

ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

▼ This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. See section 4.8 for how to report adverse reactions.

1. NAME OF THE MEDICINAL PRODUCT

Padcev 20 mg powder for concentrate for solution for infusion

Padcev 30 mg powder for concentrate for solution for infusion

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Padcev 20 mg powder for concentrate for solution for infusion

One vial of powder for concentrate for solution for infusion contains 20 mg enfortumab vedotin.

Padcev 30 mg powder for concentrate for solution for infusion

One vial of powder for concentrate for solution for infusion contains 30 mg enfortumab vedotin.

After reconstitution, each mL of solution contains 10 mg of enfortumab vedotin.

Enfortumab vedotin is 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 as monotherapy is indicated for the treatment of adult patients with locally advanced or metastatic urothelial cancer who have previously received a platinum-containing chemotherapy and a programmed death receptor-1 or programmed death-ligand 1 inhibitor (see section 5.1).

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. Ensure good venous access prior to starting treatment (see section 4.4).

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 reductions for adverse reactions

	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. Dose interruption, reduction and discontinuation in patients with locally advanced or metastatic urothelial cancer

Adverse reaction	Severity*	Dose modification*
Skin reactions	Suspected Stevens-Johnson syndrome (SJS) or toxic epidermal necrolysis (TEN) or bullous lesions	Immediately withhold and refer to specialised care.
	Confirmed SJS or TEN; Grade 4 or recurrent Grade 3	Permanently discontinue.
	Grade 2 worsening Grade 2 with fever Grade 3	<ul style="list-style-type: none"> • Withhold until Grade ≤ 1 • Referral to specialised care should be considered • Resume at the same dose level or consider dose reduction by one dose level (see Table 1)
Hyperglycaemia	Blood glucose >13.9 mmol/L (>250 mg/dL)	<ul style="list-style-type: none"> • Withhold until elevated blood glucose has improved to ≤ 13.9 mmol/L (≤ 250 mg/dL) • Resume treatment at the same dose level
Pneumonitis/ interstitial lung disease (ILD)	Grade 2	<ul style="list-style-type: none"> • Withhold until Grade ≤ 1, then resume at the same dose or consider dose reduction by one dose level (see Table 1)
	Grade ≥ 3	Permanently discontinue.
Peripheral neuropathy	Grade 2	<ul style="list-style-type: none"> • Withhold until Grade ≤ 1 • For first occurrence, resume treatment at the same dose level • For a recurrence, withhold until Grade ≤ 1, then resume treatment reduced by one dose level (see Table 1)
	Grade ≥ 3	Permanently discontinue.

*Toxicity was graded per National Cancer Institute Common Terminology Criteria for Adverse Events Version 5.0 (NCI-CTCAE v5.0) where Grade 1 is mild, Grade 2 is moderate, Grade 3 is severe and Grade 4 is life-threatening

Special populations

Elderly

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

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 15 – <30 mL/min) renal impairment. Enfortumab vedotin has not been evaluated in patients with end stage renal disease (CrCL <15 mL/min) (see section 5.2).

Hepatic impairment

No dose adjustment is necessary in patients with mild hepatic impairment [total bilirubin of 1 to $1.5 \times$ upper limit of normal (ULN) and AST any, or total bilirubin \leq ULN and AST $>$ ULN]. Enfortumab vedotin has only been evaluated in a limited number of patients with moderate hepatic impairment and has not been evaluated in patients with severe hepatic impairment (see section 5.2).

Paediatric population

There is no relevant use of enfortumab vedotin in the paediatric population for the indication of locally advanced or metastatic urothelial cancer.

Method of administration

Padcev is for intravenous use. The recommended dose 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 or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

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.

Skin reactions

Skin reactions are associated with enfortumab vedotin as a result of enfortumab vedotin binding to Nectin-4 expressed in the skin. Fever or flu-like symptoms may be the first sign of a severe skin reaction, and patients should be observed, if this occurs.

Mild to moderate skin reactions, predominantly maculopapular rash, have been reported (see section 4.8). 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. In clinical trials, the median time to onset of severe skin reactions was 0.6 months (range: 0.1 to 6.4).

Patients should be monitored starting with the first cycle and throughout treatment for skin reactions. Appropriate treatment such as topical corticosteroids and antihistamines can be considered for mild to moderate skin reactions. For suspected SJS or TEN, or in case of bullous lesions onset, withhold treatment immediately and refer to specialised care; histologic confirmation, including consideration of multiple biopsies, is critical to early recognition, as diagnosis and intervention can improve prognosis. Permanently discontinue Padcev for confirmed SJS or TEN, Grade 4 or recurrent severe skin reactions. For Grade 2 worsening, Grade 2 with fever or Grade 3 skin reactions, treatment should be withheld until Grade ≤ 1 and referral for specialised care should be considered. Treatment should be resumed at the same dose level or consider dose reduction by one dose level (see section 4.2).

Pneumonitis/ILD

Severe, life-threatening or fatal pneumonitis/ILD have occurred in patients treated with enfortumab vedotin (see section 4.8).

Monitor patients for signs and symptoms indicative of pneumonitis/ILD such as hypoxia, cough, dyspnea or interstitial infiltrates on radiologic exams. Corticosteroids should be administered for Grade ≥ 2 events (e.g., initial dose of 1-2 mg/kg/day prednisone or equivalent followed by a taper). Withhold Padcev for Grade 2 pneumonitis/ILD and consider dose reduction. Permanently discontinue Padcev for Grade ≥ 3 pneumonitis/ILD (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 (see section 4.8).

