HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use PADCEV safely and effectively. See full prescribing information for PADCEV.

PADCEV® (enfortumab vedotin-ejfv) for injection, for intravenous use
Initial U.S. Approval: 2019

WARNING: SERIOUS SKIN REACTIONS
See full prescribing information for complete boxed warning.

- **PADCEV can cause severe and fatal cutaneous adverse reactions, including Stevens-Johnson syndrome (SJS) and Toxic Epidermal Necrolysis (TEN).**
- **Immediately withhold PADCEV and consider referral for specialized care for suspected SJS or TEN or severe skin reactions.**
- **Permanently discontinue PADCEV in patients with confirmed SJS or TEN; or Grade 4 or recurrent Grade 3 skin reactions. (2.2), (5.1) (6.1)**

RECENT MAJOR CHANGES

Indications and Usage (1)	4/2023
Dosage and Administration (2.2)	10/2022
Warnings and Precautions (5.1), (5.2), (5.3), (5.4), (5.6)	4/2023

INDICATIONS AND USAGE

PADCEV is a Nectin-4-directed antibody and microtubule inhibitor conjugate indicated:

- as a single agent for the treatment of adult patients with locally advanced or metastatic urothelial cancer who:
  - have previously received a programmed death receptor-1 (PD-1) or programmed death-ligand 1 (PD-L1) inhibitor and platinum-containing chemotherapy, or
  - are ineligible for cisplatin-containing chemotherapy and have previously received one or more prior lines of therapy. (1)
- in combination with pembrolizumab for the treatment of adult patients with locally advanced or metastatic urothelial cancer who are not eligible for cisplatin-containing chemotherapy.[1] (1)

[1] This indication is approved under accelerated approval based on tumor response rate and durability of response. Continued approval for this indication may be contingent upon verification and description of clinical benefit in the confirmatory trials. (14.1)

DOSAGE AND ADMINISTRATION

- *For intravenous infusion only.* Do not administer PADCEV as an intravenous push or bolus. Do not mix with, or administer as an infusion with, other medicinal products. (2.3)
- The recommended dose of PADCEV as a single agent is 1.25 mg/kg (up to a maximum dose of 125 mg) given as an intravenous infusion over 30 minutes on Days 1, 8 and 15 of a 28-day cycle until disease progression or unacceptable toxicity. (2.1)
- The recommended dose of PADCEV in combination with pembrolizumab is 1.25 mg/kg (up to a maximum dose of 125 mg) given as an intravenous infusion over 30 minutes on Days 1 and 8 of a 21-day cycle until disease progression or unacceptable toxicity. (2.1)
- Avoid use in patients with moderate or severe hepatic impairment (8.6)

DOSAGE FORMS AND STRENGTHS

For Injection: 20 mg and 30 mg of enfortumab vedotin-ejfv as a lyophilized powder in a single-dose vial for reconstitution. (3)

CONTRAINDICATIONS

None. (4)

WARNINGS AND PRECAUTIONS

- Hyperglycemia: Diabetic ketoacidosis may occur in patients with and without preexisting diabetes mellitus, which may be fatal. Closely /monitor blood glucose levels in patients with, or at risk for, diabetes mellitus or hyperglycemia. Withhold PADCEV if blood glucose is >250 mg/dL. (2.2, 5.2)
- Pneumonitis/Interstitial Lung Disease (ILD): Severe, life-threatening or fatal pneumonitis/ILD may occur. Withhold PADCEV for Grade 2 pneumonitis/ILD and consider dose reduction. Permanently discontinue PADCEV for Grade 3 or 4 pneumonitis/ILD. (2.2, 5.3)
- Peripheral Neuropathy: Monitor patients for new or worsening peripheral neuropathy and consider dose interruption, dose reduction or discontinuation of PADCEV. (2.2, 5.4)
- Ocular Disorders: Ocular disorders, including vision changes, may occur. Monitor patients for signs or symptoms of ocular disorders. Consider prophylactic artificial tears for dry eyes and treatment with ophthalmic topical steroids after an ophthalmic exam. Consider dose interruption or dose reduction of PADCEV when symptomatic ocular disorders occur. (5.5)
- Infusion Site Extravasation: Ensure adequate venous access prior to administration. Monitor the infusion site during PADCEV administration and stop the infusion immediately for suspected extravasation. (5.6)
- Embryo-Fetal Toxicity: PADCEV can cause fetal harm. Advise of the potential risk to a fetus and to use effective contraception. (5.7, 8.1, 8.3)

ADVERSE REACTIONS

The most common adverse reactions, including laboratory abnormalities, (≥20%) were:

- PADCEV as a single agent: rash, aspartate aminotransferase increased, glucose increased, creatinine increased, fatigue, peripheral neuropathy, lymphocytes decreased, alopecia, decreased appetite, hemoglobin decreased, diarrhea, sodium decreased, nausea, pruritus, phosphate decreased, dysgeusia, alanine aminotransferase increased, anemia, albumin decreased, neutrophils decreased, urate increased, lipase increased, platelets decreased, weight decreased and dry skin. (6.1)
- PADCEV in combination with pembrolizumab: glucose increased, aspartate aminotransferase increased, rash, hemoglobin decreased, creatinine increased, peripheral neuropathy, lymphocytes decreased, fatigue, alanine aminotransferase increased, sodium decreased, lipase increased, albumin decreased, alopecia, phosphate decreased, decreased weight, diarrhea, pruritus, decreased appetite, nausea, dysgeusia, potassium decreased, neutrophils decreased, urinary tract infection, constipation, potassium increased, calcium increased, peripheral edema, dry eye, dizziness, arthralgia, and dry skin. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Astellas Pharma US, Inc. at 1-800-727-7003 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DRUG INTERACTIONS

Concomitant use of dual P-gp and strong CYP3A4 inhibitors with PADCEV may increase the exposure to monomethyl auristatin E (MMAE). (7.1)

USE IN SPECIFIC POPULATIONS

- Lactation: Advise women not to breastfeed. (8.2)

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling

Revised: 4/2023

FULL PRESCRIBING INFORMATION: CONTENTS*

*Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

WARNING: SERIOUS SKIN REACTIONS

- **PADCEV can cause severe and fatal cutaneous adverse reactions including Stevens-Johnson syndrome (SJS) and Toxic Epidermal Necrolysis (TEN), which occurred predominantly during the first cycle of treatment, but may occur later.**
- **Closely monitor patients for skin reactions.**
- **Immediately withhold PADCEV and consider referral for specialized care for suspected SJS or TEN or severe skin reactions.**
- **Permanently discontinue PADCEV in patients with confirmed SJS or TEN; or Grade 4 or recurrent Grade 3 skin reactions *[see Dosage and Administration (2.2), Warnings and Precautions (5.1) and Adverse Reactions (6.1)]*.**

1 INDICATIONS AND USAGE

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, or
- are ineligible for cisplatin-containing chemotherapy and have previously received one or more prior lines of therapy.

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.

This indication is approved under accelerated approval based on tumor response rate and durability of response *[see Clinical Studies (14.1)]*. Continued approval for this indication may be contingent upon verification and description of clinical benefit in the confirmatory trials.

2 DOSAGE AND ADMINISTRATION

2.1 Recommended Dosage

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.

2.2 Dose Modifications

Table 1. Dose Modifications

Adverse Reaction	Severity[1]	Dose Modification[1]
Skin Reactions *[see Boxed Warning, Warnings and Precautions (5.1)]*	For persistent or recurrent Grade 2 skin reactions	Consider withholding until Grade ≤1, then resume treatment at the same dose level or dose reduce by one dose level.
	Grade 3 skin reactions	Withhold until Grade ≤1, then resume treatment at the same dose level or dose reduce by one dose level.
	Suspected SJS or TEN	Immediately withhold, consult a specialist to confirm the diagnosis. If not SJS/TEN, see Grade 2-4 skin reactions.
	Confirmed SJS or TEN; Grade 4 or recurrent Grade 3 skin reactions	Permanently discontinue.
Hyperglycemia *[see Warnings and Precautions (5.2)]*	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 (ILD) *[see Warnings and Precautions (5.3)]*	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 *[see Warnings and Precautions (5.4)]*	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 nonhematologic toxicity *[see Adverse Reactions (6)]*	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 *[see Adverse Reactions (6)]*	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.

