

An addendum to this public summary document has been included at the end of the document.

**7.10 ENFORTUMAB VEDOTIN,
Powder for I.V. infusion 20 mg,
Powder for I.V. infusion 30 mg,
Padcev[®],
Astellas Pharma Australia Pty Ltd**

1 Purpose

1.1 The early re-entry resubmission sought a Section 100 (Efficient Funding of Chemotherapy) listing for enfortumab vedotin for the treatment of patients with locally advanced (Stage III) or metastatic (Stage IV) urothelial cancer (la/mUC) who have progressed on or after a platinum-containing chemotherapy regimen and either a programmed cell death-1 (PD-1) inhibitor or a programmed cell death ligand-1 (PD-L1) inhibitor.

1.2 The resubmission was based on the PBAC recommendation from March 2022. Table 1 outlines the issues raised by the PBAC in March 2022 and the resubmission response.

Table 1 Summary of key matters to be addressed

Matter of concern	Response	Addressed?
The submission presented a cost-utility analysis with a 10 year time horizon and a resulting base case ICER of \$█/QALY. The PBAC agreed with the ESC that for clinical plausibility the model time horizon should be reduced to 5 years. (Para 7.6)	The resubmission presented base case results over a time horizon of 7.5 years. Noted that extrapolation (exponential) based on the OS data from the updated data cut off (30 July 2021), indicated a flattening of risk and predicted that 4.6% of patients on enfortumab vedotin are still alive at 5 years. Therefore, argued relevant differences between patients on enfortumab vedotin and chemotherapy should be captured beyond 5 years.	No
The PBAC agreed with the ESC that exclusion of vinflunine data to create the taxane subgroup used in the model may impact the validity of the estimate of the HR and hence considered the use of ITT HR results in the model more appropriate. (Para 7.6)	Accepted and presented in the economic model.	Yes
The PBAC noted the pre-PBAC response accepted that the use of non-treatment specific utilities for patients in equivalent health states regardless of treatment arm may be appropriate. (Para 7.6)	Accepted and presented in the economic model.	Yes

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Matter of concern	Response	Addressed?
The PBAC noted the PSCR and pre-PBAC response arguments that the exponential distribution provided a better fit to the EV-301 longer-term OS data for the enfortumab vedotin arm compared to the use of the Weibull extrapolation. The PBAC considered that this remained an area of uncertainty and advised that it would be appropriate in a resubmission for (i) changes as per the ESC respecified base case scenario including use of the Weibull function for OS extrapolation unless the use of an exponential distribution can be adequately justified. (Para 7.7).	Argued analysis of the extended follow-up data justified an exponential extrapolation. Stated that analysis of the extended follow-up data also informed the extent and impact of cross-over to the enfortumab vedotin arm; the prespecified adjusted hazard ratio analysis for cross-over was hence proposed in the revised base case.	Unclear
....and (ii) if the ICER was in the order of \$ ² /QALY (Para 7.7)	Proposed an SRA (together with the original SPA) to reduce the ICER. SRA involves a cap on the PBS subsidised treatment at ¹ months treatment or ¹ treatment cycles if treatment is of greater duration (¹ months continuous treatment = ¹ cycles). After this cap, enfortumab vedotin will be administered at a ¹ % rebate by the sponsor. The proposed SRA (and SPA) stated to reduce the ICER in the proposed base case to \$ ³ /QALY from \$ ¹ without the SRA.	No
The PBAC noted the advice from DUSC that the approach taken to the application of relative dosing intensity in the financial estimates likely underestimated costs by around 5%. The PBAC considered that this should be corrected in any resubmission. (Para 7.8)	Accepted and presented in the financial model.	Yes
The PBAC considered it would be appropriate for a resubmission to address any residual uncertainty regarding the number of patients treated with enfortumab vedotin by data triangulation. The PBAC considered this would involve verifying the submission's estimate of patient numbers against those derived from using current pembrolizumab utilisation data for this indication and an assumption that 80% of such patients would subsequently receive enfortumab vedotin. (Para 7.8)	Estimates verified as per PBAC recommendation.	Yes
Revision of the financial estimates as outlined in paragraph 7.8 and recalculation of the financial implications using the revised enfortumab vedotin price. (Para 7.10)	Revised financial estimates have been presented based on the SRA agreement proposed above, including the SPA.	Unclear as enfortumab vedotin price not revised

Source: Table 1, pvii-x of the submission

HR: Hazard ratio, ICER: incremental cost-effectiveness ratio, ITT: Intention-to-treat, OS: overall survival, QALY: Quality-adjusted life year, SPA: Special pricing arrangement, RDI: relative dose intensity, SRA: Special revenue arrangement, PSCR: Pre-Sub-Committee Response.

The redacted values correspond to the following ranges:

¹ \$95,000 to < \$115,000

² \$55,000 to < \$75,000

³ \$75,000 to < \$95,000

- 1.3 The resubmission requested a special pricing arrangement (SPA), with an effective ex-manufacturer price of \$| per 20 mg vial and \$| per 30 mg vial. The effective ex-manufacturer prices were identical to those proposed in the original submission. In March 2022, the PBAC advised that a revised enfortumab vedotin price be used to recalculate the financial estimates (paragraph 7.10, enfortumab vedotin Public Summary Document (PSD), March 2022 PBAC meeting). The pre-PBAC response proposed a |% reduction in the effective ex-manufacturer price (\$| per 20 mg vial and \$| per 30 mg vial).

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

2 Background

- 2.1 Enfortumab vedotin was TGA registered on 7 July 2022 for the treatment of adult patients with la/mUC who have previously received a platinum-containing chemotherapy and a programmed death receptor-1 or programmed death-ligand-1 inhibitor.¹
- 2.2 The PICO from the previous submission is presented below.

Table 2: Key components of the clinical issue addressed by the submission

Component	Description
Population	Patients with locally advanced (Stage III) or metastatic (Stage IV) urothelial cancer and WHO performance status of 0 or 1 who have progressed on or after treatment with a platinum-containing chemotherapy regimen and either a programmed cell death-1 (PD-1) inhibitor or a programmed cell death ligand-1 (PD-L1) inhibitor
Intervention	Enfortumab vedotin 1.25 mg/kg (to a maximum of 125 mg) on Days 1, 8 and 15 of each 28-day treatment cycle until disease progression or unacceptable toxicity
Comparator	Docetaxel 75 mg/m ² on Day 1 of each 21-day treatment cycle or paclitaxel 175 mg/m ² on Day 1 of each 21-day treatment cycle until disease progression or unacceptable toxicity
Outcomes	Overall survival, progression-free survival, quality-adjusted survival, overall response rates, safety
Clinical claim	In patients with locally advanced (Stage III) or metastatic (Stage IV) urothelial cancer and WHO performance status of 0 or 1 who have progressed on or after treatment with a platinum-containing chemotherapy regimen and either a PD-1 inhibitor or a PD-L1 inhibitor, enfortumab vedotin has superior clinical efficacy and non-inferior safety compared with docetaxel or paclitaxel.

Source: Table 1, p1 enfortumab vedotin March 2022 PBAC PSD

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

3 Requested listing

- 3.1 The resubmission accepted amendments to the previously considered PBS restriction. Suggestions and additions proposed by the Secretariat are added in italics and suggested deletions are crossed out with strikethrough.

¹ [PADCEV \(Astellas Pharma Australia Pty Ltd\) | Therapeutic Goods Administration \(TGA\)](#)