Hyperglycaemia occurred more frequently in patients with pre-existing hyperglycaemia or a high body mass index (≥ 30 kg/m²). Patients with baseline HbA1c $\geq 8\%$ were excluded from clinical trials. Blood glucose levels should be monitored prior to dosing and periodically throughout the course of treatment as clinically indicated 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 (see section 4.8). Patients with preexisting peripheral neuropathy Grade ≥ 2 were excluded from clinical trials. 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 (see Table 1). 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 (see section 4.8). 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 (see section 4.8). 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 12 months after stopping treatment. Men being treated with enfortumab vedotin are advised not to father a child during treatment and for up to 9 months following the last dose of Padcev.

4.5 Interaction with other medicinal products and other forms of interaction

Formal drug-drug interaction studies with enfortumab vedotin have not been conducted. Concomitant administration of enfortumab vedotin and CYP3A4 (substrates) metabolised medicinal products, has no clinically relevant risk of inducing pharmacokinetic interactions (see section 5.2).

Effects of other medicinal products on enfortumab vedotin

CYP3A4 inhibitors, substrates or inducers

Based on physiologically-based pharmacokinetic (PBPK) modeling, concomitant use of enfortumab vedotin with ketoconazole (a combined P-gp and strong CYP3A inhibitor) is predicted to increase unconjugated MMAE C_{max} and AUC exposure to a minor extent, with no change in ADC exposure. Caution is advised in case of concomitant treatment with CYP3A4 inhibitors. Patients receiving concomitant strong CYP3A4 inhibitors (e.g. boceprevir, clarithromycin, cobicistat, indinavir, itraconazole, nefazodone, nelfinavir, posaconazole, ritonavir, saquinavir, telaprevir, telithromycin, voriconazole) should be monitored more closely for signs of toxicities.

Unconjugated MMAE is not predicted to alter the AUC of concomitant medicines that are CYP3A4 substrates (e.g. midazolam).

Strong CYP3A4 inducers (e.g. rifampicin, carbamazepine, phenobarbital, phenytoin, St. John's wort [*Hypericum perforatum*]) may decrease the exposure of unconjugated MMAE with moderate effect (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 12 months after stopping treatment. Men being treated with

enfortumab vedotin are advised not to father a child during treatment and for up to 9 months following 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 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

In rats, repeat dose administration of enfortumab vedotin, resulted in testicular toxicity and may alter male fertility. MMAE has been shown to have aneugenic properties (see section 5.3). Therefore, men being treated with this medicinal product are advised to have sperm samples frozen and stored before treatment. 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 most common 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%).

The most common serious adverse reactions were diarrhoea (2%) and hyperglycaemia (2%). Nine percent of patients permanently discontinued enfortumab vedotin for adverse reactions; the most common adverse reaction ($\geq 2\%$) leading to dose discontinuation was peripheral sensory neuropathy (4%). Adverse reactions leading to dose interruption occurred in 44% of patients; the most common adverse reactions ($\geq 2\%$) leading to dose interruption were peripheral sensory neuropathy (15%), fatigue (7%), rash maculo-papular (4%), aspartate aminotransferase increased (4%), alanine aminotransferase increased (4%), anaemia (3%), diarrhoea (3%) and hyperglycaemia (3%). Thirty percent of patients required a dose reduction due to an adverse reaction; the most common adverse reactions ($\geq 2\%$) leading to a dose reduction were peripheral sensory neuropathy (10%), fatigue (5%), rash maculo-papular (4%) and decreased appetite (2%).

Tabulated summary of adverse reactions

The safety of enfortumab vedotin as monotherapy has been evaluated in 680 patients with locally advanced or metastatic urothelial cancer receiving 1.25 mg/kg on Days 1, 8 and 15 of a 28-day cycle in clinical studies (see Table 3). Patients were exposed to enfortumab vedotin for a median duration of 4.7 months (range: 0.3 to 34.8 months).

Adverse reactions observed during clinical studies are listed in this section by frequency category. Frequency categories are defined as follows: very common ($\geq 1/10$); common ($\geq 1/100$ to $< 1/10$); uncommon ($\geq 1/1,000$ to $< 1/100$); rare ($\geq 1/10,000$ to $< 1/1,000$); very rare ($< 1/10,000$); not known (cannot be estimated from the available data). Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

Table 3. Adverse reactions

Blood and lymphatic system disorders	
Very common	Anaemia
Not known ¹	Neutropenia, febrile neutropenia, neutrophil count decreased
Metabolism and nutrition disorders	
Very common	Hyperglycaemia, decreased appetite
Nervous system disorders	
Very common	Peripheral sensory neuropathy, dysgeusia
Common	Neuropathy peripheral, peripheral motor neuropathy, peripheral sensorimotor neuropathy, paraesthesia, hypoaesthesia, gait disturbance, muscular weakness
Uncommon	Demyelinating polyneuropathy, polyneuropathy, neurotoxicity, motor dysfunction, dysaesthesia, muscle atrophy, neuralgia, peroneal nerve palsy, sensory loss, skin burning sensation, burning sensation
Eye disorders	
Very common	Dry eye
Respiratory, thoracic, and mediastinal disorders	
Common	Pneumonitis
Uncommon	Interstitial lung disease
Gastrointestinal disorders	
Very common	Diarrhoea, vomiting, nausea
Skin and subcutaneous tissue disorders	
Very common	Alopecia, pruritus, rash, rash maculo-papular, dry skin
Common	Drug eruption, skin exfoliation, conjunctivitis, dermatitis bullous, blister, stomatitis, palmar-plantar erythrodysesthesia syndrome, eczema, erythema, rash erythematous, rash macular, rash papular, rash pruritic, rash vesicular
Uncommon	Dermatitis exfoliative generalised, erythema multiforme, exfoliative rash, pemphigoid, rash maculovesicular, dermatitis, dermatitis allergic, dermatitis contact, intertrigo, skin irritation, stasis dermatitis, blood blister
Not known ¹	Toxic epidermal necrolysis, Stevens-Johnson syndrome, epidermal necrosis, symmetrical drug-related intertriginous and flexural exanthema

