Summary Report of Benefit-Risk Assessment

PADCEV POWDER FOR CONCENTRATE FOR SOLUTION FOR INFUSION 20MG and 30MG

NEW DRUG APPLICATION

Active Ingredient(s)	Enfortumab vedotin
Product Registrant	Astellas Pharma Singapore Pte. Ltd.
Product Registration Number	SIN16502P, SIN16503P
Application Route	Abridged evaluation
Date of Approval	30 May 2022

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A INTRODUCTION

Padcev is indicated for the treatment of adult patients with locally advanced (LA) or metastatic urothelial cancer (mUC) who have previously received a programmed death receptor-1 (PD-1) or programmed death-ligand 1 (PD-L1) inhibitor, and a platinum-containing chemotherapy in the neoadjuvant/adjuvant, locally advanced or metastatic setting.

The active substance, enfortumab vedotin, is an antibody drug conjugate (ADC) containing humanised anti-Nectin-4 immunoglobulin G1 kappa monoclonal antibody (mAb) conjugated to the small molecule microtubule-disrupting agent monomethyl auristatin E (MMAE), via a protease-cleavable maleimidocaproyl valine-cituline (vc) linker. Enfortumab vedotin targets and binds to the Nectin-4 adhesion protein expressed in multiple cancers including urothelial cancers and induces cytotoxicity in cancer cells by releasing MMAE which disrupts tubulin polymerization resulting in G2/M phase cell cycle arrest and apoptosis.

Padcev is available as a powder for concentrate for solution for infusion containing either 20 mg or 30 mg enfortumab vedotin. Other ingredients in the vial are histidine, histidine hydrochloride monohydrate, trehalose dihydrate and polysorbate 20.

B ASSESSMENT OF PRODUCT QUALITY

The drug substance, Enfortumab vedotin, is manufactured at [redacted]. The drug products, Padcev Powder for Concentrate for Solution for Injection 20 mg/vial and 30 mg/vial, are manufactured at Baxter Oncology GmbH.

Drug substance:

Adequate controls have been presented for the starting materials, intermediates, reagents and cell banks. The in-process control tests and acceptance criteria applied during the manufacturing of the drug substance are considered appropriate. The drug substance manufacturer is compliant with Good Manufacturing Practice (GMP). Process validation was conducted on three consecutive production-scale batches.

The characterisation of the drug substance and its impurities have been appropriately performed. Potential and actual impurities are adequately controlled in the manufacturing process.

The drug substance specifications were established in accordance with ICH Q6B, and the impurity limits have been appropriately qualified. The analytical methods used were adequately described and non-compendial methods have been appropriately validated in accordance with ICH Q2. Information on the reference standards used for identity, assay and impurities testing is presented.

The stability data presented was adequate to support the storage of the drug substance at ≤ -60ºC with a shelf life of 60 months. The packaging is a 2L square sterile polycarbonate container with a white silicone lined polypropylene screw closure.

Drug product:
The manufacturing process involves pooling and mixing of the drug substance, followed by sterile filtration and aseptic filling. This is considered to be a standard manufacturing process.

The manufacturing site is compliant with GMP. Proper development and validation studies were conducted. It has been demonstrated that the manufacturing process is reproducible and consistent. Adequate in-process controls are in place.

The specifications have been established in accordance with ICH Q6B, and impurity limits were adequately qualified. The analytical methods used were adequately described and non-compendial methods have been appropriately validated in accordance with ICH Q2. Information on the reference standards used for identity, assay and impurities testing is presented.

The stability data submitted was adequate to support the approved shelf-life of 36 months when stored at 2 – 8 ºC. After reconstitution with sterile water for injection, the in-use period is up to 24 hours at 2 – 8 °C. Following this, the reconstituted drug product is further diluted with either sterile 5% Dextrose Injection, 0.9% Sodium Chloride Injection or sterile Lactated Ringer's Injection. The diluted product has been demonstrated to be stable for up to 16 hours at 2 – 8 °C. The container closure system consists of a 10 ml Clear Type I tubular injection vial with bromobutyl rubber stopper and aluminium flip off seal.

C ASSESSMENT OF CLINICAL EFFICACY

The efficacy of enfortumab vedotin for the treatment of LA or mUC in patients previously treated with platinum-based therapies and PD-1/PDL-1 inhibitors was based on one pivotal Phase III study, Study EV-301, and 3 supportive studies: one Phase II study, EV-201 and two Phase I studies, EV-101 and EV-102.

Study EV-101 was an open-label, multicentre, dose escalation (0.5, 0.75, 1.0 and 1.25 mg/kg) and expansion study of enfortumab vedotin in subjects with Nectin-4 expressing solid tumours, including mUC. The study determined 1.25mg/kg as the recommended dose for subsequent studies based on the objective response rate (ORR) and safety profile.

Study EV-102 was an open-label, randomised study to assess the safety, tolerability, and pharmacokinetics of enfortumab vedotin in Japanese subjects with LA or mUC. The confirmed ORR was 35.3% (6 of 17 subjects), with 1 subject achieving complete response (CR).

Study EV-201 was a single-arm, multi-cohort, open-label study to assess the efficacy and safety of enfortumab vedotin. Cohort 1 included subjects with LA or mUC who were previously treated with a PD-1 or PD-L1 inhibitor and platinum-containing chemotherapy in the locally advanced or metastatic setting. The confirmed ORR per blinded independent committee review (BICR) assessment for Cohort 1 subjects was 44% (55 of 125 subjects), with 15 subjects (12%) achieving CR. Due to the single-arm nature of studies EV-201 and EV-102, the clinical relevance of the ORR could not be assessed, but it was generally consistent with that observed in the pivotal study.

The pivotal study, Study EV-301, was an open-label, randomised (1:1), multicentre (158 sites in 19 countries in North America, South America, Europe, Asia-Pacific region), active controlled (docetaxel, or paclitaxel or vinflunine) study in adult subjects with histologically or cytologically confirmed LA or mUC who progressed on platinum-based regimens and PD-1/PD L1 inhibitors. Subjects who discontinued PD-1 or PD-L1 inhibitor treatment because of toxicity were also eligible, provided that they had evidence of disease progression following

discontinuation. Subjects were stratified by geographic region (US vs EU vs rest of the world), Eastern Cooperative Oncology Group (ECOG) performance status (Performance status [PS] 0 or 1) and the presence of liver metastasis (Yes or No). Subjects were randomised to enfortumab vedotin 1.25 mg/kg on days 1, 8 and 15 of a 28-day cycle or investigator's choice of either docetaxel [75 mg/m^2], paclitaxel [175 mg/m^2] or vinflunine [320 mg/m^2] on day 1 of each 3-week treatment cycle. The active comparators were considered appropriate for this patient population who have failed platinum-based chemotherapies and PD-1/PDL-1 immunotherapy. Subjects were evaluated for response as per investigator assessment according to RECIST v1.1 based on imaging performed at baseline and every 56 days (± 7 days) which was considered acceptable and aligned with the RECIST v1.1 guidelines.

The primary efficacy endpoint was overall survival (OS). The secondary endpoints were progression free survival (PFS1) by RECIST v1.1 per investigator, objective response rate (ORR; CR + partial response [PR]) by RECIST v1.1 per investigator, disease control rate (DCR; CR +PR +stable disease [SD]) by RECIST v1.1 and duration of response (DoR). OS was formally tested at both the interim and final analyses according to the O'Brien-Fleming boundary using the Lan and DeMets method in the full analysis set (FAS). Formal hypothesis testing for the selected secondary endpoints was performed hierarchically in the order of PFS1, ORR, and DCR, provided that the null hypothesis for OS was rejected. PFS1 was planned to be tested at either the interim analysis or final analysis. The significance level of PFS1 at the interim and final analysis was based on the Pocock boundary using the Lan and DeMets method. ORR and DCR were tested only after both the null hypothesis for OS and PFS1 were rejected (at either interim analysis or final analysis).

