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 30 mg powder for concentrate for solution for infusion

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

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 Grade 2 with fever Grade 3	• Withhold until Grade ≤1 • Referral to specialised care should be

Table 2. Dose interruption, reduction and discontinuation of enfortumab vedotin in patients with locally advanced or metastatic urothelial cancer

Adverse reaction	Severity*	Dose modification*
		considered • Resume at the same dose level or consider dose reduction by one dose level (see Table 1)
Hyperglycaemia	Blood glucose >13.9 mmol/L (>250 mg/dL)	• Withhold until elevated blood glucose has improved to ≤13.9 mmol/L (≤250 mg/dL) • Resume treatment at the same dose level
Pneumonitis/interstitial lung disease (ILD)	Grade 2	• 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 • For first occurrence, resume treatment at the same dose level • For a recurrence, withhold until Grade ≤1, then resume treatment reduced by one dose level (see Table 1)
	Grade ≥3	Permanently discontinue.

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

Special populations

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

Renal impairment
No dose adjustment is necessary in patients with mild [creatinine clearance (CrCL) >60-90 mL/min], moderate (CrCL 30–60 mL/min) or severe (CrCL 15–

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

Hepatic impairment
No dose adjustment is necessary in patients with mild hepatic impairment [total bilirubin of 1 to 1.5 × 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 (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 pre-existing 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 12 months after stopping treatment. Men being treated with enfortumab vedotin are advised not to father a child during treatment and for up to 9 months following the last dose of Padcev.

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) modelling, concomitant use of enfortumab vedotin with ketoconazole (a combined P-gp and strong CYP3A inhibitor) is predicted to increase unconjugated MMAE C_{max} and AUC exposure to a minor extent, with no change in ADC exposure. Caution is advised in case of concomitant treatment with CYP3A4 inhibitors. Patients receiving concomitant strong CYP3A4 inhibitors (e.g. boceprevir, clarithromycin, cobicistat, indinavir, itraconazole, nefazodone, nelfinavir, posaconazole, ritonavir, saquinavir, telaprevir, telithromycin, voriconazole) should be monitored more closely for signs of toxicities. Unconjugated MMAE is not predicted to alter the AUC of concomitant medicines that are CYP3A4 substrates (e.g. midazolam).
Strong CYP3A4 inducers (e.g. rifampicin, carbamazepine, phenobarbital, phenytoin, St John's wort [*Hypericum perforatum*]) may decrease the exposure of unconjugated MMAE with moderate effect (see section 5.2).

4.6 Fertility, pregnancy and lactation

Women of childbearing potential/ Contraception in males and females

Pregnancy testing is recommended for females of reproductive potential within 7 days prior to initiating treatment. Females of reproductive potential should be advised to use effective contraception during treatment and for at least 12 months after stopping treatment. Men being treated with enfortumab vedotin are advised not to father a child during treatment and for up to 9 months following the last dose of Padcev.

Pregnancy

Padcev can cause foetal harm when administered to pregnant women based upon findings from animal studies. Embryo-foetal development studies in female rats have shown that intravenous administration of enfortumab vedotin resulted in reduced numbers of viable foetuses, reduced litter size, and increased early resorptions (see section 5.3). Padcev is not recommended during pregnancy and in women of childbearing potential not using effective contraception.

Breast-feeding

It is unknown whether enfortumab vedotin is excreted in human milk. A risk to breast-fed children cannot be excluded. Breast-feeding 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	Sepsis
Blood and lymphatic system disorders		
Very common	Anaemia	Anaemia
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
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, Stevens-Johnson syndrome, epidermal necrosis, symmetrical	Toxic epidermal necrolysis, Stevens-Johnson syndrome, epidermal necrosis, symmetrical drug-related intertriginous and flexural exanthaema

	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 Yellow Card Scheme at: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

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.

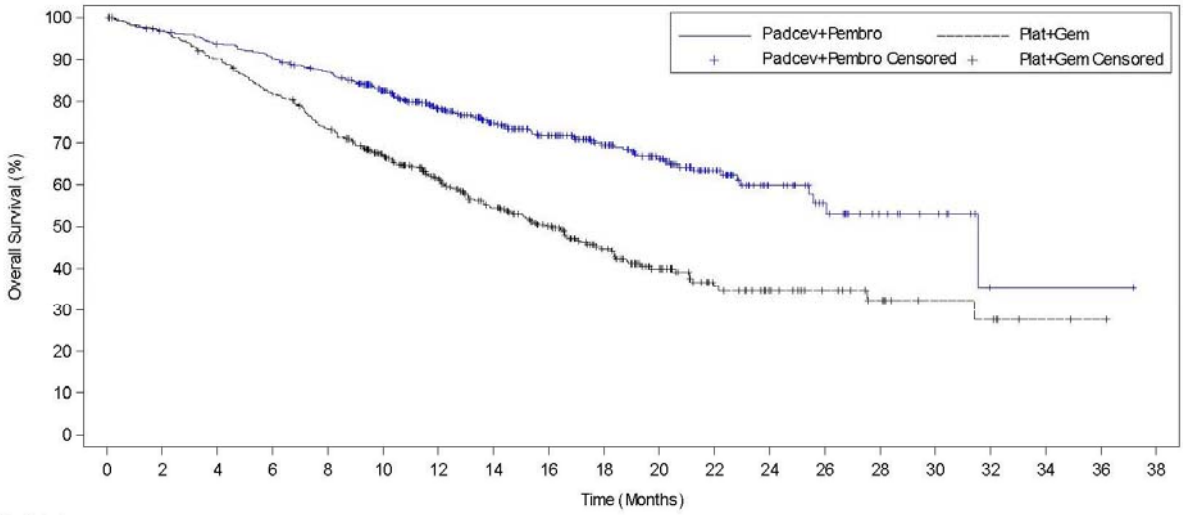
Table 4. Efficacy Results in EV-302

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.