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MEDICINAL PRODUCT Form	PBS item code	Max. Amount	No. of Rpts	Dispensed price for maximum amount
ENFORTUMAB VEDOTIN 20 mg powder for injection, 1 vial 30 mg powder for injection, 1 vial	NEW	130mg 125 mg	9	Public Hospital: \$6,210.46 (published) \$↓ (effective) Private Hospital: \$6,337.82 (published) \$↓ (effective)
Available brands				
Padcev (enfortumab vedotin 20 mg powder for injection, 1 vial)				
Padcev (enfortumab vedotin 30 mg powder for injection, 1 vial)				
Restriction Summary [new] / Treatment of Concept: [new]				
	Category / Program: Section 100 – Efficient Funding of Chemotherapy Public/Private hospitals			
	Prescriber type: <input checked="" type="checkbox"/> Medical Practitioners			
	Restriction Type: <input checked="" type="checkbox"/> Authority Required – Streamlined			
	Administrative Advice: No increase in the maximum quantity or number of units may be authorised.			
	Administrative Advice: No increase in the maximum number of repeats may be authorised.			
	Administrative Advice: Special Pricing Arrangements apply.			
	Severity: Locally advanced (Stage III) or metastatic (Stage IV)			
	Condition: Urothelial cancer			
	Indication: Locally advanced (Stage III) or metastatic (Stage IV) urothelial cancer			
	Treatment Phase: Initial treatment			
	Clinical criteria:			
	Patient must have received <i>prior treatment with platinum-based chemotherapy</i>			
	AND			
	Clinical criteria:			
	The condition must have progressed on or after either a programmed death protein 1 (PD-1) or programmed death ligand 1 (PD-L1) inhibitor; OR			
	Patient must have developed intolerance to a programmed death protein 1 (PD-1) or programmed death ligand 1 (PD-L1) inhibitor necessitating permanent treatment withdrawal,			
	AND			
	Clinical criteria			
	Patient must have a WHO performance status of 0 or 1			
	AND			
	Clinical criteria:			
	The treatment must be the sole PBS-subsidised therapy for this condition.			
	Category / Program: Section 100 – Efficient Funding of Chemotherapy Public/Private hospitals			
	Prescriber type: <input checked="" type="checkbox"/> Medical Practitioners			
	Restriction Type: <input checked="" type="checkbox"/> Authority Required – Streamlined			
	Administrative Advice: No increase in the maximum quantity or number of units may be authorised.			
	Administrative Advice: No increase in the maximum number of repeats may be authorised.			
	Administrative Advice: Special Pricing Arrangements apply.			
	Severity: Locally advanced (Stage III) or metastatic (Stage IV)			
	Condition: Urothelial cancer			

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	Indication: Locally advanced (Stage III) or metastatic (Stage IV) urothelial cancer
	Treatment Phase: Continuing treatment
	Clinical criteria:
	Patient must have previously received PBS-subsidised treatment with this drug for this condition,
	AND
	Clinical criteria:
	Patient must not have developed disease progression while being treated with this drug for this condition,
	AND
	Clinical criteria
	The treatment must be the sole PBS-subsidised therapy for this condition.

	Category / Program: Section 100 – Efficient Funding of Chemotherapy Public/Private hospitals
	Prescriber type: <input checked="" type="checkbox"/> Medical Practitioners
	Restriction Type: <input checked="" type="checkbox"/> Authority Required – Streamlined
	Administrative Advice: No increase in the maximum quantity or number of units may be authorised.
	Administrative Advice: No increase in the maximum number of repeats may be authorised.
	Administrative Advice: Special Pricing Arrangements apply.
	Severity: Locally advanced (Stage III) or metastatic (Stage IV)
	Condition: Urothelial cancer
	Indication: Locally advanced (Stage III) or metastatic (Stage IV) urothelial cancer
	Treatment Phase: Grandfather treatment
	Clinical criteria:
	Patient must have received treatment with this drug for this condition prior to [listing date],
	AND
	Clinical criteria:
	Patient must have been treated with platinum-containing chemotherapy prior to initiation of non-PBS-subsidised treatment with this drug for this condition; OR
	AND
	Clinical criteria:
	<i>Patient must have been treated with a programmed death protein 1 (PD-1) or programmed death ligand 1 (PD-L1) inhibitor prior to initiation of non-PBS-subsidised treatment with this drug for this condition,</i>
	AND
	Clinical criteria:
	Patient must have had a WHO performance status of 0 or 1 <i>at the time of initiation of non-PBS-subsidised treatment with this drug for this condition,</i>
	AND
	Clinical criteria:
	Patient must not have developed disease progression while being treated with this drug for this condition,
	AND
	Clinical criteria:
	The treatment must be the sole PBS-subsidised therapy for this condition.
	Prescribing instructions A patient may qualify for PBS-subsidised treatment under this restriction once only. For continuing PBS-subsidised treatment, a Grandfathered patient must qualify under the 'Continuing treatment' criteria.
	Administrative advice: This grandfather restriction will cease to operate from 12 months after the date specified in the clinical criteria.

- 3.2 The minimum efficient combination of vials to deliver the maximum dose of 125 mg per infusion is 2 × 20 mg vials and 3 × 30 mg vials, which equates to dispensing 130 mg of enfortumab vedotin. The proposed dispensed price for the maximum amount relates to the price for 130 mg of enfortumab vedotin.

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 an individual (1) and organisation (1) via the Consumer Comments facility on the PBS website. The comments from an individual who has used enfortumab vedotin for their own health condition described how they had experienced a complete response to the treatment. The individual noted that they had experienced a range of adverse events, some of which had reduced over time and others that were ongoing (peripheral neuropathy, dry skin, eyes affected by glare) but in general they were able to tolerate the drug well. The individual noted the prohibitive cost of treatment if they were not on a clinical trial. The PBAC also recalled the input from 1 individual and 3 organisations that were considered at the March 2022 meeting.
- 4.3 The Medical Oncology Group of Australia (MOGA) expressed its strong support for the enfortumab vedotin submission, categorising it as one of the therapies of “highest priority for PBS listing” on the basis of the EV-301 trial. The PBAC noted that the MOGA presented a European Society for Medical Oncology Magnitude of Clinical Benefit Scale (ESMO-MCBS) for enfortumab vedotin, which was limited to 4 (out of a maximum of 5, where 5 and 4 represent the grades with substantial improvement)², based on a comparison with chemotherapy.

Comparative effectiveness

- 4.4 The March 2022 consideration of enfortumab vedotin was based on one head-to-head Phase III, multicentre, randomised, controlled, open-label trial comparing enfortumab vedotin with chemotherapy (investigator’s choice of docetaxel, paclitaxel or vinflunine; the selection was nominated before randomisation) in patients with

² Cherny NI, Dafni U, Bogaerts J, et al: ESMO-Magnitude of Clinical Benefit Scale version 1.1. *Annals of Oncology* 2017;28:2340-2366

la/mUC who had previously been treated with a platinum-containing regimen and a PD-(L)1 inhibitor (n=608) (EV-301) (paragraph 6.4, enfortumab vedotin PSD, March 2022 PBAC meeting).

- 4.5 In March 2022, the PBAC noted that at the interim data cut-off (15 July 2020), treatment with enfortumab vedotin reduced the risk of death (hazard ratio (HR) 0.70, 95% CI 0.56, 0.89) compared with chemotherapy, and median OS was extended by approximately 4 months. At that time, the PBAC agreed with the ESC that while the overall survival (OS) data presented in the submission were immature, the updated OS data provided in the Pre-Sub-Committee Response (PSCR)(data cut-off 30 July 2021) suggested the treatment effect in the original submission was accurate and reduced the uncertainty associated with the initial data presented. At the interim data cut-off, the PBAC in March 2022 noted that treatment with enfortumab vedotin reduced the risk of progression or death (HR 0.62, 95% CI 0.51, 0.75) and increased the overall response rate (40.6% vs 17.9%) compared to chemotherapy. Although there was a trend favouring enfortumab vedotin, at that time the PBAC noted that no statistically significant differences in EORTC QLQ-C30 scores between enfortumab vedotin and chemotherapy arms were identified. The PBAC considered the claim of superior comparative effectiveness was reasonable with a moderate OS benefit observed (paragraph 7.4, enfortumab vedotin PSD, March 2022 PBAC meeting).
- 4.6 In March 2022, the PBAC considered that the claim of non-inferior comparative safety was not well supported by the data presented in the submission. However, the PBAC agreed with the ESC that enfortumab vedotin had significant potential adverse events but overall an acceptable safety profile (paragraph 7.5, enfortumab vedotin PSD, March 2022 PBAC meeting).
- 4.7 The resubmission provided the Clinical Study Report regarding the updated analysis presented in the March 2022 PSCR (EV-301 data cut-off 30 July 2021). The resubmission presented the OS and progression-free survival (PFS) results and Kaplan-Meier plots for the interim and updated data cut-off. The OS data are presented in Figure 1 and Figure 2. The PFS data are presented in Table 3.