A total of 608 subjects were randomised to enfortumab vedotin (n=296) and chemotherapy arms (n=291), respectively. Out of the 291 subjects who received treatment in the chemotherapy arm, 109 (37%) received docetaxel, 107 (37%) paclitaxel and 75 (26%) vinflunine. The demographic and baseline characteristics were generally well balanced across the two arms. The median age of the subjects was 68 years, with 75.8% having received 2 prior lines of therapy and 12.5% of subjects having received 3 or more prior lines of therapy in the locally advanced or metastatic setting. The most commonly used PD-1/PDL-1 inhibitors were pembrolizumab (47%) and atezolizumab (28%). Overall, 16.6% of patients had normal renal function, 35.7% had mild renal impairment, and 45.2% had moderate renal impairment at baseline. Renal impairment was expected given the origin of the tumour. A total of 60% of subjects had a ECOG PS status of 1 and 30.5% subjects had liver metastasis. Subsequent anti-cancer therapies were received by a slightly lower proportion of subjects in enfortumab vedotin arm (35.9%) compared to chemotherapy arm (38.4%). The median duration of treatment was also longer in enfortumab vedotin arm (4.99 months) compared to chemotherapy arm (3.45 months). The H-score of NECTIN-4 was calculated as the percentage of positive cells (0–100%) multiplied by the staining intensity (0–3+), resulting in a final score ranging from 0 to 300. Specimens were then classified as negative (H-score 0– 14), weak (H-score 15–99), moderate (H-score 100–199), and strong (H-score 200–300). Nectin H-score was over 150 in majority of the subjects (85%) with a median score of 250, ranging from 0 to 300. Overall, the study recruited an appropriate patient population that reflected the proposed patient population.

The study met its primary efficacy endpoint by demonstrating statistically significant superiority in terms of OS (68.6% maturity) based on the pre-defined interim analyses with a 30% reduction in the risk of death (Hazard ratio [HR]: 0.702, 95% CI: 0.556, 0.886; 1-sided P = 0.00142) and an improvement of 3.9 months in the median OS with enfortumab vedotin compared to the chemotherapy regimens (12.88 [95% CI: 10.58, 15.21] versus 8.97 [95% CI: 8.05, 10.74] respectively). Median follow-up of OS at data cutoff was 11.10 months across

both the arms. The subgroup analyses consistently favoured the enfortumab vedotin arm (HR < 1) in the prespecified subgroups stratified by age, geographic region, baseline ECOG performance status, liver metastasis, preselected control therapy by the investigator, primary site of tumour, and prior lines of therapy.

The key secondary endpoint of PFS also showed statistically significant improvements favouring enfortumab vedotin with 38% reduction in the risk of progression or death (HR: 0.615, 95% CI: 0.505, 0.748; 1-sided P < 0.00001) and median PFS of 5.55 [95% CI: 5.32, 5.82] versus 3.71 [95% CI: 3.52, 3.94], respectively, Δ = 1.8 months. ORR per investigator assessment was statistically significantly higher for the enfortumab vedotin arm (40.6% [95% CI: 34.90, 46.54]) compared to the chemotherapy arm (17.9% [95% CI: 13.71, 22.76]), with a 1-sided P value < 0.001. The median DoR was numerically longer in the chemotherapy arm (8.1 months) compared to the enfortumab vedotin arm (7.4 months).

The open-label design of the study might have introduced potential bias for the investigator-assessed PFS and ORR endpoints due to the lack of a Blinded Independent Review Committee assessment. However, the favourable overall survival outcome, being an objective endpoint, provided reassurance regarding the study's results. Additionally, despite the numerically longer median DoR in the chemotherapy arm, the higher proportion of responded subjects with neither progressive disease nor death at 12 months in the enfortumab vedotin arm (28% vs 20%) suggested a potentially more durable response in a subset of patients. This observation of numerically higher longer-term response rates, considered alongside the positive overall survival outcomes, contributed to a favourable overall assessment of the treatment's efficacy.

While the number of subjects with locally advanced disease enrolled in the study was very small (n=10), consistent results were observed with respect to the primary and secondary endpoints (OS: NE vs 8.38 months; PFS: 9.17 months vs 5.39 months; ORR: 70% vs 11.1% in enfortumab vedotin vs chemotherapy arms respectively). In addition, based on clinical practice guidelines, patients with locally advanced UC and metastatic UC are treated with similar regimens. Hence, the efficacy observed in the metastatic UC population could be extrapolated to the locally advanced population.

Subjects with Nectin-4 H-score ≥ 150 consistently exhibited favourable ORR 45.8% versus 19.2%), PFS (HR: 0.602 [95% CI: 0.481, 0.754]), and OS (HR: 0.636 [95% CI: 0.482, 0.839]) in the enfortumab vedotin arm compared to chemotherapy arm. For subjects with Nectin-4 H-score < 150, the ORR (20% vs 5.7%) and PFS (Hazard ratio: 0.896; [95% CI:0.545,1.474] numerically favoured the enfortumab vedotin arm but the median OS was slightly lower (7.5 months [95% CI: 4.6,9.5]) in enfortumab vedotin arm compared to chemotherapy arm (8.0 months [95% CI: 5.9, 13.6]). This should be interpreted with caution due to the exploratory nature of this endpoint and the small sample size (n=45). It was noted that the 95% CI of the median OS was overlapping between the two arms and the ORR and PFS results numerally favoured the enfortumab vedotin arm. Taken together, the data did not suggest a detrimental effect and screening for Nectin-4 expression was considered not required.

Overall, the pivotal study EV-301 provided adequate evidence supporting of the efficacy of enfortumab vedotin in the post-platinum and post-immunotherapy setting of advanced urothelial cancer. The observed benefit was consistent across the subgroups, and also further supported by superiority across PFS and response-related endpoints.

Summary of Key Efficacy Results (Study EV-301)-FAS population

	Study EV-301	
	Enfortumab vedotin (N = 301)	**Chemotherapy (N =307)**
Primary efficacy endpoint-Overall survival (OS)		
Deaths, n (%)	134 (44.5%)	167 (54.4%)
Median OS, months (95% CI)	12.88 (10.58, 15.21)	8.97 (8.05,10.74)
Hazard ratio (95% CI)	0.702 (0.556, 0.886)	
1-sided p -valus	0.00142	
Secondary efficacy endpoints		
Progression free survival (PFS)		
PFS events, n (%)	201 (66.8%)	231 (75.2%)
Median PFS, months (95% CI)	5.55 (5.32, 5.82)	3.71 (3.52,3.94)
Hazard ratio (95% CI)	0.615 (0.505, 0.748)	
1-sided p value	<0.00001	
Objective response rate (ORR)		
Proportion (%) [b]	117 (40.6%)	53 (17.9%)
Stratified 1-sided p value	<0.001 (-1.6%, 10.1%)	
Disease Control Rate (DCR)		
Proportion (%)	207 (71.9%)	158 (53.4%)
Stratified 1-sided p value	<0.001	
Duration of response (DoR)		
Median, months (95% CI)	7.39 (5.59, 9.46)	8.11 (5.65,9.56)

D ASSESSMENT OF CLINICAL SAFETY

The overall safety evaluation was based on the 680 subjects from Study EV-301, Study EV-201 and all subjects who received a starting dose of enfortumab vedotin of 1.25 mg/kg in EV-101 and EV-102. The median duration of treatment for enfortumab vedotin was approximately 5 months across the safety analysis groups with 27.1% of subjects in the enfortumab vedotin 1.25 mg/kg group staying on treatment for 6 to 12 months and 9.4% of subjects staying on treatment for a year or longer.

Overview of treatment emergent adverse events (TEAEs)

Number (%) of patients with:	**Study EV-301**		**Pooled data**
	Enfortumab vedotin (N = 296)	**Chemotherapy (N = 291)**	**Enfortumab vedotin (N = 680)**
TEAEs	290 (98.0%)	288 (99.0%)	673 (99.0%)
Drug related TEAEs	278 (93.9%)	267 (91.8 %)	639 (94.0%)
Serious TEAEs	138 (46.6%)	128 (44.0 %)	306 (45.0%)
Drug-related Serious TEAEs	67 (22.6%)	68 (23.4%)	132 (19.4%)
TEAEs leading to death	21 (7.1 %)	16 (5.5 %)	47 (6.9%)
Drug related TEAEs leading to death	7 (2.4%)	3 (1.0%)	14 (2.1%)

TEAE leading to permanent withdrawal of study drug	51 (17.2%)	51 (17.5%)	126 (18.5%)
Drug related TEAE leading to permanent withdrawal of study drug	40 (13.5 %)	33 (11.3%)	84 (12.4%)
TEAE with NCI-CTCAE ≥ Grade 3	210 (70.9%)	193 (66.3%)	468 (68.8%)
Drug related TEAE with NCI-CTCAE ≥ Grade 3	152 (51.4%)	145 (49.8%)	332 (48.8%)

In Study EV-301, the overall incidences of TEAEs (98% vs 99%) and drug-related TEAEs (93.9% vs 91.8%) were comparable between the two arms. This was consistent with the overall incidence observed in the pooled population (99%). In the enfortumab vedotin arm, the most common TEAEs occurring in ≥ 20% of subjects by PT were alopecia, decreased appetite, fatigue, diarrhea, peripheral sensory neuropathy, pruritus, nausea, constipation, dysgeusia, and pyrexia.