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

Table 2. Recommended Dose Reduction Schedule

	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

2.3 Instructions for Preparation and Administration

- Administer PADCEV as an intravenous infusion only.
- PADCEV is a hazardous drug. Follow applicable special handling and disposal procedures.[1]

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 either 5% Dextrose Injection, USP, 0.9% Sodium Chloride Injection, USP, or Lactated Ringer's Injection, USP.

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 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 PADCEV.
    b. 30 mg vial: Add 3.3 mL of SWFI, resulting in 10 mg/mL PADCEV.
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. Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit. 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.
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). 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 either 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 PADCEV.
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 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.
12. Discard any unused portion left in the single-dose vials.

Administration

13. Immediately administer the infusion over 30 minutes through an intravenous line.
14. If the infusion is not administered immediately, the prepared infusion bag should not be stored longer than 8 hours at 2°C to 8°C (36 °F to 46 °F). DO NOT FREEZE.

DO NOT administer PADCEV as an intravenous push or bolus.

DO NOT mix PADCEV with, or administer as an infusion with, other medicinal products.

3 DOSAGE FORMS AND STRENGTHS

For Injection: 20 mg and 30 mg of enfortumab vedotin-ejfv as a white to off-white lyophilized powder in a single-dose vial for reconstitution.

4 CONTRAINDICATIONS

None.

5 WARNINGS AND PRECAUTIONS

5.1 Skin Reactions

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

Skin reactions occurred in 56% (all grades) of the 753 patients treated with PADCEV as a single agent in clinical trials. Twenty-four percent (24%) of patients had maculo-papular rash and 33% had pruritus. Grade 3-4 skin reactions occurred in 12% of patients, including maculo-papular rash, erythematous rash, rash or drug eruption, symmetrical drug-related intertriginous and flexural exanthema (SDRIFE), bullous dermatitis, exfoliative dermatitis, and palmar-plantar erythrodysesthesia. The median time to onset of severe skin reactions was 0.7 months (range: 0.1 to 6 months). Among patients experiencing a skin reaction leading to dose interruption who then restarted PADCEV (n=59), 24% of patients restarting at the same dose and 16% of patients restarting at a reduced dose experienced recurrent severe skin reactions. Skin reactions led to discontinuation of PADCEV in 2.6% of patients *[see Adverse Reactions (6.1)]*.

When PADCEV was given in combination with pembrolizumab, the incidence of skin reactions, including severe events, occurred at a higher rate. Skin reactions occurred in 72% (all grades) of the 121 patients treated with PADCEV in combination with pembrolizumab in clinical trials. The majority of the skin reactions that occurred with combination therapy included maculo-papular rash, macular rash and papular rash. Grade 3-4 skin reactions occurred in 20% of patients (Grade 3: 19%, Grade 4: 0.8%), including maculo-papular rash, bullous dermatitis, dermatitis, exfoliative dermatitis, pemphigoid, rash, erythematous rash, macular rash, and papular rash. A fatal reaction of bullous dermatitis occurred in one patient (0.8%). The median time to onset of severe skin reactions was 2.6 months (range: 0.3 to 16 months). Skin reactions led to discontinuation of PADCEV in 6% of patients *[see Adverse Reactions (6.1)]*.

Monitor patients closely throughout treatment for skin reactions. Consider topical corticosteroids and antihistamines, as clinically indicated.

For persistent or recurrent Grade 2 skin reactions, consider withholding PADCEV until Grade ≤1. Withhold PADCEV and refer for specialized care for suspected SJS, TEN or for Grade 3 skin reactions.

Permanently discontinue PADCEV in patients with confirmed SJS or TEN; or Grade 4 or recurrent Grade 3 skin reactions *[see Dosage and Administration (2.2)]*.

5.2 Hyperglycemia

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

Patients with baseline hemoglobin A1C ≥8% were excluded from clinical trials.

In clinical trials of PADCEV as a single agent, 14% of the 753 patients treated with PADCEV developed hyperglycemia; 7% of patients developed Grade 3-4 hyperglycemia. Fatal events of hyperglycemia and diabetic ketoacidosis occurred in one patient each (0.1%). The incidence of Grade 3-4 hyperglycemia increased consistently in patients with higher body

mass index and in patients with higher baseline A1C. Five percent (5%) 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 months). Hyperglycemia led to discontinuation of PADCEV in 0.4% of patients *[see Adverse Reactions (6.1)]*.

Closely monitor blood glucose levels in patients with, or at risk for, diabetes mellitus or hyperglycemia.

If blood glucose is elevated (>250 mg/dL), withhold PADCEV *[see Dosage and Administration (2.2)]*.

5.3 Pneumonitis/Interstitial Lung Disease (ILD)

Severe, life-threatening or fatal pneumonitis/ILD occurred in patients treated with PADCEV.

In clinical trials of PADCEV as a single agent, 2.9% of the 753 patients treated with PADCEV had pneumonitis/ILD of any grade and 0.8% had Grade 3-4. The median time to onset of pneumonitis/ILD was 2.7 months (range: 0.6 to 6 months).

The incidence of pneumonitis/ILD, including severe events occurred at a higher rate when PADCEV was given in combination with pembrolizumab. When PADCEV was given in combination with pembrolizumab, 9% of the 121 patients treated with combination therapy had pneumonitis/ILD of any grade and 3.3% had Grade 3. A fatal event of pneumonitis occurred in one patient (0.8%). The median time to onset of pneumonitis/ILD was 6 months (range: 0.6 to 26 months).

Monitor patients for signs and symptoms indicative of pneumonitis/ILD 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 patients who develop Grade 2 pneumonitis/ILD and consider dose reduction. Permanently discontinue PADCEV in all patients with Grade 3 or 4 pneumonitis/ILD *[see Dosage and Administration (2.2)]*.

5.4 Peripheral Neuropathy

Peripheral neuropathy occurred in 53% of the 753 patients treated with PADCEV as a single agent in clinical trials including 40% with sensory neuropathy, 7% with muscular weakness and 7% with motor neuropathy. Thirty percent of patients experienced Grade 2 reactions and 5% experienced Grade 3-4 reactions. Peripheral neuropathy occurred in patients treated with PADCEV with or without preexisting peripheral neuropathy. The median time to onset of Grade ≥2 peripheral neuropathy was 4.9 months (range: 0.1 to 20 months). Neuropathy led to treatment discontinuation in 7% of patients *[see Adverse Reactions (6.1)]*. Of the patients who experienced neuropathy who had data regarding resolution (N = 319) 14% had complete resolution, 46% had partial improvement, and 40% had no improvement at the time of their last evaluation. Of the 86% of patients with residual neuropathy at last evaluation, 51% had Grade 2 or greater neuropathy at the time of their last evaluation.

The incidence of peripheral neuropathy occurred at a higher rate when PADCEV was given in combination with pembrolizumab. When PADCEV was given in combination with pembrolizumab, 65% of the 121 patients treated with combination therapy had peripheral neuropathy of any grade, 45% had Grade 2 neuropathy, and 3.3% had Grade 3 neuropathy. The median time to onset of Grade ≥2 peripheral neuropathy was 6 months (range: 0.3 to 25 months).

Monitor patients for symptoms of new or worsening peripheral neuropathy and consider dose interruption or dose reduction of PADCEV when peripheral neuropathy occurs.

Permanently discontinue PADCEV in patients who develop Grade ≥3 peripheral neuropathy *[see Dosage and Administration (2.2)]*.

5.5 Ocular Disorders

Ocular disorders were reported in 40% of the 384 patients treated with PADCEV as a single agent in clinical trials in which ophthalmologic exams were scheduled. The majority of these 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.

