astellas

PADCEV™ 20 mg
PADCEV™ 30 mg

1. NAME OF THE MEDICINAL PRODUCT

Padcev 20 mg
Padcev 30 mg

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each vial contains either 20 mg or 30 mg enfortumab vedotin active ingredient that is reconstituted to a final concentration of 10 mg/mL.

Enfortumab vedotin is an antibody-drug conjugate (ADC) comprised of a Nectin-4 directed, fully human Chinese Hamster Ovary (CHO)-expressed IgG1-kappa monoclonal antibody conjugated to the microtubule-disrupting agent monomethyl auristatin E (MMAE) via a protease-cleavable maleimidocaproyl valine-citrulline (vc) linker.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Padcev is supplied as single-dose vials containing sterile, preservative-free, white to off-white lyophilized powder for reconstitution for intravenous infusion.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Padcev, in combination with pembrolizumab, is indicated for the treatment of adult patients with locally advanced or metastatic urothelial cancer (mUC) who are not eligible for cisplatin-containing chemotherapy.

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

4.2 Posology and method of administration

Treatment with Padcev should be initiated and supervised by a physician experienced in the use of anti-cancer therapies. Ensure good venous access prior to starting treatment (see section 4.4).

Posology

The recommended dose of Padcev as a single agent 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 Padcev 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 a 21-day cycle until disease progression or unacceptable toxicity. Refer to the pembrolizumab Prescribing Information for the recommended dosing information of pembrolizumab.

Refer to Table 1 for Recommended Dose Reduction Schedule for Adverse Events for Padcev.

Table 1. Recommended dose reductions for adverse events

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

Dose Modifications

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

Adverse Reaction	**Severity***	**Dose Modification***
Skin Reactions	Grade 2 worsening, Grade 2 with fever, Grade 3	• Withhold until Grade ≤1 • Referral to specialized care should be considered • Resume at the same dose level or consider dose reduction by one dose level (see Table 1)
	Suspected Stevens-Johnson syndrome (SJS) or toxic epidermal necrolysis (TEN), or bullous lesions	• Immediately withhold and refer to specialized care
	Confirmed SJS or TEN; Grade 4 or recurrent Grade 3	Permanently discontinue.
Hyperglycemia	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	Grade 2	• Withhold until Grade ≤1 • Resume at the same dose level 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 required in patients ≥65 years of age (see section 5.2).

Patients with Renal Impairment

No dose adjustment is required 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 (see section 5.2). Enfortumab vedotin has not been evaluated in patients with end stage renal disease.

Patients with Hepatic Impairment

No dose adjustment is required 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 hepatic impairment and has not been evaluated in patients with severe hepatic impairment (see section 5.2).

Pediatric population
There is no relevant use of enfortumab vedotin in the paediatric population for the indication of locally advanced or metastatic urothelial cancer. The safety and efficacy of enfortumab vedotin in pediatric patients have not been established.

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 Padcev 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 maculopapular, have been reported. The incidence of skin reactions occurred at a higher rate when Padcev was given in combination with pembrolizumab (see section 4.8). Severe cutaneous adverse reactions, including SJS and TEN, with fatal outcome have also occurred in patients treated with Padcev, predominantly during the first cycle of treatment. In clinical trials, the median time to onset of severe skin reactions was 0.7 months (range: 0.1 to 6.4).

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

Hyperglycemia

Hyperglycemia and diabetic ketoacidosis (DKA), including fatal events, occurred in patients with and without pre-existing diabetes mellitus, treated with Padcev (see section 4.8). Hyperglycemia occurred more frequently in patients with pre-existing hyperglycemia or a high body mass index (≥30 kg/m^2). Patients with baseline hemoglobin A1C (HbA1c) ≥8% were excluded from clinical trials. Blood glucose levels should be monitored prior to dosing and periodically throughout the course of treatment as clinically indicated in patients with or at risk for diabetes mellitus or hyperglycemia. 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 sections 4.2 and 5.1).

Pneumonitis/interstitial lung disease

Severe, life-threatening or fatal pneumonitis/interstitial lung disease have occurred in patients receiving Padcev (see section 4.8). Monitor patients for signs and symptoms indicative of pneumonitis/interstitial lung disease such as hypoxia, cough, dyspnea or interstitial infiltrates on radiologic exams. Withhold Padcev for Grade 2 pneumonitis/interstitial lung disease and consider dose reduction. Permanently discontinue Padcev for Grade ≥3 pneumonitis/interstitial lung disease (see section 4.2).

