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PRODUCT MONOGRAPH
INCLUDING PATIENT MEDICATION INFORMATION

Pr PADCEV®

enfortumab vedotin for injection

lyophilized powder for solution for intravenous infusion only

20 mg and 30 mg single-use vials

Antineoplastic Agent

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RECENT MAJOR LABEL CHANGES

4 Dosage and Administration, 4.2 Recommended Dose and Dosage Adjustment MM/YYYY

7 Warnings and Precautions MM/YYYY

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PART I: HEALTH PROFESSIONAL INFORMATION

1 INDICATIONS

PADCEV (enfortumab vedotin for injection) is indicated for the treatment of adult patients with unresectable locally advanced or metastatic urothelial cancer (mUC) who have previously received a platinum-containing chemotherapy and programmed death receptor-1 (PD-1) or programmed death-ligand 1 (PD-L1) inhibitor therapy.

1.1 Pediatrics

Pediatrics (<18 years of age): No data are available to Health Canada; therefore, Health Canada has not authorized an indication for pediatric use.

1.2 Geriatrics

Geriatrics (≥65 years of age): No clinically relevant differences in efficacy were observed between patients ≥65 years and those younger than 65 years. Evidence from clinical studies suggests the use in the geriatric population may be associated with differences in safety. See 7 WARNINGS AND PRECAUTIONS, Special Populations.

2 CONTRAINDICATIONS

- PADCEV is contraindicated in patients who are hypersensitive to this drug or to any ingredient in the formulation, including any non-medicinal ingredient, or component of the container. For a complete listing, see 6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING.

3 SERIOUS WARNINGS AND PRECAUTIONS BOX

Serious Warnings and Precautions

Clinically significant and/or life-threatening adverse events include:

- Severe cutaneous adverse reactions, including Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN), with fatal outcome have occurred in patients treated with PADCEV (see 7 WARNINGS AND PRECAUTIONS).

- Hyperglycemia and diabetic ketoacidosis (DKA), including fatal events, have occurred in patients with and without pre-existing diabetes mellitus treated with PADCEV (see 7 WARNINGS AND PRECAUTIONS).

4 DOSAGE AND ADMINISTRATION

4.1 Dosing Considerations

- PADCEV is for intravenous infusion and must be reconstituted and diluted prior to administration. **Do not administer as an intravenous push or bolus**.

4.2 Recommended Dose and Dosage Adjustment

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, 8, and 15 of a 28-day cycle until disease progression or unacceptable toxicity.

Patients with Hepatic Impairment

Avoid use of PADCEV in patients with moderate (Child-Pugh B) or severe (Child-Pugh C) hepatic impairment. No dose adjustment is required in patients with mild hepatic impairment. PADCEV 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. Patients with moderate or severe hepatic impairment are likely to have increased exposure to MMAE (see 10 CLINICAL PHARMACOLOGY, Pharmacokinetics).

Patients with Renal Impairment

No dose adjustment is required in patients with mild (CrCl >60-90 mL/min), moderate (CrCl 30-60 mL/min) or severe (CrCl <30 mL/min) renal impairment (see 10 CLINICAL PHARMACOLOGY, Pharmacokinetics).

Concomitant Use with Strong P-gp and CYP3A4 Inhibitors

No dose adjustment of PADCEV is required with concomitant use of strong inhibitors of P-gp and CYP3A4. The concomitant use of strong inhibitors of P-gp and CYP3A4 with PADCEV may result in an increase in unconjugated MMAE exposure. Closely monitor for adverse reactions when PADCEV is given concomitantly with strong P-gp and CYP3A4 inhibitors (see 9 DRUG INTERACTIONS).

Pediatrics (<18 years of age)

Health Canada has not authorized an indication for pediatric use.

Geriatrics (≥65 years of age)

No dose adjustment of PADCEV is required in patients ≥ 65 years of age (see 10 CLINICAL PHARMACOLOGY, Pharmacokinetics).

Dose Modifications for Adverse Reactions

The recommended PADCEV dose reduction schedule is provided in Table 1.

Table 1: PADCEV Dose Reduction Schedule

Dose Level	**PADCEV Dose**
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

The recommended PADCEV dose modifications for patients with adverse reactions are provided in Table 2.

Table 2: PADCEV Dose Modifications for Adverse Reactions

Adverse Reaction	Severity*	PADCEV Dose Modification*
Skin Reactions	Suspected Stevens-Johnson syndrome (SJS) or toxic epidermal necrolysis (TEN), worsening or Grade 3 (severe)	Withhold until Grade ≤1, then resume treatment at the same dose level or consider dose reduction by one dose level.
	Confirmed SJS or TEN; Grade 4 or recurrent Grade 3	Permanently discontinue.
Hyperglycemia	Blood glucose >250 mg/dL	Withhold until elevated blood glucose has improved to ≤ 250 mg/dL, then resume treatment at the same dose level.
Pneumonitis/Interstitial Lung Disease	Grade 2	Withhold until Grade ≤1, then resume treatment at the same dose level or consider dose reduction by one dose level.
	Grade ≥3	Permanently discontinue.
Peripheral Neuropathy	Grade 2	Withhold until Grade ≤1, then resume treatment at the same dose level (if first occurrence). For a recurrence, withhold until Grade ≤1, then resume treatment reduced by one dose level.
	Grade ≥3	Permanently discontinue.
Other Non-hematologic Toxicity	Grade 3	Withhold until Grade ≤1, then resume treatment at the same dose level or consider dose reduction by one dose level.
	Grade 4	Permanently discontinue.
Hematologic Toxicity	Grade 3, or Grade 2 thrombocytopenia	Withhold until Grade ≤1, then resume treatment at the same dose level or consider dose reduction by one dose level.
	Grade 4	Withhold until Grade ≤1, then reduce dose by one dose level or discontinue treatment.

*Grade 1 is mild, Grade 2 is moderate, Grade 3 is severe, Grade 4 is life-threatening.

4.3 Reconstitution

Prior to administration, the PADCEV vial is reconstituted with Sterile Water for Injection (SWFI). The reconstituted solution is subsequently diluted in an intravenous infusion bag containing sterile 5% Dextrose Injection, sterile 0.9% Sodium Chloride injection or sterile Lactated Ringer's injection.

Reconstitution in a 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 of and strength (20 mg or 30 mg) of vials needed.
4. Reconstitute each vial according to Table 3 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.

Table 3 - Reconstitution

Vial Size	Volume of Diluent to be Added to Vial	Approximate Available Volume	Concentration per mL
20 mg	2.3 mL of SWFI	2.0 mL of reconstituted solution	10 mg/mL enfortumab vedotin
30 mg	3.3 mL of SWFI	3.0 mL of reconstituted solution	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.
7. Based upon the calculated dose amount, the reconstituted solution from the vial(s) should be added to the infusion bag immediately. This product does not contain a preservative. If not used immediately, reconstituted vials may be stored for up to 24 hours in refrigeration at 2°C to 8°C (36 °F to 46 °F) (see 11 STORAGE, STABILITY AND DISPOSAL). DO NOT FREEZE. Discard unused vials with reconstituted solution beyond the recommended storage time.

Dilution in infusion bag

8. Withdraw the calculated dose amount of reconstituted solution from the vial(s) and transfer into an infusion bag.
9. Dilute PADCEV with 5% Dextrose Injection, 0.9% Sodium Chloride Injection or Lactated Ringer's Injection. The infusion bag size should allow enough diluent to achieve a final concentration of 0.3 mg/mL to 4 mg/mL enfortumab vedotin.
10. Mix diluted solution by gentle inversion. DO NOT SHAKE THE BAG. Do not expose to direct sunlight.
11. Visually inspect the infusion bag for any particulate matter or discolouration 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 discolouration is observed.