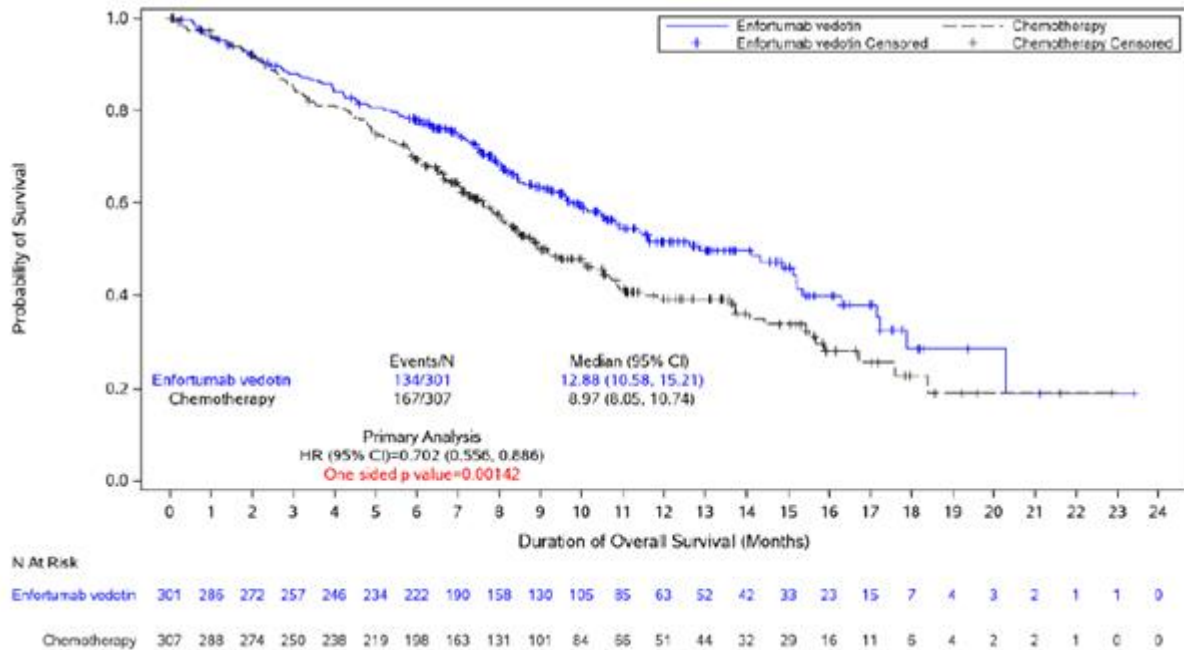
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Table 3: OS and PFS results from the EV-301 trial (ITT population, interim and updated data cut-off)

	Updated data cut-off 30 July 2021		Interim data cut-off 15 July 2020	
	Enfortumab Vedotin (n=301)	Chemotherapy (n=307)	Enfortumab Vedotin (n=301)	Chemotherapy (n=307)
Overall Survival				
Deaths, n (%)	207 (68.8)	237 (77.2)	134 (44.5)	167 (54.4)
Censored, n (%)				
Censored within 14 days of Cut-off Date	76 (25.2)	53 (17.3)	154 (51.2)	124 (40.4)
Censored More Than 14 days before Cut-off Date	18 (6.0)	17 (5.5)	13 (4.3)	16 (5.2)
Overall Survival Rate				
At 6 Months - % (95%CI)	77.9 (72.74, 82.25)	69.5 (63.88, 74.40)	77.9 (72.74, 82.25)	69.5 (63.85, 74.38)
At 12 Months - % (95% CI)	53.0 (47.05, 58.56)	38.7 (33.12, 44.28)	51.5 (44.63, 58.03)	39.2 (32.60, 45.64)
At 24 Months - % (95% CI)	29.3 (23.92, 34.89)	19.8 (15.28, 24.84)	NR	NR
Duration of Overall Survival (months)				
Median (95% CI)	12.91 (11.01, 14.92)	8.94 (8.25, 10.25)	12.88 (10.58, 15.21)	8.97 (8.05, 10.74)
Range	0.30, 35.81	0.03, 32.13	0.30, 23.39	0.03, 22.87
Hazard Ratio (95% CI)	0.704 (0.581, 0.852)		0.702 (0.556, 0.886)	
Median (95% CI) Follow-up of OS, Months	23.52 (22.11, 24.51)	24.18 (23.49, 25.82)	11.10 (10.35, 11.93)	11.07 (9.99, 12.12)
Overall	23.75 (23.10, 24.51)		11.10 (10.55, 11.60)	
Adjusting in Chemotherapy arm based on the RPSFT method				
Duration of Overall Survival (months)				
Median (95% CI)	12.91 (11.01, 14.92)	8.94 (8.05, 10.15)	12.88 (10.58, 15.21)	8.94 (8.05, NE)
Range	0.30, 35.81	0.03, 12.25	0.30, 23.39	0.03, 12.55
Hazard Ratio (95% CI)	0.624 (0.488, 0.849)		0.705 (0.516, 0.853)	
Progression free survival				
PFS events – n (%)	231 (76.7)	248 (80.8)	201 (66.8)	231 (75.2)
Radiographic progression – n (%)	201 (66.8)	211 (68.7)	172 (57.1)	195 (63.5)
Death without documented progression – n (%)	30 (10.0)	37 (12.1)	29 (9.6)	36 (11.7)
Censored, n (%)	70 (23.3)	59 (19.2)	100 (33.2)	76 (24.8)
PFS Rate - % (95% CI)				
At 6 Months	44.7 (38.69, 50.44)	29.2 (23.85, 34.68)	44.0 (37.96, 49.84)	28.2 (22.85, 33.76)
At 12 Months	24.8 (19.82, 30.15)	9.8 (6.43, 13.92)	21.7 (16.26, 27.71)	8.3 (4.61, 13.36)
At 24 Months	13.0 (8.88, 17.83)	5.8 (3.25, 9.45)	NR	NR
Duration of PFS (months)				
Median (95% CI)	5.55 (5.32, 6.28)	3.71 (3.52, 3.94)	5.55 (5.32, 5.82)	3.71 (3.52, 3.94)
HR (95% CI)	0.632 (0.525, 0.762)		0.615 (0.505, 0.748)	

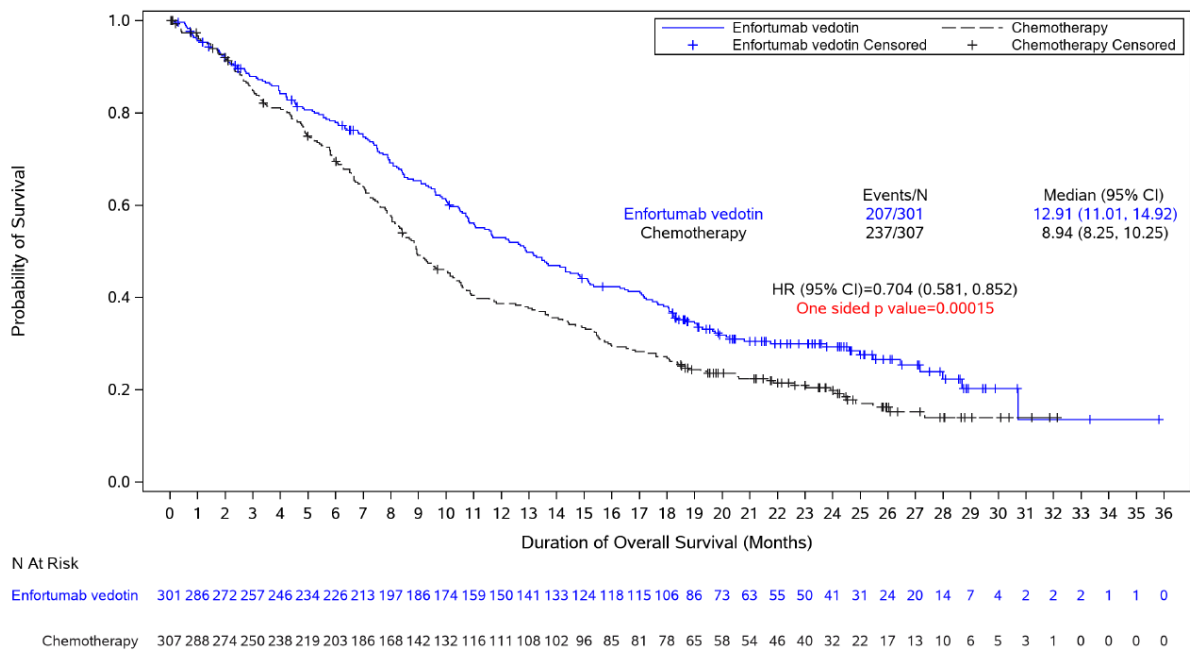
Source: Table 3, p xiv, Table 4, p xvii, enfortumab vedotin resubmission. Blue shading indicates data previously seen by the PBAC. Orange shading indicates data used in the resubmission economic model
RPSFT: rank preserving structural failure time

Figure 1: Kaplan-Meier plot of OS by treatment group in the EV-301 trial (ITT population, interim data cut-off)



Source: Figure 1, enfortumab vedotin PSD, March 2022 PBAC meeting.

