	1	1	1	1	2026	1	1	1	1	
	2027	1	1	1	1	2027	1	1	1	1	
	2028	1	1	1	1	2028	1	1	1	1	
	2029	1	1	1	1	2029	1	1	1	1	
Uptake rates	Induction 1: 82.5% Induction 2: 59.4% Consolidation 1: 70.9% Consolidation 2: 68.6%					Induction 1: Yr 1: 85%, Yr 2: 90% Yrs 3-6: 95% Induction 2: Yrs 1-6: 35% Consolidation 1 and 2: Yr 1: 85%, Yr 2: 90% Yrs 3-6: 95%					July 2023: based on averages from the KOL survey. November 2023: assumptions based on PBAC feedback.  The increased rates of uptake applied in consolidation do not align with the PBAC's July 2023 view that the claim of superior efficacy in this setting was not supported (see paragraph 4.3). The pre-PBAC response stated that the increased consolidation rates were due to the increased use of liposomal daunorubicin and cytarabine in the induction setting which results in more patients achieving a response requiring consolidation.
Patients receiving treatment		Ind 1	Ind 2	Con 1	Con 2		Ind 1	Ind 2	Con 1	Con 2	-
	2024	1	1	1	1	2024	1	1	1	1	
	2025	1	1	1	1	2025	1	1	1	1	
	2026	1	1	1	1	2026	1	1	1	1	
	2027	1	1	1	1	2027	1	1	1	1	
	2028	1	1	1	1	2028	1	1	1	1	
	2029	1	1	1	1	2029	1	1	1	1	
Total patients	2024:	1				2024:	1				-
	2025:	1				2025:	1				
	2026:	1				2026:	1				
	2027:	1				2027:	1				
	2028:	1				2028:	1				
	2029:	1				2029:	1				
Public vs private hospital split	46.8% vs 53.2%					83% public hospital inpatient setting (i.e. non-PBS supply) vs 17% public hospital outpatient and private hospital in/outpatient setting (i.e. PBS supply)					July 2023: based on PBS utilisation estimates for cytarabine in 2022. November 2023: previously accepted for gemtuzumab ozogamicin (Nov 2021).
Total patients receiving PBS/RPBS liposomal daunorubicin and cytarabine	2024:	1				2024:	1				November 2023: █% of prescriptions dispensed
	2025:	1				2025:	1				
	2026:	1				2026:	1				
	2027:	1				2027:	1				
	2028:	1				2028:	1				
	2029:	1				2029:	1				

Input	July 2023 value	November 2023 value	Sources
Average number of vials treatment	Induction: 2.44 vials Consolidation: 1.97	Induction: 2.44 vials Consolidation: 1.97	Derived from economic analysis
Effective DPMA	Induction: Public = \$ [redacted] Private = \$ [redacted] Consolidation: Public = \$ [redacted] Private = \$ [redacted]	Induction: Public = \$ [redacted] Private = \$ [redacted] Consolidation: Public = \$ [redacted] Private = \$ [redacted]	-

Source: Table 8, p12 of the November 2023 resubmission and Tables 4.1.1 and 4.2.1 of the July 2023 commentary  
 AIHW = Australian Institute of Health and Welfare; AML = acute myeloid leukaemia; AML-MCR = acute myeloid leukaemia with myelodysplasia-related changes; Con = consolidation; Ind = induction; KOL = key opinion leader; t-AML = therapy-related acute myeloid leukaemia; Yr = year

The redacted values correspond to the following ranges:

<sup>1</sup> < 500

**Table 6: Estimated use and financial implications**

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
<b>Estimated extent of use</b>						
Number of patients treated	[redacted] <sup>1</sup>	[redacted] <sup>1</sup>	[redacted] <sup>1</sup>	[redacted] <sup>1</sup>	[redacted] <sup>1</sup>	[redacted] <sup>1</sup>
Number of scripts dispensed <sup>a</sup>	[redacted] <sup>1</sup>	[redacted] <sup>1</sup>	[redacted] <sup>1</sup>	[redacted] <sup>1</sup>	[redacted] <sup>1</sup>	[redacted] <sup>1</sup>
<b>Estimated financial implications</b>						
<b>Cost to PBS/RPBS</b>	[redacted] <sup>2</sup>	[redacted] <sup>2</sup>	[redacted] <sup>2</sup>	[redacted] <sup>2</sup>	[redacted] <sup>2</sup>	[redacted] <sup>2</sup>
Cost to MBS	[redacted] <sup>3</sup>	[redacted] <sup>3</sup>	[redacted] <sup>3</sup>	[redacted] <sup>3</sup>	[redacted] <sup>3</sup>	[redacted] <sup>3</sup>
Net cost to PBS/RPBS/MBS	[redacted] <sup>2</sup>	[redacted] <sup>2</sup>	[redacted] <sup>2</sup>	[redacted] <sup>2</sup>	[redacted] <sup>2</sup>	[redacted] <sup>2</sup>
<b>July 2023 submission</b>						
Net cost to PBS/RPBS	[redacted] <sup>2</sup>	[redacted] <sup>2</sup>	[redacted] <sup>2</sup>	[redacted] <sup>2</sup>	[redacted] <sup>2</sup>	[redacted] <sup>2</sup>

<sup>a</sup> Assuming induction requires 2.44 vials and consolidation requires 1.97 vials.

The redacted values correspond to the following ranges:

<sup>1</sup> < 500

<sup>2</sup> \$0 to < \$10 million

<sup>3</sup> net cost saving

4.11 The net cost of listing liposomal daunorubicin and cytarabine on the PBS/RPBS was estimated to be \$0 to < \$10 million in Year 1, \$0 to < \$10 million in Year 6 and total \$0 to < \$10 million over the first six years of listing.

4.12 The resubmission also estimated the financial implications for:

- (i) the supply of liposomal daunorubicin and cytarabine to inpatients of public hospitals (Table 7); and
- (ii) the additional costs for HSCT to the public hospital setting, as a higher proportion of patients in Study 301 received HSCT when treated with liposomal daunorubicin and cytarabine (34%) compared to when treated with daunorubicin and cytarabine (25%) (Table 8).

**Table 7: Cost of liposomal daunorubicin and cytarabine outside of the PBS/RPBS (i.e. dispensed to inpatients of public hospitals)**

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
Number of scripts dispensed <sup>a</sup>	█ <sup>1</sup>	█ <sup>1</sup>	█ <sup>1</sup>	█ <sup>1</sup>	█ <sup>1</sup>	█ <sup>1</sup>
Cost (\$)	█ <sup>2</sup>	█ <sup>2</sup>	█ <sup>2</sup>	█ <sup>2</sup>	█ <sup>2</sup>	█ <sup>2</sup>

Source: Table 17, p17 of the November 2023 resubmission

<sup>a</sup> Assuming induction requires 2.44 vials and consolidation requires 1.97 vials.

The redacted values correspond to the following ranges:

<sup>1</sup> < 500

<sup>2</sup> \$0 to < \$10 million

**Table 8: Additional cost of HSCT to the public hospital setting**

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
Patients initiating treatment with LDC (i.e. receiving first induction treatment)	█ <sup>1</sup>	█ <sup>1</sup>	█ <sup>1</sup>	█ <sup>1</sup>	█ <sup>1</sup>	█ <sup>1</sup>
Additional % receiving HSCT	9%					
Cost of HSCT	\$123,980					
Cost (\$)	█ <sup>2</sup>	█ <sup>2</sup>	█ <sup>2</sup>	█ <sup>2</sup>	█ <sup>2</sup>	█ <sup>2</sup>

Source: Table 18, p17 of the November 2023 resubmission

LDC = liposomal daunorubicin and cytarabine; HSCT = haematopoietic stem cell transplant

The redacted values correspond to the following ranges:

<sup>1</sup> < 500

<sup>2</sup> \$0 to < \$10 million

For more detail on PBAC’s view, see section 5 PBAC outcome.