12. Discard any unused portion left in the single-dose vials.
13. The prepared infusion bag should not be stored longer than 16 hours under refrigeration at 2°C to 8°C (36 °F to 46 °F). DO NOT FREEZE.

4.4 Administration

Immediately administer the infusion over 30 minutes though an intravenous line.

DO NOT administer PADCEV as an IV push or bolus.

DO NOT co-administer other drugs through the same infusion line.

4.5 Missed Dose

A missed dose should be administered as soon as possible. Subsequent doses should not be administered less than 1 week apart.

5 OVERDOSAGE

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 for the antibody-drug conjugate (ADC) and 2.6 days for monomethyl auristatin E (MMAE).

For management of a suspected drug overdose, contact your regional poison control centre.

6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING

To help ensure the traceability of biologic products, including biosimilars, health professionals should recognise the importance of recording both the brand name and the non-proprietary (active ingredient) name as well as other product-specific identifiers such as the Drug Identification Number (DIN) and the batch/lot number of the product supplied.

Table 4 – Dosage Forms, Strengths, Composition and Packaging

Route of Administration	Dosage Form / Strength/Composition	Non-medicinal Ingredients
Intravenous infusion	Powder for concentrate for solution for infusion / 10 mg per mL	Histidine, histidine hydrochloride monohydrate, polysorbate 20, trehalose dihydrate

PADCEV is supplied as single-dose vials containing 20 mg and 30 mg of enfortumab vedotin as a sterile, preservative-free, white to off-white lyophilized powder for reconstitution for intravenous infusion.

7 WARNINGS AND PRECAUTIONS

Please see 3 SERIOUS WARNINGS AND PRECAUTIONS BOX

General

PADCEV should be administered under the supervision of physicians experienced in the treatment of cancer.

The pooled safety population described in 7 WARNINGS AND PRECAUTIONS reflect exposure to PADCEV as a single agent at 1.25 mg/kg in 680 patients in EV-301 (NCT03474107), EV-201 (NCT03219333), EV-101 (NCT02091999), and EV-102 (NCT03070990). Ocular disorders reflect 384 patients in EV-201, EV-101, and EV-102 with scheduled ophthalmological exams.

Infusion Site Extravasation

Skin and soft tissue injury following PADCEV administration has been observed when extravasation occurred. Extravasation events occurred in 1% (8) of the 680 patients treated with PADCEV 1.25 mg/kg, including 0.3% (2) who experienced Grade 3-4 reactions. Reactions may be delayed. Erythema, swelling, increased temperature, and pain worsened until 2-7 days after extravasation and resolved within 1-4 weeks of peak. Two patients (0.3%) developed extravasation reactions with secondary cellulitis, bullae, or exfoliation. 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.

Endocrine and Metabolism

Hyperglycemia

Hyperglycemia and diabetic ketoacidosis (DKA) including fatal events, occurred in patients with and without pre-existing diabetes mellitus treated with PADCEV. In clinical studies, hyperglycemia occurred in 14% (98) of the 680 patients treated with PADCEV 1.25 mg/kg. Seven percent of patients who received PADCEV 1.25 mg/kg developed severe (Grade 3 or 4) hyperglycemia. Two patients experienced fatal events, one event each of hyperglycemia and diabetic ketoacidosis. The incidence of Grade 3 or 4 hyperglycemia increased consistently in patients with higher body mass index and in patients with higher baseline hemoglobin A1C. Five percent (32) of patients required initiation of insulin therapy for treatment of hyperglycemia. The median time to onset of hyperglycemia was 0.6 months (range: 0.1 to 20.3). Hyperglycemia led to discontinuation of PADCEV in 0.6% (4) of patients and dose interruptions in 3.5% (24) of the 680 patients treated with PADCEV. Seven (30%) of 23 patients had recrudescence after dose restart. Patients with baseline hemoglobin A1C ≥8% were excluded from clinical trials.

Hyperglycemia occurred more frequently in patients with pre-existing hyperglycemia or a high body mass index (≥30 kg/m2). Blood glucose levels should be monitored regularly in patients with or at risk for diabetes mellitus or hyperglycemia. If blood glucose is elevated (>13.9 mmol/L; >250 mg/dL), withhold PADCEV (see 4 DOSAGE AND ADMINISTRATION, Recommended Dose and Dose Adjustment).

Neurologic

Peripheral Neuropathy

Peripheral neuropathy, predominantly sensory, has occurred with PADCEV, including Grade ≥3 reactions. Peripheral neuropathy occurred in patients treated with PADCEV with or without pre-existing peripheral neuropathy. In clinical studies, peripheral neuropathy occurred in 52% (352) of

the 680 patients treated with PADCEV 1.25 mg/kg including 39% with sensory neuropathy, 7% with muscular weakness and 6% with motor neuropathy. Four percent of patients experienced severe (Grade 3 or 4) peripheral neuropathy including sensory and motor events. The median time to onset of Grade ≥2 was 4.6 months (range 0.1 to 15.8 months). There were 135 (20%) patients that experienced peripheral neuropathy adverse events leading to dose interruption. Of these patients, 102 restarted at any dose, with 81 (79.4%) of patients experiencing recrudescence. Five percent of patients discontinued treatment due to peripheral neuropathy. Patients with pre-existing peripheral neuropathy Grade ≥2 were excluded from clinical studies.

Monitor patients for symptoms of new or worsening peripheral neuropathy as these patients may require a delay, dose reduction or discontinuation of PADCEV.

Permanently discontinue PADCEV in patients who develop Grade ≥3 peripheral neuropathy (see 4 DOSAGE AND ADMINISTRATION, Recommended Dose and Dose Adjustment).

Ophthalmologic

Ocular Disorders

Ocular disorders, predominately dry eye, occurred in 40% of the 384 patients treated with PADCEV in clinical trials in which ophthalmologic exams were performed. The majority of ocular events involved the cornea and included events associated with dry eye such as keratitis, blurred vision, increased lacrimation, conjunctivitis, limbal stem cell deficiency, and keratopathy. In clinical studies, 14 (2.1%) patients interrupted, and 1 (0.1%) patient permanently discontinued treatment for ocular disorders. Severe (Grade 3) ocular disorders occurred only in 3 patients (0.4%). Thirteen percent of patients experienced dry eye symptoms during treatment with PADCEV 1.25 mg/kg and the median time to onset was 1.7 months (range 0 to 19.1 months).

Monitor patients for ocular disorders such as dry eye and blurred vision. Consider artificial tears for prophylaxis of dry eye and refer patient for ophthalmologic evaluation if ocular symptoms do not resolve or worsen. Consider dose interruption or dose reduction of PADCEV for symptomatic ocular disorders (see 4 DOSAGE AND ADMINISTRATION, Recommended Dose and Dose Adjustment).

Reproductive Health: Female and Male Potential

Pregnancy Testing

Pregnancy testing is recommended for females of reproductive potential within 7 days prior to initiating PADCEV treatment (see 7 WARNINGS AND PRECAUTIONS, Special Populations, Pregnant Women and 16 NON-CLINICAL TOXICOLOGY).

Contraception

Advise females of reproductive potential to use effective contraception during treatment with PADCEV and for at least 6 months after the last dose of PADCEV (see 7 WARNINGS AND PRECAUTIONS, Special Populations, Pregnant Women and 16 NON-CLINICAL TOXICOLOGY).

Advise males of reproductive potential to use effective contraception during treatment with PADCEV and for at least 4 months after the last dose of PADCEV.

Fertility

Testicular toxicity was observed in rats following repeat dosing at systemic exposures that were approximately equal to the human systemic exposure at the clinically recommended dose (see 16 NON-

CLINICAL TOXICOLOGY). There are no data on the effect of PADCEV on human fertility.