Peripheral neuropathy

Peripheral neuropathy, predominantly peripheral sensory neuropathy, has occurred with Padcev, including Grade ≥3 reactions (see section 4.8). Patients with pre-existing peripheral neuropathy Grade ≥2 were excluded from clinical trials. Monitor patients for symptoms of new or worsening peripheral neuropathy as these patients may require a delay, dose reduction or discontinuation of Padcev (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 Padcev (see section 4.8). Monitor patients for ocular disorders such as dry eye. 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 Padcev 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-fetal toxicity and contraception

Pregnant women should be informed of the potential risk to a fetus (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 Padcev, to use effective contraception during treatment and for at least 12 months after stopping treatment. Men being treated with Padcev are advised not to father a child during treatment and for up to 9 months following the last dose of Padcev.

4.5 Interaction with other medicinal products and other forms of interaction

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

Effects of Other Drugs on enfortumab vedotin

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

4.6 Fertility, pregnancy and lactation

Women of childbearing potential/ Contraception in males and females

Pregnancy testing is recommended for females of reproductive potential within 7 days prior to initiating treatment. Females of reproductive potential should be advised to use effective contraception during treatment and for at least 12 months after stopping treatment. Men being treated with Padcev 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 fetal harm when administered to pregnant women based upon findings from animal studies. Embryo-fetal development studies in female rats have shown that intravenous administration of enfortumab vedotin resulted in reduced numbers of viable fetuses, 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

Padcev as a single agent

The most common adverse reactions with Padcev were alopecia (48.3%), fatigue (47.5%), decreased appetite (46.1%), peripheral sensory neuropathy (40.1%), diarrhea (38.4%), nausea (37.1%), pruritus (33.3%), dysgeusia (30.7%), anemia (26.6%), weight decreased (25.0%), rash maculo-papular (24.0%), dry skin (22.4%), vomiting (18.1%), aspartate aminotransferase increased (14.3%), hyperglycemia (13.0%), dry eye (12.9%), alanine aminotransferase increased (11.0%) and rash (10.0%).

The most common serious adverse reactions were diarrhea (2%) and hyperglycemia (2%). Twenty percent of patients permanently discontinued Padcev for adverse events; the most common adverse reaction (≥2%) leading to dose discontinuation was peripheral sensory neuropathy (5%). Adverse events leading to dose interruption occurred in 62% of patients; the most common adverse reactions (≥2%) leading to dose interruption were peripheral sensory neuropathy (15%), fatigue (7%), rash maculo-papular (4%), aspartate aminotransferase increased (4%), alanine aminotransferase increased (3%), anemia (3%), diarrhea (3%), hyperglycemia (3%), neutrophil count decreased (3%) and rash (2%). Thirty-six percent of patients required a dose reduction due to an adverse event; the most common adverse reactions (≥2%) leading to a dose reduction were peripheral sensory neuropathy (11%), fatigue (5%), rash maculo-papular (4%) and decreased appetite (2%).

Tabulated summary of adverse reactions

The safety of Padcev as a single agent has been evaluated in 753 patients with locally advanced or metastatic urothelial cancer receiving 1.25 mg/kg on Days 1, 8 and 15 of a 28-day cycle in clinical studies (see Table 3). Patients were exposed to Padcev for a median duration of 4.7 months (range: 0.3 to 52.1 months).

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

Table 3. Adverse Reactions, Integrated Safety Set, Padcev Single Agent

Enfortumab vedotin 1.25 mg/kg	
Blood and lymphatic system disorders	
Very common	Anemia
Not known[1]	Neutropenia, febrile neutropenia, neutrophil count decreased
Respiratory, thoracic, and mediastinal disorders	
Not known[1]	Pneumonitis, interstitial lung disease
Gastrointestinal disorders	
Very common	Diarrhea, vomiting, nausea
General disorders and administration site conditions	
Very common	Fatigue
Common	Infusion site extravasation
Metabolism and nutrition disorders	
Very common	Hyperglycemia, decreased appetite
Nervous system disorders	