Dry eye symptoms occurred in 34% of patients, and blurred vision occurred in 13% of patients, during treatment with PADCEV. The median time to onset to symptomatic ocular disorder was 1.6 months (range: 0 to 19 months). Monitor patients for ocular disorders. Consider artificial tears for prophylaxis of dry eyes and ophthalmologic evaluation if ocular symptoms occur or do not resolve. Consider treatment with ophthalmic topical steroids, if indicated after an ophthalmic exam. Consider dose interruption or dose reduction of PADCEV for symptomatic ocular disorders.

5.6 Infusion Site Extravasation

Skin and soft tissue reactions secondary to extravasation have been observed after administration of PADCEV. Of the 753 patients treated with PADCEV as a single agent in clinical trials, 1.5% of patients experienced skin and soft tissue reactions, including 0.3% 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 adequate venous access prior to starting PADCEV and monitor for possible extravasation during administration. If extravasation occurs, stop the infusion and monitor for adverse reactions.

5.7 Embryo-Fetal Toxicity

Based on the mechanism of action and findings in animals, PADCEV can cause fetal harm when administered to a pregnant woman. In animal reproduction studies, administration of enfortumab vedotin-ejfv to pregnant rats during the period of organogenesis caused maternal toxicity, embryo-fetal lethality, structural malformations and skeletal anomalies at maternal exposures similar to the clinical exposures at the recommended human dose of 1.25 mg/kg.

Advise patients of the potential risk to the fetus. Advise female patients of reproductive potential to use effective contraception during treatment with PADCEV and for 2 months after the last dose. Advise male patients with female partners of reproductive potential to use effective contraception during treatment with PADCEV and for 4 months after the last dose *[see Use in Specific Populations (8.1, 8.3) and Clinical Pharmacology (12.1)]*.

6 ADVERSE REACTIONS

The following serious adverse reactions are described elsewhere in the labeling:

- Skin Reactions *[see Boxed Warning, Warnings and Precautions (5.1)]*
- Hyperglycemia *[see Warnings and Precautions (5.2)]*
- Pneumonitis/Interstitial Lung Disease (ILD) *[see Warnings and Precautions (5.3)]*
- Peripheral Neuropathy *[see Warnings and Precautions (5.4)]*
- Ocular Disorders *[see Warnings and Precautions (5.5)]*
- Infusion Site Extravasation *[see Warnings and Precautions (5.6)]*

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

The pooled safety population described in the WARNINGS AND PRECAUTIONS reflect exposure to PADCEV as a single agent at 1.25 mg/kg in 753 patients in EV-301, EV-201, EV-103, EV-101 (NCT02091999), and EV-102 (NCT03070990). In addition, certain subsections in the WARNINGS AND PRECAUTIONS describe adverse reactions observed with exposure to PADCEV in combination with pembrolizumab at 1.25 mg/kg in 121 patients in EV-103. Ocular disorders reflect 384 patients in EV-201, EV-101, and EV-102. Among 753 patients receiving PADCEV as a single agent, 25% were exposed for ≥6 months, and 13% were exposed for ≥12 months. In this pooled population, the most common (≥20%) adverse reactions, including laboratory abnormalities, were rash, aspartate aminotransferase increased, glucose increased, creatinine increased, fatigue, peripheral neuropathy, lymphocytes decreased, alopecia, decreased appetite, hemoglobin decreased, diarrhea, sodium decreased, nausea, pruritus, phosphate decreased, dysgeusia, alanine aminotransferase increased, anemia, albumin decreased, neutrophils decreased, urate increased, lipase increased, platelets decreased, decreased weight and dry skin.

The data described in the following sections reflect exposure to PADCEV as a single agent from an open-label, randomized, study (EV-301); Cohort 1 and Cohort 2 of an open-label, single arm, two cohort study (EV-201); and Cohort K of an open-label, multi-cohort study (EV-103). Patients received PADCEV 1.25 mg/kg until disease progression or unacceptable toxicity.

The data described in the following section also reflects exposure to PADCEV in combination with pembrolizumab from the dose escalation cohort, Cohort A and Cohort K of EV-103. Patients received PADCEV 1.25 mg/kg in combination with pembrolizumab until disease progression or unacceptable toxicity.

Previously Treated Locally Advanced or Metastatic Urothelial Cancer

EV-301

The safety of PADCEV was evaluated as a single agent in EV-301 in patients with locally advanced or metastatic urothelial cancer (n=296) who received at least one dose of PADCEV 1.25 mg/kg and who were previously treated with a PD-1 or PD-L1 inhibitor and a platinum-based chemotherapy *[see Clinical Studies (14)]*. Routine ophthalmologic exams were not conducted in EV-301. The median duration of exposure to PADCEV was 5 months (range: 0.5 to 19 months).

Serious adverse reactions occurred in 47% of patients treated with PADCEV. The most common serious adverse reactions (≥2%) were urinary tract infection, acute kidney injury (7% each) and pneumonia (5%). Fatal adverse reactions occurred in 3% of patients, including multiorgan dysfunction (1.0%), hepatic dysfunction, septic shock, hyperglycemia, pneumonitis and pelvic abscess (0.3% each).

Adverse reactions leading to discontinuation occurred in 17% of patients; the most common adverse reactions (≥2%) leading to discontinuation were peripheral neuropathy (5%) and rash (4%).

Adverse reactions leading to dose interruption occurred in 61% of patients; the most common adverse reactions (≥4%) leading to dose interruption were peripheral neuropathy (23%), rash (11%) and fatigue (9%).

Adverse reactions leading to dose reduction occurred in 34% of patients; the most common adverse reactions (≥2%) leading to dose reduction were peripheral neuropathy (10%), rash (8%), decreased appetite (3%) and fatigue (3%).

Table 3 summarizes the most common (≥15%) adverse reactions in EV-301.

Table 3. Adverse Reactions (≥15%) in Patients Treated with PADCEV in EV-301

Adverse Reaction	PADCEV n=296		Chemotherapy n=291	
	All Grades %	Grade 3-4 %	All Grades %	Grade 3-4 %
Skin and subcutaneous tissue disorders				
Rash[1]	54	14	20	0.3
Alopecia	47	0	38	0
Pruritus	34	2	7	0
Dry skin	17	0	4	0
General disorders and administration site conditions				
Fatigue[2]	50	9	40	7
Pyrexia[3]	22	2	14	0
Nervous system disorders				
Peripheral neuropathy[4]	50	5	34	3
Dysgeusia[5]	26	0	8	0
Metabolism and nutrition disorders				
Decreased appetite	41	5	27	2
Gastrointestinal disorders				
Diarrhea[6]	35	4	23	2
Nausea	30	1	25	2
Constipation	28	1	25	2
Abdominal Pain[7]	20	1	14	3
Musculoskeletal and connective tissue disorders				
Musculoskeletal Pain[8]	25	2	35	5
Eye Disorders				
Dry eye[9]	24	0.7	6	0.3
Blood and lymphatic system disorders				
Anemia	20	6	30	12
Infections and infestations				
Urinary Tract Infection[10]	17	6	13	3
Vascular disorders				
Hemorrhage[11]	17	3	13	2
Investigations				
Weight decreased	16	0.3	7	0

1. Includes: blister, blood blister, conjunctivitis, dermatitis, dermatitis bullous, 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
2. Includes: fatigue, asthenia
3. Includes: pyrexia, hyperthermia, hyperpyrexia, body temperature increased
4. 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
5. Includes: dysgeusia, ageusia, hypogeusia
6. Includes: diarrhea, colitis, enterocolitis
7. Includes: abdominal pain, abdominal pain upper, abdominal pain lower, abdominal discomfort, hepatic pain, abdominal tenderness, gastrointestinal pain
8. Includes: myalgia, arthralgia, back pain, bone pain, pain in extremity, musculoskeletal pain, arthritis, neck pain, non-cardiac chest pain, musculoskeletal chest pain, spinal pain, musculoskeletal stiffness, musculoskeletal discomfort

9. Includes: blepharitis, conjunctivitis, dry eye, eye irritation, keratitis, keratopathy, lacrimation increased, Meibomian gland dysfunction, ocular discomfort, punctate keratitis
10. 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
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

Clinically relevant adverse reactions (<15%) include vomiting (14%), aspartate aminotransferase increased (12%), hyperglycemia (10%), alanine aminotransferase increased (9%), pneumonitis (3%) and infusion site extravasation (0.7%).