With respect to drug-related TEAEs which occurred at a higher incidence in enfortumab vedotin arm versus chemotherapy arm were increased lacrimation (7.8% vs 2.7%), dry eye (5.1% vs 0), blurred vision (4.1% vs 1.4%), nausea (22.6% vs 21.6%), diarrhoea (24.3% vs 16.5%), stomatitis (7.1% vs 6.5%), dry mouth (6.4% vs 1.7%), abdominal pain (6.1% vs 5.5%), fatigue (31.1% vs 22.7%), decreased weight (11.8% vs 3.8%), increased aspartate aminotransferase (8.8% vs 1%), increased alanine aminotransferase (6.8% vs 1.4%), decreased appetite (30.7% vs 23.4%), hyperglycemia (5.1% vs 0.3%), sensory peripheral neuropathy (33.8% vs 21.3%), dysgeusia (24.3% vs 7.2%), peripheral motor neuropathy (3.4% vs 0), alopecia (45.3% vs 36.4%), pruiritis (32.1% vs 4.5%), maculopapular rash (16.2% vs 1.7%), dry skin (14.2% vs 0.7%), rash (15.2% vs 3.8%) and skin hyperpigmentation (6.1% vs 0.3%). Drug-related TEAEs with Grade 3 or 4 were also comparable between the two arms (49.7% vs 48.8%). Of the Grade 3 or 4 TEAEs (anemia, fatigue, neutrophil count decreased, hyperglycemia, decreased appetite, and rash maculo-papular) that occurred in ≥ 5% of subjects in either arm, the incidences of all events except fatigue and rash maculo-papular were lower in the enfortumab vedotin arm.

There were 7.1% of subjects in the enfortumab vedotin arm and 5.5% of subjects in the chemotherapy arm died with the most common cause being underlying disease progression. A total of 2.4% in the enfortumab vedotin arm and 1% in the chemotherapy arm experienced drug-related TEAE leading to death. In the enfortumab vedotin arm, the drug-related TEAE leading to death that occurred in > 1 subject was multiple organ dysfunction syndrome (2 subjects). A similar proportion of subjects experienced drug related serious TEAEs in the enfortumab vedotin arm (22.6%) and in the chemotherapy arm (23.4%). In the enfortumab vedotin arm the most common drug-related serious TEAEs occurring in ≥ 2% subjects were diarrhoea (2.4%) and acute kidney injury (2.0%).

The adverse events of special interest (AESIs) reported for enfortumab vedotin were skin reactions (severe cutaneous adverse reactions and rash), hyperglycemia, peripheral neuropathy, diarrhoea, nausea, vomiting, dry eye, anaemia, extravasation events, neutropenia, infusion-related reactions (other than extravasation events), corneal disorders, blurred vision. Of these, nausea, vomiting, neutropenia and anaemia were observed at a lower incidence in the enfortumab vedotin arm compared to the chemotherapy arm. These AESIs were expected toxicities based on the on-target effects of enfortumab on Nectin-4 expression and microtubules inhibition, and were mostly of higher incidence compared to the chemotherapy arm.

Skin reactions occurred in 53.7% of subjects in the enfortumab vedotin arm and 19.9% of subjects in the chemotherapy arm. The median time to first onset of any grade skin reaction was 0.46 months (range 0 to 12.7) in the enfortumab vedotin arm, and 0.66 months (range 0.1 to 9.6) in the chemotherapy arm. In the enfortumab vedotin arm, the majority of severe cutaneous adverse reaction events were Grades 1 or 2 (20.6% each), with 5.1% of subjects reporting Grade 3 events and one subject with a Grade 4 event (dermatitis bullous). The incidence of any rash event was higher in the enfortumab vedotin arm (48.0%) compared with the chemotherapy arm (13.1%).

Peripheral neuropathy events were more frequent in the enfortumab vedotin arm (50.3%) compared with the chemotherapy arm (34.4%), with the majority being Grade 1 or 2. Hyperglycaemia was reported in 11.8% of subjects treated with enfortumab vedotin and 2.7% in the chemotherapy arm, most frequently at Grade 3 (6.4%) severity, with most events resolving. Extravasation events (Grade 1 or 2) occurred in 1.0% of subjects in the enfortumab vedotin arm and 2.4% in the chemotherapy arm. Infusion-related reactions were observed in 9.1% of subjects in the enfortumab vedotin arm and 5.8% in the chemotherapy arm. The incidence of diarrhoea was higher in the enfortumab vedotin arm (34.8%) compared with the chemotherapy arm (22.7%). Ocular disorder events were more frequent in the enfortumab vedotin arm (28%) compared to the chemotherapy arm (7.9%), with the majority being Grade 1 or 2, and two subjects reporting Grade 3 events in the enfortumab vedotin arm. The incidence of nausea and vomiting was similar in both treatment arms (nausea: 30.1% vs 25.4%; vomiting: 14.2% vs 15.1% in the enfortumab vedotin and chemotherapy arms, respectively). Anaemia occurred less frequently in the enfortumab vedotin arm (19.9%) compared to the chemotherapy arm (29.9%). Similarly, neutropenia was observed at a lower rate in the enfortumab vedotin arm (18.2%) than in the chemotherapy arm (29.6%).

Overall, the AE profile was as expected based on the mechanism of action and were considered to be associated with the on-target toxicity of enfortumab vedotin due to Nectin-4 expression except for hyperglycemia. Adequate warnings and precautions regarding the AEs have been included in the package insert. The AE profile was deemed manageable through treatment, dose modifications, or drug discontinuations, and was considered acceptable in the context of the disease severity, particularly given that these patients with LA/mUC have progressed after prior lines of systemic therapies and have limited treatment options.

E ASSESSMENT OF BENEFIT-RISK PROFILE

Patients with locally advanced and metastatic urothelial carcinoma who progress after platinum-based chemotherapy and PD-1/PD-L1 inhibitors face poor prognosis and limited subsequent chemotherapy options.

Enfortumab vedotin is an ADC directed against Nectin-4 which is highly expressed in bladder cancer. The pivotal study EV-301 demonstrated a survival benefit of 3.9 months and a statistically significant reduction in the risk of death by 30% (HR = 0.702, 95% CI: 0.556, 0.886; 1-sided P = 0.00142) with enfortumab vedotin when compared to chemotherapy regimens of investigator's choice (docetaxel/paclitaxel/vinflunine). The OS data was supported by consistent results favouring enfortumab vedotin for the secondary efficacy endpoints in respect of PFS (HR: 0.615, 95% CI: 0.51, 0.75; 1-sided P < 0.00001) and ORR (40.6% vs 17.9%). The subgroup analyses were consistent with the overall analysis.

In subjects with Nectin-4 H-score ≥ 150, enfortumab vedotin consistently showed favourable ORR, PFS and OS compared to chemotherapy. For subjects with Nectin-4 H-score < 150, enfortumab vedotin numerically favoured ORR and PFS but OS benefit was not observed. Nevertheless, the results did not suggest any detrimental effect in this patient subgroup hence screening for Nectin-4 expression was not considered necessary.

The most common adverse reactions included alopecia, peripheral sensory neuropathy, pruritus, fatigue, decreased appetite, diarrhoea, dysgeusia and nausea. AESIs for enfortumab vedotin included skin reactions (severe cutaneous adverse reactions and rash), hyperglycemia, peripheral neuropathy, dry eye, diarrhoea, nausea, vomiting, anaemia, extravasation events, infusion-related reactions (other than extravasation events), corneal disorders, blurred vision. Most of these were mild to moderate and were identified risk of on-target toxicity associated with Nectin-4 expression. The AEs could be managed with treatment or drug discontinuations and adequate warnings have been included in the package insert.