Very common	Peripheral sensory neuropathy, dysgeusia
Common	Neuropathy peripheral, peripheral motor neuropathy, peripheral sensorimotor neuropathy, paresthesia, hypoesthesia, gait disturbance, muscular weakness
Uncommon	Demyelinating polyneuropathy, polyneuropathy, neurotoxicity, motor dysfunction, dysesthesia, muscle atrophy, neuralgia, peroneal nerve palsy, sensory loss, skin burning sensation, burning sensation
Eye disorders	
Very common	Dry eye
Skin and subcutaneous tissue disorders	
Very common	Alopecia, pruritus, rash, rash maculo-papular, dry skin
Common	Drug eruption, skin exfoliation, conjunctivitis, dermatitis bullous, blister, stomatitis, palmar-plantar erythrodysesthesia syndrome, eczema, erythema, rash erythematous, rash macular, rash papular, rash pruritic, rash vesicular
Uncommon	Dermatitis exfoliative generalised, erythema multiforme, exfoliative rash, pemphigoid, rash maculovesicular, dermatitis, dermatitis allergic, dermatitis contact, intertrigo, skin irritation, stasis dermatitis, blood blister
Not known[1]	Toxic epidermal necrolysis, Stevens-Johnson syndrome, epidermal necrosis, symmetrical drug-related intertriginous and flexural exanthema
Investigations	
Very common	Alanine aminotransferase increased, aspartate aminotransferase increased, weight decreased

[1] Based on global post-marketing experience.

Padcev with pembrolizumab

Serious adverse reactions occurred in 50% of patients. The most common serious adverse reactions (≥2%) were anemia (2%) and diarrhea (2%).
Adverse reactions leading to discontinuation of either Padcev, pembrolizumab, or both occurred in 49% of patients; 22% Padcev only, 20% pembrolizumab only, and 12% both. The most common adverse reactions (≥2%) leading to discontinuation of Padcev, pembrolizumab or the combination were peripheral sensory neuropathy (14%), pneumonitis (5%), rash maculo-papular (5%), myasthenia gravis (3%) and peripheral motor neuropathy (3%).
Adverse reactions leading to dose interruption of Padcev, pembrolizumab, or both occurred in 80% of patients; 39% Padcev only, 37% pembrolizumab only, and 50% both. The most common adverse reactions (≥2%) leading to dose interruption of Padcev, pembrolizumab or the combination were peripheral sensory neuropathy (23%), rash maculo-papular (12%), fatigue (7%), lipase increased (7%), neutropenia (7%), diarrhea (6%), pneumonitis (6%), anemia (3%), alanine aminotransferase increased (3%), dermatitis bullous (3%), hyperglycemia (3%), peripheral motor neuropathy (3%) and peripheral sensorimotor neuropathy (3%).
Adverse reactions leading to dose reduction of Padcev occurred in 46% of patients. The most common adverse reactions (≥2%) leading to dose reduction of Padcev were peripheral sensory neuropathy (14%), rash maculo-papular (8%), neutropenia (5%), fatigue (5%) and diarrhea (4%).

Tabulated summary of adverse reactions

The safety of Padcev was evaluated in combination with pembrolizumab in 121 patients who received at least one dose of Padcev 1.25 mg/kg and pembrolizumab in one phase 2 study (EV-103) (see Table 4).
Adverse reactions observed during the clinical study 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 4. Adverse Reactions, Padcev, combination with Pembrolizumab

Enfortumab vedotin 1.25 mg/kg with Pembrolizumab	
Blood and lymphatic system disorders	
Very common	Anemia
Not known[1]	Neutropenia, febrile neutropenia, neutrophil count decreased
Endocrine disorders	
Very common	Hypothyroidism
Respiratory, thoracic, and mediastinal disorders	
Common	Pneumonitis
Not known[1]	Interstitial lung disease
Gastrointestinal disorders	
Very common	Diarrhea, vomiting, nausea
General disorders and administration site conditions	
Very common	Fatigue
Uncommon	Infusion site extravasation
Metabolism and nutrition disorders	
Very common	Hyperglycemia, decreased appetite
Nervous system disorders	
Very common	Peripheral sensory neuropathy, peripheral motor neuropathy, dysgeusia, muscular weakness
Common	Peripheral sensorimotor neuropathy, gait disturbance, myasthenia gravis
Uncommon	Dysesthesia, paresthesia, hypoesthesia
Eye disorders	
Very common	Dry eye
Skin and subcutaneous tissue disorders	
Very common	Alopecia, pruritus, rash maculo-papular, rash macular, dry skin
Common	Skin exfoliation, conjunctivitis, dermatitis, dermatitis bullous, blister, stomatitis, palmar-plantar erythrodysesthesia syndrome, erythema, rash, rash erythematous, rash papular, rash pruritic
Uncommon	Dermatitis exfoliative generalised, erythema multiforme, exfoliative rash, rash vesicular, pemphigoid
Not known[1]	Toxic epidermal necrolysis, Stevens-Johnson syndrome, epidermal necrosis, symmetrical drug-related intertriginous and flexural exanthema
Musculoskeletal disorders	
Common	Myositis
Investigations	
Very common	Alanine aminotransferase increased, aspartate aminotransferase increased, weight decreased, lipase increased

