

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

Boxed Warning, Serious Skin Reactions	7/2021
Indications and Usage (1)	7/2021
Dosage and Administration (2.2)	3/2021
Warnings and Precautions (5.1), (5.2), (5.3), (5.4), (5.5), (5.6)	7/2021

INDICATIONS AND USAGE

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

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 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)
- 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: Severe, life-threatening or fatal pneumonitis may occur. Withhold PADCEV for persistent or recurrent Grade 2 pneumonitis and consider dose reduction. Permanently discontinue PADCEV for Grade 3 or 4 pneumonitis. (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%) included 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)

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: 7/2021

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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® 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.

2 DOSAGE AND ADMINISTRATION

2.1 Recommended Dosage

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.

2.2 Dose Modifications

Table 1. Dose Modifications

Adverse Reaction	Severity*	Dose Modification*
Skin Reactions <i>[see Boxed Warning, Warnings and Precautions (5.1)]</i>	Suspected SJS or TEN	Immediately withhold, consult a specialist to confirm the diagnosis. If not SJS/TEN, see Grade 3 skin reactions.
	Confirmed SJS or TEN; Grade 4 or recurrent Grade 3 skin reactions	Permanently discontinue.
	Grade 3 (severe) skin reactions	Withhold until Grade ≤ 1 , then resume treatment at the same dose level or consider dose reduction by one dose level.
Hyperglycemia <i>[see Warnings and Precautions (5.2)]</i>	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 <i>[see Warnings and Precautions (5.3)]</i>	Grade 2	Withhold until Grade ≤ 1 for persistent or recurrent Grade 2 pneumonitis, consider dose reduction by one dose level.
	Grade ≥ 3	Permanently discontinue.
Peripheral Neuropathy <i>[see Warnings and Precautions (5.4)]</i>	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 <i>[see Adverse Reactions (6)]</i>	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 <i>[see Adverse Reactions (6)]</i>	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.

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 55% of the 680 patients treated with PADCEV in clinical trials. Twenty-three percent (23%) of patients had maculopapular rash and 33% had pruritus. Grade 3-4 skin reactions occurred in 13% of patients, including 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. In clinical trials, the median time to onset of severe skin reactions was 0.6 months (range: 0.1 to 6.4 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](#))].

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

Withhold PADCEV and refer for specialized care for suspected SJS, TEN or for severe (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 $\geq 8\%$ were excluded from clinical trials. In clinical trials, 14% of the 680 patients treated with PADCEV developed hyperglycemia; 7% of patients developed Grade 3-4 hyperglycemia. 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 20.3 months). Hyperglycemia led to discontinuation of PADCEV in 0.6% 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

Severe, life-threatening or fatal pneumonitis occurred in patients treated with PADCEV. In clinical trials, 3.1% of the 680 patients treated with PADCEV had pneumonitis of any grade and 0.7% had Grade 3-4. In clinical trials, the median time to onset of pneumonitis was 2.9 months (range: 0.6 to 6 months).

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

5.4 Peripheral Neuropathy

Peripheral neuropathy occurred in 52% of the 680 patients treated with PADCEV in clinical trials including 39% with sensory neuropathy, 7% with muscular weakness and 6% with motor neuropathy; 4% 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 4.6 months (range: 0.1 to 15.8 months). Neuropathy led to treatment discontinuation in 5% of patients. [see *Adverse Reactions* (6.1)].

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 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 19.1 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 680 patients, 1.6% 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 approximately 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 [*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 680 patients in EV-301, EV-201, EV-101 (NCT02091999), and EV-102 (NCT03070990). Ocular disorders reflect 384 patients in EV-201, EV-101, and EV-102. Among 680 patients receiving PADCEV, 36% were exposed for ≥ 6 months, and 9% were exposed for ≥ 12 months. In this pooled population, the most common ($\geq 20\%$) 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, weight decreased and dry skin.

The data described in the following sections reflect exposure to PADCEV from an open-label, randomized, study (EV-301); and Cohort 1 and Cohort 2 of an open-label, single arm, two cohort study (EV-201). Patients received PADCEV 1.25 mg/kg on Days 1, 8 and 15 of a 28-day cycle until disease progression or unacceptable toxicity.

Previously Treated Locally Advanced or Metastatic Urothelial Cancer

EV-301

The safety of PADCEV was evaluated 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 19.4 months).

