**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, in combination with pembrolizumab, is indicated for the first-line treatment of adult patients with unresectable or metastatic urothelial cancer who are eligible for platinum-containing chemotherapy.

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

As monotherapy, 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.

When given in combination with pembrolizumab, 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 and 8 of every 3-week (21-day) cycle until disease progression or unacceptable toxicity. The recommended dose of pembrolizumab is either 200 mg every 3 weeks or 400 mg every 6 weeks administered as an intravenous infusion over 30 minutes. Patients should be administered pembrolizumab after enfortumab vedotin when given on the same day. Refer to the pembrolizumab SmPC for additional dosing information of pembrolizumab.

**Table 1. Recommended dose reductions of enfortumab vedotin 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 of enfortumab vedotin 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<br>Grade 2 with fever<br>Grade 3 | • Withhold until Grade ≤1.<br>• Referral to specialised care should be considered.<br>• 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) | • Withhold until elevated blood glucose has improved to ≤13.9 mmol/L (≤250 mg/dL).<br>• Resume treatment at the same dose level. |
| **Pneumonitis/ interstitial lung disease (ILD)** | Grade 2 | • 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 | • Withhold until Grade ≤1.<br>• For first occurrence, resume treatment at the same dose level.<br>• 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 × upper limit of normal (ULN) and AST any, or total bilirubin ≤ ULN and AST > ULN]. Enfortumab vedotin has only been evaluated in a limited number of patients with moderate and severe hepatic impairment. Hepatic impairment is expected to increase the systemic exposure to MMAE (the cytotoxic drug); therefore, patients should be closely monitored for potential adverse events. Due to the sparsity of the data in patients with moderate and severe hepatic impairment, no specific dose recommendation can be given (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 rash maculo-papular, have been reported with enfortumab vedotin. The incidence of skin reactions occurred at a higher rate when enfortumab vedotin was given in combination with pembrolizumab compared to enfortumab vedotin as monotherapy (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.

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 Grade 3 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. The incidence of pneumonitis/ILD, including severe events occurred at a higher rate when enfortumab vedotin was given in combination with pembrolizumab compared to enfortumab vedotin as monotherapy (see section 4.8).
Monitor patients for signs and symptoms indicative of pneumonitis/ILD such as hypoxia, cough, dyspnoea 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/m$^2$). Patients with baseline HbA1c ≥8% were excluded from clinical studies.
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).

Serious infections

Serious infections such as sepsis or pneumonia (including fatal outcomes) have been reported in patients treated with Padcev. Patients should be carefully monitored during treatment for the emergence of possible serious infections.

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 studies. 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 6 months after stopping treatment. Men being treated with enfortumab vedotin are advised not to father a child during treatment and for at least 4 months following the last dose of Padcev.

Patient information pack

The prescriber must discuss the risks of Padcev therapy, including combination therapy with pembrolizumab, with the patient. The patient should be provided with the patient information leaflet and patient card with each prescription.

## 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 6 months after stopping treatment. Men being treated with enfortumab vedotin are advised not to father a child during treatment and for at least 4 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

*Enfortumab vedotin as monotherapy*

The safety of enfortumab vedotin was evaluated as monotherapy in 793 patients who received at least one dose of enfortumab vedotin 1.25 mg/kg in two phase 1 studies (EV-101 and EV-102), three phase 2 studies (EV-103, EV-201 and EV-203) and one phase 3 study (EV-301) (see Table 3). Patients were exposed to enfortumab vedotin for a median duration of 4.7 months (range: 0.3 to 55.7 months).

The most common adverse reactions with enfortumab vedotin were alopecia (47.7%), decreased appetite (47.2%), fatigue (46.8%), diarrhoea (39.1%), peripheral sensory neuropathy (38.5%), nausea (37.8%), pruritus (33.4%), dysgeusia (30.4%), anaemia (29.1%), weight decreased (25.2%), rash maculo-papular (23.6%), dry skin (21.8%), vomiting (18.7%), aspartate aminotransferase increased (17%), hyperglycaemia (14.9%), dry eye (12.7%), alanine aminotransferase increased (12.7%) and rash (11.6%).

The most common serious adverse reactions (≥2%) were diarrhoea (2.1%) and hyperglycaemia (2.1%). Twenty-one percent of patients permanently discontinued enfortumab vedotin for adverse reactions; the most common adverse reaction (≥2%) leading to dose discontinuation was peripheral sensory neuropathy (4.8%). Adverse reactions leading to dose interruption occurred in 62% of patients; the most common adverse reactions (≥2%) leading to dose interruption were peripheral sensory neuropathy (14.8%), fatigue (7.4%), rash maculo-papular (4%), aspartate aminotransferase increased (3.4%), alanine aminotransferase increased (3.2%), anaemia (3.2%), hyperglycaemia (3.2%), neutrophil count decreased (3%), diarrhoea (2.8%), rash (2.4%) and peripheral motor neuropathy (2.1%). Thirty-eight percent of patients required a dose reduction due to an adverse reaction; the most common adverse reactions (≥2%) leading to a dose reduction were peripheral sensory neuropathy (10.3%), fatigue (5.3%), rash maculo-papular (4.2%) and decreased appetite (2.1%).

*Enfortumab vedotin in combination with pembrolizumab*

When enfortumab vedotin is administered in combination with pembrolizumab, refer to the SmPC for pembrolizumab prior to initiation of treatment.