Figure 2: Kaplan Meier plots of OS for the updated cut of data (data cut-off: 30 July 2021) for the EV-301 trial (ITT analysis)



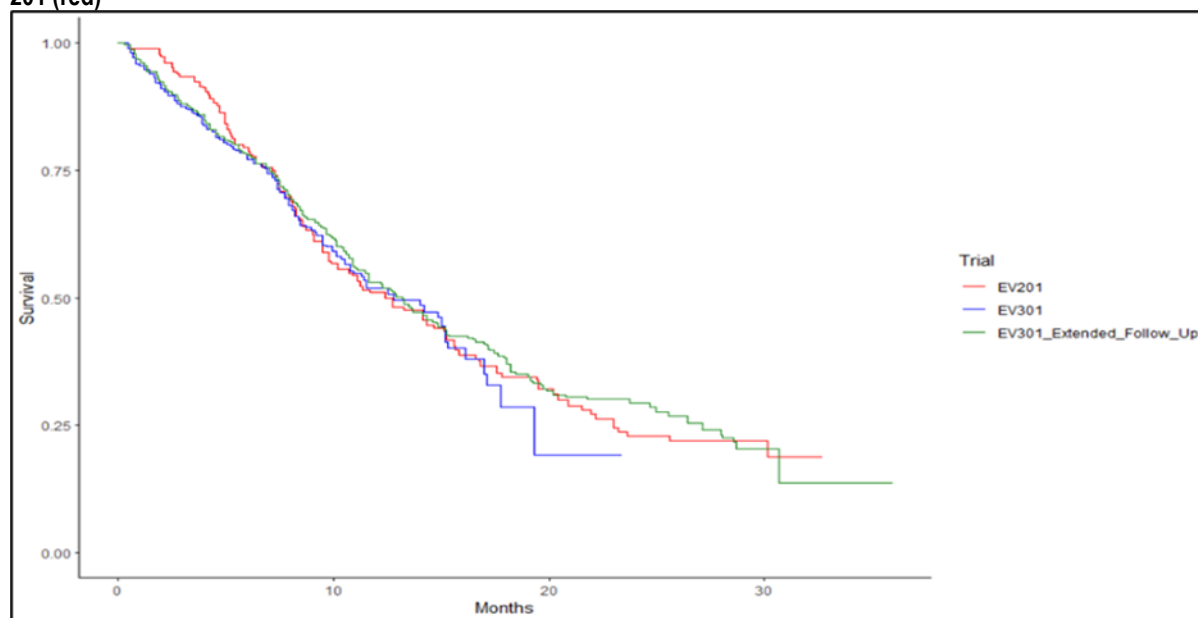
Source: Figure 3, enfortumab vedotin PSD, March 2022 PBAC meeting

4.8 The resubmission stated that since the interim data cut-off (15 July 2020) of the EV-301 trial demonstrated a statistically significant treatment effect in favour of

enfortumab vedotin, the protocol was amended (Substantial Protocol Amendment 5.0) to allow subjects randomized to the chemotherapy arm to receive enfortumab vedotin in the cross-over extension period. At the time of interim data cut-off, there was minimal cross-over (only 4 [1.3%] subjects in the chemotherapy arm received enfortumab vedotin as a subsequent therapy). However, as per updated data cut-off (30 July 2021), 18 [5.9%] subjects in the chemotherapy arm received enfortumab vedotin as a subsequent therapy. The Rank Preserving Structural Failure Time (RPSFT) method was used to assess the impact of chemotherapy arm subjects who took enfortumab vedotin specifically. This 'cross-over adjusted' OS based on interim and updated data cut-off of the EV-301 trial is presented in Table 3. The resubmission noted this analysis indicated a significant effect on the HR for OS from cross-over to enfortumab vedotin, which is lower at HR=0.624 (95% CI 0.488,0.849, p=0.001) than the overall full analysis set (FAS) estimate of HR=0.704 (95% CI 0.581, 0.852). The resubmission noted that the Inverse Probability of Censoring Weights (IPCW) method was also used to determine the robustness of the primary OS results with a further improved HR reported (HR 0.578, 95% CI 0.406, 0.823).

- 4.9 The previous submission had compared the Kaplan-Meier survival functions for enfortumab vedotin-treated patients in EV-201 and the EV-301 interim data. With greater follow-up available in the EV-301 trial, this comparison has been updated (Figure 3). The resubmission argued that this indicated that survival risk with the EV-301 extended follow-up is consistent with the EV-201 trial Cohort 1 providing greater confidence in the survival benefit for enfortumab vedotin-treated patients.

Figure 3 Overall survival comparison update: EV-301 [primary follow-up (blue), extended follow-up (green)] and EV-201 (red)



Source: Figure 6, p xxiii, enfortumab vedotin resubmission

4.10 The resubmission provided the duration of exposure (time on treatment, ToT) and the relative dose intensity (RDI) with the updated data cut-off (Table 4). The resubmission stated the updated ToT data are used in the economic model.

Table 4 Study drug exposure and treatment compliance as per interim and updated data cut-off of EV-301

Parameter Statistics/Criteria	Updated data-cut 30 July 2021		Interim data cut-off 15 July 2020	
	Enfortumab Vedotin (n=296)	Chemotherapy (n=291)	Enfortumab Vedotin (n=296)	Chemotherapy (n=291)
Duration of Exposure (months)				
Mean (SD)	6.46 (5.78)	4.46 (4.39)	5.36 (3.72)	3.96 (2.95)
Median (min, max)	4.99 (0.5, 29.9)	3.45 (0.2, 26.4)	4.99 (0.5, 19.4)	3.45 (0.2, 15.0)
Relative Dose Intensity (%)				
Mean (SD)	78.33 (18.02)	91.68 (11.63)	79.35 (17.52)	91.76 (11.61)
Median (min, max)	78.95 (30.6, 104.9)	97.31 (32.5, 114.2)	80.73 (30.6, 104.9)	97.36 (32.5, 114.2)

Source: Table 6, p xxiii, enfortumab vedotin resubmission. Orange shading indicates data used in the economic model

4.11 The PBAC noted the results of a retrospective cohort study (UNITE) of 260 patients with advanced urothelial cancer treated with enfortumab vedotin.³ At the time of analysis, the median follow-up from the start of enfortumab vedotin was 7.2 months (interquartile range, 3.7-11.6 months), and the median treatment duration was 4.1 months (interquartile range, 1.6-6.9 months). The PBAC noted that of the 212 evaluable for a response, 24% (50/212) were still on enfortumab vedotin at the time of analysis.

4.12 The PBAC reaffirmed its March 2022 advice regarding comparative effectiveness and safety claims (see paragraphs 4.5 and 4.6).

Economic analysis

4.13 In March 2022, the submission presented a cost-utility analysis with a 10 year time horizon and a resulting base case ICER of \$95,000 to < \$115,000/quality-adjusted life year (QALY). At that time, the PBAC noted the ESC proposed a respecified base case that incorporated a 5 year time horizon, ITT HRs data for OS and PFS (along with time on treatment), non-treatment specific utilities for both the progression free and progressed health states and applied a Weibull extrapolation for OS. The PBAC noted this increased the ICER to \$155,000 to < \$255,000/QALY. In March 2022, the PBAC considered the ICER proposed in the submission was uncertain and the respecified ICERs were high at the proposed price (paragraph 7.6, enfortumab vedotin PSD, March 2022 PBAC meeting).

4.14 In March 2022, the PBAC noted the PSCR and pre-PBAC response arguments that the exponential distribution provided a better fit to the EV-301 longer-term OS data for

³ Koshkin VS, Henderson N, James M, et al: Efficacy of enfortumab vedotin in advanced urothelial cancer: analysis from the Urothelial Cancer Network to Investigate Therapeutic Experiences (UNITE) study. Cancer 2022;128:1194-1205

the enfortumab vedotin arm compared to the use of the Weibull extrapolation. The PBAC considered that this remained an area of uncertainty and advised that it would be appropriate in a resubmission for (i) changes as per the ESC respecified base case scenario including use of the Weibull function for OS extrapolation unless the use of an exponential distribution can be adequately justified, which may include provision of additional information, including the Clinical Study Report, for the analysis using the July 2021 data cut-off for the EV-301 trial, and (ii) if the ICER was in the order of \$55,000 to < \$75,000/QALY (paragraph 7.7, enfortumab vedotin PSD, March 2022 PBAC meeting).