General disorders and administration site conditions	
Very common	Fatigue
Common	Infusion site extravasation
Investigations	
Very common	Alanine aminotransferase increased, aspartate aminotransferase increased, weight decreased

¹Based on global post-marketing experience.

Description of selected adverse reactions

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-drug antibody (ADA), 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.

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). Serious skin reactions occurred in 3.8% (26) of patients.

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).

Pneumonitis/ILD

In clinical studies, pneumonitis occurred in 15 (2.2%) and ILD occurred in 2 (0.3%) of the 680 patients treated with enfortumab vedotin 1.25 mg/kg. Less than 1% of patients experienced severe (Grade 3-4) pneumonitis or ILD. Pneumonitis or ILD led to discontinuation of enfortumab vedotin in 0.1% and 0.3% of patients, respectively. There were no deaths from ILD or pneumonitis. The median time to onset of any grade pneumonitis or ILD was 3.6 months (range: 0.8 to 6.0 months) and the median duration was 1.4 months (range: 0.2 to 27.5 months). Of the 17 patients who experienced pneumonitis or ILD, 6 (35.3%) had resolution of symptoms.

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. Serious events of hyperglycaemia occurred in 2.2% of patients, 7% of patients developed severe (Grade 3-4) hyperglycaemia and 0.3% of 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 hyperglycemia was 0.6 months (range: 0.1 to 20.3).

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).

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, 30% of patients experienced dry eye during treatment with enfortumab vedotin 1.25 mg/kg. Treatment was interrupted in 1.3% of patients and 0.1% of patients permanently discontinued treatment due to dry eye. Severe (Grade 3) dry eye only occurred in 3 patients (0.4%). The median time to onset of dry eye 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 listed in [Appendix V](#).

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: Antineoplastic agents, other antineoplastic agents, monoclonal antibodies, ATC code: L01FX13

Mechanism of action

Enfortumab vedotin is an antibody drug conjugate (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 maleimidocaproyl valine-citrulline 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.

Cardiac electrophysiology

At the recommended dose of 1.25 mg/kg, enfortumab vedotin did not prolong the mean QTc interval to any clinically relevant extent based on ECG data from a study in patients with advanced urothelial cancer.

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 have previously received a platinum-containing chemotherapy and a programmed death receptor 1 (PD-1) or programmed death ligand 1 (PD-L1) inhibitor. The primary endpoint of the study was Overall Survival (OS) and secondary endpoints included Progression Free Survival (PFS) and Objective Response Rate (ORR) [PFS and ORR were evaluated by investigator assessment using RECIST v1.1]. 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/m² (38%), paclitaxel 175 mg/m² (36%) or vinflunine 320 mg/m² (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 \geq Grade 2, known history of human immunodeficiency virus (HIV) infection (HIV 1 or 2), active Hepatitis B or C, or uncontrolled diabetes defined as HbA1c \geq 8% or HbA1c \geq 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 performance status of 0 (40%) or 1 (60%). Ninety-five percent (95%) of patients had metastatic disease and 5% had locally advanced disease. 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, 14% had urothelial carcinoma mixed and approximately 10% had other histologic variants. A total of 76 (13%) patients had received \geq 3 lines of prior systemic therapy. Fifty-two percent (314) of patients had received prior PD-1 inhibitor, 47% (284) had received prior PD-L1 inhibitor, and an additional 1% (9) patients had 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 had received prior cisplatin-based regimens, 26% (159) had received prior carboplatin-based regimens, and an additional 11% (65) had received both cisplatin and carboplatin-based regimens.

Table 4 summarizes the efficacy results for the EV-301 study, after a median follow-up time of 11.1 months (95% CI: 10.6 to 11.6).

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*	
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 [‡]	
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
Duration of Response for responders		
Median in months (95% CI)	7.4 (5.6, 9.5)	8.1 (5.7, 9.6)