The safety of enfortumab vedotin was evaluated in combination with pembrolizumab in 564 patients who received at least one dose of enfortumab vedotin 1.25 mg/kg in combination with pembrolizumab in one phase 2 study (EV-103) and one phase 3 study (EV-302) (see Table 3). Patients were exposed to enfortumab vedotin in combination with pembrolizumab for a median duration of 9.4 months (range: 0.3 to 34.4 months).

The most common adverse reactions with enfortumab vedotin in combination with pembrolizumab were peripheral sensory neuropathy (53.4%), pruritus (41.1%), fatigue (40.4%), diarrhoea (39.2%), alopecia (38.5%), rash maculo-papular (36%), weight decreased (36%), decreased appetite (33.9%), nausea (28.4%), anaemia (25.7%), dysgeusia (24.3%), dry skin (18.1%), alanine aminotransferase increased (16.8%), hyperglycaemia (16.7%), aspartate aminotransferase increased (15.4%), dry eye (14.4%), vomiting (13.3%), rash macular (11.3%), hypothyroidism (10.5%) and neutropenia (10.1%).

The most common serious adverse reactions (≥2%) were diarrhoea (3%) and pneumonitis (2.3%). Thirty-six percent of patients permanently discontinued enfortumab vedotin for adverse reactions; the most common adverse reactions (≥2%) leading to discontinuation were peripheral sensory neuropathy (12.2%) and rash maculo-papular (2%).

Adverse reactions leading to dose interruption of enfortumab vedotin occurred in 72% of patients. The most common adverse reactions (≥2%) leading to dose interruption were peripheral sensory neuropathy (17%), rash maculo-papular (6.9%), diarrhoea (4.8%), fatigue (3.7%), pneumonitis (3.7%), hyperglycaemia (3.4%), neutropenia (3.2%), alanine aminotransferase increased (3%), pruritus (2.3%) and anaemia (2%).

Adverse reactions leading to dose reduction of enfortumab vedotin occurred in 42.4% of patients. The most common adverse reactions (≥2%) leading to dose reduction were peripheral sensory neuropathy (9.9%), rash maculo-papular (6.4%), fatigue (3.2%), diarrhoea (2.3%) and neutropenia (2.1%).

Tabulated summary of adverse reactions

Adverse reactions observed during clinical studies of enfortumab vedotin as monotherapy or in combination with pembrolizumab, or reported from post-marketing use of enfortumab vedotin 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). Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

**Table 3. Adverse reactions in patients treated with enfortumab vedotin**

| | **Monotherapy** | **In combination with pembrolizumab** |
|---|---|---|
| **Infections and infestations** | | |
| Common | Sepsis, pneumonia | Sepsis, pneumonia |
| **Blood and lymphatic system disorders** | | |
| Very common | Anaemia | Anaemia |
| Common | Thrombocytopenia | Thrombocytopenia |
| Not known[1] | Neutropenia, febrile neutropenia, neutrophil count decreased | Neutropenia, febrile neutropenia, neutrophil count decreased |
| **Endocrine disorders** | | |
| Very common | | Hypothyroidism |
| **Metabolism and nutrition disorders** | | |
| Very common | Hyperglycaemia, decreased appetite | Hyperglycaemia, decreased appetite |
| Not known[1] | Diabetic ketoacidosis | Diabetic ketoacidosis |
| **Nervous system disorders** | | |
| Very common | Peripheral sensory neuropathy, dysgeusia | Peripheral sensory neuropathy, dysgeusia |
| Common | Neuropathy peripheral, peripheral motor neuropathy, peripheral sensorimotor neuropathy, paraesthesia, hypoaesthesia, gait disturbance, muscular weakness | 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 | Neurotoxicity, dysaesthesia, myasthenia gravis, neuralgia, peroneal nerve palsy, skin burning sensation |
| **Eye disorders** | | |
| Very common | Dry eye | Dry eye |
| **Respiratory, thoracic, and mediastinal disorders** | | |
| Very common | | Pneumonitis/ILD[2] |
| Common | Pneumonitis/ILD[2] | |
| **Gastrointestinal disorders** | | |
| Very common | Diarrhoea, vomiting, nausea | Diarrhoea, vomiting, nausea |