[1] Based on global post-marketing experience.

Selected Adverse Reactions

Immunogenicity

A total of 655 patients were tested for immunogenicity to enfortumab vedotin 1.25 mg/kg as a single agent; 15 patients were confirmed to be positive at baseline for anti-therapeutic antibody (ATA), and in patients that were negative at baseline (n=640), a total of 23 (3.6%) were positive post baseline. A total of 110 patients were tested for immunogenicity against enfortumab vedotin following enfortumab vedotin in combination with pembrolizumab; 5 patients were confirmed to be positive at baseline for ATA, and in patients that were negative at baseline (n=105), a total of 3 (2.9%) were positive post baseline. The incidence of treatment-emergent anti-enfortumab vedotin antibody formation was consistent when assessed following Padcev administration as a single agent and in combination with pembrolizumab.
Due to the limited number of patients with antibodies against enfortumab vedotin, no conclusions can be drawn concerning a potential effect of immunogenicity on pharmacokinetics, pharmacodynamics, efficacy, safety or pharmacokinetics.

Skin Reactions

In clinical studies of Padcev as a single agent, skin reactions occurred in 56% (418) of the 753 patients treated with Padcev 1.25 mg/kg. Severe (Grade 3 or 4) skin reactions occurred in 12% (92) of patients and a majority of these reactions included rash maculo-papular, rash erythematous, rash or drug eruption. The time to onset of severe skin reactions ranged from 0.1 to 6.4 months (median 0.7 months). Serious skin reactions occurred in 3.7% (28) of patients.
In the EV-201 (n=214) clinical study, of the patients who experienced skin reactions, 75% had complete resolution and 14% had partial improvement.
When enfortumab vedotin 1.25 mg/kg was given in combination with pembrolizumab (n=121), skin reactions occurred in 72% (87) patients. The majority of the skin reactions that occurred with combination therapy included rash maculo-papular, rash macular and rash papular. Severe (Grade 3 or 4) skin reactions occurred in 21% (25) patients on combination therapy (Grade 3: 19%, Grade 4: 2%). The time to onset of severe skin reactions ranged from 0.3 to 16.1 months (median 2.6 months) (see section 4.4).

Hyperglycemia

In clinical studies of Padcev as a single agent, hyperglycemia (blood glucose >13.9 mmol/L) occurred in 14% (108) of the 753 patients treated with Padcev 1.25 mg/kg. Serious events of hyperglycemia occurred in 2.3% of patients, 7% of patients developed severe (Grade 3-4) hyperglycemia and 0.3% of patients experienced fatal events, one event each of hyperglycemia and diabetic ketoacidosis. The incidence of Grade 3-4 hyperglycemia increased consistently in patients with higher body mass index and in patients with higher baseline hemoglobin A1C. The time to onset of hyperglycemia ranged from 0 to 20.3 months (median 0.6 months).
In the EV-201 (n=214) clinical study, at the time of their last evaluation, 61% of patients had complete resolution, and 19% of patients had partial improvement (see section 4.4).

Pneumonitis/interstitial lung disease

In clinical studies of Padcev as a single agent, pneumonitis occurred in 17 (2.3%) and interstitial lung disease occurred in 2 (0.3%) of the 753 patients treated with Padcev 1.25 mg/kg. Less than 1% of patients experienced severe (Grade 3-4) pneumonitis or interstitial lung disease.
When Padcev 1.25 mg/kg was given in combination with pembrolizumab (n=121), pneumonitis occurred in 11 (9%) of the 121 patients treated with combination therapy. Four patients (3%) experienced severe (Grade 3) and one patient experienced a fatal event of pneumonitis. The time to onset of pneumonitis ranged from 0.6 to 26.2 months (median 6 months) (see section 4.4).