Respiratory

Pneumonitis/Interstitial Lung Disease

Severe, life-threatening or fatal pneumonitis/interstitial lung disease have occurred in patients treated with PADCEV. In clinical trials, 3.1% of the 680 patients treated with PADCEV had pneumonitis/interstitial lung disease of any grade and 0.7% had Grade 3-4. In clinical trials, the median time to onset of pneumonitis/interstitial lung disease was 2.9 months (range: 0.6 to 6 months). Two patients on trial also experienced fatal events. Monitor patients for signs and symptoms indicative of pneumonitis/interstitial lung disease such as hypoxia, cough, dyspnea or interstitial infiltrates on radiologic exams. Evaluate and exclude infectious, neoplastic and other causes for such signs and symptoms through appropriate investigations. Withhold PADCEV for Grade 2 pneumonitis/interstitial lung disease, then resume treatment at the same dose level or consider dose reduction by one dose level . Permanently discontinue PADCEV for Grade ≥3 pneumonitis/interstitial lung disease (see 4 DOSAGE AND ADMINISTRATION, Recommended Dose and Dose Adjustment).

Skin

Skin Reactions

Skin reactions are anticipated on-target events, as Nectin-4 is expressed in the skin.

Severe cutaneous adverse reactions, including SJS and TEN, with fatal outcome have occurred in patients treated with PADCEV, predominately during the first cycle of treatment, but may occur later.

Skin reactions, predominantly mild to moderate maculopapular rash, have occurred with PADCEV. In clinical studies, skin reactions occurred in 55% (375) of the 680 patients treated with PADCEV 1.25 mg/kg. Severe (Grade 3 or 4) skin reactions occurred in 13% (85) of patients and a majority of these reactions included maculo-papular rash, rash erythematous, rash or drug eruption, symmetrical drug-related intertriginous and flexural exanthema (SDRIFE), dermatitis bullous, dermatitis exfoliative, and palmar-plantar erythrodysesthesia. The median time to onset of severe skin reactions was 0.6 months (range: 0.1 to 6.4 months). Skin reactions led to dose interruption of PADCEV in 12% of patients. Of the 59 patients who restarted PADCEV after reporting a skin reaction leading to dose interruption, 24% of patients restarting at the same dose and 16% restarting at a reduced dose experienced recurrent severe skin reactions. Skin reactions led to discontinuation of PADCEV in 2.6% of patients.

Starting with the first cycle and throughout treatment, monitor patients for skin reactions. Consider appropriate therapy such as topical corticosteroids and antihistamines for mild to moderate skin reactions. For worsening or severe (Grade 3) skin reactions, suspected SJS or TEN, withhold PADCEV and consider referral for specialized care. Permanently discontinue PADCEV for confirmed SJS or TEN, Grade 4 or recurrent Grade 3 skin reactions (see 4 DOSAGE AND ADMINISTRATION, Recommended Dose and Dose Adjustment).

7.1 Special Populations

7.1.1 Pregnant Women

PADCEV can cause fetal harm based upon findings from animal studies. There are no available human data on PADCEV use in pregnant women to inform a drug-associated risk. Embryo-fetal development studies in female rats have shown that intravenous administration of enfortumab vedotin (2 or 5

mg/kg/dose; 1- and 3-fold the human C_{max}, respectively) resulted in maternal toxicity, embryo-fetal lethality, structural malformations and skeletal anomalies reduced numbers of viable fetuses, reduced litter size, and increased early resorptions at maternal exposures approximately similar to the exposures at the recommended human dose of 1.25 mg/kg (see 16 NON-CLINICAL TOXICOLOGY).

Female patients of childbearing potential treated with PADCEV should be advised of the potential risk to the fetus.

7.1.2 Breast-feeding

There is no information regarding the presence of enfortumab vedotin in human milk, the effects on the breastfed child, or the effects on milk production. Breastfeeding is not recommended during PADCEV treatment and for at least 6 months after the last dose.

7.1.3 Pediatrics

Pediatrics (<18 years of age): No data are available to Health Canada; therefore, Health Canada has not authorized an indication for pediatric use.

7.1.4 Geriatrics

Geriatrics (≥ 65 years of age): Of the 748 patients treated with PADCEV in clinical trials, 449 (60%) were 65 years or older and 142 (19%) were 75 years or older. No overall differences in efficacy were observed between these patients and younger patients (see 10 CLINICAL PHARMACOLOGY, Pharmacokinetics). In the PADCEV arm of the EV-301 study, serious adverse events were reported in 40% of patients < 65 (n=106), 51% of patients ≥ 65 and < 75 (n=139), and 49% of patients ≥ 75 (n=51). Adverse events leading to treatment discontinuation were reported in 13%, 18% and 23% of patients < 65, ≥ 65 and < 75 and ≥ 75, respectively.

8 ADVERSE REACTIONS

8.1 Adverse Reaction Overview

The data described in the following section reflect exposure to PADCEV from one open-label, randomized, phase 3 study (EV-301). Patients received PADCEV 1.25 mg/kg on Days 1, 8 and 15 of a 28-day cycle until disease progression or unacceptable toxicity.

Study EV-301

EV-301 included 296 patients with unresectable locally advanced or metastatic urothelial cancer who received at least one dose of PADCEV 1.25 mg/kg and were previously treated with a PD-1 or PD-L1 inhibitor and a platinum-based chemotherapy. The median duration of exposure to PADCEV was 5 months (range: 0.5 to 19.4 months). The median duration of exposure to chemotherapy was 3.5 months (range: 0.2 to 15 months).

Serious adverse events, regardless of causality, occurred in 47% of patients treated with PADCEV. The most common serious adverse events were acute kidney injury (6%), malignant neoplasm progression and pneumonia (4% each), urinary tract infection bacterial (3%), diarrhoea, urinary tract infection, and pyrexia (2% each). Grade 3 or higher adverse events, regardless of causality, occurred in 71% of patients treated with PADCEV. The most common Grade ≥3 adverse events (≥5%) were rash

maculopapular, hyperglycaemia, neutrophil count decreased, fatigue (7% each), anaemia (6%), and decreased appetite (5%). Adverse events, regardless of causality, resulting in death occurred in 7% (21/296) of patients, including malignant neoplasm progression (3%), multiple organ dysfunction syndrome (1%), pneumonia (0.7%), and hepatic dysfunction, septic shock, hyperglycemia, pneumonitis and pelvic abscess (0.3% each).

Adverse events leading to discontinuation occurred in 17% of patients; the most common adverse event (≥2%) leading to discontinuation was peripheral neuropathy (2%). Adverse events leading to dose interruption occurred in 61% of patients; the most common adverse events (≥4%) leading to dose interruption were peripheral sensory neuropathy 16%), fatigue (6%), neutrophil count decreased (5%), and rash maculopapular (4%). Adverse events leading to dose reduction occurred in 34% of patients; the most common adverse events (≥2%) leading to dose reduction were peripheral sensory neuropathy (7%), rash maculopapular (4%), decreased appetite (3%) and fatigue (3%), neutrophil count decreased and neuropathy peripheral (2%).

8.2 Clinical Trial Adverse Reactions

Clinical trials are conducted under very specific conditions. The adverse reaction rates observed in the clinical trials; therefore, may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse reaction information from clinical trials may be useful in identifying and approximating rates of adverse drug reactions in real-world use.

Table 5 summarizes the all grade and Grade ≥3 treatment emergent adverse events reported in patients in EV-301.