| | Monotherapy | In combination with pembrolizumab |
|---|---|---|
| **Skin and subcutaneous tissue disorders** | | |
| Very common | Alopecia, pruritus, rash, rash maculo-papular, dry skin | Alopecia, pruritus, rash maculo-papular, dry skin, rash macular |
| Common | Drug eruption, skin exfoliation, conjunctivitis, dermatitis bullous, blister, stomatitis, palmar-plantar erythrodysesthesia syndrome, eczema, erythaema, rash erythaematous, rash macular, rash papular, rash pruritic, rash vesicular | Rash, skin exfoliation, conjunctivitis, dermatitis bullous, blister, stomatitis, palmar-plantar erythrodysesthesia syndrome, eczema, erythaema, rash erythaematous, rash papular, rash pruritic, rash vesicular, erythaema multiforme, dermatitis |
| Uncommon | Dermatitis exfoliative generalised, erythaema multiforme, exfoliative rash, pemphigoid, rash maculovesicular, dermatitis, dermatitis allergic, dermatitis contact, intertrigo, skin irritation, stasis dermatitis, blood blister | Drug eruption, dermatitis exfoliative generalised, exfoliative rash, pemphigoid, dermatitis contact, intertrigo, skin irritation, stasis dermatitis |
| Not known[1] | Toxic epidermal necrolysis, skin hyperpigmentation, skin discoloration, pigmentation disorder, Stevens-Johnson syndrome, epidermal necrosis, symmetrical drug-related intertriginous and flexural exanthaema | Toxic epidermal necrolysis, skin hyperpigmentation, skin discoloration, pigmentation disorder, Stevens-Johnson syndrome, epidermal necrosis, symmetrical drug-related intertriginous and flexural exanthaema |
| **Musculoskeletal and connective tissue disorders** | | |
| Common | | Myositis |
| **General disorders and administration site conditions** | | |
| Very common | Fatigue | Fatigue |
| Common | Infusion site extravasation | Infusion site extravasation |
| **Investigations** | | |
| Very common | Alanine aminotransferase increased, aspartate aminotransferase increased, weight decreased | Alanine aminotransferase increased, aspartate aminotransferase increased, weight decreased |
| Common | | Lipase increased |
| **Injury, poisoning and procedural complications** | | |
| Common | Infusion related reaction | Infusion related reaction |

[1]Based on global post-marketing experience.

[2]Includes: acute respiratory distress syndrome, autoimmune lung disease, immune-mediated lung disease, interstitial lung disease, lung opacity, organising pneumonia, pneumonitis, pulmonary fibrosis, pulmonary toxicity and sarcoidosis.

Description of selected adverse reactions

*Immunogenicity*

A total of 697 patients were tested for immunogenicity to enfortumab vedotin 1.25 mg/kg as monotherapy; 16 patients were confirmed to be positive at baseline for anti-drug antibody (ADA), and in patients that were negative at baseline (N=681), a total of 24 (3.5%) were positive post baseline.

A total of 490 patients were tested for immunogenicity against enfortumab vedotin following enfortumab vedotin in combination with pembrolizumab; 24 patients were confirmed to be positive at baseline for ADA, and in patients that were negative at baseline (N=466), a total of 14 (3%) were positive post baseline. The incidence of treatment-emergent anti-enfortumab vedotin antibody formation was consistent when assessed following enfortumab vedotin administration as monotherapy and in combination with pembrolizumab.

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 of enfortumab vedotin as monotherapy, skin reactions occurred in 57% (452) of the 793 patients treated with enfortumab vedotin 1.25 mg/kg. Severe (Grade 3 or 4) skin reactions occurred in 14% (108) of patients and a majority of these reactions included rash maculo-papular, stomatitis, rash erythematous, rash or drug eruption. The median time to onset of severe skin reactions was 0.7 months (range: 0.1 to 8.2 months). Serious skin reactions occurred in 4.3% (34) of patients. Of the patients who experienced skin reactions and had data regarding resolution (N=366), 61% had complete resolution, 24% had partial improvement, and 15% had no improvement at the time of their last evaluation. Of the 39% of patients with residual skin reactions at last evaluation, 38% had Grade ≥2 events.

In clinical studies of enfortumab vedotin in combination with pembrolizumab, skin reactions occurred in 70% (392) of the 564 patients and a majority of these skin reactions included rash maculo-papular, rash macular and rash papular. Severe (Grade 3 or 4) skin reactions occurred in 17% (97) of patients (Grade 3: 16%, Grade 4: 1%). The median time to onset of severe skin reactions was 1.7 months (range: 0.1 to 17.2 months). Of the patients who experienced skin reactions and had data regarding resolution (N=391), 59% had complete resolution, 30% had partial improvement, and 10% had no improvement at the time of their last evaluation. Of the 41% of patients with residual skin reactions at last evaluation, 27% had Grade ≥2 events.

*Pneumonitis/ILD*

In clinical studies of enfortumab vedotin as monotherapy, pneumonitis/ILD occurred in 26 (3.3%) of the 793 patients treated with enfortumab vedotin 1.25 mg/kg. Less than 1% of patients experienced severe (Grade 3 or 4) pneumonitis/ILD (Grade 3: 0.5%, Grade 4: 0.3%). Pneumonitis/ILD led to discontinuation of enfortumab vedotin in 0.5% of patients. There were no deaths from pneumonitis/ILD. The median time to onset of any grade pneumonitis/ILD was 2.7 months (range: 0.6 to 6.0 months) and the median duration for pneumonitis/ILD was 1.6 months (range: 0.1 to

43.0 months). Of the 26 patients who experienced pneumonitis/ILD, 8 (30.8%) had resolution of symptoms.

In clinical studies of enfortumab vedotin in combination with pembrolizumab, pneumonitis/ILD occurred in 58 (10.3%) of the 564 patients. Severe (Grade 3 or 4) pneumonitis/ILD occurred in 20 patients (Grade 3: 3.0%, Grade 4: 0.5%). Pneumonitis/ILD led to discontinuation of enfortumab vedotin in 2.1% of patients. Two patients experienced a fatal event of pneumonitis/ILD. The median time to onset of any grade pneumonitis/ILD was 4 months (range: 0.3 to 26.2 months).