Overall, the benefit-risk profile of enfortumab vedotin for use in locally advanced and metastatic urothelial carcinoma who have previously received a programmed death receptor- 1 (PD-1) or programmed death-ligand 1 (PD-L1) inhibitor, and a platinum-containing chemotherapy in the neoadjuvant/adjuvant, locally advanced or metastatic setting was considered favourable.

F CONCLUSION

Based on the review of quality, safety and efficacy data, the benefit-risk balance of enfortumab vedotin was deemed favourable for the treatment locally advanced or metastatic urothelial carcinoma who have previously received a programmed death receptor-1 (PD-1) or programmed death-ligand 1 (PD-L1) inhibitor, and a platinum-containing chemotherapy in the neoadjuvant/adjuvant, locally advanced or metastatic setting. Approval of the product registration was granted on 30 May 2022.

APPROVED PACKAGE INSERT AT REGISTRATION

1. NAME OF THE MEDICINAL PRODUCT

PADCEV® POWDER FOR CONCENTRATE FOR SOLUTION FOR INFUSION 20MG
PADCEV® POWDER FOR CONCENTRATE FOR SOLUTION FOR INFUSION 30MG

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each vial of powder for concentrate for infusion contains either 20 mg or 30 mg enfortumab vedotin. After reconstitution, each mL contains 10 mg of enfortumab vedotin.

Enfortumab vedotin is a Nectin-4 targeted antibody drug conjugate (ADC) comprised of a fully human IgG1 kappa antibody, conjugated to the microtubule-disrupting agent monomethyl auristatin E (MMAE) via a protease-cleavable maleimidocaproyl valine-citrulline linker.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Powder for concentrate for solution for infusion.
White to off-white lyophilized powder.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Padcev is indicated for the treatment of adult patients with locally advanced (LA) or metastatic urothelial cancer (mUC) who have previously received a programmed death receptor-1 (PD-1) or programmed death-ligand 1 (PD-L1) inhibitor, and a platinum-containing chemotherapy in the neoadjuvant/adjuvant, locally advanced or metastatic setting.

4.2 Posology and method of administration

Treatment with Padcev should be initiated and supervised by a physician experienced in the use of anti-cancer therapies.

Posology

The recommended dose of enfortumab vedotin is 1.25 mg/kg (up to a maximum of 125 mg for patients ≥100 kg) administered as an intravenous infusion over 30 minutes on Days 1, 8 and 15 of a 28-day cycle until disease progression or unacceptable toxicity.

Table 1. Recommended Dose Reduction Schedule for Adverse Events

	Dose Level
Starting dose	1.25 mg/kg up to 125 mg
First dose reduction	1.0 mg/kg up to 100 mg
Second dose reduction	0.75 mg/kg up to 75 mg
Third dose reduction	0.5 mg/kg up to 50 mg

Dose Modifications

Table 2. Padcev dose interruption, reduction and discontinuation recommendations in patients with LA or mUC

Adverse Reaction	Severity*	Dose Modification*
Skin Reactions	Grade 2 worsening skin reactions	Consider withhold until Grade ≤1
	Suspected Stevens-Johnson syndrome (SJS) or toxic epidermal necrolysis (TEN), or Grade 3 (severe) skin reactions	Withhold until Grade ≤1, then resume treatment at the same dose level or consider dose reduction by one dose level (see Table 1)
	Confirmed SJS or TEN; Grade 4 or recurrent Grade 3 skin reactions	Permanently discontinue.
Hyperglycaemia	Blood glucose >13.9 mmol/L (>250 mg/dL)	Withhold until elevated blood glucose has improved to ≤13.9 mmol/L (≤250 mg/dL), then resume treatment at the same dose level
Peripheral Neuropathy	Grade 2	Withhold until Grade ≤1, then resume treatment at the same dose level (if first occurrence). For a recurrence, withhold until Grade ≤1 then, resume treatment reduced by one dose level (see Table 1)
	Grade ≥3	Permanently discontinue.
Other nonhaematologic toxicity	Grade 3	Withhold until Grade ≤1, then resume treatment at the same dose level or consider dose reduction by one dose level (see Table 1)
	Grade 4	Permanently discontinue.
Haematologic toxicity	Grade 3, or Grade 2 thrombocytopenia	Withhold until Grade ≤1, then resume treatment at the same dose level or consider dose reduction by one dose level (see Table 1)
	Grade 4	Withhold until Grade ≤1, then reduce dose by one dose level (see Table 1) or discontinue treatment

*Grade 1 is mild, Grade 2 is moderate, Grade 3 is severe, Grade 4 is life-threatening.

Special Populations

Elderly
No dose adjustment is necessary in patients ≥65 years of age (see section 5.2).

Patients with Renal Impairment
No dose adjustment is necessary in patients with mild [creatinine clearance (CrCL) >60–90 mL/min], moderate (CrCL 30–60 mL/min) or severe (CrCL <30 mL/min) renal impairment (see section 5.2).

Patients with Hepatic Impairment
No dose adjustment is necessary in patients with mild hepatic impairment (bilirubin of 1 to 1.5 × ULN and AST < ULN, or bilirubin ≤ ULN and AST > ULN). Padcev is not recommended in patients with

moderate or severe hepatic impairment (AST or ALT >2.5 × ULN or total bilirubin >1.5 × ULN) as there is limited to no safety and efficacy in these patient populations (see section 5.2).

Paediatric population
There is no relevant use of enfortumab vedotin in the paediatric population for the indication of LA or mUC.

Method of administration

The recommended dose of enfortumab vedotin must be administered by intravenous infusion over 30 minutes. Enfortumab vedotin must not be administered as an intravenous push or bolus injection.

For instructions on reconstitution and dilution of the medicinal product before administration, see section 6.6.

4.3 Contraindications

Hypersensitivity to the active substance(s) or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

Skin Reactions

Skin reactions are associated with enfortumab vedotin as a result of enfortumab vedotin binding to Nectin-4 expressed in the skin.

Mild to moderate skin reactions, predominantly maculopapular rash, have been reported. Severe cutaneous adverse reactions, including SJS and TEN, with fatal outcome have also occurred in patients treated with enfortumab vedotin, predominantly during the first cycle of treatment.

Patients should be monitored starting with the first cycle and throughout treatment for skin reactions. Consider appropriate treatment such as topical corticosteroids and antihistamines for mild to moderate skin reactions. For Grade 2 worsening skin reactions, consider withholding enfortumab vedotin until toxicity is Grade ≤1. For worsening or severe (Grade 3) skin reactions, suspected SJS or TEN, withhold Padcev and consider referral for specialised care. Permanently discontinue Padcev for confirmed SJS or TEN, Grade 4 or recurrent severe skin reactions (see section 4.2).

Hyperglycaemia

Hyperglycaemia and diabetic ketoacidosis (DKA), including fatal events, occurred in patients with and without pre-existing diabetes mellitus, treated with enfortumab vedotin. Hyperglycaemia occurred more frequently in patients with pre-existing hyperglycaemia or a high body mass index (≥30 kg/m^2). Blood glucose levels should be monitored regularly in patients with or at risk for diabetes mellitus or hyperglycaemia. If blood glucose is elevated >13.9 mmol/L (>250 mg/dL), Padcev should be withheld until blood glucose is <13.9 mmol/L (<250 mg/dL) and treat as appropriate (see section 4.2).

Peripheral neuropathy

Peripheral neuropathy, predominantly peripheral sensory neuropathy, has occurred with enfortumab vedotin, including Grade ≥3 reactions. Patients should be monitored for symptoms of new or worsening peripheral neuropathy as these patients may require a delay, dose reduction or discontinuation of enfortumab vedotin. Padcev should be permanently discontinued for Grade ≥3 peripheral neuropathy (see section 4.2).

Ocular disorders

Ocular disorders, predominantly dry eye, have occurred in patients treated with enfortumab vedotin. Patients should be monitored for ocular disorders. Consider artificial tears for prophylaxis of dry eye and referral for ophthalmologic evaluation if ocular symptoms do not resolve or worsen.

Infusion Site Extravasation

Skin and soft tissue injury following enfortumab vedotin administration has been observed when extravasation occurred. Ensure good venous access prior to starting Padcev and monitor for possible infusion site extravasation during administration. If extravasation occurs, stop the infusion and monitor for adverse reactions.