Table 5: Treatment Emergent Adverse Events Reported in ≥10% (All Grades) in Patients Treated with PADCEV in EV-301

	PADCEV N = 296		**Chemotherapy N = 291**	
SOC Preferred Term	All Grade n (%)	Grade ≥3 n (%)	All Grade n (%)	Grade ≥3 n (%)
Blood and lymphatic system disorders				
Anemia	59 (20)	19 (6)	87 (30)	34 (12)
Neutrophil count decreased	33 (11)	21 (7)	54 (19)	43 (15)
Eye disorders				
Dry eye[1]	71 (24)	2 (0.7)	17 (6)	1 (0.3)
Gastrointestinal disorders				
Nausea	89 (30)	3 (1)	74 (25)	5 (2)
Diarrhea[2]	105 (35)	12 (4)	67 (23)	6 (2)
Vomiting	42 (14)	4 (1)	44 (15)	3 (1)
Constipation	82 (28)	3 (1)	73 (25)	6 (2)
Abdominal Pain[3]	59 (20)	2 (1)	41 (14)	8 (3)
General disorders and administration site conditions				

SOC Preferred Term	PADCEV N = 296		Chemotherapy N = 291	
	All Grade n (%)	Grade ≥3 n (%)	All Grade n (%)	Grade ≥3 n (%)
Fatigue[4]	147 (50)	27 (9)	116 (40)	20 (7)
Pyrexia[5]	65 (22)	7 (2)	42 (14)	0
Infections and infestations				
Urinary Tract Infection[6]	49 (17)	19 (6)	38 (13)	10 (3)
Investigations				
Weight decreased	47 (16)	1 (0.3)	20 (7)	0
Aspartate aminotransferase increased	36 (12)	3 (1)	5 (2)	0
Metabolism and nutrition disorders				
Decreased appetite	121 (41)	16 (5)	78 (27)	7 (2)
Hyperglycaemia	31 (11)	21 (7)	6 (2)	2 (1)
Musculoskeletal and connective tissue disorders				
Musculoskeletal Pain[7]	74 (25)	7 (2)	101 (35)	15 (5)
Nervous system disorders				
Peripheral neuropathy[8]	149 (50)	15 (5)	99 (34)	8 (3)
Dysgeusia[9]	76 (26)	0	23 (8)	0
Psychiatric disorders				
Insomnia	31 (11)	0	23 (8)	0
Skin and subcutaneous tissue disorders				
Rash[10]	159 (54)	42 (14)	58 (20)	1 (0.3)
Alopecia	139 (47)	0	110 (38)	0
Dry skin	50 (17)	0	11 (4)	0
Pruritus	102 (34)	5 (2)	20 (7)	0
Vascular disorders				
Hemorrhage[11]	51 (17)	8 (3)	37(13)	7 (2)

[1]Includes: blepharitis, conjunctivitis, conjunctivitis allergic, dry eye, eye irritation, keratitis, keratopathy, lacrimation increased, Meibomian gland dysfunction, ocular discomfort, punctate keratitis

[2]Includes: diarrhea, colitis, enterocolitis

[3]Includes: abdominal pain, abdominal pain upper, abdominal pain lower, abdominal discomfort, hepatic pain, abdominal tenderness, gastrointestinal pain

[4]Includes: fatigue, asthenia

[5]Includes: pyrexia, hyperthermia, hyperpyrexia, body temperature increased

[6]Includes: urinary tract infection, urinary tract infection bacterial, urinary tract infection enterococcal, streptococcal urinary tract infection, escherichia urinary tract infection, pyelonephritis acute, escherichia pyelonephritis, urinary tract infection fungal, cystitis, urinary tract infection staphylococcal, urinary tract infection pseudomonal

[7]Includes: myalgia, arthralgia, back pain, bone pain, pain in extremity, musculoskeletal pain, arthritis, neck pain, noncardiac chest pain, musculoskeletal chest pain, spinal pain, musculoskeletal stiffness, musculoskeletal discomfort

[8]Includes: burning sensation, demyelinating polyneuropathy, dysesthesia, hypoesthesia, muscular weakness, neuralgia, neuropathy peripheral, neurotoxicity, paresthesia, peripheral motor neuropathy, peripheral sensorimotor neuropathy, peroneal nerve palsy, peripheral sensory neuropathy, gait disturbance, polyneuropathy, sensory loss

[9]Includes: dysgeusia, ageusia, hypogeusia

[10]Includes: blister, blood blister, conjunctivitis, dermatitis, dermatitis bullous, dermatitis contact, drug eruption, eczema, erythema, erythema multiforme, exfoliative rash, intertrigo, palmar-plantar erythrodysesthesia syndrome, rash, rash erythematous, rash macular, rash maculo-papular, rash papular, rash pruritic, rash vesicular, skin irritation, skin exfoliation, stomatitis

[11]Includes: hematuria, rectal hemorrhage, gastrointestinal hemorrhage, epistaxis, upper gastrointestinal hemorrhage, tumor hemorrhage, hemoptysis, vaginal hemorrhage, anal hemorrhage, hemorrhagic stroke, urethral hemorrhage, infusion site hemorrhage, conjunctival hemorrhage, hemorrhagic ascites, hemorrhoidal hemorrhage

8.3 Less Common Clinical Trial Adverse Reactions

Other clinically important adverse events, regardless of relationship to PADCEV, that occurred in < 10% of recipients of PADCEV in EV-301 included:

Blood and lymphatic disorders: neutropenia, febrile neutropenia
Cardiac disorders: tachycardia
General disorders and administrative site conditions: infusion site extravasation, multiple organ dysfunction syndrome
Infections and infestations: sepsis
Monitoring and laboratory tests: alanine aminotransferase increased
Respiratory, thoracic, and mediastinal disorders: pneumonitis/ILD

8.4 Abnormal Laboratory Findings: Hematologic, Clinical Chemistry and Other Quantitative Data

Table 6: Selected Laboratory Abnormalities Reported in ≥15% (All Grades) or ≥5% (Grade 3-4) of Patients Treated with PADCEV in EV-301

		PADCEV			Chemotherapy	
Laboratory Abnormality	**N**	**All Grades n (%)**	**Grade 3-4 n (%)**	**N**	**All Grades n (%)**	**Grade 3-4 n (%)**
Hematology						
Hemoglobin decreased	281	116 (41)	5 (2)	268	137 (51)	26 (10)
Lymphocytes decreased	281	130 (46)	26 (9)	268	124 (46)	34 (13)
Neutrophils decreased	281	68 (24)	11 (4)	268	31 (12)	4 (2)
Platelets decreased	279	61 (22)	0	268	26 (10)	4 (2)
Chemistry						
Phosphate decreased	285	75 (26)	13 (5)	271	56 (21)	12 (4)
Glucose increased (non-fasting)	285	135 (47)	20 (7)	271	112 (41)	13 (5)
Creatinine increased	285	143 (50)	1 (0.4)	271	122 (45)	0
Potassium increased	285	38 (13)	8 (3)	271	48 (18)	4 (2)
Lipase increased	251	43 (17)	16 (6)	257	37 (14)	10 (4)
Sodium decreased	285	92 (32)	19 (7)	271	57 (21)	11 (4)
Alanine aminotransferase increased	281	57 (20)	0	270	20 (7)	1 (0.4)
Aspartate aminotransferase increased	282	133 (47)	2 (0.7)	269	38 (14)	2 (0.7)

8.5 Post-Market Adverse Reactions

The following adverse reactions have been identified during post-approval use of PADCEV. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Skin and subcutaneous tissue disorders: epidermal necrosis, Stevens-Johnson syndrome, toxic epidermal necrolysis, symmetrical drug-related intertriginous and flexural exanthema [see 7 WARNINGS AND PRECAUTIONS].

9 DRUG INTERACTIONS

9.2 Drug Interactions Overview

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 free MMAE.