Table 4. Selected Laboratory Abnormalities Reported in ≥15% (Grades 2-4) or ≥5% (Grade 3-4) of Patients Treated with PADCEV in EV-301

Laboratory Abnormality	PADCEV[1]		Chemotherapy[1]	
	Grades 2-4 %	Grade 3-4 %	Grades 2-4 %	Grade 3-4 %
Hematology				
Lymphocytes decreased	41	14	34	18
Hemoglobin decreased	28	4	42	14
Neutrophils decreased	27	12	25	17
Chemistry				
Phosphate decreased	39	8	24	6
Glucose increased (non-fasting)	33	9	27	6
Creatinine increased	18	2	13	0
Potassium decreased	16	2	7	3
Lipase increased	13	8	7	4
Sodium decreased	8	8	5	5

1. The denominator used to calculate the rate varied from 262 to 287 based on the number of patients with a baseline value and at least one post-treatment value.

EV-201, Cohort 1

The safety of PADCEV was evaluated as a single agent in EV-201, Cohort 1 in patients (n=125) with locally advanced or metastatic urothelial cancer who had received prior treatment with a PD-1 or PD-L1 inhibitor and platinum-based chemotherapy *[see Clinical Studies (14)]*. Patients received PADCEV 1.25 mg/kg on Days 1, 8 and 15 of a 28-day cycle until disease progression or unacceptable toxicity. The median duration of exposure to PADCEV was 4.6 months (range: 0.5-15.6).

Serious adverse reactions occurred in 46% of patients treated with PADCEV. The most common serious adverse reactions (≥3%) were urinary tract infection (6%), cellulitis (5%), febrile neutropenia (4%), diarrhea (4%), sepsis (3%), acute kidney injury (3%), dyspnea (3%), and rash (3%). Fatal adverse reactions occurred in 3.2% of patients, including acute respiratory failure, aspiration pneumonia, cardiac disorder, sepsis and pneumonitis (each 0.8%).

Adverse reactions leading to discontinuation occurred in 16% of patients; the most common adverse reaction leading to discontinuation was peripheral neuropathy (6%).

Adverse reactions leading to dose interruption occurred in 64% of patients; the most common adverse reactions leading to dose interruption were peripheral neuropathy (18%), rash (9%) and fatigue (6%).

Adverse reactions leading to dose reduction occurred in 34% of patients; the most common adverse reactions leading to dose reduction were peripheral neuropathy (12%), rash (6%) and fatigue (4%).

Laboratory Abnormality	PADCEV in combination with pembrolizumab	
	All Grades[1] %	Grade 3-4[1] %
Calcium increased	27	4.2

1. The denominator used to calculate the rate varied from 114 to 121 based on the number of patients with a baseline value and at least one post-treatment value.

6.2 Post Marketing Experience

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 *[see Warnings and Precautions (5.1)]*.

7 DRUG INTERACTIONS

7.1 Effects of Other Drugs on PADCEV

Dual P-gp and Strong CYP3A4 Inhibitors

Concomitant use with dual P-gp and strong CYP3A4 inhibitors may increase unconjugated MMAE exposure *[see Clinical Pharmacology (12.3)]*, which may increase the incidence or severity of PADCEV toxicities. Closely monitor patients for signs of toxicity when PADCEV is given concomitantly with dual P-gp and strong CYP3A4 inhibitors.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Based on the mechanism of action and findings in animals, PADCEV can cause fetal harm when administered to a pregnant woman *[see Clinical Pharmacology (12.1)]*. There are no available human data on PADCEV use in pregnant women to inform a drug-associated risk. In an animal reproduction study, administration of enfortumab vedotin-ejfv to pregnant rats during organogenesis caused maternal toxicity, embryo-fetal lethality, structural malformations and skeletal anomalies at maternal exposures similar to the exposures at the recommended human dose of 1.25 mg/kg *(see Data)*. Advise patients of the potential risk to the fetus.

The background risk of major birth defects and miscarriage for the indicated population is unknown. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2%-4% and 15%-20%, respectively.

Data

Animal Data

In a rat pilot embryo-fetal development study, administration of enfortumab vedotin-ejfv on gestation day 6 and 13 during the period of organogenesis resulted in a complete litter loss in all pregnant rats at the maternally toxic dose of 5 mg/kg (approximately 3 times the exposure at the recommended human dose). A dose of 2 mg/kg (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.

8.2 Lactation

Risk Summary

There are no data on the presence of enfortumab vedotin-ejfv in human milk, the effects on the breastfed child, or the effects on milk production. Because of the potential for serious adverse reactions in a breastfed child, advise lactating women not to breastfeed during treatment with PADCEV and for at least 3 weeks after the last dose.

8.3 Females and Males of Reproductive Potential

Pregnancy Testing

Verify pregnancy status in females of reproductive potential prior to initiating PADCEV treatment *[see Use in Specific Populations (8.1)]*.

Contraception

Females

PADCEV can cause fetal harm when administered to a pregnant woman *[see Use in Specific Populations (8.1)]*. Advise females of reproductive potential to use effective contraception during treatment with PADCEV and for 2 months after the last dose.

Males

Advise male patients with female partners of reproductive potential to use effective contraception during treatment with PADCEV and for 4 months after the last dose.

Infertility

Females

Based on findings in animal studies with MMAE-containing antibody-drug conjugates (ADCs), PADCEV may impair female fertility. The effect on fertility is reversible *[see Nonclinical Toxicology (13.1)]*.

Males

Based on findings from animal studies, PADCEV may impair male fertility *[see Nonclinical Toxicology (13.1)]*.

8.4 Pediatric Use

Safety and effectiveness of PADCEV in pediatric patients have not been established.

8.5 Geriatric Use

Of the 753 patients treated with PADCEV as a single agent in clinical trials, 40% (n=300) were 65-74 years and 27% (n=202) were 75 years or older. Of the 121 patients treated with PADCEV in combination with pembrolizumab, 43% (n=52) were 65-74 years and 33% (n=40) were 75 years or older. No overall differences in effectiveness were observed between patients 65 years of age or older and younger patients.

Patients 65 years of age or older treated with PADCEV as a single agent experienced a higher incidence of serious and fatal adverse reactions than younger patients. In clinical trials, the incidence of serious adverse reactions was 42% in patients younger than 65 years, 45% in patients ages 65-74 years, and 49% in patients 75 years or older. The incidence of

fatal adverse reactions was 4.4% in patients younger than 65 years, 6% in patients ages 65-74 years, and 11% in patients 75 years or older. The incidence of treatment discontinuations of PADCEV due to adverse reactions was 17% in patients younger than 65 years, 20% in patients ages 65-74 years, and 26% in patients 75 years or older.

There were an insufficient number of patients treated with PADCEV in combination with pembrolizumab in clinical trials to accurately characterize safety by age.

No significant difference was observed in the pharmacokinetics of PADCEV between patients 65 years and older and younger patients *[see Clinical Pharmacology (12.3)]*.

8.6 Hepatic Impairment

Avoid the use of PADCEV in patients with moderate or severe hepatic impairment (total bilirubin >1.5 x ULN and AST any). PADCEV 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 *[see Clinical Pharmacology (12.3)]*. In another ADC that contains MMAE, the frequency of ≥ Grade 3 adverse reactions and deaths was greater in patients with moderate (Child-Pugh B) or severe (Child-Pugh C) hepatic impairment compared to patients with normal hepatic function. No adjustment in the starting dose is required when administering PADCEV to patients with mild hepatic impairment (total bilirubin 1 to 1.5 × ULN and AST any, or total bilirubin ≤ULN and AST >ULN).

8.7 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 Clinical Pharmacology (12.3)]*.