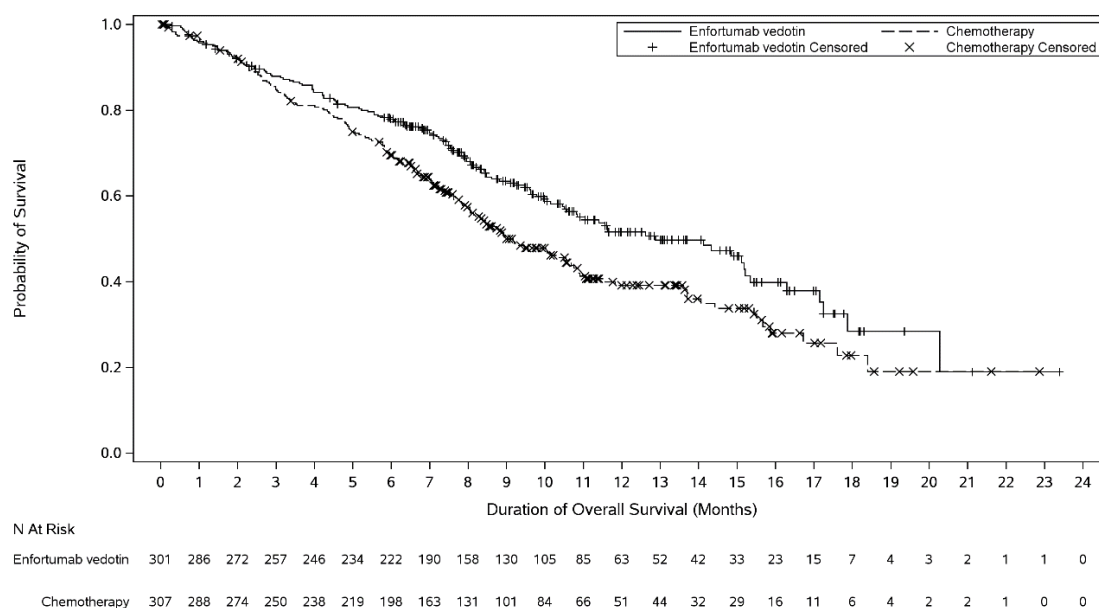
*pre-determined efficacy boundary = 0.00679, 1-sided (adjusted by observed deaths of 301)

[†]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)

Figure 1. Kaplan Meier plot of overall survival



Paediatric population

The European Medicines Agency has waived the obligation to submit the results of studies with enfortumab vedotin in all subsets of the paediatric population in urothelial cancer (see section 4.2 for information on paediatric use).

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 medicinal products. *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 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.

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 (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 $1.5 \times$ ULN and AST any, or total bilirubin \leq 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 x ULN and AST any) or liver transplantation on the pharmacokinetics of ADC or unconjugated MMAE is unknown.

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} and AUC exposure to a minor extent, 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} and AUC exposure with moderate effect, with no change in ADC exposure. The full impact of rifampin on the C_{max} of MMAE may be underestimated in the PBPK model.

Concomitant use of enfortumab vedotin is predicted not to affect exposure to midazolam (a sensitive CYP3A 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

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 repeat dose studies in rats (4- and 13-weeks) and in monkeys (4-weeks). 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 (reduced litter size or complete litter loss) was observed and 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. A dose of 2 mg/kg (approximately similar to the exposure at the recommended human dose) resulted in maternal toxicity, embryo-foetal lethality and structural malformations that included gastroschisis, malrotated hindlimb, absent forepaw, malpositioned internal organs and fused cervical arch. Additionally, skeletal anomalies (asymmetric, fused, incompletely ossified, and misshapen sternbrae, misshapen cervical arch, and unilateral ossification of the thoracic centra) and decreased foetal weight were observed.

Testicular toxicity observed, only in rats, was partially reversed by the end of a 24-week recovery period.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Histidine
Histidine hydrochloride monohydrate
Trehalose dihydrate
Polysorbate 20

6.2 Incompatibilities

In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products.

6.3 Shelf life

Unopened vial
3 years.

Reconstituted solution in the vial

From a microbiological point of view, after reconstitution, the solution from the vial(s) should be added to the infusion bag immediately. If not used immediately, storage times and conditions prior to

use of the reconstituted vials are the responsibility of the user and would normally not be longer than 24 hours in refrigeration at 2°C to 8°C. Do not freeze.

Diluted dosing solution in the infusion bag

From a microbiological point of view, after dilution into the infusion bag, the diluted solution in the bag should be administered to the patient immediately. If not used immediately, storage times and conditions prior to use of the diluted dosing solution is the responsibility of the user and would normally not be longer than 16 hours in refrigeration at 2°C to 8°C including infusion time. Do not freeze.

6.4 Special precautions for storage

Unopened vials

Store in a refrigerator (2°C to 8°C).

Do not freeze.

For storage conditions after reconstitution and dilution of the medicinal product, see section 6.3.

6.5 Nature and contents of container

Padcev 20 mg powder for concentrate for solution for infusion vial

10 mL Type I glass vial with gray bromobutyl rubber stopper, 20 mm aluminum seal with a green ring and green cap. Each carton contains 1 vial.

Padcev 30 mg powder for concentrate for solution for infusion vial

10 mL Type I glass vial with gray bromobutyl rubber stopper, 20 mm aluminum seal with a silver ring and yellow cap. Each carton contains 1 vial.

6.6 Special precautions for disposal and other handling

Instructions for preparation and administration

Reconstitution in single-dose vial

1. Follow procedures for proper handling and disposal of anticancer medicinal products.
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 sterile water for injection along the walls of the vial and not directly onto the lyophilized powder:
 - a. 20 mg vial: Add 2.3 mL of sterile water for injection, resulting in 10 mg/mL enfortumab vedotin.
 - b. 30 mg vial: Add 3.3 mL of sterile water for injection, 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.

Dilution in infusion bag

7. Withdraw the calculated dose amount of reconstituted solution from the vial(s) and transfer into an infusion bag.
8. Dilute enfortumab vedotin with dextrose 50 mg/mL (5%), sodium chloride 9 mg/mL (0.9%) or Lactated Ringer's solution for injection. The infusion bag size should allow enough solvent to achieve a final concentration of 0.3 mg/mL to 4 mg/mL enfortumab vedotin.