9.3 Drug-Behavioural Interactions

Not applicable.

9.4 Drug-Drug Interactions

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.

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 MMAE inhibits CYP3A4/5 but not other CYP450 isoforms. MMAE did not induce major CYP450 enzymes in human hepatocytes.

In vitro studies indicate that MMAE is a substrate and not an inhibitor of the efflux transporter P-glycoprotein (P-gp). *In vitro* studies determined that MMAE was not a substrate of breast cancer resistance protein (BCRP), multidrug resistance-associated protein 2 (MRP2), organic anion transporting polypeptide 1B1 or 1B3 (OATP1B1 or OATP1B3), organic cation transporter 2 (OCT2), or organic anion transporter 1 or 3 (OAT1 or OAT3). MMAE was not an inhibitor of the bile salt export pump (BSEP), P-gp, BCRP, MRP2, OCT1, OCT2, OAT1, OAT3, OATP1B1, or OATP1B3 at clinically relevant concentrations.

9.5 Drug-Food Interactions

Not applicable as PADCEV is administered by IV infusion.

9.6 Drug-Herb Interactions

Interactions with herbal products have not been established.

9.7 Drug-Laboratory Test Interactions

Interactions with laboratory tests have not been established.

10 CLINICAL PHARMACOLOGY

10.1 Mechanism of Action

Enfortumab vedotin is an ADC directed against Nectin-4, an adhesion protein located on the surface of most 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 apoptotic cell death.

AGS-22M6E, an antibody drug conjugate (ADC) that is biologically equivalent to enfortumab vedotin, is a high affinity humanized IgG1κ monoclonal antibody drug conjugate that binds human Nectin-4 antigen. AGS-22M6E demonstrated dose-dependent cytotoxic activity against Nectin-4 expressing cancer cells *in vitro* and inhibited tumour growth in various human Nectin-4 positive cancer xenograft models.

Pharmacodynamic bridging studies of AGS-22M6E (hybridoma-derived) and enfortumab vedotin (CHO-derived) confirmed comparable binding affinity, cytotoxicity and *in vivo* efficacy between the 2 antibody drug conjugates. In addition, the safety profile and pharmacokinetics of AGS-22M6E and enfortumab vedotin were comparable in cynomolgus monkeys.

10.2 Pharmacodynamics

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

10.3 Pharmacokinetics

Population pharmacokinetic analysis included data from 748 patients based on three phase 1 studies,

one phase 2 study and one phase 3 study. Enfortumab vedotin pharmacokinetics were characterized after single and multiple doses in patients with unresectable locally advanced or metastatic urothelial carcinoma and other solid tumours.

Peak ADC concentrations were observed near the end of intravenous infusion administration [median estimate of 0.03 days (~0.72 hours)] and peak 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, minimal to no accumulation of ADC or MMAE was observed. ADC and MMAE concentrations appeared to reach steady state after 1 cycle.

Table 7 - Summary of Enfortumab Vedotin Pharmacokinetic Parameters in Unresectable Locally Advanced or Metastatic Urothelial Cancer

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

Absorption:

PADCEV is administered as an IV infusion and therefore is immediately and completely bioavailable.

Distribution:

The mean estimate of steady-state volume of distribution of ADC was 12.8 L following 1.25 mg/kg of enfortumab vedotin.

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

Metabolism:

A small fraction of MMAE released from enfortumab vedotin is metabolized. *In vitro* data indicate that the metabolism of MMAE occurs primarily via oxidation by CYP3A4.

Elimination:

The mean clearance (CL) of ADC and unconjugated MMAE in patients was 0.114 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 MMAE appeared to be limited by its rate of release from enfortumab vedotin. MMAE elimination exhibited a multi-exponential decline with a half-life of 2.6 days.

The excretion of MMAE occurs mainly in feces with a smaller proportion in urine. After a single dose of another ADC that contained MMAE, approximately 24% of the total MMAE administered was

recovered in feces and urine as unchanged MMAE over a 1-week period. The majority of recovered MMAE was excreted in feces (72%). A similar excretion profile is expected for MMAE after enfortumab vedotin administration.

Special Populations and Conditions

Race: 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] does not have a clinically meaningful effect on the pharmacokinetics of enfortumab vedotin.

Gender: Based on population pharmacokinetic analysis, gender [73% (544/748) male] does not have a clinically meaningful effect on the pharmacokinetics of enfortumab vedotin.

Pediatrics: Pharmacokinetics of enfortumab vedotin have not been evaluated in children and adolescents <18 years of age.

Geriatrics**:** 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.

Hepatic Insufficiency: Avoid use of PADCEV in patients with moderate (Child-Pugh B) or severe (Child-Pugh C) hepatic impairment. Based on population pharmacokinetics analysis using data from clinical studies in patients with metastatic UC, there were no significant differences in ADC exposure and a 37% increase in unconjugated MMAE AUC were observed in patients with mild hepatic impairment (bilirubin of 1 to 1.5 × ULN and AST < ULN, or bilirubin ≤ ULN and AST > ULN, n=65) compared to patients with normal hepatic function. Also, in the PADCEV arm of the EV-301 study, 53.6% of patients with mild hepatic impairment and 45.3% of patients with normal hepatic function had serious treatment-emergent adverse events. 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 liver transplantation on the pharmacokinetics of ADC or unconjugated MMAE is unknown.

Renal Insufficiency**:** The pharmacokinetics of ADC and unconjugated MMAE were evaluated after the administration of 1.25 mg/kg of enfortumab vedotin to patients with mild (creatinine clearance; CrCL >60–90 mL/min; n=272), moderate (CrCL 30–60 mL/min; n=315) and severe (CrCL <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. The effect of end stage renal disease with or without dialysis on the pharmacokinetics of ADC or unconjugated MMAE is unknown.

11 STORAGE, STABILITY AND DISPOSAL

Store PADCEV vials refrigerated at 2°C to 8°C (36°F to 46°F) in the original carton. Do not freeze. Do not shake.

12 SPECIAL HANDLING INSTRUCTIONS

PADCEV is an antineoplastic product. Follow local handling and disposal procedures.

PART II: SCIENTIFIC INFORMATION

13 PHARMACEUTICAL INFORMATION

Drug Substance

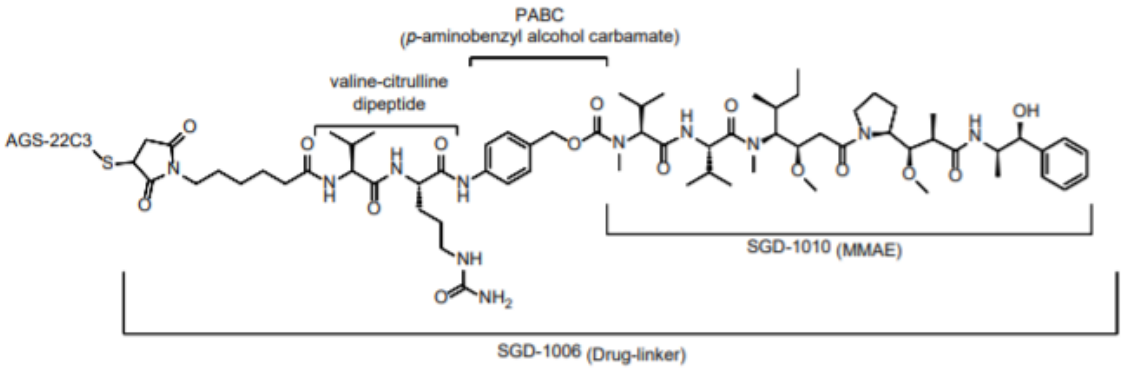
Proper name: enfortumab vedotin

Chemical name: IgG_1-k AGS-22C3 covalently linked to MMAE

Molecular formula and molecular mass: $C_{6754}H_{10442}N_{1750}O_{2144}S_{46}$

Average mass: 151,935 Da

Structural formula:



Product Characteristics

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 (AGS-22C3) conjugated to the microtubule-disrupting agent monomethyl auristatin E (MMAE) via a protease-cleavable maleimidocaproyl valine-citrulline (vc) linker.