Serious adverse reactions occurred in 47% of patients treated with PADCEV. The most common serious adverse reactions ($\geq 2\%$) 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 ($\geq 2\%$) 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 ($\geq 4\%$) 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 ($\geq 2\%$) leading to dose reduction were peripheral neuropathy (10%), rash (8%), decreased appetite (3%) and fatigue (3%).

Table 3 summarizes the most common ($\geq 15\%$) 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

¹Includes: 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.

²Includes: fatigue, asthenia

³Includes: pyrexia, hyperthermia, hyperpyrexia, body temperature increased

⁴Includes: 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

⁵Includes: dysgeusia, ageusia, hypogeusia

⁶Includes: diarrhea, colitis, enterocolitis

⁷Includes: abdominal pain, abdominal pain upper, abdominal pain lower, abdominal discomfort, hepatic pain, abdominal tenderness, gastrointestinal pain

⁸Includes: 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

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

¹⁰Includes: 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

¹¹Includes: 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

¹The 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 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 ($\geq 3\%$) 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%).

Table 5 summarizes the All Grades and Grades 3-4 adverse reactions reported in patients in EV-201, Cohort 1.

Table 5. Adverse Reactions Reported in $\geq 15\%$ (All Grades) or $\geq 5\%$ (Grade 3-4) of Patients Treated with PADCEV in EV-201 Cohort 1

Adverse Reaction	PADCEV n=125	
	All Grades %	Grade 3-4 %
Any	100	73
General disorders and administration site conditions		
Fatigue ¹	56	6
Nervous system disorders		
Peripheral neuropathy ²	56	4
Dysgeusia	42	0
Metabolism and nutrition disorders		
Decreased appetite	52	2
Skin and subcutaneous tissue disorders		
Rash ³	52	13
Alopecia	50	0
Dry skin	26	0
Pruritus ⁴	26	2
Gastrointestinal disorders		
Nausea	45	3
Diarrhea ⁵	42	6
Vomiting	18	2
Eye disorders		
Dry eye ⁶	40	0

¹Includes: asthenia and fatigue

²Includes: hypoesthesia, gait disturbance, muscular weakness, neuralgia, paresthesia, peripheral motor neuropathy, peripheral sensory neuropathy and peripheral sensorimotor neuropathy.

³Includes: dermatitis acneiform, dermatitis bullous, dermatitis contact, dermatitis exfoliative, drug eruption, erythema, erythema multiforme, exfoliative rash, palmar-plantar erythrodysesthesia syndrome, photosensitivity reaction, rash, rash erythematous, rash generalized, rash macular, rash maculo-papular, rash papular, rash pustular, rash pruritic, rash vesicular, skin exfoliation, stasis dermatitis, and symmetrical drug-related intertriginous and flexural exanthema (SDRIFE) and urticaria.

⁴Includes: pruritus and pruritus generalized

⁵Includes: colitis, diarrhea and enterocolitis

⁶Includes: blepharitis, conjunctivitis, dry eye, eye irritation, keratitis, keratopathy, lacrimation increased, limbal stem cell deficiency, Meibomian gland dysfunction, ocular discomfort, punctate keratitis, tear break up time decreased

Clinically relevant adverse reactions (<15%) include herpes zoster (3%), pneumonitis (2%) and infusion site extravasation (2%).

Table 6. Selected Laboratory Abnormalities Reported in ≥15% (Grades 2-4) or ≥5% (Grade 3-4) of Patients Treated with PADCEV in EV-201, Cohort 1

Laboratory Abnormality	PADCEV	
	Grades 2-4 ¹ %	Grade 3-4 ¹ %
Hematology		
Hemoglobin decreased	34	10
Lymphocytes decreased	32	10
Neutrophils decreased	14	5
Chemistry		
Phosphate decreased	34	10
Glucose increased (non-fasting)	27	8
Creatinine increased	20	2
Potassium decreased	19 ²	1
Lipase increased	14	9
Sodium decreased	8	8
Urate increased	7	7

¹Denominator for each laboratory parameter is based on the number of patients with a baseline and post-treatment laboratory value available for 121 or 122 patients.

²Includes Grade 1 (potassium 3.0-3.5 mmol/L) – Grade 4.

EV-201, Cohort 2

The safety of PADCEV was evaluated in EV-201, Cohort 2 in patients with locally advanced or metastatic urothelial cancer (n=89) who received at least one dose of PADCEV 1.25 mg/kg and had prior treatment with a PD-1 or PD-L1 inhibitor and were not eligible for cisplatin-based chemotherapy. The median duration of exposure was 5.98 months (range: 0.3 to 24.6 months).