4.15 The resubmission provided an updated economic model that included the following amendments:

- Reducing the time horizon to 7.5 years from 10 years (rationale provided in Table 1). In March 2022 the PBAC considered that for clinical plausibility the model time horizon should be reduced to 5 years (paragraph 7.6, enfortumab vedotin PSD, March 2022 PBAC meeting). Using the new economic model provided in the resubmission the use of a 5 year time horizon increased the incremental cost-effectiveness ratio (ICER) from \$75,000 to < \$95,000/QALY to \$75,000 to < \$95,000/QALY.
- Using updated data cut-off (30 July 2021) of EV-301 trial, replacing the interim data cut-off (15 July 2020). This involved using updated OS, PFS, ToT and RDI values in the economic model. For enfortumab vedotin arm, health state allocation is determined by PFS and OS curves directly from EV-301 to 25 months for OS (up from 15 months in March 2022) and 20 months for PFS (up from 15 months) followed by extrapolation of the curves using parametric functions (exponential and loglogistic respectively [same as March 2022]). For the chemotherapy arm, health state allocation is determined by PFS and OS curves generated by applying the HR from EV-301 to the enfortumab PFS and OS curves and extrapolations. The OS and PFS HR used for the chemotherapy arm of the model are highlighted in orange in Table 3. Time on treatment curves for both enfortumab vedotin and chemotherapy are derived from EV-301 and extrapolated using lognormal function (same as March 2022). The RDI values used in both arms of the model are highlighted in orange in Table 4. These changes were not specified by the PBAC in March 2022 and as the resubmission was submitted via the early re-entry pathway they were unable to be evaluated.
- Using outcomes from all chemotherapy patients (including vinflunine data) for OS and PFS. The use of ITT HR data for OS and PFS is consistent with the March 2022 PBAC recommendations (see paragraph 4.13).
- Applying a cross-over adjusted HR for OS. The resubmission argued use of this HR is justified as enfortumab vedotin had been demonstrated as superior for OS in the interim analysis and hence there is a directional bias against the study therapy during the period of extended follow-up where cross-over was permitted (see paragraph 4.8). Using the ITT HR for OS increased the ICER from \$75,000 to < \$95,000/QALY to

\$95,000 to < \$115,000 /QALY gained. This change was not specified by the PBAC in March 2022 and as the resubmission was submitted using the early re-entry pathway the analysis adjusting for cross-over could not be evaluated.

- Using non-treatment specific utility for PFS health state, instead of using PFS utility by treatment arm. The use of non-treatment specific utilities for both the progression free and progressed health states is consistent with the March 2022 PBAC recommendations (see paragraph 4.13).
- Proposing a Special Revenue Arrangement (SRA) to lower the ICER and, according to the sponsor, to provide certainty in the maximum per patient treatment cost of enfortumab vedotin. The resubmission states that the sponsor will rebate |% of the expenditure beyond | months (or after | treatment cycles) per patient with the rebate pertaining only to the cost of enfortumab vedotin itself. The resubmission noted that in the context of the proposed SRA the ToT data is not applied beyond | months in the base case. Removal of the SRA discount increased the ICER from \$75,000 to < \$95,000/QALY to \$95,000 to < \$115,000/QALY gained.

4.16 The resubmission argued that OS from the extended follow-up of the EV-301 trial is supportive of the clinical benefit and the use of the exponential function for OS extrapolation because:

- Consistent OS benefit and with a marked level of right-censoring (i.e., those alive at this new cut-off) in the enfortumab vedotin arm indicated a ‘flattening’ of risk.
- The OS hazards fall after 6 months; which is not consistent with the Weibull extrapolation (increasing hazards) but consistent with functions that have reducing hazards. The selection of the exponential (constant hazards) is hence reasonable and may represent a conservative estimate of the survival benefit (see paragraph 4.17).
- The extension period of the trial permitted cross-over to enfortumab vedotin from the chemotherapy arm at discretion; a pre-planned analysis for cross-over (and use of enfortumab vedotin prior to the extension) estimated an improved HR (see paragraph 4.8)
- Comparison with the EV-201 trial (Cohort 1), previously presented as more mature data, showed that survival risk with the EV-301 extended follow-up is consistent with the EV-201 trial exhibiting a ‘flatter tail’ than the interim EV-301 data (see paragraph 4.9).

4.17 In terms of the OS hazards, the resubmission reported that the updated EV-301 trial data cut-off indicated the enfortumab vedotin arm hazard rates for OS (and PFS) increase initially for approximately 6 months and then decrease. The resubmission stated that this pattern was consistent with the log-logistic and log-normal functions which also decrease over time. However, the Weibull function increases hazards over time. Hence, the resubmission argued the use of the exponential function was a reasonable and conservative selection.

- 4.18 The resubmission also provided graphical comparisons of the parametric functions fitted to the enfortumab vedotin KM OS data and statistical goodness of fit tests and argued these supported the use of the exponential function for extrapolating OS data.
- 4.19 The resubmission noted the base case ICER has been reduced from \$95,000 to < \$115,000 /QALY in the previous submission to \$75,000 to < \$95,000/QALY gained (see Table 5). The resubmission stated that even though the ICER estimated in this re-entry submission is not in the order of \$55,000 to < \$75,000 /QALY, as recommended at the March 2022 PBAC meeting (paragraph 7.7, enfortumab vedotin PSD, March 2022 PBAC meeting), it argued that the PBAC has recently considered the listing of oncology drugs with a recommended ICER of the range of \$75,000 to less than \$95,000/QALY gained^{4,5,6}.
- 4.20 In addition to the base case ICER provided in the resubmission, Table 5 provides the base case ICER excluding the SRA proposal along with the ESC respecified base case from the March 2022 PBAC meeting.
- 4.21 The pre-PBAC response provided a revised base case that reduced the time horizon to 5 years, removed the cross-over adjusted HR for OS (used the July 2021 data cut-off HR 0.704, 95% CI 0.581, 0.852), proposed a new SRA to lower the ICER (a cap on the PBS subsidised treatment of | cycles with a |% rebate of the excess) and incorporated the proposed |% reduction in the effective ex-manufacturer price (\$| per 20 mg vial and \$| per 30 mg vial). The pre-PBAC response noted the model retained exponential OS extrapolation. The revised base case provided an ICER of \$55,000 to < \$75,000/QALY gained including the proposed SRA and \$115,000 to < \$135,000/QALY gained without the SRA (see Table 5).

⁴ July 2021 PBAC public summary document for ripretinib. Available at <https://www.pbs.gov.au/info/industry/listing/elements/pbac-meetings/psd/2021-07/ripretinib-tablet-50-mg-ginlock> [Last accessed: 10 August 2022].

⁵ March 2021 PBAC public summary document for tucatinib. Available at <https://www.pbs.gov.au/info/industry/listing/elements/pbac-meetings/psd/2021-03/tucatinib-tablet-150-mg-tablet-50-mg-tukyasa> [Last accessed: 10 August 2022].

⁶ March 2021 PBAC public summary document for venetoclax. Available at <https://www.pbs.gov.au/info/industry/listing/elements/pbac-meetings/psd/2021-03/venetoclax-tablet-100-mg-venclaxta> [Last accessed: 10 August 2022].

Table 5 Summary of revised base case results

Parameters	Enfortumab vedotin	Chemotherapy	Incremental	ICER
Base case (including SRA proposal) – EMP \$ (30 mg vial) ^a				
Total cost	\$	\$	\$	
LYs	1.53	1.00	0.53	\$ ¹
QALYs	1.04	0.67	0.37	\$ ²
If EMP price reduced to \$ (30 mg vial)				
Base case (excluding SRA proposal) – EMP \$ (30 mg vial) ^a				
Total cost	\$	\$	\$	
LYs	1.53	1.00	0.53	\$ ²
QALYs	1.04	0.67	0.37	\$ ³
If EMP price reduced to \$ (30 mg vial)				
Revised base case in pre-PBAC response (including SRA proposal) – EMP \$ (30 mg vial) ^b				
Total cost	\$	\$	\$	
LYs	1.49	1.11	0.38	\$ ⁴
QALYs	1.01	0.73	0.28	\$ ²
If EMP price reduced to \$ (30 mg vial)				
Revised base case in pre-PBAC response (excluding SRA proposal) - EMP \$ (30 mg vial) ^b - equivalent to March 2022 respecified base case (exponential for OS) with use of data with longer follow-up				
Total cost	\$	\$	\$	
LYs	1.49	1.11	0.38	\$ ²
QALYs	1.01	0.73	0.28	\$ ⁵
If EMP price reduced to \$ (30 mg vial)				
ESC respecified base case – March 2022 (exponential for OS) – EMP \$ (30 mg vial) ^a				
Total cost	\$	\$	\$	
LYs	1.487	1.103	0.383	\$ ³
QALYs	0.994	0.725	0.270	\$ ⁵
If EMP price reduced to \$ (30 mg vial)				
ESC respecified base case – March 2022 (weibull for OS) – EMP \$ (30 mg vial) ^a				
Total cost	\$	\$	\$	
LYs	1.311	1.001	0.309	\$ ⁵
QALYs	0.886	0.662	0.224	\$ ⁶
If EMP price reduced to \$ (30 mg vial)				

Source: Table 11, p xxxiv, enfortumab vedotin resubmission, PADCEV_la-muc_Early Re-entry Economic Analysis_vFinal.xlsx, Economic analysis - enfortumab vedotin (PADCEV) - la-mUC - March 2022 PBAC meeting.xlsx