14 CLINICAL TRIALS

14.1 Trial Design and Study Demographics

Previously Treated Unresectable Locally Advanced or Metastatic Urothelial Carcinoma

Study EV-301

Table 8 - Summary of Trial Design of EV-301, enfortumab vedotin versus Chemotherapy in Patients with Previously Treated Unresectable Locally Advanced or Metastatic Urothelial Carcinoma

Study #	Study design	Dosage, route of administration and duration	Study subjects (n)
EV-301	Randomized, open-label, phase 3, multicenter Subjects randomized in a 1:1 ratio to receive enfortumab vedotin or chemotherapy	PADCEV (enfortumab vedotin for injection) 1.25 mg/kg IV over approximately 30 minutes on Days 1, 8 and 15 of a 28-day cycle was administered until disease progression or unacceptable toxicity	PADCEV (n=301) Chemotherapy (n=307) Total (n=608)

The efficacy of PADCEV was evaluated in EV-301, an open-label, randomized, phase 3, multicenter study that enrolled 608 patients with unresectable locally advanced or metastatic urothelial cancer who received prior treatment with a platinum-containing chemotherapy and PD-1 or PD-L1 inhibitor. Patients were randomized 1:1 to receive either PADCEV or one of the following chemotherapies as decided by the investigator prior to randomization: docetaxel (38%), paclitaxel (36%) or vinflunine (26%). Randomization was stratified by ECOG PS (0 vs 1), regions of the world (Western EU vs. US vs. rest of world), and presence of liver metastasis (yes or no).

Patients were excluded from the trial if they had active CNS metastases, cardiac symptoms (including congestive heart failure) consistent with New York Heart Association Class III-IV, severe renal impairment, ongoing sensory or motor neuropathy ≥ Grade 2, or uncontrolled diabetes defined as hemoglobin A1C (HbA1c) ≥8% or HbA1c ≥7% with associated diabetes symptoms.

Table 9: Summary of Patient Demographics and Baseline Disease Characteristics in EV-301

	PADCEV (n=301)	Chemotherapy (n=307)	Total (n=608)
Median Age, years (range)	68.0 (34.0, 85.0)	68.0 (30.0, 88.0)	68.0 (30.0, 88.0)
Age Category, n (%)			
< 65 years	108 (35.9)	111 (36.2)	219 (36.0)
65 to < 75 years	141 (46.8)	128 (41.7)	269 (44.2)
≥ 75 years	52 (17.3)	68 (22.1)	120 (19.7)
Gender, n (%)			
Male	238 (79.1)	232 (75.6)	470 (77.3)

	PADCEV (n=301)	Chemotherapy (n=307)	Total (n=608)
Female	63 (20.9)	75 (24.4)	138 (22.7)
Race			
White	159 (52.8)	155 (50.5)	314 (51.6)
Asian	97 (32.2)	103 (33.6)	200 (32.9)
Black	2 (0.7)	2 (0.7)	4 (0.7)
Baseline ECOG, n (%)			
0	120 (39.9)	124 (40.4)	244 (40.1)
1	181 (60.1)	183 (59.6)	364 (59.9)
Visceral Metastasis, n (%)	234 (77.2)	250 (81.7)	484 (79.7)
Liver Metastasis, n (%)	93 (30.9)	95 (30.9)	188 (30.9)
Type of Prior Platinum-based Treatment Received, n (%)			
Cisplatin-based only	193 (64.1)	190 (61.9)	383 (63.0)
Carboplatin-based only	74 (24.6)	85 (27.7)	159 (26.2)
Both Cisplatin-based and Carboplatin-based	34 (11.3)	31 (10.1)	65 (10.7)

Thirty-four percent of patients had tumors located in the upper tract that included the renal pelvis and ureter. Seventy-six percent of patients had pure transitional cell carcinoma (TCC) histology; 14% had TCC with other histologic variants; and 10% had other tumor histologies including adenocarcinoma and squamous cell carcinoma. The median number of prior therapies was 2 (range 1 to ≥3). For patients with prior therapies in the PADCEV arm, 13% had 1 line of prior therapy, 74% had 2 lines, and 13% had ≥3 lines of prior therapy. Additionally, more than 98% of patients in this arm used one checkpoint inhibitor; 55% received a PD-1 inhibitor and 44% received a PD-L1 inhibitor.

14.2 Study Results

Previously Treated Unresectable Locally Advanced or Metastatic Urothelial Carcinoma

Study EV-301

The major efficacy outcome measure was overall survival (OS). Progression free survival (PFS) and overall response rate (ORR) as assessed by investigator using RECIST v1.1 were secondary objectives. The median follow-up time for this study was 11.1 months. Findings are summarized in Table 10 and Figures 1-2.

Table 10 - Results of Study EV-301 in Previously Treated Unresectable Locally Advanced or Metastatic Urothelial Cancer

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)	0.70 (0.56, 0.89)	
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)	0.62 (0.51, 0.75)	
1-sided p-value	<0.00001[‡]	
Overall 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

*Based on stratified log-rank test. Stratification factors were ECOG PS, region and liver metastasis. Pre-determined efficacy boundary = 0.00679.

[‡] Based on stratified log-rank test. Stratification factors were ECOG PS, region and liver metastasis. Pre-determined efficacy boundary = 0.02189.