Diluted dosing solution of enfortumab vedotin is compatible with intravenous infusion bags composed of polyvinyl chloride (PVC), ethylvinyl acetate, polyolefin such as polypropylene (PP), or IV bottles comprised of polyethylene (PE), polyethylene terephthalate glycol-modified, and infusion sets composed of PVC with either plasticizer (bis(2-ethylhexyl) phthalate (DEHP) or tris(2-ethylhexyl) trimellitate (TOTM)), PE and with filter membranes (pore size: 0.2-1.2 µm) composed of polyethersulfone, polyvinylidene difluoride, or mixed cellulose esters.

9. Mix diluted solution by gentle inversion. Do not shake the bag.
10. 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.
11. Discard any unused portion left in the single-dose vials.

Administration

12. Administer the infusion over 30 minutes through an intravenous line. Do not administer as an intravenous push or bolus.

No incompatibilities have been observed with closed system transfer device composed of acrylonitrile butadiene styrene (ABS), acrylic, activated charcoal, ethylene propylene diene monomer, methacrylate ABS, polycarbonate, polyisoprene, polyoxymethylene, PP, silicone, stainless steel, thermoplastic elastomer for reconstituted solution.

13. Do not co-administer other medicinal products through the same infusion line.
14. In-line filters or syringe filters (the pore size: 0.2-1.2 µm, recommended materials: polyethersulfone, polyvinylidene difluoride, mixed cellulose esters) are recommended to be used during administration.

Disposal

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

Astellas Pharma Europe B.V.
Sylviusweg 62
2333 BE Leiden
The Netherlands

8. MARKETING AUTHORISATION NUMBER

EU/1/21/1615/001

EU/1/21/1615/002

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 13 April 2022

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency <http://www.ema.europa.eu>.

ANNEX II

- A. MANUFACTURER OF THE BIOLOGICAL ACTIVE
SUBSTANCE AND MANUFACTURER RESPONSIBLE FOR
BATCH RELEASE**
- B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY
AND USE**
- C. OTHER CONDITIONS AND REQUIREMENTS OF THE
MARKETING AUTHORISATION**
- D. CONDITIONS OR RESTRICTIONS WITH REGARD TO
THE SAFE AND EFFECTIVE USE OF THE MEDICINAL
PRODUCT**

**A. MANUFACTURER OF THE BIOLOGICAL ACTIVE SUBSTANCE AND<
MANUFACTURER RESPONSIBLE FOR BATCH RELEASE**

Name and address of the manufacturer of the biological active substance

Lonza AG
Lonzastrasse
Visp, 3930
Switzerland

Name and address of the manufacturer responsible for batch release

Astellas Ireland Co. Limited,
Killorglin, Co. Kerry
V93 FC86
Ireland

The printed package leaflet of the medicinal product must state the name and address of the manufacturer responsible for the release of the concerned batch.

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

– **Periodic safety update reports (PSURs)**

The requirements for submission of PSURs for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

The marketing authorisation holder (MAH) shall submit the first PSUR for this product within 6 months following authorisation.

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

– **Risk management plan (RMP)**

The marketing authorisation holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP. An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

– **Additional risk minimization measures**

Prior to use of Padcev in each Member State, the MAH should agree on the content and format of the educational programme, including communication media, distribution modalities, and any other aspects of the programme, with the National Competent Authority.

The MAH should ensure that in each Member State where Padcev is marketed, all healthcare professionals who are expected to prescribe Padcev are provided with the following materials:

The patient information pack:

- Patient information leaflet
- Patient card
 - Patient card:
 - Information for patients that Padcev treatment may cause skin reactions including severe skin reactions such as SJS, TEN or other severe rashes.
 - Description of the symptoms of skin reactions and to immediately seek medical care as these may be signs of a severe skin reaction.
 - A warning message for healthcare professionals treating the patient at any time, including in conditions of emergency, that the patient is using Padcev.
 - Contact details of the treating physician who has prescribed Padcev.
 - Needs to be carried all the time and presented to any healthcare professional.

The MAH should also provide a patient card in each pack of the medicinal product, the text of which is included in Annex III.

ANNEX III
LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING**OUTER CARTON****1. NAME OF THE MEDICINAL PRODUCT**

PADCEV 20 mg powder for concentrate for solution for infusion
enfortumab vedotin

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each vial contains 20 mg enfortumab vedotin.
After reconstitution each mL contains 10 mg of enfortumab vedotin.

3. LIST OF EXCIPIENTS

Contains histidine, histidine hydrochloride monohydrate, trehalose dihydrate and polysorbate 20

4. PHARMACEUTICAL FORM AND CONTENTS

Powder for concentrate for solution for infusion
1 vial

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
For intravenous use after reconstitution and dilution.
Do not shake.
For single use only.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY**8. EXPIRY DATE**

EXP:

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator.
Store in the original packaging.
Do not freeze.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE
--

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Astellas Pharma Europe B.V.
Sylviusweg 62
2333 BE Leiden
The Netherlands

12. MARKETING AUTHORISATION NUMBER(S)
--

EU/1/21/1615/001

13. BATCH NUMBER

Lot:

14. GENERAL CLASSIFICATION FOR SUPPLY
--

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Justification for not including Braille accepted.

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA
--

PC
SN
NN

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS VIAL
--

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION
--

PADCEV 20 mg powder for concentrate for solution for infusion
enfortumab vedotin
Intravenous use

2. METHOD OF ADMINISTRATION

For IV use after reconstitution and dilution.

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT
--

10 mg /mL

6. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING**OUTER CARTON****1. NAME OF THE MEDICINAL PRODUCT**

PADCEV 30 mg powder for concentrate for solution for infusion
enfortumab vedotin

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each vial contains 30 mg enfortumab vedotin.
After reconstitution each mL contains 10 mg of enfortumab vedotin.