## 5 PBAC Outcome

- 5.1 The PBAC recommended liposomal daunorubicin and cytarabine for the treatment of therapy-related acute myeloid leukaemia (t-AML) or acute myeloid leukaemia with myelodysplasia-related changes (AML-MRC). The PBAC’s recommendation for listing was based on, among other matters, its assessment that the cost-effectiveness of daunorubicin and cytarabine would be acceptable at the price proposed in the resubmission. The PBAC considered that the revised estimated utilisation and financial impact were reasonable.
- 5.2 The PBAC acknowledged the advice received via the consumer comments facility which noted the unmet need for alternate AML treatments and was supportive of the submission.
- 5.3 The PBAC recalled that in July 2023 it had:
- accepted that daunorubicin was an acceptable proxy for idarubicin when given at the recommended dose for the 7+3 regimen in the induction setting;
  - considered that liposomal daunorubicin and cytarabine was superior in terms of effectiveness compared to daunorubicin/idarubicin plus cytarabine in the first induction setting;
  - considered that the claim that liposomal daunorubicin and cytarabine was non-inferior in terms of safety compared to daunorubicin/idarubicin and cytarabine was not supported in the first induction setting; and

- considered that the claim that liposomal daunorubicin and cytarabine was superior in terms of efficacy and non-inferior in terms of safety compared to daunorubicin/idarubicin and cytarabine was uncertain, but likely to be reasonable, for second induction and consolidation due to the use of a non-standard regimen (5+2) in the context of use in only a proportion of patients.
- 5.4 The PBAC recalled that in July 2023 it had considered that the base case ICER of \$75,000 to < \$95,000 per quality adjusted life year (QALY) was high and uncertain. The PBAC recalled that it had requested a revised economic model which (i) applied convergence so that the OS curves converged within the 25-year time horizon; (ii) increased the costs associated with haematopoietic stem cell transplant (HSCT) by 50% to be indicative of the increased costs associated with liposomal daunorubicin and cytarabine; and (iii) incorporated a price reduction so that the resultant ICER was no more than \$60,000 per QALY.
- 5.5 The PBAC noted that the requested changes were partially addressed, as convergence was not applied in the revised economic model and the costs associated with HSCT were increased by 25% (rather than 50%). The PBAC noted that for the model scenario presented in the resubmission the ICER was \$75,000 to < \$95,000 per QALY and that, to result in an ICER of \$55,000 to < \$75,000 per QALY, the effective ex-manufacturer price of liposomal daunorubicin and cytarabine was reduced by  $\frac{1}{3}$  (from \$ $\frac{1}{3}$  per vial to \$ $\frac{1}{6}$  per vial). The PBAC noted that if the requested changes as advised in July 2023 were implemented, the required price reduction was  $\frac{1}{3}$ . On balance, the PBAC considered that the economic model as presented in the resubmission was reliable and that liposomal daunorubicin and cytarabine was likely to be cost effective at the price proposed.
- 5.6 The PBAC noted that the revised utilisation and financial estimates had addressed the issues identified in July 2023 (see paragraph 4.9). The PBAC considered that the increased rates of consolidation applied in the resubmission, which were due to the increased use of liposomal daunorubicin and cytarabine in the induction setting, were reasonable. The PBAC were satisfied that the majority of use of liposomal daunorubicin and cytarabine would be in the public hospital inpatient setting (83%). Overall, the PBAC considered that the estimated cost to the PBS/RPBS of \$0 to < \$10 million over the first 6 years of listing for use in the public hospital outpatient and the private hospital settings (17%) was reasonable.
- 5.7 In terms of the restriction, the PBAC advised that it would be appropriate to include a prescribing instruction requiring documentation of diagnosis in the patient's file and a caution advising that liposomal daunorubicin and cytarabine should not be used interchangeably with daunorubicin injection and cytarabine injection.
- 5.8 The PBAC noted that combination chemotherapy products present system challenges for Services Australia and prescribing and dispensing software. The PBAC noted that significant changes to software, the Efficient Funding of Chemotherapy calculation

algorithm and Services Australia would be required and that this will be a lengthy process.