Serious adverse reactions occurred in 39% of patients treated with PADCEV. The most common serious adverse reactions (≥3%) were pneumonia, sepsis and diarrhea (5% each). Fatal adverse reactions occurred in 8% of patients, including acute kidney injury (2.2%), metabolic acidosis, sepsis, multiorgan dysfunction, pneumonia and pneumonitis (1.1% each).

Adverse reactions leading to discontinuation occurred in 20% of patients; the most common adverse reaction (≥2%) leading to discontinuation was peripheral neuropathy (7%).

Adverse reactions leading to dose interruption occurred in 60% of patients; the most common adverse reactions ($\geq 3\%$) leading to dose interruption were peripheral neuropathy (19%), rash (9%), fatigue (8%), diarrhea (5%), aspartate aminotransferase increased (3%) and hyperglycemia (3%).

Adverse reactions leading to dose reduction occurred in 49% of patients; the most common adverse reactions ($\geq 3\%$) leading to dose reduction were peripheral neuropathy (19%), rash (11%) and fatigue (7%).

Table 7 summarizes the All Grades and Grades 3-4 adverse reactions reported in patients in EV-201, Cohort 2.

Table 7. Adverse Reactions $\geq 15\%$ (All Grades) or $\geq 5\%$ (Grades 3-4) in Patients Treated with PADCEV in EV-201, Cohort 2

Adverse Reaction	PADCEV n=89	
	All Grades (%)	Grades 3-4 (%)
Skin and subcutaneous tissue disorders		
Rash ¹	66	17
Alopecia	53	0
Pruritus	35	3
Dry skin	19	1
Nervous system disorders		
Peripheral neuropathy ²	58	8
Dysgeusia ³	29	0
General disorders and administration site conditions		
Fatigue ⁴	48	11
Metabolism and nutrition disorders		
Decreased appetite	40	6
Hyperglycemia	16	9
Blood and lymphatic disorders		
Anemia	38	11
Gastrointestinal disorders		
Diarrhea ⁵	36	8
Nausea	30	1
Investigations		
Weight decreased	35	1
Eye disorders		
Dry eye ⁶	30	0

¹Includes: blister, conjunctivitis, dermatitis bullous, dermatitis exfoliative generalized, eczema, erythema, erythema multiforme, intertrigo, palmar-plantar erythrodysesthesia syndrome, rash, rash erythematous, rash macular, rash maculo-papular, rash papular, rash vesicular, skin exfoliation, stomatitis

²Includes: demyelinating polyneuropathy, gait disturbance, hypoesthesia, motor dysfunction, muscle atrophy, muscular weakness, paresthesia, peripheral motor neuropathy, peripheral sensorimotor neuropathy, peroneal nerve palsy, peripheral sensory neuropathy

³Includes: dysgeusia, ageusia, hypogeusia

⁴Includes: fatigue, asthenia

⁵Includes: diarrhea, colitis, enterocolitis

⁶Includes: blepharitis, conjunctivitis, dry eye, eye irritation, keratitis, keratopathy, lacrimation increased, limbal stem cell deficiency, Meibomian gland dysfunction, ocular discomfort, punctate keratitis, tear break up time decreased

Clinically relevant adverse reactions (<15%) include vomiting (13%), aspartate aminotransferase increased (12%), lipase increased (11%), alanine aminotransferase increased (10%), pneumonitis (4%) and infusion site extravasation (1%).

Table 8. Selected Laboratory Abnormalities Reported in ≥15% (Grades 2-4) or ≥5% (Grades 3-4) of Patients Treated with PADCEV in EV-201, Cohort 2

Laboratory Abnormality	PADCEV N=88 ¹	
	Grades 2-4 ¹ %	Grade 3-4 ¹ %
Hematology		
Lymphocytes decreased	43	15
Hemoglobin decreased	34	5
Neutrophils decreased	20	9
Chemistry		
Glucose increased (non-fasting)	36	13
Phosphate decreased	25	7
Creatinine increased	23	3
Lipase increased	18	11
Urate increased	9	9
Potassium increased	8	6
Sodium decreased	7	7

¹Based 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)*].