*Hyperglycaemia*

In clinical studies of enfortumab vedotin as monotherapy, hyperglycaemia (blood glucose >13.9 mmol/L) occurred in 17% (133) of the 793 patients treated with enfortumab vedotin 1.25 mg/kg. Serious events of hyperglycaemia occurred in 2.5% of patients, 7% of patients developed severe (Grade 3 or 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 hyperglycaemia was 0.5 months (range: 0 to 20.3). Of the patients who experienced hyperglycaemia and had data regarding resolution (N=106), 66% had complete resolution, 19% had partial improvement, and 15% had no improvement at the time of their last evaluation. Of the 34% of patients with residual hyperglycaemia at last evaluation, 64% had Grade ≥2 events.

*Peripheral neuropathy*

In clinical studies of enfortumab vedotin as monotherapy, peripheral neuropathy occurred in 53% (422) of the 793 patients treated with enfortumab vedotin 1.25 mg/kg. Five percent of patients experienced severe (Grade 3 or 4) peripheral neuropathy including sensory and motor events. The median time to onset of Grade ≥2 peripheral neuropathy was 5 months (range: 0.1 to 20.2). Of the patients who experienced neuropathy and had data regarding resolution (N=340), 14% had complete resolution, 46% had partial improvement, and 41% had no improvement at the time of their last evaluation. Of the 86% of patients with residual neuropathy at last evaluation, 51% had Grade ≥2 events.

*Ocular disorders*

In clinical studies of enfortumab vedotin as monotherapy, 30% of patients experienced dry eye during treatment with enfortumab vedotin 1.25 mg/kg. Treatment was interrupted in 1.5% 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 30.6 months).

Special populations

*Elderly*

Enfortumab vedotin in combination with pembrolizumab has been studied in 173 patients <65 years and 391 patients ≥65 years. Generally, adverse event frequencies were higher in patients ≥65 years of age compared to <65 years of age, particularly for serious adverse events (56.3%, and 35.3%,

respectively) and Grade ≥3 events (80.3% and 64.2%, respectively), similar to observations with the chemotherapy comparator.

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, apoptosis, and immunogenic cell death. MMAE released from enfortumab vedotin targeted cells can diffuse into nearby Nectin-4 low-expressing cells resulting in cytotoxic cell death. Combination of enfortumab vedotin with PD-1 inhibitors results in enhanced anti-tumour activity, consistent with the complementary mechanisms of MMAE induced cell cytotoxicity and induction of immunogenic cell death, plus the up-regulation of immune function by PD-1 inhibition.

*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

*Enfortumab vedotin in combination with pembrolizumab*

Previously untreated locally advanced or metastatic urothelial cancer

*EV-302 (KEYNOTE-A39)*

The efficacy of Padcev in combination with pembrolizumab was evaluated in study EV-302 (KEYNOTE-A39), an open-label, randomised, phase 3, multicentre study that enrolled 886 patients with unresectable or metastatic urothelial cancer who had not received prior systemic therapy for locally advanced or metastatic disease. Patients that received neoadjuvant chemotherapy or patients that received adjuvant chemotherapy following cystectomy were included in the study if recurrence was >12 months from completion of therapy. Patients were considered cisplatin-ineligible if they had at least one of the following criteria: glomerular filtration rate (GFR) between 30-59 mL/min, Eastern Cooperative Oncology Group (ECOG) performance status ≥2, Grade ≥2 hearing loss or New York Heart Association (NYHA) Class III heart failure.

Patients were randomised 1:1 to receive either enfortumab vedotin in combination with pembrolizumab (arm A) or gemcitabine and platinum-based chemotherapy (cisplatin or carboplatin) (arm B). Patients in arm A received enfortumab vedotin 1.25 mg/kg as an intravenous infusion over 30 minutes on Days 1 and 8 of a 21-day cycle followed by pembrolizumab 200 mg on Day 1 of a 21-day cycle approximately 30 minutes after enfortumab vedotin. Patients in arm B received gemcitabine 1000 mg/m$^2$ administered on Days 1 and 8 of a 21-day cycle with cisplatin 70 mg/m$^2$ or carboplatin (AUC = 4.5 or 5 mg/mL/min according to local guidelines) administered on Day 1 of a 21-day cycle. Treatment was continued until disease progression, unacceptable toxicity or completion of the maximum number of treatment cycles (chemotherapy, 6 cycles; pembrolizumab, 35 cycles; enfortumab vedotin, no set maximum).

Patients randomised to the gemcitabine and platinum-based chemotherapy arm were permitted to receive maintenance immunotherapy (e.g., avelumab). Randomisation was stratified by cisplatin eligibility (eligible versus ineligible), PD-L1 expression (CPS≥10 versus CPS<10), and presence of liver metastases (present versus absent). PD-L1 expression was based on the PD-L1 IHC 22C3 pharmDx kit.

Patients were excluded from the study if they had active CNS metastases, ongoing sensory or motor neuropathy Grade ≥2, uncontrolled diabetes defined as haemoglobin A1C (HbA1c) ≥8% or HbA1c ≥7% with associated diabetes symptoms, autoimmune disease or a medical condition that required immunosuppression, pneumonitis or other forms of interstitial lung disease.