Figure 1: Kaplan Meier Plot of Overall Survival

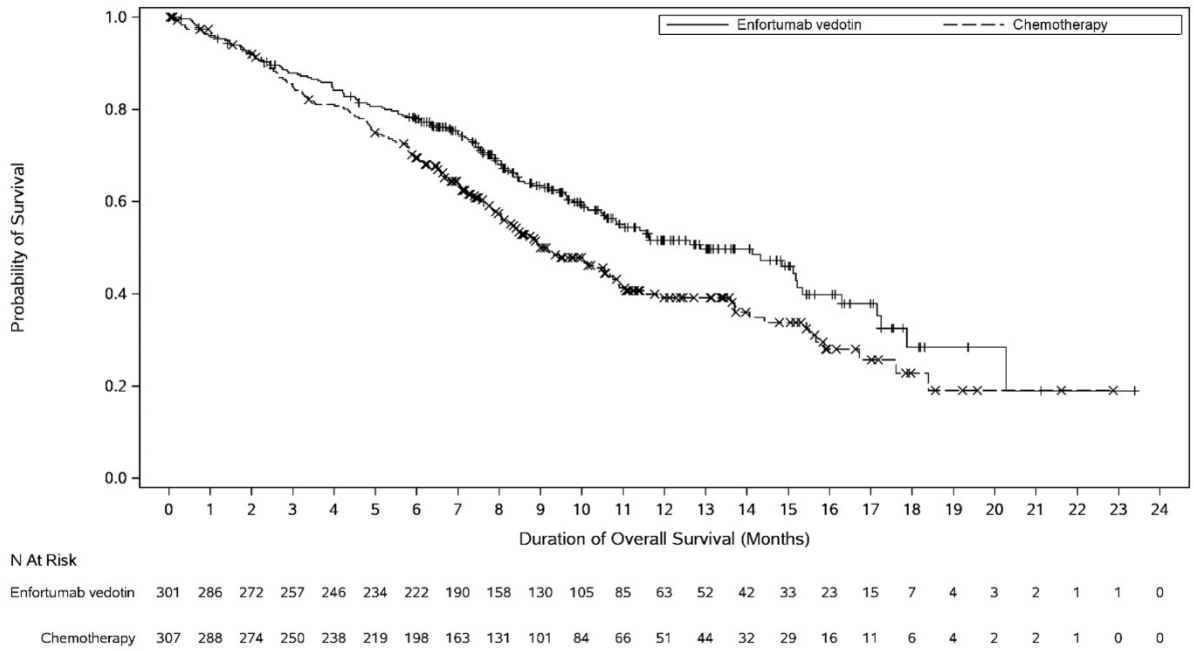


Figure 2: Kaplan Meier Plot of Progression Free Survival

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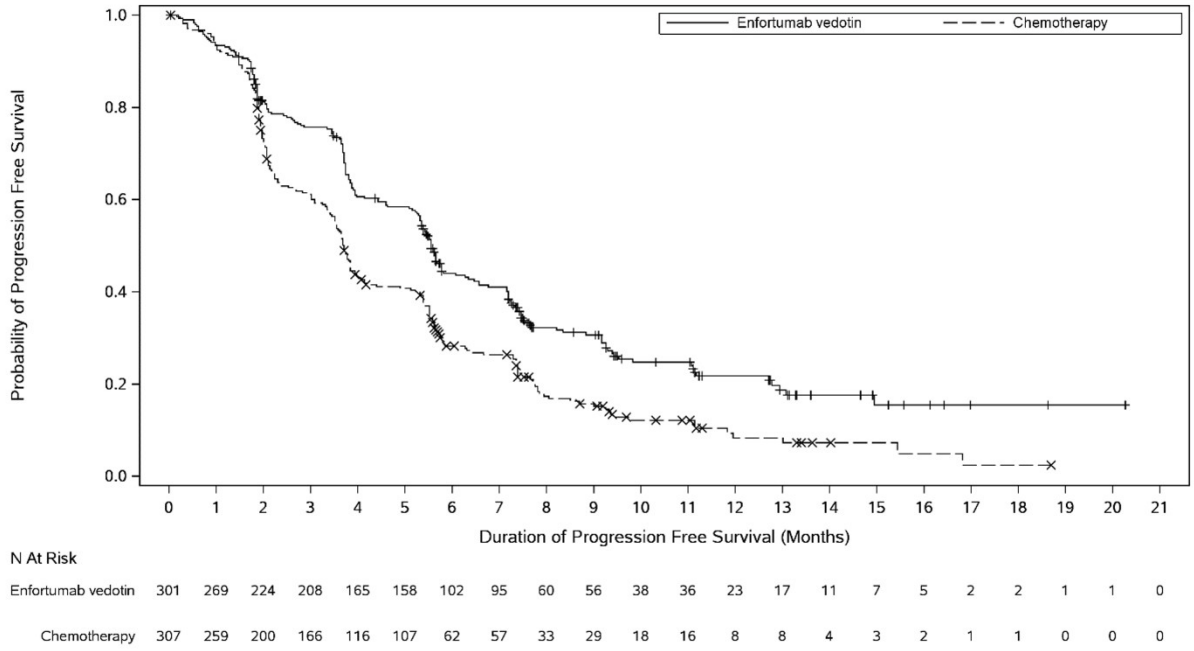

14.4 Immunogenicity

A total of 590 patients were tested for immunogenicity to enfortumab vedotin 1.25 mg/kg; 15 patients were confirmed to be positive at baseline for anti-therapeutic antibody (ATA), and in patients that were negative at baseline (N=575), a total of 16 (2.8%) were positive post-baseline (13 transiently and 3 persistently). Due to the limited number of patients with antibodies against PADCEV, no conclusions can be drawn concerning a potential effect of immunogenicity on efficacy, safety or pharmacokinetics.

15 MICROBIOLOGY

No microbiological information is required for this drug product.

16 NON-CLINICAL TOXICOLOGY

General Toxicology:

Good laboratory practice (GLP)-compliant repeat dose toxicity studies were conducted in rats intravenously administered 2, 5, or 10 mg/kg given once weekly for 4 total doses, followed by a 6-week recovery period or 0.5, 2, and 5 mg/kg given once weekly for 13 total doses. GLP-compliant repeat dose toxicity studies were also conducted in cynomolgus monkeys intravenously administered 1, 3 or 6 mg/kg, given once weekly for 4 total doses, followed by a 6-week recovery period. The toxicity profile in monkey was comparable to rat. Mortality was observed in both rats and monkeys at initial exposure levels that were at least 6-fold higher than the human exposure at the recommended clinical dose.

Predominant target organs of toxicity in rats and monkeys include skin and injection site (abrasions, sores, reddened/dry skin, coupled with inflammation, epidermal hyperplasia, hyperkeratosis, ulcers, single-cell necrosis of the epidermis and/or adnexa), bone marrow (hypocellularity and reductions red blood cells, hemoglobin, hematocrit, neutrophils and eosinophils) and male sex organs (testes, epididymis, prostate, mammary gland, and seminal vesicle including increased mitotic figures and seminiferous tubule degeneration and hypospermia in the epididymis). Additional toxicological target organs identified include, mammary gland, lymphoid tissue (decreased cellularity and increased mitotic figures), liver (transient elevations in liver enzymes and single cell increased mitotic figures), eye (minimal increased corneal mitotic figures in the 13-week rat study without correlate in ophthalmological examinations), and gastrointestinal tract (increased epithelial mitotic figures in the intestines).

Dose-dependent skin findings were observed at approximately 2- to 3-fold and 1-fold the human exposure at the recommended clinical dose in rats and cynomolgus monkeys, respectively. Dose-dependent bone marrow findings were observed at approximately 2- to 3-fold the human exposure at the recommended clinical dose. Male reproductive toxicity was observed across all dose level in rats. All findings were reversible following a 6-week recovery period except for testes toxicity. The AUC in rats at 5 mg/kg, the maximum tolerated dose, was approximately 2- to 3-fold higher than the human exposure at the recommended clinical dose. The AUC in monkey at the NOAEL, 3 mg/kg, was approximately 3-fold higher than the human exposure at the recommended clinical dose.

Carcinogenicity:

Carcinogenicity studies with enfortumab vedotin or the small molecule cytotoxic agent (MMAE) have not been conducted.

Genotoxicity:

MMAE was genotoxic in the rat bone marrow micronucleus study through an aneugenic mechanism. This effect is consistent with the pharmacological effect of MMAE as a microtubule-disrupting agent. MMAE was not mutagenic in the bacterial reverse mutation assay (Ames test) or the L5178Y mouse lymphoma forward mutation assay.

Reproductive and Developmental Toxicology:

Impairment of Fertility

Fertility studies with enfortumab vedotin or MMAE have not been conducted. However, results of repeat-dose toxicity studies in rats indicate the potential for enfortumab vedotin to impair male reproductive function and fertility.

Administration of weekly doses of ≥2 mg/kg (approximately 1-fold the human exposure at the recommended dose) was associated with reduced weights in testis and epididymis. Histopathological findings included degeneration/atrophy and loss of germ cells in seminiferous tubules, abnormal spermatids and abnormal mitotic figures in the testis. Microscopic findings in the epididymis included luminal cell debris, hypospermia and abnormal spermatids. Changes in the testes and epididymis were not reversed following the recovery period.

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.

Developmental Toxicity

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.

Maternal toxicities, embryo-fetal lethality, reduced fetal body weight and structural malformations were observed with enfortumab vedotin at 2 mg/kg (an exposure similar to clinical exposure at the recommended dose) and with MMAE at 0.2 mg/kg (C_{max} 1.1-fold the human Cmax at the recommended clinical dose) administered on gestational days 6 and 13. The findings included structural malformations (malrotated hindlimb, absent digit of the forepaw, protruding tongue gastroschisis and agnathia) and skeletal abnormalities (asymmetric sternebrae, fused sternebrae, incomplete ossification of the sternebrae and misshapen sternebra, unilateral ossification of the thoracic centra, misshapen or fused cervical arch).