Embryo-foetal Toxicity and Contraception

Pregnant women should be informed of the potential risk to a foetus (see sections 4.6 and 5.3). Females of reproductive potential should be advised to have a pregnancy test within 7 days prior to starting treatment with enfortumab vedotin, to use effective contraception during treatment and for at least 6 months after stopping treatment. Males with female partners of reproductive potential should be advised to use effective contraception during treatment and for at least 4 months after the last dose of Padcev.

Traceability

In order to improve the traceability of biological medicinal products, the name and the batch number of the administered product should be clearly recorded.

4.5 Interaction with other medicinal products and other forms of interaction

Formal drug-drug interaction studies with enfortumab vedotin have not been conducted. To evaluate the drug-drug interaction potential of unconjugated MMAE, physiologically-based pharmacokinetic (PBPK) modeling was conducted to predict the drug-drug interaction potential of enfortumab vedotin following coadministration with other drugs.

Effects of Other Drugs on enfortumab vedotin

CYP3A4 inhibitors
Concomitant use of enfortumab vedotin with ketoconazole (a combined P-gp and strong CYP3A inhibitor) is predicted to increase unconjugated MMAE C_{max} by 15% and AUC by 38%, with no change in ADC exposure. Closely monitor for adverse reactions when Padcev is given concomitantly with strong CYP3A4 inhibitors (see section 5.2).

4.6 Fertility, pregnancy and lactation

Women of childbearing potential/ Contraception in males and females

Pregnancy testing is recommended for females of reproductive potential within 7 days prior to initiating treatment. Females of reproductive potential should be advised to use effective contraception during treatment and for at least 6 months after stopping treatment. Males with female partners of reproductive potential should be advised to use effective contraception during treatment and for at least 4 months after the last dose of Padcev.

Pregnancy

Padcev can cause foetal harm when administered to pregnant women based upon findings from animal studies. Embryo-foetal development studies in female rats have shown that intravenous administration of enfortumab vedotin (2 or 5 mg/kg/dose; 1- and 3-fold the human C_{max}, respectively) resulted in reduced numbers of viable foetuses, reduced litter size, and increased early resorptions (see

section 5.3). Padcev is not recommended during pregnancy and in women of childbearing potential not using effective contraception.

Breast-feeding

It is unknown whether enfortumab vedotin is excreted in human milk. A risk to breast-fed children cannot be excluded. Breastfeeding should be discontinued during Padcev treatment and for at least 6 months after the last dose.

Fertility

Testicular toxicity was observed in rats following repeat dosing at systemic exposures that were approximately equal to the human systemic exposure at the clinically recommended dose (see section 5.3). There are no data on the effect of Padcev on human fertility.

4.7 Effects on ability to drive and use machines

Padcev has no or negligible influence on the ability to drive and use machines.

4.8 Undesirable effects

Summary of the safety profile

The safety of enfortumab vedotin was evaluated as monotherapy in 680 patients who received at least one dose of enfortumab vedotin 1.25 mg/kg in two phase 1 studies (EV-101 and EV-102), one phase 2 study (EV-201) and one phase 3 study (EV-301).

The most frequent (≥10%) adverse reactions with enfortumab vedotin were alopecia (48.8%), fatigue (46.8%), decreased appetite (44.9%), peripheral sensory neuropathy (38.7%), diarrhoea (37.6%), nausea (36%), pruritus (33.4%), dysgeusia (29.9%), anaemia (26.5%), weight decreased (23.4%), rash maculo-papular (22.9%), dry skin (21.6%), vomiting (18.4%), aspartate aminotransferase increased (15.3%), hyperglycaemia, (13.1%), dry eye (12.8%), alanine aminotransferase increased (12.1%) and rash (10.4%).

Serious adverse events occurred in 45% of patients. The most frequent (≥2%) serious adverse reactions were diarrhoea (2%) and hyperglycaemia (2%).

Tabulated summary of adverse reactions

Adverse reactions observed during clinical studies are listed in this section by frequency category. Frequency categories are defined as follows: very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000); very rare (<1/10,000); not known (cannot be estimated from the available data).

Table 3. Adverse Reactions

Enfortumab vedotin monotherapy*	
Blood and lymphatic system disorders	
Very common	Anaemia
Not known	Neutropenia†, febrile neutropenia†, neutrophil count decreased†
Gastrointestinal disorders	
Very common	Diarrhoea, nausea, vomiting, constipation
General disorders and administration site conditions	
Very common	Fatigue
Common	Infusion site extravasation, asthenia

Metabolism and nutrition disorders	
Very common	Decreased appetite, hyperglycaemia
Nervous system disorders	
Very common	Dysgeusia, peripheral sensory neuropathy
Common	Gait disturbance, hypoaesthesia, neuropathy peripheral, muscular weakness, paraesthesia, peripheral motor neuropathy, peripheral sensorimotor neuropathy
Uncommon	Burning sensation, demyelinating polyneuropathy, dysaesthesia, motor dysfunction, muscle atrophy, neuralgia, neurotoxicity, peroneal nerve palsy, polyneuropathy, skin burning sensation, sensory loss
Eye disorders	
Very common	Dry eye
Skin and subcutaneous tissue disorders	
Very common	Alopecia, dry skin, pruritus, rash, rash maculo-papular
Common	Blister, conjunctivitis, dermatitis bullous, drug eruption, erythaema, eczema, palmar-plantar erythrodysesthesia syndrome, rash erythaematous, rash macular, rash papular, rash pruritic, rash vesicular, skin exfoliation, stomatitis
Uncommon	Blood blister, dermatitis, dermatitis allergic, dermatitis contact, dermatitis exfoliative generalised, erythaema multiforme, exfoliative rash, intertrigo, pemphigoid, rash maculovesicular, skin irritation, stasis dermatitis
Not known	Epidermal necrosis[†], Stevens-Johnson syndrome[†], symmetrical drug-related intertriginous and flexural exanthaema[†], toxic epidermal necrolysis[†]
Investigations	
Very common	Alanine aminotransferase increased, aspartate aminotransferase increased, weight decreased

[*]Preferred term in MedDRA (v23.0). The above-mentioned listed adverse reactions have been observed during clinical studies (EV-101, EV-102, EV-201 and EV-301).

[†]Based on global post-marketing experience.

Description of selected adverse reactions

Skin Reactions

In clinical studies, skin reactions occurred in 55% (375) of the 680 patients treated with enfortumab vedotin 1.25 mg/kg. Severe (Grade 3 or 4) skin reactions occurred in 13% (85) of patients and a majority of these reactions included maculo-papular rash, rash erythematous, rash or drug eruption. The median time to onset of severe skin reactions was 0.62 months (range: 0.1 to 6.4 months).

In the EV-201 (N=214) clinical study, of the patients who experienced skin reactions, 75% had complete resolution and 14% had partial improvement (see section 4.4).

Hyperglycaemia

In clinical studies, hyperglycaemia (blood glucose >13.9 mmol/L) occurred in 14% (98) of the 680 patients treated with enfortumab vedotin 1.25 mg/kg. Seven percent of patients developed severe (Grade 3-4) hyperglycaemia. Two patients experienced fatal events, one event each of hyperglycaemia and diabetic ketoacidosis. The incidence of Grade 3-4 hyperglycaemia increased consistently in

patients with higher body mass index and in patients with higher baseline haemoglobin A1C (HbA1c). The median time to onset of hyperglycaemia was 0.6 months (range: 0.1 to 20.3). Patients with baseline HbA1c ≥8% were excluded from clinical studies.

In the EV-201 (N=214) clinical study, at the time of their last evaluation, 61% of patients had complete resolution, and 19% of patients had partial improvement (see section 4.4).

Peripheral Neuropathy

In clinical studies peripheral neuropathy occurred in 52% (352) of the 680 patients treated with enfortumab vedotin 1.25 mg/kg. Four percent of patients experienced severe (Grade 3-4) peripheral neuropathy including sensory and motor events. The median time to onset of Grade ≥2 was 4.6 months (range: 0.1 to 15.8). Patients with pre-existing peripheral neuropathy Grade ≥2 were excluded from clinical studies.

In the EV-201 (N=214) clinical study, at the time of their last evaluation, 19% of patients had complete resolution, and 39% of patients had partial improvement (see section 4.4).