The median age was 69 years (range: 22 to 91); 77% were male; and most were White (67%) or Asian (22%). Patients had a baseline ECOG performance status of 0 (49%), 1 (47%) or 2 (3%). Forty-seven percent of patients had a documented baseline HbA1c of <5.7%. At baseline, 95% of patients had metastatic urothelial cancer and 5% of patients had unresectable urothelial cancer. Seventy-two percent of patients had visceral metastasis at baseline including 22% with liver metastases. Eighty-five percent of patients had urothelial carcinoma (UC) histology, 6% had UC mixed squamous differentiation and 2% had UC mixed other histologic variants. Forty-six percent of patients were cisplatin-ineligible and 54% were cisplatin-eligible at time of randomisation. Of the 877 patients tested who had tissue evaluable for PD-L1 expression, 58% of patients had tumours that expressed PD-L1 with a CPS ≥10 and 42% had tumours that expressed PD-L1 with a CPS <10. The median follow-up time was 17.3 months (range: 0.3 to 37.2).

The primary efficacy outcome measures were Overall Survival (OS) and Progression Free Survival (PFS) as assessed by BICR according to RECIST v1.1. Secondary efficacy outcome measures included Objective Response Rate (ORR) as assessed by BICR according to RECIST v1.1.

The study showed statistically significant improvements in OS, PFS and ORR for patients randomised to enfortumab vedotin in combination with pembrolizumab as compared to gemcitabine and platinum-based chemotherapy.

Table 4, Figures 1 and 2 summarise the efficacy results for EV-302.

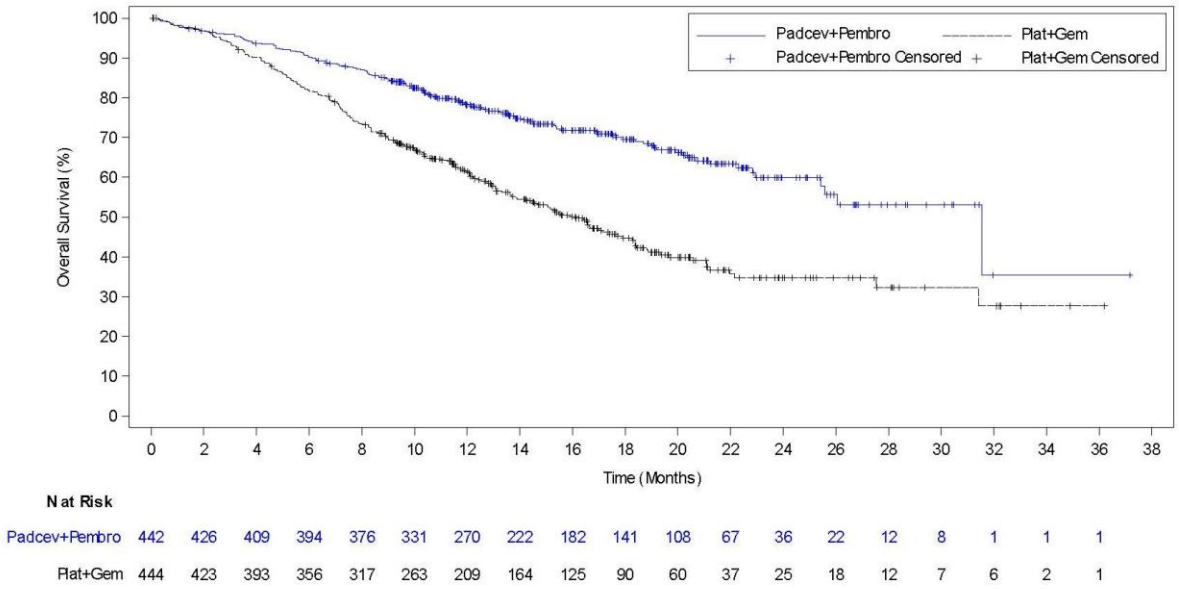
**Table 4. Efficacy Results in EV-302**

| Endpoint | Padcev + pembrolizumab n=442 | Gemcitabine +platinum n=444 |
|---|---|---|
| **Overall Survival** | | |
| Number (%) of patients with events | 133 (30.1) | 226 (50.9) |
| Median in months (95% CI)[a] | 31.5 (25.4, -) | 16.1 (13.9, 18.3) |
| Hazard ratio[b] (95% CI) | 0.468 (0.376, 0.582) | |
| 2-sided p-value[c] | <0.00001 | |
| **Progression Free Survival**[d] | | |
| Number (%) of patients with events | 223 (50.5) | 307 (69.1) |
| Median in months (95% CI)[a] | 12.5 (10.4, 16.6) | 6.3 (6.2, 6.5) |
| Hazard ratio[b] (95% CI) | 0.450 (0.377, 0.538) | |
| 2-sided p-value[c] | <0.00001 | |
| **Objective Response Rate (CR + PR)**[d,f] | | |
| Confirmed ORR (%) (95% CI)[e] | 67.7 (63.1, 72.1) | 44.4 (39.7, 49.2) |
| 2-sided p-value[g] | <0.00001 | |
| **Duration of Response**[d,f] | | |
| Median in months (95% CI)[a] | NR (20.2, -) | 7.0 (6.2, 10.2) |

NR = Not reached.