Peripheral Neuropathy

In clinical studies of Padcev as a single agent, peripheral neuropathy occurred in 53% (401) of the 753 patients treated with Padcev 1.25 mg/kg. Five percent of patients experienced severe (Grade 3-4) peripheral neuropathy including sensory and motor events. The time to onset of Grade ≥2 ranged from 0.1 to 20.2 months (median 4.9 months).

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

Ocular Disorders

In clinical studies of Padcev as a single agent, 30.8% of patients experienced dry eye during treatment with enfortumab vedotin 1.25 mg/kg. Treatment was interrupted in 1.3% of patients and 0.1% of patients permanently discontinued treatment due to dry eye. Severe (Grade 3) dry eye only occurred in 3 patients (0.4%). The time to onset ranged from 0 to 19.1 months (median 1.6 months) (see section 4.4).

4.9 Overdose

There is no known antidote for overdosage with Padcev. 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 ADC targeting Nectin-4, an adhesion protein located on the surface of the urothelial cancer cells. It is comprised of a fully human IgG1-kappa antibody conjugated to the microtubule-disrupting agent, MMAE, via a protease-cleavable linker. Nonclinical data suggest that the anticancer activity of enfortumab vedotin is due to the binding of the ADC to Nectin-4-expressing cells, followed by internalization of the ADC-Nectin-4 complex, and the release of MMAE via proteolytic cleavage. Release of MMAE disrupts the microtubule network within the cell, subsequently inducing cell cycle arrest and 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-tumor 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.

Pharmacodynamic effects

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

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

Clinical efficacy and safety

Urothelial Cancer

Previously Untreated Cisplatin Ineligible Patients with Locally Advanced or Metastatic Urothelial Carcinoma
EV-103

The efficacy of Padcev in combination with pembrolizumab was evaluated in a phase 2, open-label, multi-cohort (dose escalation cohort, Cohort A, Cohort K) study in patients with locally advanced or metastatic urothelial cancer who were ineligible for cisplatin-containing chemotherapy and received no prior systemic therapy for locally advanced or metastatic disease.
Patients in the dose escalation cohort (n=5) and Cohort A (n=40) received Padcev 1.25 mg/kg in combination with pembrolizumab 200 mg. Patients in Cohort K received Padcev 1.25 mg/kg as a single agent (n=73) or in combination with pembrolizumab 200 mg (n=76).
Patients received Padcev 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 Padcev until disease progression or unacceptable toxicity.
Reasons for cisplatin ineligibility in patients enrolled in EV-103 included: ECOG PS of 2, creatinine clearance ≥30 and <60 mL/min, hearing loss/dysfunction and/or age.
Patients with active CNS metastases, ongoing sensory or motor neuropathy Grade ≥2, or uncontrolled diabetes defined as HbA1c ≥8% or HbA1c ≥7% with associated diabetes symptoms were excluded from participating in the study.
A total of 121 patients received Padcev 1.25 mg/kg in combination with pembrolizumab. The median age was 71 years (range: 51 to 91); 74% were male; 85% were White; and 45% of patients had an ECOG performance status of 1 and 15% had an ECOG performance status of 2. Forty-seven percent of patients had a documented baseline HbA1c of <5.7%. At baseline, 98% of patients had metastatic urothelial cancer and 2.5% of patients had locally advanced urothelial cancer. Eighty four percent of patients had visceral metastasis at baseline including 22% with liver metastases. Of the 108 patients tested who had tissue evaluable for PD-L1 expression, 43% of patients had tumors that expressed PD-L1 with a CPS ≥10 and 57% had tumors that expressed PD-L1 with a CPS <10. The median follow-up time for the dose escalation cohort + Cohort A was 44.7 months (range: 0.7 to 52.4) and for Cohort K was 14.8 months (range: 0.6 to 26.2).
Confirmed ORR was evaluated by BICR using RECIST v1.1. The median time to response was 1.94 months (range: 1.1 to 13.2) for the dose escalation cohort + Cohort A and was 2.07 months (range: 1.1 to 6.6) for Cohort K.