- 5.9 The PBAC advised that liposomal daunorubicin and cytarabine was not suitable for prescribing by nurse practitioners.
- 5.10 The PBAC advised that the Early Supply Rule should not apply.
- 5.11 The PBAC advised that liposomal daunorubicin and cytarabine should not be treated as interchangeable with any other drugs.
- 5.12 The PBAC found that the criteria prescribed by the *National Health (Pharmaceuticals and Vaccines – Cost Recovery) Regulations 2022* for Pricing Pathway A were not met. Specifically, the PBAC found that in the circumstances of its recommendation for liposomal daunorubicin and cytarabine:
- a) Liposomal daunorubicin and cytarabine was expected to provide a clinically relevant improvement in efficacy over currently available alternative therapies;
  - b) The treatment is not expected to address a high and urgent unmet clinical need due to the availability of alternative therapies;
  - c) It was not necessary to make a finding in relation to whether it would be in the public interest for the subsequent pricing application to be progressed under Pricing Pathway A because one or more of the preceding tests had failed.
- 5.13 The PBAC noted that this submission is not eligible for an Independent Review as it received a positive recommendation.

**Outcome:**

Recommended

## 6 Recommended listing

### 6.7 Add new item:

MEDICINAL PRODUCT Form	PBS item code	Max. Amount	No. of Rpts
Liposomal DAUNORUBICIN + CYTARABINE Injection	NEW (Public) NEW (Private)	132 mg/300 mg (3 vials) daunorubicin – 132mg	4
<b>Available brands</b>			
Vyxeos (liposomal daunorubicin hydrochloride 44 mg + cytarabine 100 mg injection, 1 vial)			
<b>Restriction Summary [new] / Treatment of Concept: [new]</b>			
	<b>Category / Program:</b> Section 100 – Efficient Funding of Chemotherapy Public/Private hospitals		
	<b>Prescriber type:</b> <input checked="" type="checkbox"/> Medical Practitioners		
	<b>Restriction type:</b> <input checked="" type="checkbox"/> Authority Required (telephone/online PBS Authorities system)		
	<b>Indication:</b> Acute myeloid leukaemia		
	<b>Treatment phase:</b> Induction		
	<b>Clinical criteria:</b>		
	Patient must not have received prior chemotherapy as induction therapy for this condition		
	<b>AND</b>		
	<b>Clinical criteria:</b>		
	The condition must be either (i) newly diagnosed therapy-related acute myeloid leukaemia (AML), (ii) newly diagnosed AML with myelodysplasia-related changes (MRC) (prior myelodysplastic syndromes (MDS) or MDS-related cytogenetic or molecular abnormality),		
	<b>AND</b>		
	<b>Clinical criteria:</b>		
	The condition must not be either (i) internal tandem duplication (ITD), or (ii) tyrosine kinase domain (TKD) FMS tyrosine kinase 3 (FLT3), mutation positive		
	<b>AND</b>		
	<b>Clinical criteria:</b>		
	Patient must not have favourable cytogenetic risk AML		
	<b>AND</b>		
	<b>Clinical criteria:</b>		
	Patient must have a World Health Organization (WHO) performance status score of 2 or less.		
	<b>Treatment criteria:</b>		
	The treatment must not exceed two cycles of induction therapy under this restriction.		
	<b>Prescribing Instructions:</b> This product is not PBS-subsidised if it is administered to an in-patient in a public hospital setting.		
	<b>Prescribing Instructions:</b> The prescriber must confirm whether the patient has newly diagnosed therapy-related AML or AML-MRC. The test result and date of testing must be provided at the time of application and documented in the patient's file.		
	<b>Caution:</b> Liposomal daunorubicin and cytarabine (Vyxeos) must not be substituted or interchanged with other daunorubicin and/or cytarabine containing products. Due to substantial differences in the pharmacokinetic parameters, the dose and schedule recommendations for Vyxeos are different from other medications that contain daunorubicin and/or cytarabine in other forms.		