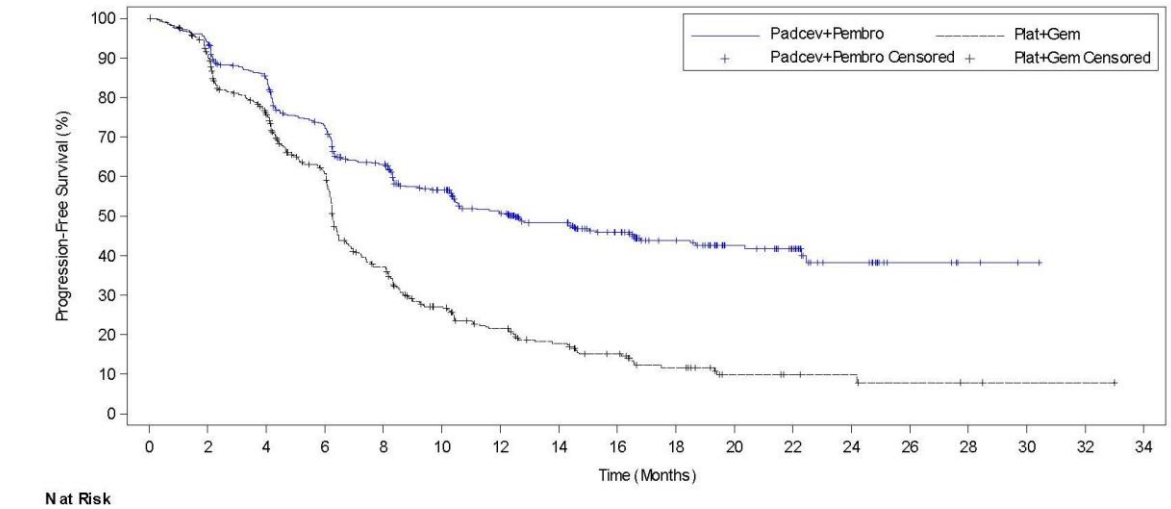
a. Based on the complementary log-log transformation method (Collett, 1994).
b. Based on stratified Cox proportional hazards model. A hazard ratio <1 favors the enfortumab vedotin in combination with pembrolizumab arm.
c. Based on stratified log-rank test.
d. Evaluated by BICR using RECIST v1.1.
e. Based on the Clopper-Pearson method (Clopper 1934).
f. Includes only patients with measurable disease at baseline (n=437 for enfortumab vedotin in combination with pembrolizumab, n=441 for gemcitabine plus platinum). The duration of response was estimated for responders.
g. Based on Cochran-Mantel-Haenszel test stratified by PD-L1 expression, cisplatin eligibility and liver metastases.

**Figure 1. Kaplan Meier plot of overall survival, EV-302**




| N at Risk | | | | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Padcev+Pembro | 442 | 426 | 409 | 394 | 376 | 331 | 270 | 222 | 182 | 141 | 108 | 67 | 36 | 22 | 12 | 8 | 1 | 1 | 1 |
| Plat+Gem | 444 | 423 | 393 | 356 | 317 | 263 | 209 | 164 | 125 | 90 | 60 | 37 | 25 | 18 | 12 | 7 | 6 | 2 | 1 |

**Figure 2. Kaplan Meier plot of progression-free survival, EV-302**




| N at Risk | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Padcev+Pembro | 442 | 409 | 361 | 303 | 253 | 204 | 167 | 132 | 102 | 73 | 45 | 33 | 17 | 6 | 3 | 1 |
| Plat+Gem | 444 | 380 | 297 | 213 | 124 | 78 | 56 | 41 | 30 | 19 | 8 | 6 | 5 | 3 | 2 | 1 | 1 |

*Enfortumab vedotin as monotherapy*

Previously treated locally advanced or metastatic urothelial cancer

*EV-301*

The efficacy of Padcev as monotherapy 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/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, known history of human immunodeficiency virus (HIV) infection (HIV 1 or 2), active Hepatitis B or C, 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 ECOG 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 ≥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 5 summarises 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 5. 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) |

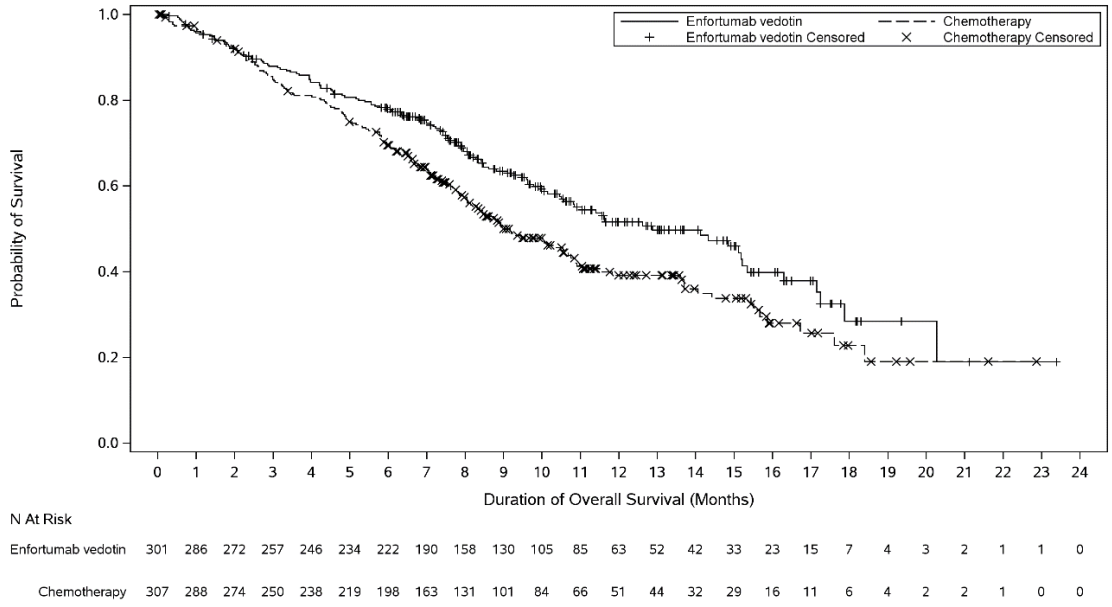
*pre-determined efficacy boundary = 0.00679, 1-sided (adjusted by observed deaths of 301)