11 DESCRIPTION

Enfortumab vedotin-ejfv is a Nectin-4 directed antibody-drug conjugate (ADC) comprised of a fully human anti-Nectin-4 IgG1 kappa monoclonal antibody (AGS-22C3) conjugated to the small molecule microtubule disrupting agent, monomethyl auristatin E (MMAE) via a protease-cleavable maleimidocaproyl valine-citrulline (vc) linker (SGD-1006). Conjugation takes place on cysteine residues that comprise the interchain disulfide bonds of the antibody to yield a product with a drug-to-antibody ratio of approximately 3.8:1. The molecular weight is approximately 152 kDa.

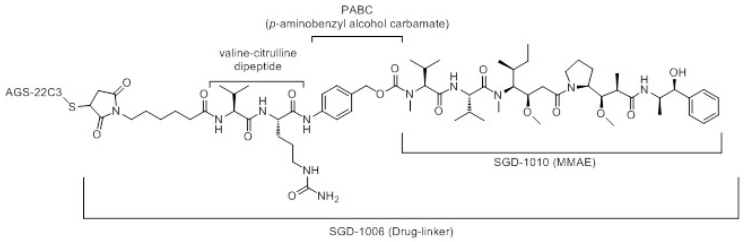

Figure 1. Structural Formula

Approximately 4 molecules of MMAE are attached to each antibody molecule. Enfortumab vedotin-ejfv is produced by chemical conjugation of the antibody and small molecule components. The antibody is produced by mammalian (Chinese hamster ovary) cells and the small molecule components are produced by chemical synthesis.

PADCEV (enfortumab vedotin-ejfv) for injection is provided as a sterile, preservative-free, white to off-white lyophilized powder in single-dose vials for intravenous use. PADCEV is supplied as a 20 mg per vial and a 30 mg per vial and requires reconstitution with Sterile Water for Injection, USP, (2.3 mL and 3.3 mL, respectively) resulting in a clear to slightly opalescent, colorless to slightly yellow solution with a final concentration of 10 mg/mL *[see Dosage and Administration (2.3)]*. After reconstitution, each vial allows the withdrawal of 2 mL (20 mg) and 3 mL (30 mg). Each mL of reconstituted solution contains 10 mg of enfortumab vedotin-ejfv, histidine (1.4 mg), histidine hydrochloride monohydrate (2.31 mg), polysorbate 20 (0.2 mg) and trehalose dihydrate (55 mg) with a pH of 6.0.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Enfortumab vedotin-ejfv is an ADC. The antibody is a human IgG1 directed against Nectin-4, an adhesion protein located on the surface of cells. The small molecule, MMAE, is a microtubule-disrupting agent, attached to the antibody via a protease-cleavable linker. Nonclinical data suggest that the anticancer activity of enfortumab vedotin-ejfv 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. The combination of enfortumab vedotin-ejfv with a PD-1 blocking antibody resulted in up-regulation of immune function and increased anti-tumor activity in syngeneic mouse tumor models expressing Nectin-4.

12.2 Pharmacodynamics

In an exposure-response analysis, higher enfortumab vedotin-ejfv exposure was associated with higher incidence of some adverse reactions (e.g., Grade ≥2 peripheral neuropathy, Grade ≥3 hyperglycemia). The exposure-response relationship for efficacy has not been fully characterized.

Cardiac Electrophysiology

At the recommended dose, PADCEV had no large QTc prolongation (>20 msec).

12.3 Pharmacokinetics

Population pharmacokinetic analysis included data from 748 patients treated with PADCEV as a single agent in clinical trials. Enfortumab vedotin-ejfv 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 PADCEV administration as a single agent and in combination with pembrolizumab.

The exposure parameters of ADC and unconjugated MMAE (the cytotoxic component of enfortumab vedotin-ejfv) are summarized in Table 11 below. Peak ADC concentrations were observed near the end of intravenous infusion while peak unconjugated MMAE concentrations were observed approximately 2 days after enfortumab vedotin-ejfv dosing. Minimal accumulation of the ADC and unconjugated MMAE was observed following repeat administration of enfortumab vedotin-ejfv in patients. Steady-state concentrations of ADC and unconjugated MMAE were reached after 1 treatment cycle.

Table 11. Exposure parameters of ADC and unconjugated MMAE after first treatment cycle of 1.25 mg/kg of enfortumab vedotin-ejfv dose of Days 1, 8 and 15

	ADC **Mean (± SD)**	**Unconjugated MMAE** **Mean (± SD)**
C_{max}	28 (6.1) µg/mL	5.5 (3.0) ng/mL
$AUC_{0\text{-}28d}$	110 (26) µg·d/mL	85 (50) ng·d/mL
$C_{trough,0\text{-}28d}$	0.31 (0.18) µg/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 estimated mean steady-state volume of distribution of ADC was 12.8 liters following administration of enfortumab vedotin-ejfv. Plasma protein binding of unconjugated MMAE ranged from 68% to 82%, *in vitro*.

Elimination

ADC and unconjugated MMAE exhibited multi-exponential declines with an elimination half-life of 3.6 days and 2.6 days, respectively. The mean clearance (CL) of enfortumab vedotin-ejfv and unconjugated MMAE in patients was 0.11 L/h and 2.11 L/h, respectively, in patients. Elimination of unconjugated MMAE appeared to be limited by its rate of release from enfortumab vedotin-ejfv.

Metabolism

Enfortumab vedotin-ejfv catabolism has not been studied in humans; however, it is expected to undergo catabolism to small peptides, amino acids, unconjugated MMAE, and unconjugated MMAE-related catabolites. Enfortumab vedotin-ejfv releases unconjugated MMAE via proteolytic cleavage, and unconjugated MMAE is primarily metabolized by CYP3A4 *in vitro*.

Excretion

The excretion of enfortumab vedotin-ejfv is not fully characterized. Following a single-dose of another ADC that contains unconjugated MMAE, 17% of the total unconjugated MMAE administered was recovered in feces and 6% in urine over a 1-week period, primarily as unchanged drug. A similar excretion profile of unconjugated MMAE is expected after enfortumab vedotin-ejfv administration.

Specific Populations

Based on population pharmacokinetic analysis, no clinically significant differences in the pharmacokinetics of enfortumab vedotin-ejfv were observed based on age (24 to 90 years), sex, or race/ethnicity (Caucasian, Asian, Black, or others).

Hepatic Impairment

Based on population pharmacokinetics analysis, there was a 37% $AUC_{0\text{-}28d}$ increase in unconjugated MMAE exposure observed in patients with mild hepatic impairment (total bilirubin of 1 to 1.5 × ULN and AST any, or total bilirubin ≤ULN and AST >ULN, n=65) compared to normal hepatic function. Enfortumab vedotin-ejfv has only been studied in limited number of patients with moderate hepatic impairment and has not been evaluated in patients with severe hepatic impairment. The effect of moderate or severe hepatic impairment (total bilirubin >1.5 x ULN and AST any) or liver transplantation on the pharmacokinetics of ADC or unconjugated MMAE is unknown.

Renal Impairment

The pharmacokinetics of enfortumab vedotin-ejfv and unconjugated MMAE were evaluated after the administration of 1.25 mg/kg of enfortumab vedotin-ejfv 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 exposure (AUC) of ADC and 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.

Drug Interaction Trials

No clinical trials evaluating the drug-drug interaction potential of enfortumab vedotin-ejfv have been conducted.

Physiologically Based Pharmacokinetic (PBPK) Modeling Predictions:

Dual P-gp and Strong CYP3A4 Inhibitor: Concomitant use of enfortumab vedotin-ejfv with ketoconazole (a dual P-gp and strong CYP3A4 inhibitor) is predicted to increase unconjugated MMAE C_{max} by 15% and AUC by 38%.

Dual P-gp and Strong CYP3A4 Inducer: Concomitant use of enfortumab vedotin-ejfv with rifampin (a dual P-gp and strong CYP3A4 inducer) is predicted to decrease unconjugated MMAE C_{max} by 28% and AUC by 53%.

Sensitive CYP3A substrates: Concomitant use of enfortumab vedotin-ejfv is predicted not to affect exposure to midazolam (a sensitive CYP3A substrate).

In Vitro Studies

Transporter Systems: MMAE is a substrate of P-glycoprotein (P-gp), but not an inhibitor of P-gp.