Ocular Disorders

In clinical studies, 14 (2.1%) patients interrupted, and 1 (0.1%) patient permanently discontinued treatment for ocular disorders. Severe (Grade 3) ocular disorders only occurred in 3 patients (0.4%). Thirteen percent of patients experienced dry eye symptoms during treatment with enfortumab vedotin 1.25 mg/kg and the median time to onset was 1.7 months (range: 0 to 19.1 months) (see section 4.4).

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system.

4.9 Overdose

There is no known antidote for overdosage with enfortumab vedotin. In case of overdosage, the patient should be closely monitored for adverse reactions, and supportive treatment should be administered as appropriate taking into consideration the half-life of 3.6 days (ADC) and 2.6 days (MMAE).

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Nectin-4-directed antibody drug conjugate, ATC code: L01FX13
Enfortumab vedotin is a Nectin-4 targeted ADC comprised of a fully human IgG1 kappa antibody, conjugated to the microtubule-disrupting agent MMAE via a protease-cleavable maleimidocaproyl valine-citrulline linker.

The clinical pharmacology of enfortumab vedotin was evaluated in patients with solid tumors who received enfortumab vedotin administered by intravenous infusion.

Mechanism of action

Enfortumab vedotin is an ADC targeting Nectin-4, an adhesion protein located on the surface of the urothelial cancer cells. It is comprised of a fully human IgG1-kappa antibody conjugated to the microtubule-disrupting agent MMAE via a protease-cleavable linker. Nonclinical data suggest that the anticancer activity of enfortumab vedotin is due to the binding of the ADC to Nectin-4-expressing cells, followed by internalisation of the ADC-Nectin-4 complex, and the release of MMAE via proteolytic cleavage. Release of MMAE disrupts the microtubule network within the cell,

subsequently inducing cell cycle arrest and apoptotic cell death. MMAE released from enfortumab vedotin targeted cells can diffuse into nearby Nectin-4 low-expressing cells resulting in cytotoxic cell death.

Pharmacodynamic effects

In an exposure-response analysis, a higher exposure was associated with higher incidence of some adverse reactions (e.g., Grade ≥2 peripheral neuropathy, Grade ≥3 hyperglycaemia).

Cardiac Electrophysiology

The effect of enfortumab vedotin on the duration of cardiac ventricular repolarisation was evaluated in 17 patients with locally advanced or metastatic urothelial carcinoma who received enfortumab vedotin on Days 1, 8, and 15 of each 28-day cycle. Based on concentration – QTcF modeling, a population mean change in QTcF interval (change from baseline QTcF; upper 1-sided 95% CI) of 6.17 (10.5) msec was estimated to occur at a geometric mean C_{max} of 20.1 mcg/mL for the ADC. For MMAE, a population mean change in QTcF interval (upper 1-sided 95% CI) of -3.14 (9.52) msec was estimated to occur at a geometric mean C_{max} of 3.94 ng/mL. At the recommended dose of 1.25 mg/kg, enfortumab vedotin had no large effect on QTc prolongation (>20 msec).

Clinical efficacy and safety

Metastatic Urothelial Cancer

EV-301
The efficacy of Padcev was evaluated in study EV-301, an open-label, randomised, phase 3, multicentre study that enrolled 608 patients with locally advanced or metastatic urothelial cancer who received prior treatment with a PD-1 or PD-L1 inhibitor and a platinum-containing chemotherapy. Patients were randomised 1:1 to receive either enfortumab vedotin 1.25 mg/kg on Days 1, 8 and 15 of a 28-day cycle, or one of the following chemotherapies as decided by the investigator: docetaxel 75 mg/m^2 (38%), paclitaxel 175 mg/m^2 (36%) or vinflunine 320 mg/m^2 (25%) on Day 1 of a 21-day cycle.

Patients were excluded from the study if they had active CNS metastases, ongoing sensory or motor neuropathy ≥ Grade 2, or uncontrolled diabetes defined as HbA1c ≥8% or HbA1c ≥7% with associated diabetes symptoms.

The median age was 68 years (range: 30 to 88 years), 77% were male, and most patients were White (52%) or Asian (33%). All patients had a baseline Eastern Cooperative Oncology Group (ECOG) performance status of 0 (40%) or 1 (60%). Eighty percent of patients had visceral metastases including 31% with liver metastases. Seventy-six percent of patients had urothelial carcinoma/transitional cell carcinoma (TCC) histology and 14% had urothelial carcinoma mixed. A total of 527 out of 608 subjects had evaluable Nectin-4 results; of these 527 subjects, 516 (98%) had detectable Nectin-4 (H-score > 0) as assessed by a validated immunohistochemistry (IHC) assay. A total of 76 (13%) of patients received ≥3 lines of prior systemic therapy. Fifty-two percent (314) of patients received prior PD-1 inhibitor, 47% (284) received prior PD-L1 inhibitor, and an additional 1% (9) patients received both PD-1 and PD-L1 inhibitors. Only 18% (111) of patients had a response to prior therapy with a PD-1 or PD-L1 inhibitor. Sixty-three percent (383) of patients received prior cisplatin-based regimens, 26% (159) received prior carboplatin-based regimens, and an additional 11% (65) received both cisplatin and carboplatin-based regimens.

The study demonstrated statistically significant improvements in Overall Survival (OS), Progression Free Survival (PFS), Objective Response Rate (ORR) and Disease Control Rate (DcR) for patients randomised to enfortumab vedotin as compared to chemotherapy (PFS, ORR and DcR were evaluated by investigator assessment using RECIST v1.1). The median follow-up time for this study was 11.1 months (95% CI: 10.6 to 11.6). Patients randomised to the enfortumab vedotin arm had a statistically significantly improvement in OS compared to the chemotherapy arm with a median OS of 12.9 months

versus 9 months, respectively (HR= 0.702; 95% CI: 0.556, 0.886; 1-sided p-value: 0.00142). Patients randomised to receive enfortumab vedotin experienced longer PFS compared to those randomised to receive chemotherapy with a median PFS of 5.6 months versus 3.7 months, respectively (HR= 0.615; 95% CI: 0.505, 0.748; 1-sided p-value: <0.00001).

The median time to response was 1.87 months (range: 1.1 to 5.7 months) for patients randomised to enfortumab vedotin. Efficacy results were consistent across most patient subgroups such as, age, geographic region, baseline ECOG PS, liver metastasis, preselected control therapy, primary site of tumor, prior lines of therapy in locally advanced or metastatic setting and best response to prior PD1 or PD-L1.

Table 4 summarizes the efficacy results for the EV-301 study.

Table 4. Efficacy Results in EV-301

Endpoint	Padcev n=301	Chemotherapy n=307
Overall Survival		
Number (%) of patients with events	134 (44.5)	167 (54.4)
Median in months (95% CI)	12.9 (10.6, 15.2)	9.0 (8.1, 10.7)
Hazard ratio (95% CI)	0.702 (0.556, 0.886)	
1-sided p-value	0.00142*	
6-month OS (%) (95% CI)	77.9 (72.7, 82.3)	69.5 (63.9, 74.4)
12-month OS (%) (95% CI)	51.5 (44.6, 58.0)	39.2 (32.6, 45.6)
Progression Free Survival[†]		
Number (%) of patients with events	201 (66.8)	231 (75.2)
Median in months (95% CI)	5.6 (5.3, 5.8)	3.7 (3.5, 3.9)
Hazard ratio (95% CI)	0.615 (0.505, 0.748)	
1-sided p-value	<0.00001[‡]	
6-month PFS (%) (95% CI)	44.0 (38.0, 49.8)	28.2 (22.9, 33.8)
12-month PFS (%) (95% CI)	21.7 (16.3, 27.7)	8.3 (4.6, 13.4)
Objective Response Rate (CR + PR)[†]		
ORR (%) (95% CI)	40.6 (35.0, 46.5)	17.9 (13.7, 22.8)
1-sided p-value	<0.001[§]	
Complete response rate (%)	4.9	2.7
Partial response rate (%)	35.8	15.2
Disease Control Rate (DcR)[†,¶]		
DcR (%) (95% CI)	71.9 (66.3, 77.0)	53.4 (47.5, 59.2)
1-sided p-value	<0.001[§]	
Duration of Response for responders		
Median in months (95% CI)	7.4 (5.6, 9.5)	8.1 (5.7, 9.6)

*pre-determined efficacy boundary = 0.00679, 1-sided (adjusted by observed deaths of 301).
†evaluated by investigator assessment using RECIST v1.1.
‡pre-determined efficacy boundary = 0.02189, 1-sided (adjusted by observed PFS1 events of 432).
§pre-determined efficacy boundary = 0.025, 1-sided (adjusted by 100% information fraction).
¶DCR was defined as the proportion of subjects who had a best overall response of confirmed CR, confirmed PR, or stable disease (≥ 7 weeks).

