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.
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#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)