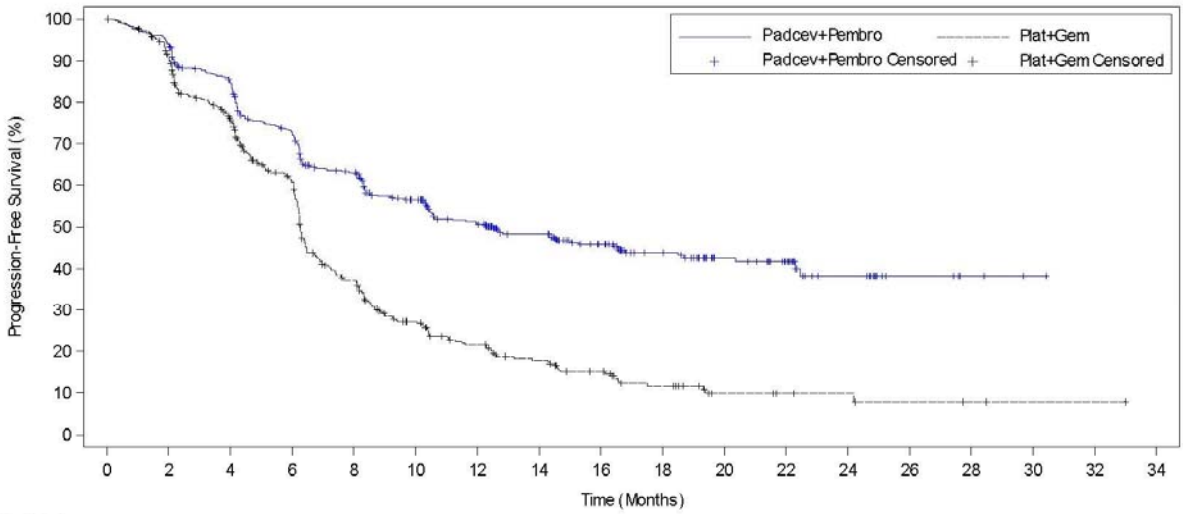
a. Based on the complementary log-log transformation method (Collett, 1994).
b. Based on stratified Cox proportional hazards model. A hazard ratio <1 favors the enfortumab vedotin in combination with pembrolizumab arm.
c. Based on stratified log-rank test.
d. Evaluated by BICR using RECIST v1.1
e. Based 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)

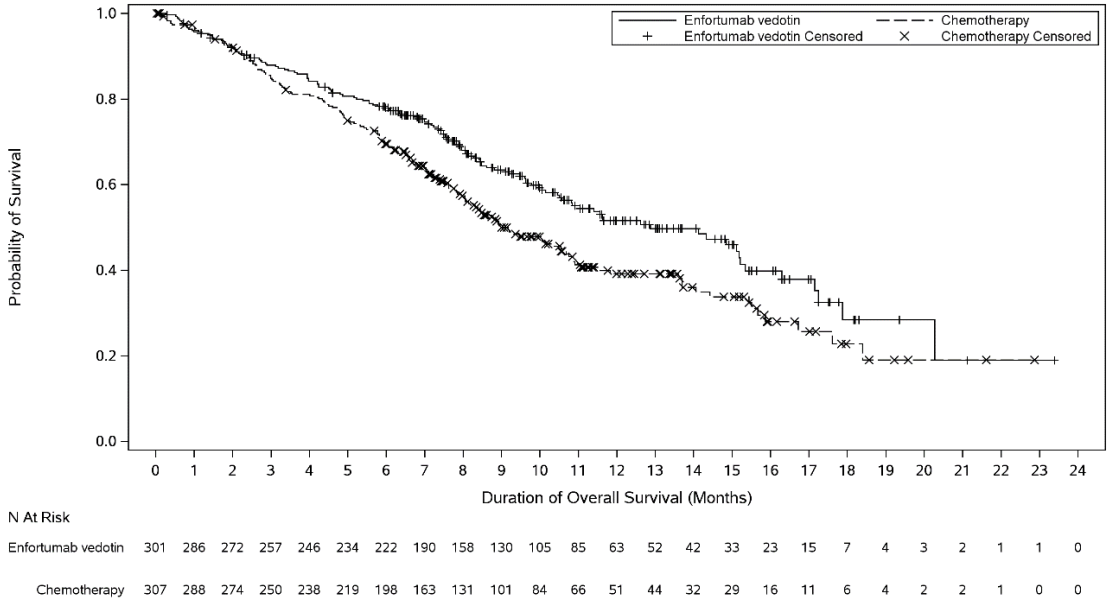
*pre-determined efficacy boundary = 0.00679, 1-sided (adjusted by observed deaths of 301)

†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 Licensing Authority 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

3 years.

Reconstituted solution in the vial

From a microbiological point of view, after reconstitution, the solution from the vial(s) should be added to the infusion bag immediately. If not used immediately, storage times and conditions prior to use of the reconstituted vials are the responsibility of the user and would normally not be longer than 24 hours in refrigeration at 2°C to 8°C. Do not freeze.

Diluted dosing solution in the infusion bag

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

6.4 Special precautions for storage

Unopened vials

Store in a refrigerator (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

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

6.6 Special precautions for disposal

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

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8 MARKETING AUTHORISATION NUMBER(S)

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9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

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10 DATE OF REVISION OF THE TEXT

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