3. LIST OF EXCIPIENTS

Contains histidine, histidine hydrochloride monohydrate, trehalose dihydrate and polysorbate 20

4. PHARMACEUTICAL FORM AND CONTENTS

Powder for concentrate for solution for infusion
1 vial

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
For intravenous use after reconstitution and dilution.
Do not shake.
For single use only.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY**8. EXPIRY DATE**

EXP:

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator.
Store in the original packaging.
Do not freeze.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Astellas Pharma Europe B.V.
Sylviusweg 62
2333 BE Leiden
The Netherlands

12. MARKETING AUTHORISATION NUMBER(S)
--

EU/1/21/1615/002

13. BATCH NUMBER

Lot:

14. GENERAL CLASSIFICATION FOR SUPPLY
--

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Justification for not including Braille accepted.

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA
--

PC
SN
NN

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS**VIAL****1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION**

PADCEV 30 mg powder for concentrate for solution for infusion
enfortumab vedotin
Intravenous use

2. METHOD OF ADMINISTRATION

For IV use after reconstitution and dilution.

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

10 mg /mL

6. OTHER

CONTENT OF PATIENT CARD

PATIENT CARD

PADCEV (enfortumab vedotin)

- Carry this card with you **at all times**, especially when you travel or when you see another doctor.
- Please ensure you show this card to any doctor, pharmacist or nurse for any medical treatment or at any visits to the hospital or clinic.
- Please contact your doctor **immediately**, if you develop any side effects, in particular those listed on this card.

IMPORTANT SAFETY INFORMATION FOR PATIENTS

Padcev may cause serious side effects, including severe skin reactions (Stevens-Johnson syndrome (SJS), Toxic Epidermal Necrolysis (TEN) and other severe rashes such as symmetrical drug related intertriginous and flexural exanthema).

Talk to your doctor, pharmacist or nurse **immediately** if you have any of the following symptoms:

- rash or itching that continues to get worse or comes back after treatment,
- skin blistering or peeling,
- painful sores or ulcers in mouth or nose, throat, or genital area,
- fever or flu like symptoms,
- or swollen lymph nodes.

These may be signs of a severe skin reaction that can happen while receiving this medicine, particularly during the first few weeks of treatment. If it occurs, your doctor will monitor you and may give you medicine to treat your skin condition. She or he may pause or stop treatment if your skin reaction worsens. If you have any further questions about your treatment, please contact your doctor.

IMPORTANT INFORMATION FOR HEALTHCARE PROVIDERS

- This patient is being treated with Padcev (enfortumab vedotin), which can cause severe skin reactions, including SJS and TEN (predominantly during the first cycle of treatment).
- Symptoms include rash or itching that continues to get worse or comes back after treatment, skin blistering or peeling, painful sores or ulcers in mouth or nose, throat, or genital area, fever or flu-like symptoms or swollen lymph nodes.
- Fever or flu-like symptoms may be the first sign of a skin reaction. Patients should be monitored starting with the first cycle and throughout treatment for skin reactions. Topical corticosteroids/antihistamines can be considered for mild to moderate skin reactions.
- If SJS or TEN is suspected or if bullous lesions occur, **immediately** withhold treatment and refer for specialised care; histologic confirmation is critical to early recognition, as diagnosis and intervention can improve prognosis.
- If SJS or TEN, Grade 4 or recurrent Grade 3 skin reactions occur, permanently discontinue treatment.
- Withhold treatment for Grade 2 with fever, worsening Grade 2 or Grade 3 skin reactions until Grade ≤ 1 and resume at the same dose level or consider dose reduction by one dose level; consider referral to specialised care.

Please contact the patient's Haematologist/Oncologist for more information and consult the Product Information for enfortumab vedotin available at <https://www.ema.europa.eu/>.

My name: _____
My contact number: _____
Emergency contact: _____
Emergency contact number: _____
Name of Haematologist/Oncologist/Oncology Nurse: _____
Contact number: _____
After-hours contact number: _____
Name of my Hospital: _____
My Hospital contact number: _____
PADCEV start date: _____

B. PACKAGE LEAFLET

Package leaflet: Information for the patient

Padcev 20 mg powder for concentrate for solution for infusion Padcev 30 mg powder for concentrate for solution for infusion enfortumab vedotin

▼ This medicine is subject to additional monitoring. This will allow quick identification of new safety information. You can help by reporting any side effects you may get. See the end of section 4 for how to report side effects.

Read all of this leaflet carefully before you are given this medicine because it contains important information for you.

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor.
- If you get any side effects, talk to your doctor. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Padcev is and what it is used for
2. What you need to know before you are given Padcev
3. How to use Padcev
4. Possible side effects
5. How to store Padcev
6. Contents of the pack and other information

1. WHAT PADCEV IS AND WHAT IT IS USED FOR

Padcev contains the active substance enfortumab vedotin which is made up of a monoclonal antibody linked to a substance intended to kill cancer cells. The monoclonal antibody recognises certain cancer cells and delivers the substance to the cancer cells.

This medicine is used in adults to treat a kind of cancer called bladder cancer (urothelial carcinoma). People get Padcev when their cancer has spread or cannot be taken out by surgery.

Padcev is given to people that have received an immunotherapy medicine and also received a chemotherapy-containing platinum medicine.

2. WHAT YOU NEED TO KNOW BEFORE YOU ARE GIVEN PADCEV

You must not be given Padcev

- if you are allergic to enfortumab vedotin or any of the other ingredients of this medicine (listed in section 6).