†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 3. Kaplan Meier plot of overall survival, EV-301**




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 unconjugated MMAE to human plasma proteins ranged from 68% to 82%. Unconjugated MMAE is not likely to displace or to be displaced by highly protein-bound medicinal products. *In vitro* studies indicate that unconjugated MMAE is a substrate of P-glycoprotein.

Biotransformation

A small fraction of unconjugated MMAE released from enfortumab vedotin is metabolised. *In vitro* data indicate that the metabolism of unconjugated 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 unconjugated MMAE appeared to be limited by its rate of release from enfortumab vedotin. Unconjugated MMAE elimination exhibited a multi-exponential decline with a half-life of 2.6 days.

Excretion

The excretion of unconjugated MMAE occurs mainly in faeces with a smaller proportion in urine. After a single dose of another ADC that contained unconjugated MMAE, approximately 24% of the total unconjugated MMAE administered was recovered in faeces and urine as unchanged unconjugated MMAE over a 1-week period. The majority of recovered unconjugated MMAE was excreted in faeces (72%). A similar excretion profile is expected for unconjugated 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), moderate (CrCL 30-60 mL/min) and severe (CrCL 15–<30 mL/min) 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% and 16% increase in unconjugated MMAE average concentrations in patients with previously treated and previously untreated locally advanced or metastatic urothelial cancer, respectively, with mild hepatic impairment (total bilirubin of 1 to 1.5 × ULN and AST any, or total bilirubin ≤ ULN and AST > ULN) compared to patients with normal hepatic function. Enfortumab vedotin has only been studied in a limited number of patients with moderate hepatic impairment (n=5) or severe hepatic impairment (n=1). 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 unconjugated 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 unconjugated MMAE inhibits CYP3A4/5 but not other CYP450 isoforms. Unconjugated MMAE did not induce major CYP450 enzymes in human hepatocytes.

*In vitro studies*

*In vitro* studies indicate that unconjugated MMAE is a substrate and not an inhibitor of the efflux transporter P-glycoprotein (P-gp). *In vitro* studies determined that unconjugated 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). Unconjugated 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 sternebrae, 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.

No dedicated preclinical safety studies were conducted with enfortumab vedotin in combination with pembrolizumab.

## 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
4 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 (2ºC to 8ºC).
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. Do not expose to direct sunlight.
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 either 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. Do not expose to direct sunlight.
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(S)

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 https://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(s) of the biological active substance

Lonza AG
Lonzastrasse
Visp, 3930
Switzerland

Name and address of the manufacturer(s) 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 exanthaema).**

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 $\leq$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

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 alone or in combination with pembrolizumab 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 when used alone is given to people that have received an immunotherapy medicine and also received a chemotherapy-containing platinum medicine.

This medicine may be given in combination with pembrolizumab. It is important that you also read the package leaflet for this other medicine. If you have any questions, ask your doctor.

## 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. Skin reactions may occur in more patients when this medicine is given with pembrolizumab. 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. These lung problems may occur more often when this medicine is given with pembrolizumab. 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, or think you have, an infection. Some infections may be serious and can be life threatening.

– 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 6 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 at least 4 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**

When used alone, the recommended dose of this medicine is 1.25 mg/kg on days 1, 8 and 15 every 28 days. When used with pembrolizumab, the recommended dose of this medicine is 1.25 mg/kg on days 1 and 8 every 21 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 exanthaema).** 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).

- **A serious complication of diabetes with high levels of ketones in the blood that can make blood more acidic (diabetic ketoacidosis)** (frequency not known).

- **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, sensimotor 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).

- **Serious infection (sepsis) when bacteria and their toxins circulate in the blood leading to organ damage** (may affect up to 1 in 10 people).

- **Infection of the lungs (pneumonia)** (may affect up to 1 in 10 people).

- **Infusion related reaction**
  Medicines of this type (monoclonal antibodies) can cause infusion related reactions such as:
  - low blood pressure
  - tongue swelling
  - difficulty breathing (dyspnoea)
  - fever
  - chills
  - redding of the skin (flushing)
  - itching
  - rash
  - being sick (vomiting)
  - feeling generally unwell (malaise)

- In general, these types of reactions occur within minutes to several hours following completion of the infusion. However, they may develop more than several hours after completion of the infusion but this is uncommon. Infusion-related reactions may affect up to 1 in 10 people.