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	<b>Administrative advice:</b> No increase in the maximum number of repeats may be authorised.
	<b>Administrative advice:</b> Special Pricing Arrangements apply.
	<b>Administrative advice:</b> Applications for authorisation under this restriction may be made in real time using the Online PBS Authorities system (see <a href="http://www.servicesaustralia.gov.au/HPOS">www.servicesaustralia.gov.au/HPOS</a> ) or by telephone by contacting Services Australia on 1800 700 270 (hours of operation 8 a.m. to 5 p.m. Monday to Friday).

MEDICINAL PRODUCT Form	PBS item code	Max. Amount	No. of Rpts
Liposomal DAUNORUBICIN + CYTARABINE Injection	NEW (Public) NEW (Private)	88 mg/200 mg (2 vials) daunorubicin – 88mg	3
<b>Available brands</b>			
Vyxeos (liposomal daunorubicin hydrochloride 44 mg + cytarabine 100 mg injection, 1 vial)			
<b>Restriction Summary [new] / Treatment of Concept: [new]</b>			
	<b>Category / Program:</b> Section 100 – Efficient Funding of Chemotherapy Public/Private hospitals		
	<b>Prescriber type:</b> <input checked="" type="checkbox"/> Medical Practitioners		
	<b>Restriction type:</b> <input checked="" type="checkbox"/> Authority Required (telephone/online PBS Authorities system)		
	<b>Indication:</b> Acute myeloid leukaemia		
	<b>Treatment phase:</b> Consolidation		
	<b>Clinical criteria:</b>		
	The treatment must be for consolidation treatment following induction treatment with this product.		
	<b>AND</b>		
	<b>Clinical criteria:</b>		
	The condition must be either (i) newly diagnosed therapy-related acute myeloid leukaemia (AML), (ii) newly diagnosed AML with myelodysplasia-related changes (MRC) (prior myelodysplastic syndromes (MDS) or MDS-related cytogenetic or molecular abnormality),		
	<b>Treatment criteria:</b>		
	The treatment must not exceed two cycles of consolidation therapy under this restriction.		
	<b>Prescribing Instructions:</b> This product is not PBS-subsidised if it is administered to an in-patient in a public hospital setting.		
	<b>Caution:</b> Liposomal daunorubicin and cytarabine (Vyxeos) must not be substituted or interchanged with other daunorubicin and/or cytarabine containing products. Due to substantial differences in the pharmacokinetic parameters, the dose and schedule recommendations for Vyxeos are different from other medications that contain daunorubicin and/or cytarabine in other forms.		
	<b>Administrative advice:</b> No increase in the maximum number of repeats may be authorised.		
	<b>Administrative advice:</b> Special Pricing Arrangements apply.		
	<b>Administrative advice:</b> Applications for authorisation under this restriction may be made in real time using the Online PBS Authorities system (see <a href="http://www.servicesaustralia.gov.au/HPOS">www.servicesaustralia.gov.au/HPOS</a> ) or by telephone by contacting Services Australia on 1800 700 270 (hours of operation 8 a.m. to 5 p.m. Monday to Friday).		

***This restriction may be subject to further review. Should there be any changes made to the restriction the Sponsor will be informed.***

## **7 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.

## **8 Sponsor's Comment**

The sponsor had no comment.