Warnings and precautions

Talk to your doctor immediately if you:

- have any of the following skin reaction symptoms:
 - rash or itching that continues to get worse or comes back after treatment,
 - skin blistering or peeling,

- painful sores or ulcers in mouth or nose, throat, or genital area,
 - fever or flu-like symptoms,
 - or swollen lymph nodes.
- these may be signs of a severe skin reaction that can happen while receiving this medicine, particularly during the first few weeks of your treatment. If it occurs, your doctor will monitor you and may give you a medicine to treat your skin condition. She or he may pause treatment until symptoms are reduced. If your skin reaction worsens, your doctor may stop your treatment. You will also find this information in the Patient Card that is included in the packaging. It is important that you keep this Patient Card with you and show it to any healthcare professional you see.
 - have any symptoms of high blood sugar, including frequent urination, increased thirst, blurred vision, confusion, drowsiness, loss of appetite, fruity smell on your breath, nausea, vomiting, or stomach pain. You can develop high blood sugar during treatment.
 - have lung problems (pneumonitis/interstitial lung disease) or if you get new or worsening symptoms, including trouble breathing, shortness of breath, or cough. If it occurs, your doctor may pause treatment until symptoms are improved or reduce your dose. If your symptoms worsen, your doctor may stop your treatment.
 - have any symptoms of nerve problems (neuropathy) such as numbness, tingling or a tingling sensation in your hands or feet or muscle weakness. If it occurs, your doctor may pause treatment until symptoms are improved or reduce your dose. If your symptoms worsen, your doctor may stop your treatment.
 - have eye problems such as dry eyes during your treatment. You can develop dry eye problems while receiving Padcev.

Children and adolescents

This medicine should not be used in children and adolescents below 18 years of age.

Other medicines and Padcev

Tell your doctor if you are taking, have recently taken or might take any other medicines.

Tell your doctor if you take medicines for fungal infections (e.g., ketoconazole) as they can increase the amount of Padcev in your blood. If you normally take these medicines, your doctor might change it and prescribe a different medicine for you during your treatment.

Pregnancy and breast-feeding and fertility

If you are pregnant, think you may be pregnant or are planning to have a baby, ask your doctor for advice before starting this medicine.

You should not use this medicine if you are pregnant. Padcev may harm your unborn baby.

If you are a woman starting this medicine who is able to become pregnant, you should use effective contraception during treatment and for at least 12 months after stopping Padcev.

It is not known if this medicine passes into your breast milk and could harm your baby. Do not breast-feed during treatment and for at least 6 months after stopping Padcev.

Men being treated with this medicine are advised to have sperm samples frozen and stored before treatment. Men are advised not to father a child during treatment with this medicine and for up to 9 months following the last dose of this medicine.

Driving and using machines

Do not drive or operate machines if you feel unwell during treatment.

3. HOW TO USE PADCEV

You will receive Padcev in a hospital or clinic, under the supervision of a doctor experienced in giving such treatments.

How much Padcev you will receive

The recommended dose of this medicine is 1.25 mg/kg on days 1, 8 and 15 every 28 days. Your doctor will decide how many treatments you need.

How you will receive Padcev

You will receive Padcev by intravenous infusion into your vein over 30 minutes. Padcev will be added to an infusion bag containing either glucose, sodium chloride or Lactated Ringer's solution before use.

If you miss a dose of Padcev

It is very important for you to keep all of your appointments to receive Padcev. If you miss an appointment, ask your doctor when to schedule your next dose.

If you stop receiving Padcev

Do not stop treatment with Padcev unless you have discussed this with your doctor. Stopping your treatment may stop the effect of the medicine.

4. POSSIBLE SIDE EFFECTS

Like all medicines, this medicine can cause side effects, although not everybody gets them.

Some possible side effects may be serious:

- **Skin reactions (Stevens-Johnson syndrome, toxic epidermal necrolysis and other severe rashes such as symmetrical drug related intertriginous and flexural exanthema).** Tell your doctor right away if you have any of these signs of a severe skin reaction: rash or itching that continues to get worse or comes back after treatment, skin blistering or peeling, painful sores or ulcers in mouth or nose, throat, or genital area, fever or flu-like symptoms or swollen lymph nodes (frequency not known).
- **High blood sugar (hyperglycaemia).** Tell your doctor right away if you have any symptoms of high blood sugar, including: frequent urination, increased thirst, blurred vision, confusion,

drowsiness, loss of appetite, fruity smell on your breath, nausea, vomiting or stomach pain (may affect more than 1 in 10 people).

- **Lung problems (pneumonitis/interstitial lung disease).** Tell your doctor right away if you get new or worsening symptoms, including trouble breathing, shortness of breath, or cough (may affect up to 1 in 10 people).
- **Nerve problems (peripheral neuropathy such as motor neuropathy, sensorimotor neuropathy, paraesthesia, hypoaesthesia and muscular weakness).** Tell your doctor right away if you get numbness, tingling or a tingling sensation in your hands or feet or muscle weakness (may affect more than 1 in 10 people).
- **Leakage of Padcev out of your vein into the tissues around your infusion site (extravasation).** Tell your doctor or get medical help right away if you notice any redness, swelling, itching, or discomfort at the infusion site. If Padcev leaks from the injection site or the vein into the nearby skin and tissues, it could cause an infusion site reaction. These reactions can happen right after you receive an infusion, but sometimes may happen days after your infusion (may affect up to 1 in 10 people).