6.3 Immunogenicity

As with all therapeutic proteins, there is a potential for immunogenicity. The detection of antibody formation is highly dependent on the sensitivity and specificity of the assay. Additionally, the observed incidence of antibody (including neutralizing antibody) positivity in an assay may be influenced by several factors including assay methodology, sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, comparison of the incidence of antibodies in the trials described below with the incidence of antibodies in other trials or other enfortumab vedotin-ejfv products may be misleading.

Following administration of PADCEV 1.25 mg/kg; 16/590 (2.7%) patients tested positive for anti-therapeutic antibody (ATA) against enfortumab vedotin-ejfv at one or more post-baseline time points. Due to the limited

number of patients with ATA against enfortumab vedotin-ejfv, no conclusions can be drawn concerning a potential effect of immunogenicity on efficacy, safety or pharmacokinetics.

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 approximately 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 (approximately similar to the exposure at the recommended human dose) resulted in maternal toxicity, embryo-fetal lethality and structural malformations that included gastroschisis, malrotated hindlimb, absent forepaw, malpositioned internal organs and fused cervical arch. Additionally, skeletal anomalies (asymmetric, fused, incompletely ossified, and misshapen sternebrae, misshapen cervical arch, and unilateral ossification of the thoracic centra) and decreased fetal weight were observed.

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

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 680 patients treated with PADCEV in clinical trials, 440 (65%) were 65 years or older and 168 (25%) were 75 years or older. No overall differences in safety or effectiveness were observed between these patients 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 $>1.5 \times$ 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 \geq 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 $1.5 \times$ ULN and AST any, or total bilirubin \leq 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.

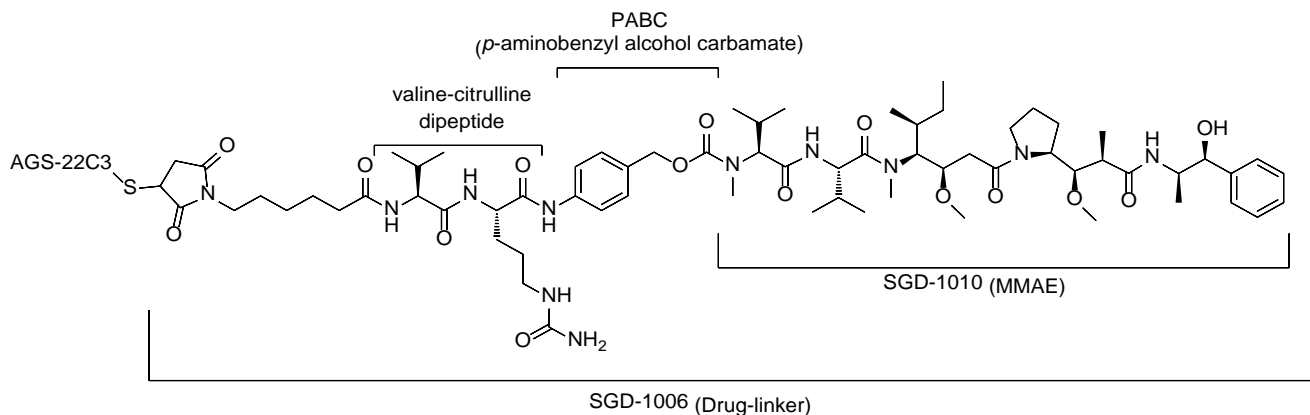


Figure 1. Structural Formula

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 apoptotic cell death.

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 based on five studies. 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 exposure parameters of ADC and unconjugated MMAE (the cytotoxic component of enfortumab vedotin-ejfv) are summarized in Table 9 below. Peak ADC concentrations were observed near the end of intravenous infusion while peak MMAE concentrations were observed approximately 2 days after enfortumab vedotin-ejfv dosing. Minimal accumulation of the ADC and MMAE was observed following repeat administration of enfortumab vedotin-ejfv in patients. Steady-state concentrations of ADC and MMAE were reached after 1 treatment cycle.

Table 9. 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 (\pm SD)	Unconjugated MMAE Mean (\pm SD)
C_{\max}	28 (6.1) $\mu\text{g/mL}$	5.5 (3.0) ng/mL
$\text{AUC}_{0-28\text{d}}$	110 (26) $\mu\text{g}\cdot\text{d/mL}$	85 (50) $\text{ng}\cdot\text{d/mL}$
$C_{\text{trough},0-28\text{d}}$	0.31 (0.18) $\mu\text{g/mL}$	0.81 (0.88) ng/mL

C_{\max} = maximum concentration, $\text{AUC}_{0-28\text{d}}$ = area under the concentration-time curve from time zero to 28 days, $C_{\text{trough},0-28\text{d}}$ = 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 MMAE ranged from 68% to 82%, *in vitro*.