^a EMP for 20 mg vial \$

^b EMP for 20 mg vial \$

The redacted values correspond to the following ranges:

¹ \$55,000 to < \$75,000

² \$75,000 to < \$95,000

³ \$95,000 to < \$115,000

⁴ \$45,000 to < \$55,000

⁵ \$115,000 to < \$135,000

⁶ \$155,000 to < \$255,000

Estimated PBS usage & financial implications

4.22 In March 2022, the PBAC noted the advice from DUSC that the approach taken to the application of relative dosing intensity (RDI) in the financial estimates likely underestimated costs by around 5%. The PBAC considered that this should be corrected in any resubmission. In addition, the PBAC noted DUSC advice that, while

the estimated number of patients predicted to use pembrolizumab was consistent with current utilisation data, the predicted number of patients treated with avelumab was a source of uncertainty. Despite this uncertainty, DUSC considered that overall, the financial estimates presented in the submission were reasonable. In March 2022, the PBAC considered it would be appropriate for a resubmission to address any residual uncertainty regarding the number of patients treated with enfortumab vedotin by data triangulation. The PBAC considered this would involve verifying the submission's estimate of patient numbers against those derived from using current pembrolizumab utilisation data for this indication and an assumption that 80% of such patients would subsequently receive enfortumab vedotin (paragraph 7.8, enfortumab vedotin PSD, March 2022 PBAC meeting).

- 4.23 In the financial model of the March 2022 submission, the RDI of enfortumab vedotin treatment in the EV-301 trial was applied to the number of scripts. This contrasted with the approach used in the economic model of the March 2022 submission, wherein the RDI was applied to the dose dispensed. The resubmission financial model applied RDI on average dose dispensed. The RDI adjusted average amount of enfortumab vedotin dispensed in revised financial model is 77.3 mg based on updated mean RDI value of 78.33%.
- 4.24 The resubmission estimated a net cost to the PBS/RPBS of \$20 million to < \$30 million in Year 6 of listing, with a total net cost to the PBS/RPBS of \$100 million to < \$200 million over the first 6 years of listing; see Table 6.
- 4.25 The resubmission stated that the correct application of RDI in the revised model resulted in a 26% increase in the total number of enfortumab vedotin prescriptions and increased the net cost to the PBS/RPBS by 2.1%, as compared to the estimates in the March 2022 submission (see Table 6).
- 4.26 The resubmission stated that with the proposed SRA, the mean duration of treatment per patient reduced from | months to | months. The resubmission argued that this would result in a 22% reduction in the total expected number of enfortumab vedotin prescriptions.
- 4.27 The pre-PBAC response provided revised financial estimates that incorporated the |% reduction in the effective ex-manufacturer price (\$| per 20 mg vial and \$| per 30 mg vial) and the proposed new SRA (a cap on the PBS subsidised treatment of | cycles with a |% rebate for use exceeding the caps) which claimed a net cost to the PBS/RPBS of \$10 million to < \$20 million in Year 6 and \$50 million to < \$60 million over 6 years.

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Table 6: Estimated use and financial implications (effective price)

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
Estimated extent of use – resubmission						
Number of patients treated	1	1	2	2	2	2
Number of scripts dispensed – without SRA treatment cap ^a	3	3	4	4	4	4
Number of scripts dispensed – with SRA treatment cap ^b	3	3	4	4	4	4
Estimated extent of use – March 2022 submission						
Number of patients treated	1	1	2	2	2	2
Number of scripts dispensed ^c	3	3	4	4	4	4
Estimated financial implications of enfortumab vedotin – resubmission						
Cost to PBS/RPBS less copayments ^d (\$)	5	5	6	6	6	6
Estimated financial implications of enfortumab vedotin – resubmission with SRA						
Cost to PBS/RPBS less copayments ^d (\$)	7	5	5	5	5	5
Estimated financial implications of enfortumab vedotin – pre-PBAC response with SRA						
Cost to PBS/RPBS less copayments (\$)	7	7	5	5	5	5
Net financial implications – March 2022 submission						
Net cost to PBS/RPBS ^e (\$)	5	5	6	6	6	6
Net cost to MBS (\$)	7	7	7	7	7	7
Net cost to PBS/RPBS/MBS ^e (\$)	5	5	6	6	6	6

Source: Table 13, p xxxvi, Table 14, p xxxvii enfortumab vedotin resubmission, Table 14, p32 enfortumab vedotin March 2022 PBAC PSD

^a Average treatment duration per patient █ months, 0.75 dose per week (Calculated as 3 doses per 4 weeks – day 1, 8 and 15 of a 28 day cycle) and dose intensity not applied to the number of scripts.

^b Average treatment duration per patient █ months, 0.75 dose per week (Calculated as 3 doses per 4 weeks – day 1, 8 and 15 of a 28 day cycle) and dose intensity not applied to the number of scripts.

^c Average treatment duration per patient █ months, 0.75 dose per week (Calculated as 3 doses per 4 weeks – day 1, 8 and 15 of a 28 day cycle), and 79.35% dose intensity (which has been applied to the number of scripts).

^d The RDI adjusted average amount of enfortumab vedotin dispensed is 77.3 mg based on an updated mean RDI value of 78.33%. The revised average number of 20 mg and 30 mg units per patient per administration (at RDI adjusted doses) is 1.0 vial and 1.9 vials respectively

^e Figures have been corrected to reflect the cost of an average dose of 96.5 mg (based on the dispensed efficient vial dose calculated using the distribution of patient weights in EV-301). The submission figures used the cost of 130 mg (maximum dispensed amount).

The redacted values correspond to the following ranges:

1 <500

2 500 to < 5,000

3 5,000 to < 10,000

4 10,000 to <20,000

5 \$10 million to <\$20 million

6 \$20 million to <\$30 million

7 \$0 to <\$10 million

4.28 As outlined in paragraph 4.22, in March 2022 the PBAC considered data triangulation be used to address any residual uncertainty regarding the number of patients treated with enfortumab vedotin. The resubmission presented PBS utilisation data including pembrolizumab’s listings for locally advanced (Stage III) or metastatic (Stage IV) urothelial cancer indication (PBS Items 11632F and 11646Y) sourced from the

Medicare Statistics Pharmaceutical Benefits Schedule Item Reports for each financial year 2019-20, 2020-21, 2021-22 as shown in Table 7.

Table 7 Pembrolizumab utilisation data and expected number of patients to be treated with enfortumab vedotin

Parameter	2019-20	2020-21	2021-22
No. of pembrolizumab initial and continuing scripts for la/mUC (PBS item codes: 11632F, 11646Y)	1 ¹	1 ¹	1 ¹
Patients with la/mUC treated with pembrolizumab ^a	2 ²	1 ¹	1 ¹
% of patients who would receive treatment with enfortumab vedotin in patients progressing on treatment with pembrolizumab	80%	80%	80%
Patients estimated to be treated with enfortumab vedotin	2 ²	2 ²	2 ²

Source: Table 21, p lii, enfortumab vedotin resubmission

^a Assumed an average of 8.4 scripts of pembrolizumab per patient (200 mg administered every 3 weeks with a 5.8 month duration of therapy [based on Table 3, avelumab PSD7]). Average number of scripts then divided by total pembrolizumab scripts for each year to estimate the number of patients treated with pembrolizumab.

The redacted values correspond to the following ranges:

¹ 500 to < 5,000

² < 500

- 4.29 The resubmission claimed that the number of patients to be treated with enfortumab vedotin estimated in Table 7 are comparable to patient numbers in Table 6.
- 4.30 The actual number of incident and prevalent patients for items 11632F and 11646Y were provided by the DUSC Secretariat based on the 100% PBS data: incident < 500 and prevalent 500 to < 5,000 in 2019-20; incident < 500 and prevalent 500 to < 5,000 in 2020-21; and incident < 500 and prevalent 500 to < 5,000 in 2021-22. Of the < 500 actual incident patients in 2021-22, an estimated < 500 patients (i.e. < 500 incident x 80%) would progress to enfortumab vedotin. This compares to the resubmission's estimate of < 500 initiating patients in Year 1 (Table 6). For the DUSC Secretariat analysis, the number of incident patients were identified using a lookback period to 1 January 2016 and the patient counts were based on the date of supply.

Financial Management – Risk Sharing Arrangements

- 4.31 In March 2022, the PBAC considered a risk sharing arrangement would not be required as the Committee considered the risk of use outside of the proposed population was low (paragraph 7.9, enfortumab vedotin PSD, March 2022 PBAC meeting).
- 4.32 The resubmission proposed an SRA which it stated would reduce the ICER. The sponsor proposed a cap on the PBS subsidised treatment at | months treatment or | treatment cycles. Beyond this cap, the resubmission proposed a |% rebate on Commonwealth

⁷ March 2022 PBAC public summary document for avelumab. Available at <https://www.pbs.gov.au/info/industry/listing/elements/pbac-meetings/psd/2022-03/avelumab-solution-concentrate-for-iv-infusion-200-mg-in-1> [Last accessed: 10 August 2022].

expenditure on enfortumab vedotin. The SRA proposed would rely on high confidence in the estimates and if they were overestimated the ICER may not be achieved.