Other possible side effects

Very common (may affect more than 1 in 10 people):

- low red blood cells (anaemia)
- nausea, diarrhoea and vomiting
- tiredness
- decreased appetite
- change in sense of taste
- dry eye
- hair loss
- weight loss
- dry or itchy skin
- rash
- flat or red raised bumps on the skin
- increased liver enzymes (aspartate aminotransferase [AST] or alanine aminotransferase [ALT])

Common (may affect up to 1 in 10 people):

- abnormal walking (gait disturbance)
- eye redness
- hives on the skin
- redness in the skin
- inflamed, itchy, cracked and rough patches of skin
- redness and tingling on the palms or soles of feet
- skin peeling
- mouth ulcer
- rash with accompanying symptoms: itchiness, redness, red bumps or red patches on the skin, fluid-filled blisters, large blisters, skin lesions

Uncommon (may affect up to 1 in 100 people):

- skin irritation
- skin burning sensation
- problems affecting nerve function causing odd sensation or problems with movement
- muscle decreasing in size

- blood blister
- allergic reaction to skin
- rash with accompanying symptoms: spots that look like bullseyes, skin peeling, flat fluid-filled blister
- skin peeling all over the body
- inflammation in skin folds including the groin
- blister or blister-like lesions on the skin
- inflammation or itchiness appearing on the legs and feet only

Reporting of side effects

If you get any side effects, talk to your doctor. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in [Appendix V](#). By reporting side effects, you can help provide more information on the safety of this medicine.

5. HOW TO STORE PADCEV

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the carton and vial label after EXP. The expiry date refers to the last day of that month.

Store in a refrigerator (2°C to 8°C). Do not freeze.

Do not store any unused portion of the infusion solution for reuse. Any unused medicine or waste material should be disposed of in accordance with local requirements.

6. CONTENTS OF THE PACK AND OTHER INFORMATION

What Padcev contains

- The active substance is enfortumab vedotin.
- One vial of 20 mg powder for concentrate for solution for infusion contains 20 mg of enfortumab vedotin
- One vial of 30 mg powder for concentrate for solution for infusion contains 30 mg of enfortumab vedotin
- After reconstitution, each mL of solution contains 10 mg of enfortumab vedotin

The other ingredients are histidine, histidine hydrochloride monohydrate, trehalose dihydrate and polysorbate 20.

What Padcev looks like and contents of the pack

Padcev powder for concentrate for solution for infusion is a white to off-white lyophilized powder. Padcev is supplied in a box containing 1 glass vial.

Marketing Authorisation Holder and Manufacturer

Marketing Authorisation Holder:

Astellas Pharma Europe B.V.
Sylviusweg 62
2333 BE Leiden
The Netherlands

Manufacturer:

Astellas Ireland Co. Ltd
Killorglin
Co Kerry
V93 FC86
Ireland

For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder:

België/Belgique/Belgien

Astellas Pharma B.V. Branch
Tél/Tel: +32 (0) 2 5580710

Lietuva

Biocodex UAB
Tel.: +370 37 408 681

България

Астелас Фарма ЕООД
Тел.: +359 2 862 53 72

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Other sources of information

Detailed information on this medicine is available on the European Medicines Agency web site:
<http://www.ema.europa.eu>

The following information is intended for healthcare professionals only:

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.

Instructions for preparation and administrationReconstitution in single-dose vial

1. Follow procedures for proper handling and disposal of anticancer medicinal products.
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 sterile water for injection along the walls of the vial and not directly onto the lyophilized powder:
 - a. 20 mg vial: Add 2.3 mL of sterile water for injection, resulting in 10 mg/mL enfortumab vedotin.

- b. 30 mg vial: Add 3.3 mL of sterile water for injection, 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.

Dilution in infusion bag

7. Withdraw the calculated dose amount of reconstituted solution from the vial(s) and transfer into an infusion bag.
8. Dilute enfortumab vedotin with dextrose 50 mg/mL (5%), sodium chloride 9 mg/mL (0.9%) or Lactated Ringer's solution for injection. The infusion bag size should allow enough solvent to achieve a final concentration of 0.3 mg/mL to 4 mg/mL enfortumab vedotin.

Diluted dosing solution of enfortumab vedotin is compatible with intravenous infusion bags composed of polyvinyl chloride (PVC), ethylvinyl acetate, polyolefin such as polypropylene (PP), or IV bottles comprised of polyethylene (PE), polyethylene terephthalate glycol-modified, and infusion sets composed of PVC with either plasticizer (bis(2-ethylhexyl) phthalate (DEHP) or tris(2-ethylhexyl) trimellitate (TOTM)), PE and with filter membranes (pore size : 0.2-1.2 µm) composed of polyethersulfone, polyvinylidene difluoride, or mixed cellulose esters.

9. Mix diluted solution by gentle inversion. Do not shake the bag.
10. 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.
11. Discard any unused portion left in the single-dose vials.

Administration

12. Administer the infusion over 30 minutes through an intravenous line. Do not administer as an intravenous push or bolus.

No incompatibilities have been observed with closed system transfer device composed of acrylonitrile butadiene styrene (ABS), acrylic, activated charcoal, ethylene propylene diene monomer, methacrylate ABS, polycarbonate, polyisoprene, polyoxymethylene, PP, silicone, stainless steel, thermoplastic elastomer for reconstituted solution.

13. Do not co-administer other medicinal products through the same infusion line.
14. In-line filters or syringe filters (the pore size: 0.2-1.2 µm, recommended materials: polyethersulfone, polyvinylidene difluoride, mixed cellulose esters) are recommended to be used during administration.

Disposal

Padcev is for single use only.

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.