Patient-reported quality of life (QoL) was assessed using the EORTC QLQ-C30. Over the first 12 weeks of treatment, patients treated with enfortumab vedotin maintained overall quality of life compared with baseline and had less variability compared to chemotherapy. Further, patients treated with enfortumab vedotin had improvements in pain compared to chemotherapy, with an average difference in change from baseline of -5.73 at week 12. Fifty-two percent of patients treated with enfortumab vedotin and 29% of patients treated with chemotherapy achieved confirmed improvement in pain (odds ratio [95% CI]: 2.76, [1.81; 4.22]) over the study period. These results should be interpreted in the context of the open-label study design.

EV-201

The efficacy of enfortumab vedotin was evaluated in EV-201, a single-arm, multi-cohort, multicentre study that enrolled 219 patients with locally advanced or metastatic urothelial cancer who received prior treatment with a PD-1 or PD-L1 inhibitor. Patients were treated with 1.25 mg/kg enfortumab vedotin over approximately 30 minutes on Days 1, 8, and 15 of each 28-day cycle.

Cohort 1 included 125 patients with locally advanced or metastatic urothelial cancer who were treated with enfortumab vedotin and received prior treatment with a PD-1 or PD-L1 inhibitor and a platinum-based chemotherapy. The ORR as established by blinded independent central review (BICR) in Cohort 1 was 44% (95% CI: 35.1, 53.2) with 15 (12%) CR, 40 (32%) PR, and a median DOR of 7.6 months (95% CI: 6.3, NE).

Cohort 2 of this study included 89 patients with locally advanced or metastatic urothelial cancer who received prior treatment with a PD-1 or PD-L1 inhibitor, are cisplatin ineligible and did not receive platinum in the locally advanced or metastatic setting.
Reasons for cisplatin ineligibility included: 66% with baseline creatinine clearance of <60 mL/min, 7% with ECOG PS of 2, 15% with Grade 2 or greater hearing loss, and 12% with more than one cisplatin-ineligibility criteria. Seventy percent of patients had TCC and 17% had TCC with other histologic variants.

Patients with active CNS metastases, ongoing sensory or motor neuropathy Grade ≥2, or uncontrolled diabetes defined as HbA1c ≥8% or HbA1c ≥7% with associated diabetes symptoms were excluded from participating in the study.
The median age was 75 years (range: 49 to 90 years), 74% were male and 70% were White. Most patients had an ECOG score of 1 (46.1%) or 0 (41.6%). Seventy-nine percent of patients had visceral metastases; 24% had liver metastases. An immunohistochemistry clinical trial assay was used to assess patients with tumor tissue available and detected Nectin-4 expression in all, but one patient tested (79/80, 98.8%).

The median number of prior systemic therapies was 1 (range: 1 to 4). Fifty-one percent of patients received prior PD-1 inhibitor, 45% received prior PD-L1 inhibitor, and an additional 4% received both PD-1 and PD-L1 inhibitors. Forty-two percent of patients did not respond to prior therapy with a PD-1 or PD-L1 inhibitor.

Efficacy was established by BICR based upon ORR and is presented in Table 5. The ORR was 50.6% (95% CI: 39.8, 61.3), the median time to response was 1.81 months (95% CI: 1.0 - 7.2) and the median duration of response was 13.8 months (95% CI: 6.41, -). The median follow-up time was 13.4 months. Responses were consistent across key patient subgroups including patients ≥75 years of age, patients with liver metastasis and patients who did not respond to prior PD-1 or PD-L1 inhibitor therapy.

Table 5. Efficacy Results in EV-201, Cohort 2

Endpoint	Enfortumab Vedotin 1.25 mg/kg n = 89
ORR (95% CI)	50.6% (39.8, 61.3)
Complete Response Rate (CR)	22.5%
Partial Response Rate (PR)	28.1%
Median Duration of Response, months (95% CI)	13.8 (6.41, -)

5.2 Pharmacokinetic properties

Distribution

The mean estimate of steady-state volume of distribution of ADC was 12.8 L following 1.25 mg/kg of enfortumab vedotin. *In vitro*, the binding of MMAE to human plasma proteins ranged from 68% to 82%. MMAE is not likely to displace or to be displaced by highly protein-bound drugs. In vitro studies indicate that MMAE is a substrate of P-glycoprotein.

Biotransformation

A small fraction of MMAE released from enfortumab vedotin is metabolised. *In vitro* data indicate that the metabolism of MMAE occurs primarily via oxidation by CYP3A4.

Elimination

The mean clearance (CL) of ADC and unconjugated MMAE in patients was 0.11 L/h and 2.11 L/h, respectively. ADC elimination exhibited a multi-exponential decline with a half-life of 3.6 days. Elimination of MMAE appeared to be limited by its rate of release from enfortumab vedotin. MMAE elimination exhibited a multi-exponential decline with a half-life of 2.6 days.

Excretion

The excretion of MMAE occurs mainly in faeces with a smaller proportion in urine. After a single dose of another ADC that contained MMAE, approximately 24% of the total MMAE administered was recovered in faeces and urine as unchanged MMAE over a 1-week period. The majority of recovered MMAE was excreted in faeces (72%). A similar excretion profile is expected for MMAE after enfortumab vedotin administration.

Immunogenicity

A total of 590 patients were tested for immunogenicity to enfortumab vedotin 1.25 mg/kg; 15 patients were confirmed to be positive at baseline for anti-therapeutic antibody (ATA), and in patients that were negative at baseline (N=575), a total of 16 (2.8%) were positive postbaseline (13 transiently and 3 persistently). Due to the limited number of patients with antibodies against Padcev, no conclusions can be drawn concerning a potential effect of immunogenicity on efficacy, safety or pharmacokinetics.

Special populations

Elderly

Population pharmacokinetic analysis indicates that age [range: 24 to 90 years; 60% (450/748) >65 years, 19% (143/748) >75 years] does not have a clinically meaningful effect on the pharmacokinetics of enfortumab vedotin.

Race and gender

Based on population pharmacokinetic analysis, race [69% (519/748) White, 21% (158/748) Asian, 1% (10/748) Black and 8% (61/748) others or unknown] and gender [73% (544/748) male] do not have a clinically meaningful effect on the pharmacokinetics of enfortumab vedotin.

Renal impairment

The pharmacokinetics of ADC and unconjugated MMAE were evaluated after the administration of 1.25 mg/kg of enfortumab vedotin to patients with mild (creatinine clearance; CrCL >60–90 mL/min; n=272), moderate (CrCL 30–60 mL/min; n=315) and severe (CrCL 15-<30 mL/min; n=25) renal impairment. No significant differences in AUC exposure of ADC or unconjugated MMAE were observed in patients with mild, moderate or severe renal impairment compared to patients with normal renal function. Enfortumab vedotin has not been evaluated in patients with end stage renal disease (CrCL <15 mL/min).

Hepatic impairment

Based on population pharmacokinetics analysis using data from clinical studies in patients with metastatic UC, there was no significant differences in ADC exposure and a 37% increase in unconjugated MMAE AUC were observed in patients with mild hepatic impairment (total bilirubin of 1 to 1.5 × ULN and AST any, or total bilirubin ≤ ULN and AST > ULN, n=65) compared to patients with normal hepatic function. Enfortumab vedotin has only been studied in a limited number of patients with moderate hepatic impairment (n=3) and has not been evaluated in patients with severe hepatic impairment. The effect of moderate or severe hepatic impairment (total bilirubin >1.5 × ULN and AST any) or liver transplantation on the pharmacokinetics of ADC or unconjugated MMAE is unknown.

Drug-drug interactions

Formal drug-drug interaction studies with enfortumab vedotin have not been conducted. Physiologically-based pharmacokinetic modeling was conducted to predict the drug-drug interaction potential of enfortumab vedotin.

Physiologically-Based Pharmacokinetic Modeling Predictions

Concomitant use of enfortumab vedotin with ketoconazole (a combined P-gp and strong CYP3A inhibitor) is predicted to increase unconjugated MMAE C_{max} by 15% and AUC by 38%, with no change in ADC exposure.