12.6 Immunogenicity

The observed incidence of anti-drug antibody (ADA) is highly dependent on the sensitivity and specificity of the assay. Differences in assay methods preclude meaningful comparisons of the incidence of ADA in the studies described below with the incidence of ADA in other studies, including those of PADCEV or of other enfortumab vedotin products.

In the 0.3-to-52.1-month treatment periods with ADA sampling in five clinical studies of PADCEV 1.25 mg/kg as a single agent in patients with locally advanced or metastatic urothelial cancer *[see Clinical Studies (14)]*, the incidence of treatment emergent anti-enfortumab vedotin-ejfv antibody formation was 3.6% [23 of 640 total PADCEV-treated patients who were tested for ADA]. When PADCEV was administered in combination with pembrolizumab, the incidence of treatment emergent ADA against enfortumab vedotin-ejfv was 2.9% [3 of 105 total PADCEV-treated patients who were tested for ADA]. The incidence of treatment-emergent anti-enfortumab-ejfv antibody formation was consistent when assessed following PADCEV administration as a single agent and in combination with pembrolizumab.

Because of the low occurrence of ADA, the effect of these antibodies on the pharmacokinetics, pharmacodynamics, safety and/or effectiveness of PADCEV is unknown.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

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

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.

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

In repeat-dose toxicology studies conducted in rats for up to 13 weeks, doses ≥2 mg/kg enfortumab vedotin-ejfv (at exposures similar to the exposures at the recommended human dose) resulted in decreases in testes and epididymis weights, seminiferous tubule degeneration, spermatid/spermatocyte depletion in the testes and cell debris, sperm granuloma and hypospermia/abnormal spermatids in the epididymis. Findings in the testes and epididymis did not reverse by the end of the recovery period.

MMAE-containing ADCs have been associated with adverse ovarian effects when administered to sexually immature animals. Adverse effects included decrease in, or absence of, secondary and tertiary ovarian follicles after weekly administration to cynomolgus monkeys in studies of 4-week duration. These effects showed a trend towards recovery 6 weeks after the end of dosing; no changes were observed in primordial follicles.

14 CLINICAL STUDIES

14.1 Metastatic Urothelial Cancer

Previously Treated Locally Advanced or Metastatic Urothelial Carcinoma

EV-301

The efficacy of PADCEV as a single agent was evaluated in EV-301 (NCT03474107), an open-label, randomized, multicenter trial that enrolled 608 patients with locally advanced or metastatic urothelial cancer who received prior treatment with a PD-1 or PD-L1 inhibitor and platinum-based 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 investigator's choice of chemotherapy. Randomization was stratified by ECOG PS (0 vs 1), region of world (Western Europe vs US vs Rest of World), and presence of liver metastasis.

Patients were excluded if they had active central nervous system (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) and 77% were male. Racial demographics were reported as White (52%), Asian (33%), Black (0.7%), Native Hawaiian or Other Pacific Islander (0.2%) or not reported (15%). Nine percent of patients were Hispanic or Latino. All patients had a baseline Eastern Cooperative Oncology Group (ECOG) performance status of 0 (40%) or 1 (60%). Thirty-four percent of patients had tumors located in the upper tract that included the renal pelvis and ureter. Eighty percent of patients had visceral metastases including 31% with liver metastases. 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). Sixty-three percent of patients received prior cisplatin-based regimens, 26% received prior carboplatin-based regimens, and an additional 11% received both cisplatin and carboplatin-based regimens. Patients on the control arm received docetaxel (38%), paclitaxel (36%) or vinflunine (25%).

The major efficacy outcome measures were overall survival (OS), progression free survival (PFS), and overall response rate (ORR) assessed by investigator using RECIST v1.1. Efficacy results were consistent across all stratified patient subgroups.

Table 12 and Figures 2-3 summarize the efficacy results for EV-301.

Table 12. Efficacy Results in EV-301

Endpoint	PADCEV n=301	Chemotherapy n=307
Overall Survival[1]		
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)	
p-value	0.0014	
Progression Free Survival[1]		
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)	
p-value	<0.0001	
Overall Response Rate (CR + PR)[2]		
ORR (%) (95% CI)	40.6 (34.9, 46.5)	17.9 (13.7, 22.8)
p-value	<0.0001	

Endpoint	PADCEV n=301	Chemotherapy n=307
Complete response rate (%)	4.9	2.7
Partial response rate (%)	35.8	15.2

1. Based on log-rank test. Stratification factors were ECOG PS, region and liver metastasis
2. Based on Cochran-Mantel-Haenszel test. Stratification factors were ECOG PS, region and liver metastasis

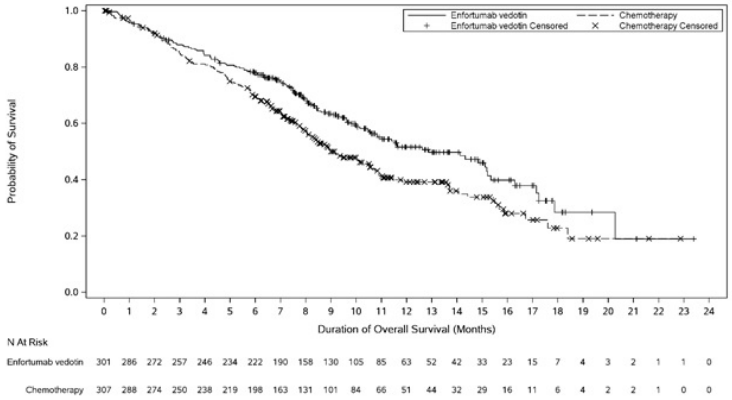

Figure 2. Kaplan Meier Plot of Overall Survival

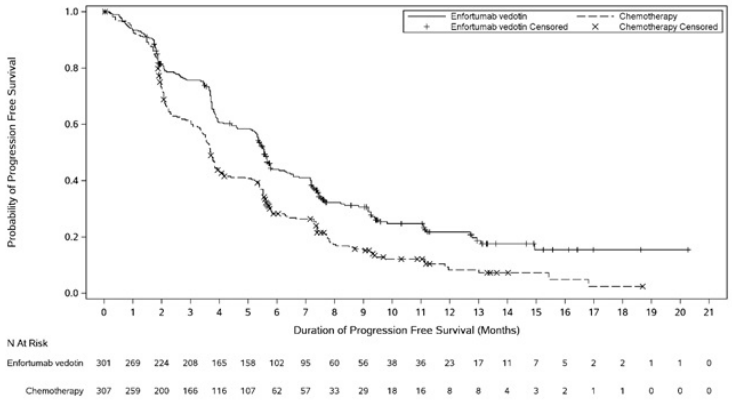

Figure 3. Kaplan Meier Plot of Progression Free Survival

EV-201, Cohort 1

The efficacy of PADCEV as a single agent was also investigated in Cohort 1 of EV-201 (NCT03219333), a single-arm, multi-cohort, multicenter trial that enrolled 125 patients with locally advanced or metastatic urothelial cancer who received prior treatment with a PD-1 or PD-L1 inhibitor and a platinum-based chemotherapy. Patients were excluded if they had active central nervous system (CNS) metastases, ongoing sensory or motor neuropathy ≥Grade 2, heart failure, or uncontrolled diabetes defined as hemoglobin A1C (HbA1c) ≥8% or HbA1c ≥7% with associated diabetes symptoms.

PADCEV was administered at a dose of 1.25 mg/kg, as an intravenous (IV) infusion on days 1, 8, and 15 of each 28-day cycle.

The median age was 69 years (range: 40 to 84 years) and 70% were male. Racial demographics were reported as White (85%), Asian (9%), Black (2%), Other (0.8%) or not reported (4%). Four percent of patients were Hispanic or Latino. All patients had a baseline Eastern Cooperative Oncology Group (ECOG) performance status of 0 (32%) or 1 (68%). Ninety percent of patients had visceral metastases including 40% with liver metastases. Approximately two-thirds (67%) of patients had pure transitional cell carcinoma (TCC) histology; 33% had TCC with other histologic variants. The median number of prior systemic therapies was 3 (range: 1 to 6). Sixty-six percent of patients received prior cisplatin-based

regimens, 26% received prior carboplatin-based regimens, and an additional 8% received both cisplatin and carboplatin-based regimens.