Table 5. Efficacy Results in EV-103

	Padcev in combination with pembrolizumab	
	Dose Escalation Cohort+ Cohort A n=45	**Cohort K n=76**
Confirmed ORR (95% CI)	73.3% (58.1, 85.4)	64.5% (52.7, 75.1)
Complete response rate (CR)	15.6%	10.5%
Partial response rate (PR)	57.8%	53.9%
Median Duration of Response, months (range)	22.1 (1.0+, 46.3+)	NR (1.2, 24.1+)
% with duration ≥6 months[1]	67%	71%

NR = Not reached

1. Based on observed duration of response

In the combined efficacy analysis of the dose escalation cohort, Cohort A and Cohort K, (n=121), confirmed ORR was 68% (95% CI: 58.7, 76.0) with complete and partial response rates of 12% and 55%, respectively. Among the responding patients, 80% had responses of 6 months or longer (based on observed duration of response).

Previously Treated Patients with Locally Advanced or Metastatic Urothelial Carcinoma
EV-301

The efficacy of Padcev as a single agent was evaluated in EV-301, an open-label, randomized, phase 3, multicenter study that enrolled 608 patients with locally advanced or metastatic urothelial cancer who received prior treatment with a PD-1 or PD-L1 inhibitor and a platinum-containing chemotherapy. Patients were randomized 1:1 to receive either Padcev 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 (38%), paclitaxel (36%) or vinflunine (26%).
Patients were excluded from the study if they had active CNS metastases, ongoing sensory or motor neuropathy Grade ≥2, or uncontrolled diabetes defined as hemoglobin A1C (HbA1c) ≥8% or HbA1c ≥7% with associated diabetes symptoms.
The median age was 68 years (range: 30 to 88 years), 77% were male, and most patients were White (52%) or Asian (33%). All patients had a baseline Eastern Cooperative Oncology Group (ECOG) performance status of 0 (40%) or 1 (60%). Eighty percent of patients had visceral metastases including 31% with liver metastases. Seventy-six percent of patients had urothelial carcinoma/transitional cell carcinoma (TCC) histology and 14% had urothelial carcinoma mixed. A total of 527 out of 608 subjects had evaluable Nectin-4 results; of these 527 subjects, 516 (98%) had detectable Nectin-4 (H-score > 0) as assessed by a validated immunohistochemistry (IHC) assay. A total of 76 (13%) of patients received ≥3 lines of prior systemic therapy. Fifty-two percent (314) of patients received prior PD-1 inhibitor, 47% (284) received prior PD-L1 inhibitor, and an additional 1% (9) patients received both PD-1 and PD-L1 inhibitors. Sixty-nine percent of patients did not respond to prior therapy with a PD-1 or PD-L1 inhibitor. Sixty-three percent (383) of patients received prior cisplatin-based regimens, 26% (159) received prior carboplatin-based regimens, and an additional 11% (65) received both cisplatin and carboplatin-based regimens.
Table 6 summarizes the efficacy results for the EV 301 study, after a median follow up time of 11.1 months (95% CI: 10.6 to 11.6).

Table 6. 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		
Median in months (95% CI)	7.4 (5.6, 9.5)	8.1 (5.7, 9.6)