- 4.33 The pre-PBAC response proposed a revised SRA with a cap on the PBS subsidised treatment of █ cycles. If the annual expenditure cap is exceeded for enfortumab vedotin, the sponsor will rebate █% for use exceeding the caps.

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

5 PBAC Outcome

- 5.1 The PBAC deferred making a recommendation for enfortumab vedotin for the treatment of patients with locally advanced (Stage III) or metastatic (Stage IV) urothelial cancer (la/mUC) who have progressed on or after a platinum-containing chemotherapy regimen and either a programmed cell death-1 (PD-1) inhibitor or a programmed cell death ligand-1 (PD-L1) inhibitor to allow further consultation with the sponsor regarding the approach to achieving a cost-effective incremental cost effectiveness ratio (ICER). In deciding to defer making a recommendation, the PBAC was concerned the proposed Special Revenue Arrangement (SRA) would not achieve a cost-effective price for enfortumab vedotin. The PBAC reaffirmed its March 2022 advice that an ICER in the order of \$55,000 to < \$75,000/QALY was appropriate.
- 5.2 The PBAC noted the input from an individual which highlighted the clinical need for treatment options for patients with this indication. In addition, the PBAC noted the Medical Oncology Group of Australia's strong support for the submission. The PBAC reaffirmed there was a moderate clinical need for more effective therapies for metastatic urothelial cancer.
- 5.3 The PBAC noted the resubmission provided the Clinical Study Report regarding the updated analysis for the EV-301 trial (data cut-off 30 July 2021) as requested by the Committee in March 2022. The PBAC noted the updated analysis results were consistent with the interim analysis results for overall survival (OS) (updated HR 0.704, 95% CI 0.581, 0.852 versus interim HR 0.702, 95% CI 0.556, 0.886) and progression-free survival (PFS) (updated HR 0.632, 95% CI 0.525, 0.762 versus interim HR 0.615, 95% 0.505, 0.748).
- 5.4 The PBAC recalled that in March 2022 it had advised that it would be appropriate for a resubmission economic model to include changes as per the ESC respecified base case scenario (see paragraph 4.13) including use of the Weibull function for OS extrapolation unless the use of an exponential distribution could be adequately justified. The PBAC considered the resubmission provided adequate justification for the use of an exponential distribution for OS extrapolation. The PBAC noted the pre-PBAC response provided a revised base case that incorporated a 5 year time horizon, ITT HRs data for OS and PFS (data cut-off 30 July 2021, see paragraph 5.3), non-treatment specific utilities for both the progression free and progressed health states

and considered these inputs were consistent with the intent of the ESC respecified base case scenario.

- 5.5 The PBAC recalled that in March 2022 it had also considered an ICER in the order of \$55,000 to < \$75,000/QALY would be appropriate. The PBAC noted the revised base case proposed in the pre-PBAC response included a █% reduction in the effective ex-manufacturer price of enfortumab vedotin along with an SRA (a cap on the PBS subsidised treatment of █ cycles with a █% rebate for use exceeding the caps which would reduce the price paid on average by approximately █%) to lower the ICER. The PBAC noted the pre-PBAC response revised base case ICER was \$55,000 to < \$75,000/QALY gained with the proposed SRA and increased to \$115,000 to < \$135,00/QALY gained when the SRA was excluded. The PBAC noted that in the updated data cut of the EV-301 trial the mean treatment duration for enfortumab vedotin was 6.46 months (SD 5.78) with a median treatment duration of 4.99 months (min 0.5, max 29.9) (see Table 4). The PBAC also noted that a lower median treatment duration of 4.1 months (interquartile range 1.6-6.9) was reported in the UNITE retrospective cohort study (see paragraph 4.11) and considered this may better reflect potential use on the PBS. As such, the PBAC was concerned that the duration of treatment with enfortumab vedotin in clinical practice would be less than that observed in the EV-301 trial. The PBAC noted this would result in a reduction in the rebates or potentially no rebate received through the proposed SRA and hence a cost-effective price for enfortumab vedotin would not be achieved.
- 5.6 The PBAC reaffirmed its March 2022 advice that an ICER in the order of \$55,000 to < \$75,000/QALY gained would be appropriate. The PBAC advised the Committee's preference would be for this to be achieved with the exclusion of the SRA from pre-PBAC response revised base case. The PBAC noted that a further price reduction would therefore be required to achieve an ICER in the order of \$55,000 to < \$75,000/QALY. However, if the SRA was to remain as a mechanism to lower the ICER, the PBAC considered that the uncertainty associated with the likely treatment duration for use through the PBS (refer to paragraph 5.5) would need to be addressed.
- 5.7 The PBAC noted that, as advised in March 2022, the resubmission provided revised financial estimates that corrected the approach taken to relative dosing intensity (see paragraph 4.23). In addition, the PBAC noted that, consistent with its March 2022 advice, the resubmission used data triangulation to address concerns regarding the number of patients treated with enfortumab vedotin (see paragraph 4.28), with additional figures provided by the DUSC Secretariat (see paragraph 4.30). The PBAC considered the estimated number of patients to be treated with enfortumab vedotin to be reasonable. The PBAC noted the financial estimates presented were updated with the price reduction proposed in the pre-PBAC response.

Outcome:

Deferred

6 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.

7 Sponsor's Comment

Astellas Pharma Australia thanks the PBAC for its further assessment of ENFORTUMAB VEDOTIN (Padcev®). We will continue to work with the PBAC seeking a listing for patients with locally advanced (Stage III) or metastatic (Stage IV) urothelial cancer, who meet the criteria's outlined in our submission.

Addendum to the November 2022 PBAC PSD:

8 Background

- 8.1 At the November 2022 meeting, the PBAC deferred making a recommendation for enfortumab vedotin for the treatment of patients with locally advanced (Stage III) or metastatic (Stage IV) urothelial cancer (la/mUC) who have progressed on or after a platinum-containing chemotherapy regimen and either a programmed cell death-1 (PD-1) inhibitor or a programmed cell death ligand-1 (PD-L1) inhibitor to allow further consultation with the sponsor regarding the approach to achieving a cost-effective incremental cost effectiveness ratio (ICER). In deciding to defer making a recommendation, the PBAC was concerned the proposed Special Revenue Arrangement (SRA) would not achieve a cost-effective price for enfortumab vedotin. The PBAC reaffirmed its March 2022 advice that an ICER in the order of \$55,000 to < \$75,000/QALY was appropriate (paragraph 5.1, enfortumab vedotin Public Summary Document [PSD], November 2022 PBAC meeting).
- 8.2 The sponsor submitted a letter for PBAC consideration on 20 December 2022.
- 8.3 Table 8 summarises the inputs made by the sponsor to address outstanding matters raised in the PBAC PSD. Table 9 provides the revised financial implications based on the proposed reduced price for enfortumab vedotin, effective ex-manufacturer price (EMP) = \$| per 30 mg vial (\$| per 20 mg vial).

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Table 8: Issues to be addressed (November 2022 PBAC PSD)

Matter of Concern Raised by PBAC	Letter from sponsor
<p>1 The PBAC noted that a further price reduction would be required to achieve an ICER in the order of \$ [redacted] /QALY.</p> <p>Using the revised base case in the pre-PBAC response an ICER of \$ [redacted] /QALY corresponds to an EMP of:</p> <ul style="list-style-type: none"> - including SPA proposal: \$ [redacted] per 30 mg vial - excluding SPA proposal: \$ [redacted] per 30 mg vial 	<p>The sponsor proposed a reduced price for enfortumab vedotin, EMP = \$ [redacted] per 30 mg vial (\$ [redacted] per 20 mg vial), representing a [redacted] % price reduction.</p> <p>The sponsor proposed to maintain the cap on PBS/RPBS subsidised enfortumab vedotin treatment at [redacted] cycles (SRA proposal). The revised ICER was \$ [redacted] /QALY using the economic model that was submitted as part of the pre-PBAC response.</p>
<p>2 If the SRA was to remain as a mechanism to lower the ICER, the PBAC considered that the uncertainty associated with the likely treatment duration for use through the PBS would need to be addressed.</p>	<p>The sponsor provided the following information on enfortumab vedotin to address this uncertainty:</p> <ul style="list-style-type: none"> - <u>EV-301 trial duration of exposure (updated data cut-off)</u> <ul style="list-style-type: none"> o Median: 4.99 months (min, max 0.5-29.9)* o Mean: 6.46 months (SD=5.78)* - <u>SPA capped duration of exposure used in model</u> <ul style="list-style-type: none"> o Mean: 4.14 months* - <u>Utilisation of enfortumab vedotin in other markets</u> Physician survey-based information on utilisation of cancer treatments (Table 3 of sponsor letter) reporting mean duration 6.4 to 8.3 months in the second line, and 5.9 to 7.2 months in the third-line treatment. - <u>UNITE study</u> <ul style="list-style-type: none"> o Median: 4.1 months (min, max 1.6-6.9)* <p>The sponsor argued the difference UNITE versus EV-301 medians could be accounted for by statistical variance</p> <p>* Information previously considered by PBAC</p>

EMP = ex-manufacturer price; ICER = incremental cost-effectiveness ratio; PSD = public summary document; QALY = quality-adjusted life-year; SPA = special pricing arrangement; SRA = special revenue arrangement.