Special Toxicity:

No special toxicity studies have been conducted.

Juvenile Animal Studies:

No juvenile toxicity studies have been conducted.

PATIENT MEDICATION INFORMATION

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

PADCEV

enfortumab vedotin for injection

Read this carefully before you start taking **PADCEV** and each time you get a refill. This leaflet is a summary and will not tell you everything about this drug.

Talk to your healthcare professional about your medical condition and treatment and ask if there is any new information about **PADCEV**.

What is PADCEV used for?

PADCEV is a medicine used to treat adults with bladder cancer and cancer of the urinary tract (renal pelvis, ureter or urethra) that has spread or cannot be removed by surgery. PADCEV may be used if you have received chemotherapy that contains platinum and an immunotherapy medicine.

Serious Warnings and Precautions

- Skin reactions: Severe and fatal skin reactions including Stevens-Johnson syndrome and toxic epidermal necrolysis have occurred in patients treated with PADCEV (see section *What are possible side effects from using PADCEV?)*
- High blood sugar: High blood sugar, a serious condition called diabetic ketoacidosis (DKA), and death have occurred in patients with and without diabetes treated with PADCEV (see section *What are possible side effects from using PADCEV?*)

How does PADCEV work?

PADCEV contains enfortumab vedotin. Enfortumab vedotin has 2 parts. One part belongs to a group of medicines called monoclonal antibodies or mAbs. The other belongs to a group of medicines called anti-mitotics. This therapy kills the cancer cell once the antibody finds it.

What are the ingredients in PADCEV?

Medicinal ingredients: enfortumab vedotin

Non-medicinal ingredients: histidine monohydrochloride monohydrate, polysorbate 20, trehalose dihydrate

PADCEV comes in the following dosage forms:

PADCEV comes in single-use vials containing 20 mg or 30 mg of enfortumab vedotin for injection.

Do not use PADCEV if:

- You are allergic to enfortumab vedotin or any of the other ingredients of this medicine.

To help avoid side effects and ensure proper use, talk to your healthcare professional before you take PADCEV. Talk about any health conditions or problems you may have, including if you:

- have a history of high blood sugar or diabetes
- have any of the following skin problems, which could be the sign of a reaction:
  - rash or itching that continues to get worse or comes back after treatment
  - skin blistering or peeling
  - painful sores or ulcers in mouth or nose, throat, or skin around your penis or vagina
  - fever or flu-like symptoms or swollen lymph nodes
- are currently experiencing numbness or tingling in your hands or feet
- have eye problems such as very dry eyes and/or blurred vision
- have or have had liver problems
- have or have had kidney problems.

Other warnings you should know about:

Female Patients:

- PADCEV may harm your unborn baby and should not be used if you are pregnant.
- If you can get pregnant, your healthcare professional should do a pregnancy test before you start treatment with PADCEV.
- You should use an effective birth control method during your treatment and for at least 6 months after stopping PADCEV.
- It is not known if PADCEV passes into your breast milk and could harm your baby. You should not breastfeed during treatment and for at least 6 months after stopping PADCEV.

Male patients with female sexual partners who are pregnant, might be pregnant or could become pregnant:

- You should use an effective contraception during your treatment and for at least 4 months after stopping PADCEV.

Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.

The following may interact with PADCEV:

- Some medicines may change the amount of the PADCEV in your body, such as ketoconazole (anti-fungal).

How to take PADCEV:

- PADCEV will be given to you by a healthcare professional in a healthcare setting.
- PADCEV will be given to you by intravenous (IV) infusion into your vein over 30 minutes.
- PADCEV will be given to you over a period of 28 days. We call this a cycle. You will receive this medicine once a week for 3 weeks in every cycle. Then you will take a week off before starting the next cycle.
- Your healthcare professional will tell you how many treatment cycles you need.
- You may have blood tests during treatment with this medicine.

Usual dose:

The dose of PADCEV depends on your body weight. The usual starting dose of this medicine is 1.25 mg for each kilogram of your body weight up to 100 kg. Your healthcare professional may need to pause, stop or lower your dose of this medicine. This can happen if you have certain side effects or if your disease gets worse.

Overdose:

It is unlikely that you will receive too much PADCEV as you will be closely monitored by healthcare professionals during your infusion.

If you think you have taken too much PADCEV contact a healthcare professional, hospital emergency department, or regional poison control centre immediately, even if there are no symptoms.

Missed Dose:

If you miss your appointment to receive PADCEV, you should make every effort to receive the missed dose as soon as possible. Doses should be given at least 1 week apart.

What are possible side effects from using PADCEV?

These are not all the possible side effects you may have when taking PADCEV. If you experience any side effects not listed here, tell your healthcare professional.

- low red blood cells (anemia)
- low numbers of a type of white blood cell called neutrophils (neutropenia)
- feeling sick to your stomach (nausea)
- watery poop (diarrhea)
- throwing up (vomiting)
- feeling tired

- not wanting to eat (decreased appetite)
- bad taste in your mouth
- rash
- hair loss
- weight loss
- high levels of enzymes called aspartate aminotransferase or alanine aminotransferase
- itching
- low platelet counts
- changes in liver & kidney tests for function
- increased uric acid in blood
- increased lipase
- dry skin
- difficulty sleeping
- difficulty pooping (constipation)
- stomach pain
- fever
- urinary tract infection
- pain in the muscles and bones
- bleeding
- Infection in the blood

Serious side effects and what to do about them			
Symptom / effect	**Talk to your healthcare professional**		**Stop taking drug and get immediate medical help**
	Only if severe	**In all cases**	
VERY COMMON			
Hyperglycemia (high blood sugar): frequent need to urinate, increased thirst, blurred vision		X	
Peripheral neuropathy (damage to nerves): Weakness, numbness and pain in hands and feet		X	
COMMON			
Cardiac problems (fast heart rate): heart beating faster than usual		x	
Eye problems: dry eye, blurry vision		x	
Infusion Site Extravasation (drug leaks outside of the blood vessels): redness, pain,			X

Serious side effects and what to do about them			
Symptom / effect	**Talk to your healthcare professional**		**Stop taking drug and get immediate medical help**
	Only if severe	**In all cases**	
swelling, bruising, infection, or blisters at the infusion site			
Respiratory symptoms and lung problems (lung inflammation): cough, shortness of breath, chest pain or discomfort		x	
RARE			
Severe skin reactions (including Stevens-Johnson syndrome, toxic epidermal necrosis): unexplained widespread skin pain, blisters on your skin and mucous membranes, hives, tongue swelling, a red or purple skin rash that spreads, or unexplained shedding of your skin			X

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, tell your healthcare professional.

Reporting Side Effects

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada.html) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

NOTE: Contact your healthcare professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

Storage:

Keep out of reach and sight of children.

PADCEV will be stored by the healthcare professional at the hospital or clinic. The storage details are as follows:

Do not use this medicine after the expiry date. This date is listed on the carton and vial label after EXP. Your healthcare professional will check this date before you receive this medicine.

Store this medicine at 2°C to 8°C. Do not freeze. Do not shake. Do not expose to sunlight. Do not store any unused portion of the infusion solution for reuse. Any unused medicine or waste material should be disposed of in accordance with local requirements.

If you want more information about PADCEV:

- Talk to your healthcare professional
- Find the full product monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website: (https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/drug-product-database.html); the manufacturer's website www.Seagen.ca, or by calling 1-833-473-2436.

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