Endpoint	Padcev n=301	Chemotherapy n=307

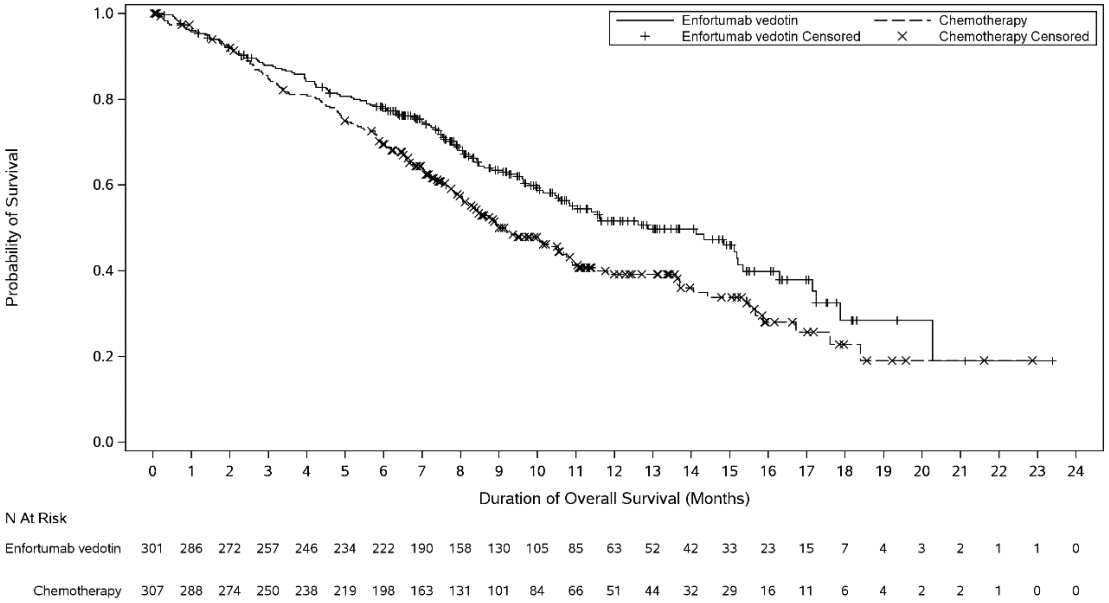
* pre-determined efficacy boundary = 0.00679, 1-sided (adjusted by observed deaths of 301).

† evaluated by investigator assessment using RECIST v1.1.

‡ pre-determined efficacy boundary = 0.02189, 1-sided (adjusted by observed PFS1 events of 432).

§ pre-determined efficacy boundary = 0.025, 1-sided (adjusted by 100% information fraction).

Figure 1. Kaplan Meier Plot of Overall Survival



5.2 Pharmacokinetic properties

Population pharmacokinetic analysis included data from 748 patients treated with enfortumab vedotin as a single agent in clinical studies. Enfortumab vedotin pharmacokinetics were characterized after single and multiple doses in patients with locally advanced or metastatic urothelial carcinoma and other solid tumors.

The pharmacokinetics of ADC and unconjugated MMAE were consistent when assessed following enfortumab vedotin as a single agent and in combination with pembrolizumab.

Peak ADC concentrations were observed near the end of intravenous infusion administration [median estimate of 0.03 days (~0.72 hours)] and peak unconjugated MMAE concentrations were observed approximately 2 days after enfortumab vedotin dosing. After repeat administration of enfortumab vedotin at 1.25 mg/kg on Days 1, 8 and 15 of a 28-day cycle or on Days 1 and 8 of a 21-day cycle, minimal to no accumulation of ADC or unconjugated MMAE was observed. ADC and unconjugated MMAE concentrations appeared to reach steady state after 1 cycle.

Table 7. Exposure parameters of ADC and unconjugated MMAE after first treatment cycle of 1.25 mg/kg of enfortumab vedotin dose of Days 1, 8 and 15

	ADC Mean (± SD)	Unconjugated MMAE Mean (± SD)
C_{max}	28 (6.1) µ/mL	5.5 (3.0) ng/mL
$AUC_{0\text{-}28d}$	110 (26) µ·d/mL	85 (50) ng·d/mL
$C_{trough,0\text{-}28d}$	0.31 (0.18) µ/mL	0.81 (0.88) ng/mL

C_{max} = maximum concentration, $AUC_{0\text{-}28d}$ = area under the concentration-time curve from time zero to 28 days, $C_{trough,0\text{-}28d}$ = pre-dose concentration on day 28.

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 drugs. *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 metabolized. *In vitro* data indicate that the metabolism of unconjugated MMAE occurs primarily via oxidation by CYP3A4.

Elimination

The mean clearance (CL) of ADC and unconjugated MMAE in patients was 0.114 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 feces 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 feces and urine as unchanged unconjugated MMAE over a 1-week period. The majority of recovered unconjugated MMAE was excreted in feces (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; n=272), moderate (CrCL 30–60 mL/min; n=315) and severe (CrCL 15-<30 mL/min; n=25) renal impairment. No significant differences in AUC exposure of ADC or unconjugated MMAE were observed in patients with mild, moderate or severe renal impairment compared to patients with normal renal function. Enfortumab vedotin has not been evaluated in patients with end stage renal disease (CrCL <15 mL/min).