Concomitant use of enfortumab vedotin with rifampin (a combined P-gp and strong CYP3A inducer) is predicted to decrease unconjugated MMAE C_{max} by 28% and AUC by 53%, with no change in ADC exposure.

Concomitant use of enfortumab vedotin is predicted not to affect exposure to midazolam (a sensitive CYP3A substrate) or digoxin (a P-gp substrate). *In vitro* studies using human liver microsomes indicate that MMAE inhibits CYP3A4/5 but not other CYP450 isoforms. MMAE did not induce major CYP450 enzymes in human hepatocytes.

In vitro studies

In vitro studies indicate that MMAE is a substrate and not an inhibitor of the efflux transporter P-glycoprotein (P-gp). *In vitro* studies determined that MMAE was not a substrate of breast cancer resistance protein (BCRP), multidrug resistance-associated protein 2 (MRP2), organic anion transporting polypeptide 1B1 or 1B3 (OATP1B1 or OATP1B3), organic cation transporter 2 (OCT2), or organic anion transporter 1 or 3 (OAT1 or OAT3). MMAE was not an inhibitor of the bile salt export pump (BSEP), P-gp, BCRP, MRP2, OCT1, OCT2, OAT1, OAT3, OATP1B1, or OATP1B3 at clinically relevant concentrations.

5.3 Preclinical safety data

AGS-22M6E, an ADC that is biologically equivalent to enfortumab vedotin, is a high affinity humanised IgG1κ monoclonal antibody drug conjugate that binds human Nectin-4 antigen. AGS-22M6E demonstrated dose-dependent cytotoxic activity against Nectin-4 expressing cancer cells in vitro and inhibited tumour growth in various human Nectin-4 positive cancer xenograft models.

Pharmacodynamic bridging studies of AGS-22M6E (hybridoma-derived) and enfortumab vedotin (CHO-derived) confirmed comparable binding affinity, cytotoxicity and in vivo efficacy between the 2 antibody drug conjugates. In addition, the safety profile and pharmacokinetics of AGS-22M6E and enfortumab vedotin were comparable in cynomolgus monkeys.

Genotoxicity studies showed that MMAE had no discernible genotoxic potential in a reverse mutation test in bacteria (Ames test) or in a L5178Y $TK^{+/-}$ mouse lymphoma mutation assay. MMAE did induce chromosomal aberrations in the micronucleus test in rats which is consistent with the pharmacological action of microtubule-disrupting agents.

Skin lesions were noted in good laboratory practice compliant toxicity studies in rats (≥5 mg/kg; 1-fold the human systemic exposure) and in monkeys (≥1 mg/kg; 0.7-fold the human systemic exposure). The skin changes were fully reversible by the end of a 6-week recovery period.
Hyperglycaemia reported in the clinical studies was absent in both the rat and monkey toxicity studies and there were no histopathological findings in the pancreas of either species.

Foetal toxicity was noted at both the 2- and 5 mg/kg dose levels (1- and 3-fold the human C_{max}, respectively) with reduced litter size noted at the 2 mg/kg dose level and complete litter loss in the 5 mg/kg/day dose group. The decrease in the litter size was reflected in an increase in early resorptions. Mean foetal body weight in the surviving foetuses at the 2 mg/kg dose level were reduced compared with control.

Enfortumab vedotin associated foetal skeletal variations were considered developmental delays related to the decreased foetal weights and included asymmetric, fused, incompletely ossified, and misshapen sternebrae, misshapen cervical arch, and unilateral ossification of the thoracic centra. There were no enfortumab vedotin related external or visceral foetal abnormalities (malformations or variations).

In addition, intravenous administration of MMAE (0.2 mg/kg; C_{max} 1.1-fold the human C_{max} at the recommended clinical dose) on Gestation Day 6 and 13 resulted in embryo-foetal lethality and foetal external malformations (protruding tongue, malrotated hindlimbs, gastroschisis, and agnathia).
Testicular toxicity was noted only in rats. Findings included seminiferous tubule degeneration and hypospermia in the epididymis (≥2.0 mg/kg; approximately 1-fold the human systemic exposure at the clinically recommended dose). These findings were partially reversed by the end of a 24-week recovery period. Testicular toxicity was not observed in sexually immature male monkeys administered enfortumab vedotin at doses up to 6 mg/kg (6-fold the human systemic exposure at the clinically recommended dose).

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Histidine
Histidine hydrochloride monohydrate
Trehalose dihydrate
Polysorbate 20

6.2 Incompatibilities

Do not co-administer other drugs through the same infusion line.

6.3 Shelf life

36 months, unopened, clear glass vial.

6.4 Special precautions for storage

Store between 2ºC and 8ºC. Do not freeze.
For storage conditions after reconstitution and dilution of the medicinal product, see section 6.6.

6.5 Nature and contents of container

Clear 10 mL Type I glass vial
Gray bromobutyl rubber stopper
20 mg vial, 20 mm aluminum seal with a green ring and green cap
30 mg vial, 20 mm aluminum seal with a silver ring and yellow cap
Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

Enfortumab vedotin is an antineoplastic product. Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

Instructions for preparation and administration

Reconstitution in single-dose vial

1. Follow procedures for proper handling and disposal of anticancer drugs.
2. Use appropriate aseptic technique for reconstitution and preparation of dosing solutions.
3. Calculate the recommended dose based on the patient's weight to determine the number and strength (20 mg or 30 mg) of vials needed.
4. Reconstitute each vial as follows and, if possible, direct the stream of SWFI along the walls of the vial and not directly onto the lyophilized powder:
   a. 20 mg vial: Add 2.3 mL of SWFI, resulting in 10 mg/mL enfortumab vedotin.
   b. 30 mg vial: Add 3.3 mL of SWFI, resulting in 10 mg/mL enfortumab vedotin.
5. Slowly swirl each vial until the contents are completely dissolved. Allow the reconstituted vial(s) to settle for at least 1 minute until the bubbles are gone. DO NOT SHAKE THE VIAL.
6. Visually inspect the solution for particulate matter and discolouration. The reconstituted solution should be clear to slightly opalescent, colourless to light yellow and free of visible particles. Discard any vial with visible particles or discolouration.
7. Based upon the calculated dose amount, the reconstituted solution from the vial(s) should be added to the infusion bag immediately. This product does not contain a preservative. If not used immediately, reconstituted vials may be stored for up to 24 hours in refrigeration between 2°C and 8°C. DO NOT FREEZE. Discard unused vials with reconstituted solution beyond the recommended storage time.

Dilution in infusion bag

8. Withdraw the calculated dose amount of reconstituted solution from the vial(s) and transfer into an infusion bag.
9. Dilute enfortumab vedotin with 5% Dextrose Injection or 0.9% Sodium Chloride Injection or Lactated Ringer's Injection. The infusion bag size should allow enough diluent to achieve a final concentration of 0.3 mg/mL to 4 mg/mL enfortumab vedotin.
10. Mix diluted solution by gentle inversion. DO NOT SHAKE THE BAG.
11. Visually inspect the infusion bag for any particulate matter or discolouration prior to use. The reconstituted solution should be clear to slightly opalescent, colourless to light yellow and free of

visible particles. DO NOT USE the infusion bag if particulate matter or discolouration is observed.
12. Discard any unused portion left in the single-dose vials.
13. The prepared infusion bag should not be stored longer than 16 hours under refrigeration between 2°C and 8°C including infusion time. DO NOT FREEZE.

Administration
14. Administer the infusion over 30 minutes through an intravenous line. DO NOT administer as an IV push or bolus.
15. DO NOT co-administer other drugs through the same infusion line.

Prior to administration, the enfortumab vedotin vial is reconstituted with Sterile Water for Injection (SWFI). The reconstituted solution is transferred to an intravenous infusion bag containing sterile 5% Dextrose Injection, sterile 0.9% Sodium Chloride injection or sterile Lactated Ringer's injection for administration.

7. PRODUCT REGISTRANT

Astellas Pharma Singapore Pte. Ltd.
6 Temasek Boulevard
#26-03/05 Suntec Tower Four
Singapore 038986
For any enquiry, please write to pv@sg.astellas.com.

8. DATE OF REVISION OF PACKAGE INSERT

MAY/2022 (CCDS v4.0)