The major efficacy outcome measures were confirmed objective response rate (ORR) and duration of response (DOR) assessed by blinded independent central review (BICR) using RECIST v1.1.

Efficacy results are presented in Table 13.

Table 13. Efficacy Results in EV-201, Cohort 1 (BICR Assessment)

Endpoint	PADCEV n=125
Confirmed ORR (95% CI)	44% (35.1, 53.2)
Complete Response Rate (CR)	12%
Partial Response Rate (PR)	32%
Median[1] Duration of Response, months (95% CI)	7.6 (6.3, NE)

NE = not estimable

1. Based on patients (n=55) with a response by BICR.

Previously Treated Cisplatin Ineligible Patients with Locally Advanced or Metastatic Urothelial Carcinoma

EV-201, Cohort 2

The efficacy of PADCEV as a single agent was also evaluated in Cohort 2 of EV-201, a single-arm, multi-cohort, multicenter trial in 89 patients with locally advanced or metastatic urothelial cancer who received prior treatment with a PD-1 or PD-L1 inhibitor and were cisplatin ineligible and did not receive platinum in the locally advanced or metastatic setting. Patients were excluded if they had active CNS metastases, ongoing sensory or motor neuropathy ≥Grade 2, heart failure, or uncontrolled diabetes defined as hemoglobin A1C (HbA1c) ≥8% or HbA1c ≥7% with associated diabetes symptoms.

PADCEV was administered at a dose of 1.25 mg/kg, as an intravenous (IV) infusion on days 1, 8, and 15 of each 28-day cycle.

The median age was 75 years (range: 49 to 90 years), 74% were male. Racial demographics were reported as White (70%), Asian (22%) or not reported (8%). One percent of patients were Hispanic or Latino. Patients had a baseline ECOG performance status of 0 (42%), 1 (46%) and 2 (12%). Forty-three percent of patients had tumors located in the upper tract that included the renal pelvis and ureter. Seventy-nine percent of patients had visceral metastases and 24% had liver metastases.

Reasons for cisplatin ineligibility included: 66% with baseline creatinine clearance of 30 – 59 mL/min, 7% with ECOG PS of 2, 15% with Grade 2 or greater hearing loss, and 12% with more than one cisplatin-ineligibility criteria. Seventy percent of patients had TCC histology; 13% had TCC with squamous differentiation and 17% had TCC with other histologic variants.

The median number of prior systemic therapies was 1 (range: 1 to 4).

Efficacy results are presented in Table 14 below.

Table 14. Efficacy Results in EV-201, Cohort 2 (BICR Assessment)

Endpoint	PADCEV n=89
Confirmed ORR (95% CI)	51% (39.8, 61.3)
Complete Response Rate (CR)	22%
Partial Response Rate (PR)	28%
Median[1] Duration of Response, months (95% CI)	13.8 (6.4, NE)

NE = not estimable

1. Based on patients (n=45) with a response by BICR

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 EV-103 (NCT03288545), an 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 with 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 were excluded from participating in the study.

Patients in the dose escalation cohort (n=5), Cohort A (n=40), and Cohort K (n=76) received PADCEV 1.25 mg/kg as an IV infusion over 30 minutes on Days 1 and 8 of a 21-day cycle followed by pembrolizumab 200 mg as an IV infusion on Day 1 of a 21-day cycle approximately 30 minutes after PADCEV. Patients were treated until disease progression or unacceptable toxicity.

A total of 121 patients received PADCEV in combination with pembrolizumab. The median age was 71 years (range: 51 to 91); 74% were male; 85% were White, 5% were Black, 4% were Asian and 6% were other, unknown or not reported. Ten percent of patients were Hispanic or Latino. Forty-five percent 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%. Reasons for cisplatin ineligibility included: 60% with baseline creatinine clearance of 30 − 59 mL/min, 10% with ECOG PS of 2, 13% with Grade 2 or greater hearing loss, and 16% with more than one cisplatin-ineligibility criteria.

At baseline, 97.5% of patients had metastatic urothelial cancer and 2.5% of patients had locally advanced urothelial cancer. Thirty-seven percent of patients had upper tract disease. Eighty-four percent of patients had visceral metastasis at baseline including 22% with liver metastases. Thirty-nine percent of patients had TCC histology; 13% had TCC with squamous differentiation and 48% had TCC with other histologic variants.

The major efficacy outcome measures were ORR and DoR as assessed by BICR according to RECIST v1.1.

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).

Efficacy results are presented in Table 15 below.

Table 15. Efficacy Results in EV-103, Combined Dose Escalation Cohort, Cohort A, and Cohort K

	PADCEV in combination with pembrolizumab n=121
Confirmed ORR (95% CI)	68% (58.7, 76.0)
Complete response rate	12%
Partial response rate	55%

The median duration of response for the dose escalation cohort + Cohort A was 22.1 months (range: 1.0+ to 46.3+) and for Cohort K was not reached (range: 1.2 to 24.1+).

15 REFERENCES

1. "OSHA Hazardous Drugs." OSHA. http://www.osha.gov/SLTC/hazardousdrugs/index.html

16 HOW SUPPLIED/STORAGE AND HANDLING

How Supplied

PADCEV (enfortumab vedotin-ejfv) 20 mg and 30 mg are supplied as a sterile, preservative-free, white to off-white lyophilized powder in single-dose vials. PADCEV vials are available in the following packages:

- Carton of one 20 mg single-dose vial (NDC 51144-020-01)
- Carton of one 30 mg single-dose vial (NDC 51144-030-01)

Storage

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

Special Handling

PADCEV is a hazardous drug. Follow applicable special handling and disposal procedures.[1]

17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Patient Information).

Skin Reactions

Inform patients that severe skin reactions including SJS and TEN with fatal outcomes have occurred after administration of PADCEV, predominantly during the first cycle of treatment but may occur later.

Advise patients to contact their healthcare provider immediately if they develop new target lesions, progressively worsening skin reactions, severe blistering or peeling of the skin *[see Boxed Warning and Warnings and Precautions (5.1)]*.

Hyperglycemia

Inform patients about the risk of hyperglycemia and how to recognize associated symptoms *[see Warnings and Precautions (5.2)]*.

Pneumonitis/Interstitial Lung Disease

Advise patients to immediately report new or worsening respiratory symptoms *[see Warnings and Precautions (5.3)]*.

Peripheral Neuropathy

Inform patients to report to their healthcare provider any numbness and tingling of the hands or feet or muscle weakness *[see Warnings and Precautions (5.4)]*.

Ocular disorders

Advise patients to contact their healthcare provider if they experience any visual changes *[see Warnings and Precautions (5.5)]*. In order to prevent or treat dry eyes, advise patients to use artificial tear substitutes.

Infusion Site Extravasation

Inform patients that infusion site reactions have occurred after administration of PADCEV. These reactions generally occurred immediately after administration but, in some instances, had a delayed onset (e.g., 24 hours). Instruct patients to contact their healthcare provider immediately if they experience an infusion site reaction *[see Warnings and Precautions (5.6)]*.

Embryo-Fetal Toxicity

Advise pregnant women and females of reproductive potential of the potential risk to the fetus. Advise females to inform their healthcare providers of a known or suspected pregnancy *[see Warnings and Precautions (5.7) and Use in Specific Population (8.1)]*.

Females and Males of Reproductive Potential

Advise female patients of reproductive potential to use effective contraception during treatment with PADCEV and for 2 months after the last dose. Advise male patients with female partners of reproductive potential to use effective contraception during treatment with PADCEV and for 4 months after the last dose *[see Use in Specific Populations (8.3)]*.

Lactation

Advise women not to breastfeed during treatment with PADCEV and for 3 weeks after the last dose *[see Use in Specific Populations (8.2)]*.

Infertility

Advise females and males of reproductive potential that PADCEV may impair fertility *[see Use in Specific Populations (8.3)]*.