Hepatic impairment

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

Drug-drug interactions

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

Effects of Other Drugs on Enfortumab Vedotin

Physiologically-Based Pharmacokinetic Modeling Predictions:
Strong CYP3A Inhibitor: Concomitant use of enfortumab vedotin with ketoconazole (a combined P-gp and strong CYP3A inhibitor) is predicted to increase unconjugated MMAE C_{max} by 15% and AUC by 38%, with no change in ADC exposure.
Strong CYP3A Inducer: Concomitant use of enfortumab vedotin with rifampin (a combined P-gp and strong CYP3A inducer) is predicted to decrease unconjugated MMAE C_{max} by 28% and AUC by 53%, with no change in ADC exposure. The full impact of rifampin on the C_{max} of MMAE may be underestimated in the PBPK model.

Effects of Enfortumab Vedotin on Other Drugs

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

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

Skin lesions were noted in repeated dose studies in both rats (4- and 13-weeks) and monkeys (4-weeks). The skin changes were fully reversible by the end of a 6-week recovery period.

Hyperglycemia 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.

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.

In a rat embryo-fetal development toxicity study, enfortumab vedotin resulted in a dose-related (2 or 5 mg/kg) decrease in maternal body weight gain and reduced food consumption at the 5 mg/kg dose level. Clinical observations included fur loss at both dose levels (one animal per dose level) as well as scabbing of the skin on the back or ventral aspect in one animal at the 5 mg/kg level.

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

Enfortumab vedotin associated fetal 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-fetal 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 fetal weight were observed.

In addition, intravenous administration of MMAE (0.2 mg/kg; C_{max} 1.1-fold the human C_{max} at the recommended clinical dose) on Gestation Day 6 and 13 resulted in embryo-fetal lethality and fetal external malformations (protruding tongue, malrotated hindlimbs, gastroschisis, and agnathia).

Testicular toxicity was noted only in rats. Findings included seminiferous tubule degeneration and hypospermia in the epididymis (≥2.0 mg/kg; approximately 1-fold the human systemic exposure at the clinically recommended dose). These findings were partially reversed by the end of a 24-week recovery period. Testicular toxicity was not observed in sexually immature male monkeys administered enfortumab vedotin at doses up to 6 mg/kg (6-fold the human systemic exposure at the clinically recommended dose).

While not observed with enfortumab vedotin, ovarian effects were observed in repeat dose toxicity studies of other MMAE-containing ADCs. A mild to moderate decrease in, or absence of, secondary and tertiary ovarian follicles was observed in young female cynomolgus monkeys at doses ≥3 mg/kg weekly for 4 weeks. No changes were observed in primordial follicles. Effects on the secondary and tertiary ovarian follicles showed evidence of recovery 6 weeks after the end of dosing.
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

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

6.3 Shelf life

The expiration date is indicated on the packaging.

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 at 2°C to 8°C including infusion time. DO NOT FREEZE.

6.4 Special precautions for storage

Unopened vial: Store at 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

Clear 10 mL Type I glass vial with Gray bromobutyl rubber stopper
- 20 mg vial, 20 mm aluminum seal with a green ring and green cap
- 30 mg vial, 20 mm aluminum seal with a silver ring and yellow cap

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 drugs.

2. Use appropriate aseptic technique for reconstitution and preparation of dosing solutions.

3. Calculate the recommended dose based on the patient's weight to determine the number and strength (20 mg or 30 mg) of vials needed.

4. Reconstitute each vial as follows and, if possible, direct the stream of sterile water for injection (SWFI) along the walls of the vial and not directly onto the lyophilized powder:

    a. 20 mg vial: Add 2.3 mL of SWFI, resulting in 10 mg/mL enfortumab vedotin.

    b. 30 mg vial: Add 3.3 mL of SWFI, resulting in 10 mg/mL enfortumab vedotin.

5. Slowly swirl each vial until the contents are completely dissolved. Allow the reconstituted vial(s) to settle for at least 1 minute until the bubbles are gone. DO NOT SHAKE THE VIAL.

6. Visually inspect the solution for particulate matter and discoloration. The reconstituted solution should be clear to slightly opalescent, colorless to light yellow and free of visible particles. Discard any vial with visible particles or discoloration.

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.

10. Visually inspect the infusion bag for any particulate matter or discoloration prior to use. The reconstituted solution should be clear to slightly opalescent, colorless to light yellow and free of visible particles. DO NOT USE the infusion bag if particulate matter or discoloration 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 drugs 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.

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