**Other possible side effects**

The following side effects have been reported with Padcev alone:

**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
- low levels of blood platelets which can lead to bleeding and bruising (thrombocytopenia)

**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

**Not known (frequency cannot be estimated from the available data):**

- low white blood cell count with or without fever
- discoloration or abnormal darkening of the skin (skin hyperpigmentation, skin discoloration, pigmentation disorder)

The following side effects have been reported with Padcev in combination with pembrolizumab:

**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
- flat or red raised bumps on the skin
- increased liver enzymes (aspartate aminotransferase [AST] or alanine aminotransferase [ALT])
- reduced thyroid gland activity (hypothyroidism)

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

- abnormal walking (gait disturbance)
- eye redness
- hives on the skin
- redness in the skin
- rash
- 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: spots that look like bullseyes, itchiness, redness, red bumps or red patches on the skin, fluid-filled blisters, large blisters, skin lesions
- increased lipase (a blood test done to check your pancreas)
- inflammation of the muscles (myositis)
- low levels of blood platelets which can lead to bleeding and bruising (thrombocytopenia)

**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
- allergic reaction to skin
- rash with accompanying symptoms: 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

**Not known (frequency cannot be estimated from the available data):**

- low white blood cell count with or without fever
- discoloration or abnormal darkening of the skin (skin hyperpigmentation, skin discoloration, pigmentation disorder)

**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 (2ºC to 8ºC). 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

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

**Česká republika**
Astellas Pharma s.r.o.
Tel: +420 221 401 500

**Danmark**
Astellas Pharma a/s
Tlf: +45 43 430355

**Deutschland**
Astellas Pharma GmbH
Tel.: +49 (0)89 454401

**Eesti**
Astellas Pharma d.o.o.
Tel: +372 6 056 014

**Ελλάδα**
Astellas Pharmaceuticals AEBE
Τηλ: +30 210 8189900

**España**
Astellas Pharma S.A.
Tel: +34 91 4952700

**France**
Astellas Pharma S.A.S.
Tél: +33 (0)1 55917500

**Hrvatska**
Astellas d.o.o
Tel: +385 1670 0102

**Ireland**
Astellas Pharma Co. Ltd.
Tel: +353 (0)1 4671555

**Ísland**
Vistor hf
Sími: +354 535 7000

**Italia**
Astellas Pharma S.p.A.
Tel: +39 (0)2 921381

**Lietuva**
Astellas Pharma d.o.o.
Tel.: +370 37 408 681

**Luxembourg/Luxemburg**
Astellas Pharma B.V. Branch
Belgique/Belgien
Tél/Tel: +32 (0)2 5580710

**Magyarország**
Astellas Pharma Kft.
Tel.: +36 1 577 8200

**Malta**
Astellas Pharmaceuticals AEBE
Tel: +30 210 8189900

**Nederland**
Astellas Pharma B.V.
Tel: +31 (0)71 5455745

**Norge**
Astellas Pharma
Tlf: +47 66 76 46 00

**Österreich**
Astellas Pharma Ges.m.b.H.
Tel.: +43 (0)1 8772668

**Polska**
Astellas Pharma Sp.z.o.o.
Tel.: +48 225451 111

**Portugal**
Astellas Farma, Lda.
Tel: +351 21 4401300

**România**
S.C. Astellas Pharma SRL
Tel: +40 (0)21 361 04 95

**Slovenija**
Astellas Pharma d.o.o
Tel: +386 14011400

**Slovenská republika**
Astellas Pharma s.r.o.
Tel: +421 2 4444 2157

**Suomi/Finland**
Astellas Pharma
Puh/Tel: +358 (0)9 85606000

**Κύπρος**
Ελλάδα
Astellas Pharmaceuticals AEBE
Τηλ: +30 210 8189900

**Latvija**
Astellas Pharma d.o.o.
Tel: +371 67 619365

**Sverige**
Astellas Pharma AB
Tel: +46 (0)40-650 15 00

**United Kingdom (Northern Ireland)**
Astellas Pharma Co., Limited
Tel: +353 (0)1 4671555
Free call from Northern Ireland: 0800783 5018

**This leaflet was last revised in MM/YYYY**

**Other sources of information**

Detailed information on this medicine is available on the European Medicines Agency web site: https://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 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. Do not expose to direct sunlight.
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 either 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. Do not expose to direct sunlight.
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.

# ANNEX IV

# SCIENTIFIC CONCLUSIONS AND GROUNDS FOR THE VARIATION TO THE TERMS OF THE MARKETING AUTHORISATION(S)

**Scientific conclusions**

Taking into account the PRAC Assessment Report on the PSUR(s) for enfortumab vedotin, the scientific conclusions of PRAC are as follows:

In view of available data on pneumonia from clinical trials and from spontaneous reports including in some cases a close temporal relationship and a positive de-challenge the PRAC considers a causal relationship between enfortumab vedotin and pneumonia is at least a reasonable possibility. The PRAC concluded that the product information of products containing enfortumab vedotin should be amended accordingly.

In view of available data on thrombocytopenia from clinical trials and from spontaneous reports including in some cases a close temporal relationship and a positive de-challenge the PRAC considers a causal relationship between enfortumab vedotin and thrombocytopenia is at least a reasonable possibility. The PRAC concluded that the product information of products containing enfortumab vedotin should be amended accordingly.

Having reviewed the PRAC recommendation, the CHMP agrees with the PRAC overall conclusions and grounds for recommendation.

**Grounds for the variation to the terms of the marketing authorisation(s)**

On the basis of the scientific conclusions for enfortumab vedotin the CHMP is of the opinion that the benefit-risk balance of the medicinal product(s) containing enfortumab vedotin is unchanged subject to the proposed changes to the product information.

The CHMP recommends that the terms of the marketing authorisation(s) should be varied.