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Northbrook, Illinois 60062

Distributed and Marketed by:
Seagen Inc.
Bothell, WA 98021
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PATIENT INFORMATION
PADCEV® (PAD-sev)
(enfortumab vedotin-ejfv)
for injection

If your healthcare provider prescribes PADCEV in combination with pembrolizumab for you, also read the Medication Guide that comes with pembrolizumab for important information about pembrolizumab.

What is the most important information I should know about PADCEV?
PADCEV may cause serious side effects, including:
Skin reactions. Skin reactions including severe skin reactions have happened in people treated with PADCEV and may be more common when PADCEV is given with pembrolizumab. In some cases, these severe skin reactions have caused death. Most severe skin reactions occurred during the first cycle of treatment but may happen later. Your healthcare provider will monitor you, may stop your treatment with PADCEV completely or for a period of time (temporarily), may change your dose, and may prescribe medicines if you get skin reactions. Tell your healthcare provider right away if you develop any of these signs of a new or worsening skin reaction:

- target lesions (skin reactions that look like rings)
- rash or itching that continues to get worse
- blistering or peeling of the skin
- painful sores or ulcers in mouth or nose, throat, or genital area
- fever or flu-like symptoms
- swollen lymph nodes

See **"What are the possible side effects of PADCEV?**" for more information about side effects.

What is PADCEV?
PADCEV is a prescription medicine used to treat adults with bladder cancer and cancers of the urinary tract (renal pelvis, ureter or urethra) that has spread or cannot be removed by surgery.

- PADCEV may be used alone if you:
  - have received an immunotherapy medicine **and** chemotherapy that contains platinum, **or**
  - are not able to receive a chemotherapy that contains the medicine cisplatin and you have received 1 or more prior therapy.
- PADCEV may be used with pembrolizumab if you:
  - are not able to receive a chemotherapy that contains the medicine cisplatin.

It is not known if PADCEV is safe and effective in children.

Before receiving PADCEV, tell your healthcare provider about all of your medical conditions, including if you:

- are currently experiencing numbness or tingling in your hands or feet
- have a history of high blood sugar or diabetes
- have liver problems
- are pregnant or plan to become pregnant. PADCEV can harm your unborn baby. Tell your healthcare provider right away if you become pregnant or think you may be pregnant during treatment with PADCEV.
  Females who are able to become pregnant:
  - Your healthcare provider should do a pregnancy test before you start treatment with PADCEV.
  - You should use an effective method of birth control during your treatment and for at least 2 months after the last dose of PADCEV.

  Males with a female sexual partner who is able to become pregnant:
  - If your female partner is pregnant, PADCEV can harm the unborn baby.
  - You should use an effective method of birth control during your treatment and for at least 4 months after the last dose of PADCEV.
- are breastfeeding or plan to breastfeed. It is not known if PADCEV passes into your breast milk. Do not breastfeed during treatment and for at least 3 weeks after the last dose of PADCEV.

Tell your healthcare provider about all the medicines you take, including prescription and over-the-counter medicines, vitamins, and herbal supplements. Taking PADCEV with certain other medicines may cause side effects.

How will I receive PADCEV?

- PADCEV will be given to you by intravenous (IV) infusion into your vein over 30 minutes.
- PADCEV is given over periods of time called "cycles".
- If you receive PADCEV alone.
  - Each PADCEV cycle is 28 days.
  - You will receive PADCEV on days 1, 8 and 15 of every cycle.
- If you receive PADCEV with pembrolizumab,
  - Each cycle is 21 days.
  - You will receive PADCEV on days 1 and 8 of every cycle.
- Your healthcare provider will decide how many treatment cycles you need.
- Your healthcare provider may do blood tests regularly during treatment with PADCEV.

What are the possible side effects of PADCEV?

PADCEV may cause serious side effects, including:

- **See "What is the most important information I should know about PADCEV?"**
- **High blood sugar (hyperglycemia).** An increase in blood sugar is common during treatment with PADCEV. Severe high blood sugar, a serious condition called diabetic ketoacidosis (DKA), and death have happened in people with and without diabetes, treated with PADCEV. Tell your healthcare provider right away if you have any symptoms of high blood sugar, including:
  - frequent urination
  - increased thirst
  - blurred vision
  - confusion
  - it becomes harder to control your blood sugar
  - drowsiness
  - loss of appetite
  - fruity smell on your breath
  - nausea, vomiting, or stomach pain
- **Lung problems.** PADCEV may cause severe or life-threatening inflammation of the lungs that can lead to death. These severe problems may happen more often when PADCEV is given in combination with pembrolizumab. Tell your healthcare provider right away if you get new or worsening symptoms, including trouble breathing, shortness of breath, or cough.
- **Nerve problems.** Nerve problems called peripheral neuropathy are common during treatment with PADCEV and can also sometimes be severe. Nerve problems may happen more often when PADCEV is given in combination with pembrolizumab. Tell your healthcare provider right away if you get new or worsening numbness or tingling in your hands or feet or muscle weakness.
- **Eye problems.** Certain eye problems are common during treatment with PADCEV. Tell your healthcare provider right away if you have dry eyes, increased tearing, blurred vision, or any vision changes. You may use artificial tear substitutes to help prevent or treat dry eyes.
- **Leakage of PADCEV out of your vein into the tissues around your infusion site (extravasation).** If PADCEV leaks from the injection site or the vein into the nearby skin and tissues, it could cause an infusion site reaction. These reactions can happen right after you receive an infusion, but sometimes may happen days after your infusion. Tell your healthcare provider or get medical help right away if you notice any redness, swelling, itching, blister, peeling skin, or discomfort at the infusion site.

Your healthcare provider may decrease your dose of PADCEV, or temporarily or completely stop your treatment with PADCEV if you have severe side effects.

The most common side effects of PADCEV when used alone include:

- rash. **See "What is the most important information I should know about PADCEV?"**
- changes in liver and kidney function tests
- increased sugar (glucose) in the blood. **See "High blood sugar (hyperglycemia)" above.**
- tiredness
- decreased white blood cell, red blood cell, and platelet counts
- hair loss
- decreased appetite
- diarrhea
- decreased sodium, phosphate and protein (albumin) in the blood
- nausea
- itching
- change in sense of taste
- increased uric acid in the blood
- increased lipase (a blood test done to check your pancreas
- decreased weight
- dry skin

The most common side effects of PADCEV when used in combination with pembrolizumab include:

- increased sugar (glucose) in the blood**. See "High blood sugar (hyperglycemia)" above.**
- changes in liver function and kidney function tests
- rash. **See "What is the most important information I should know about PADCEV?"**
- decreased red blood cell and white blood cell counts
- tiredness
- decreased sodium, phosphate and protein (albumin) in the blood
- increased lipase (a test done to check your pancreas)
- hair loss
- decreased weight
- diarrhea
- itching
- decreased appetite
- nausea
- change in sense of taste
- urinary tract infection
- constipation
- increased or decreased potassium
- increased calcium in the blood
- swelling of the arms, hands, legs and feet
- dry eye. **See "Eye problems" above.**
- dizziness
- joint aches
- dry skin

PADCEV may cause fertility problems in females and males, which may affect the ability to have children. Talk to your healthcare provider if you have concerns about fertility.

These are not all of the possible side effects of PADCEV.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

General information about the safe and effective use of PADCEV.
Medicines are sometimes prescribed for purposes other than those listed in a Patient Information leaflet. You can ask your pharmacist or healthcare provider for information about PADCEV that is written for healthcare professionals.

What are the ingredients in PADCEV?
Active ingredient: enfortumab vedotin-ejfv
Inactive ingredients: histidine, histidine hydrochloride monohydrate, polysorbate 20, and trehalose dihydrate.

Manufactured and Marketed by: Astellas Pharma US, Inc., Northbrook, Illinois 60062
Distributed and Marketed by: Seagen Inc., Bothell, WA 98021
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For more information, go to www.padcev.com or call 1-888-4-PADCEV
368762-EV-USA

This Patient Information has been approved by the U.S. Food and Drug Administration. Revised: 4/2023