The redacted values correspond to the following ranges:

¹ \$55,000 to < \$75,000

Table 9: Estimated use and financial implications

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6	Y1-Y6
Current estimates (Letter dated 20 Dec 2022) – including SRA proposal, EMP \$ [redacted] (30 mg vial)^a							
Net cost PBS / RPBS	\$ [redacted] ¹	\$ [redacted] ¹	\$ [redacted] ²	\$ [redacted] ²	\$ [redacted] ²	\$ [redacted] ²	\$ [redacted] ³
November 2022 Pre-PBAC response – including SRA proposal, \$ EMP \$ [redacted] (30mg vial)^b							
Net cost PBS / RPBS	\$ [redacted] ¹	\$ [redacted] ¹	\$ [redacted] ²	\$ [redacted] ²	\$ [redacted] ²	\$ [redacted] ²	\$ [redacted] ³

Source: Table 4 Sponsor letter

^a Capping on PBS/RPBS subsidised enfortumab vedotin treatment at [redacted] cycles, EMP for 20 mg vial \$ [redacted]

^b Capping on PBS/RPBS subsidised enfortumab vedotin treatment at [redacted] cycles, EMP for 20 mg vial \$ [redacted]

The redacted values correspond to the following ranges:

¹ \$0 to < \$10 million

² \$10 million to < \$20 million

³ \$50 million to < \$60 million

9 PBAC Outcome

9.1 The PBAC recommended the Section 100 (Efficient Funding of Chemotherapy Program) Authority Required (Streamlined) listing of enfortumab vedotin for the

treatment of patients with locally advanced (Stage III) or metastatic (Stage IV) urothelial cancer (la/mUC) who have progressed on or after a platinum-containing chemotherapy regimen and either a programmed cell death-1 (PD-1) inhibitor or a programmed cell death ligand-1 (PD-L1) inhibitor. The PBAC was satisfied that enfortumab vedotin provides, for some patients, a significant improvement in efficacy over docetaxel or paclitaxel, administered as single agents. The PBAC considered that the sponsor had addressed the outstanding issues identified at the November 2022 meeting via the proposed price reduction and the proposed Special Revenue Arrangement (SRA).

- 9.2 The PBAC's recommendation for listing was based on, among other matters, its assessment, that the cost-effectiveness of enfortumab vedotin would be acceptable at the price proposed in the revised offer of 20 December 2022 if the following additional measures were implemented:
- A SRA to cap PBS/RPBS subsidised enfortumab vedotin treatment at | cycles with a |% rebate for use exceeding the caps.
 - DUSC undertake a review of utilisation (both treatment duration and patient uptake) after an appropriate period of time post listing to ensure that the duration of treatment observed in clinical practice is consistent with the proposed SRA achieving a cost-effective price for enfortumab vedotin. The PBAC considered that updated survival data from the to-be-published final analysis of EV-301 should also be reviewed at this time to ensure that it is not less favourable than the input into the economic model that was submitted as part of the November 2022 pre-PBAC response.
- 9.3 The PBAC noted the revised offer was an effective ex-manufacturer price █████% below that proposed in November 2022 and resulted in an ICER of \$55,000 to < \$75,000/QALY gained (see Table 8). The PBAC considered that this was consistent with its March 2022 advice that an ICER in the order of \$55,000 to < \$75,000/QALY gained would be appropriate (see paragraph 8.1).
- 9.4 The PBAC noted that the ICER of \$55,000 to < \$75,000/QALY gained was achieved using the revised effective ex-manufacturer price and an SRA (a cap on the PBS subsidised treatment of | cycles with a |% rebate for use exceeding the caps which would reduce the price paid on average by approximately |%). The PBAC advised that while the use of an SRA was not a preferred approach (see paragraph **Error! Reference source not found.**), the information provided in the sponsor letter along with the additional measures outlined in paragraph 9.2 addressed the Committee's concerns regarding the likely duration of enfortumab vedotin treatment raised in November 2022.
- 9.5 The PBAC noted the financial estimates presented were updated with the price reduction proposed in the revised offer of 20 December 2022. The PBAC reiterated its November 2022 advice that the Committee considered the estimated number of

patients to be treated with enfortumab vedotin to be reasonable. The PBAC considered the inclusion of a grandfathering restriction was also reasonable.

- 9.6 The PBAC accepted the Secretariat’s suggestion to simplify the recommended PBS listing, which was to cover initial treatment, continuing treatment and ‘grandfather’ transition arrangements all in a single restriction. The Secretariat further noted that the Product Information’s dosing schedule is to administer the drug on days 1, 8 and 15 of a 28-day cycle and advised that the repeat prescriptions available should facilitate a number of doses that is a multiple of 3. The Secretariat therefore suggested 8 repeat prescriptions would be preferable compared to the 9 repeats as mentioned in Section 3 above as 8 repeats facilitates 9 doses in total (original prescription plus 8 repeats), which is adequate to complete 3 whole treatment cycles. The PBAC accepted this suggestion.
- 9.7 The PBAC advised that enfortumab vedotin is not suitable for prescribing by nurse practitioners.
- 9.8 The PBAC recommended that the Early Supply Rule should not apply.
- 9.9 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 enfortumab vedotin:
- The treatment is expected to provide a moderate improvement in efficacy, over alternative therapies, on the basis of the clinical evidence considered at the November 2022 meeting;
 - The treatment is not expected to address a high and urgent unmet clinical need;
 - 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.
- 9.10 The PBAC noted that this submission is not eligible for an Independent Review as it received a positive recommendation.

Outcome:

Recommended

10 Recommended listing

- 10.1 Add new medicinal product as follows:

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Out of Session PBAC Consideration

Category / Program: Section 100 – Efficient Funding of Chemotherapy (Public/Private hospitals)			
MEDICINAL PRODUCT Form	PBS item code	Max. Amount	No. of Rpts
ENFORTUMAB VEDOTIN Injection	New (Public) New (Private) MP	125 mg	8
Available brands			
Padcev (enfortumab vedotin 20 mg powder for injection, 1 vial)*			
Padcev (enfortumab vedotin 30 mg powder for injection, 1 vial)*			
Restriction Summary [New 1] / Treatment of Concept: [New 1.1]: Authority Required (STREAMLINED)			
Indication: Locally advanced (Stage III) or metastatic (Stage IV) urothelial cancer			
Clinical criteria:			
The condition must have progressed on/following both: (i) platinum-based chemotherapy, (ii) programmed cell death 1/ligand 1 (PD-1/PD-L1) inhibitor therapy; or			
The condition must have progressed on/following platinum-based chemotherapy, whilst PD-1/PD-L1 inhibitor therapy resulted in an intolerance that required treatment cessation			
AND			
Clinical criteria			
Patient must have/have had a WHO performance status score of no greater than 1 at treatment initiation with this drug			
AND			
Clinical criteria:			
The treatment must be the sole PBS-subsidised systemic anti-cancer therapy for this PBS indication			
Treatment criteria:			
Patient must be undergoing treatment with this drug for the first time; or			
Patient must be undergoing continuing treatment with this drug, with each of the following being true: (i) all other PBS eligibility criteria in this restriction are met, (ii) disease progression is absent.			
Administrative Advice: No increase in the maximum amount or number of units may be authorised.			
Administrative Advice: No increase in the maximum number of repeats may be authorised.			
Administrative Advice: Special Pricing Arrangements apply.			

*final details dependent on Australian Medicines Terminology (AMT) mapping

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

11 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.

12 Sponsor's Comment

Astellas Pharma Australia thanks the PBAC for its recommendation of ENFORTUMAB VEDOTIN (Padcev®). We will continue to work with the Department to gain a prompt PBS listing for patients with locally advanced (Stage III) or metastatic (Stage IV) urothelial cancer, who meet the criteria's outlined in our submission.