Elimination

ADC and 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 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 MMAE via proteolytic cleavage, and 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 MMAE, 17% of the total MMAE administered was recovered in feces and 6% in urine over a 1-week period, primarily as unchanged drug. A similar excretion profile of 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_{0-28d} increase in unconjugated MMAE exposure observed in patients with mild hepatic impairment (total bilirubin of 1 to $1.5 \times ULN$ and AST any, or total bilirubin $\leq ULN$ 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 $>1.5 \times ULN$ 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 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.

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 in rats indicate the potential for enfortumab vedotin-ejfv to impair 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.

14 CLINICAL STUDIES

14.1 Metastatic Urothelial Cancer

Previously Treated Locally Advanced or Metastatic Urothelial Carcinoma

EV-301

The efficacy of PADCEV 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 \geq Grade 2, or uncontrolled diabetes defined as hemoglobin A1C (HbA1c) $\geq 8\%$ or HbA1c $\geq 7\%$ 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 10 and Figures 2-3 summarize the efficacy results for EV-301.

Table 10. Efficacy Results in EV-301

Endpoint	PADCEV N=301	Chemotherapy N=307
Overall Survival¹		
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 Survival¹		
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	
Complete response rate (%)	4.9	2.7
Partial response rate (%)	35.8	15.2

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

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

Figure 2. Kaplan Meier Plot of Overall Survival

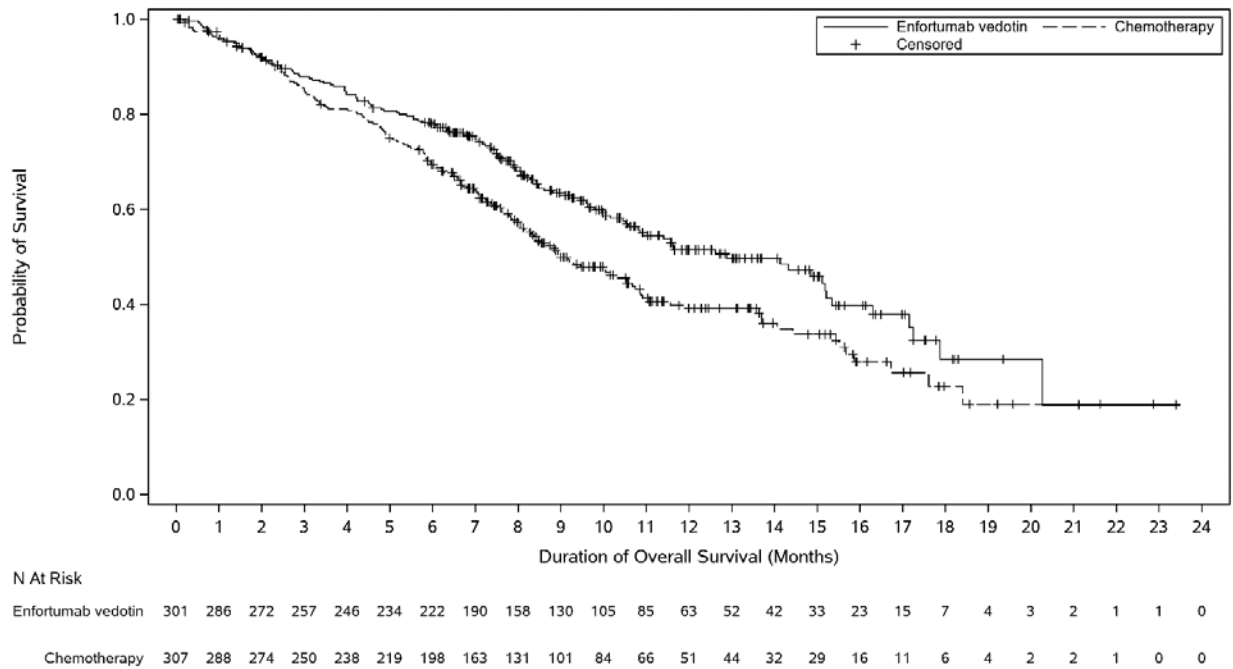
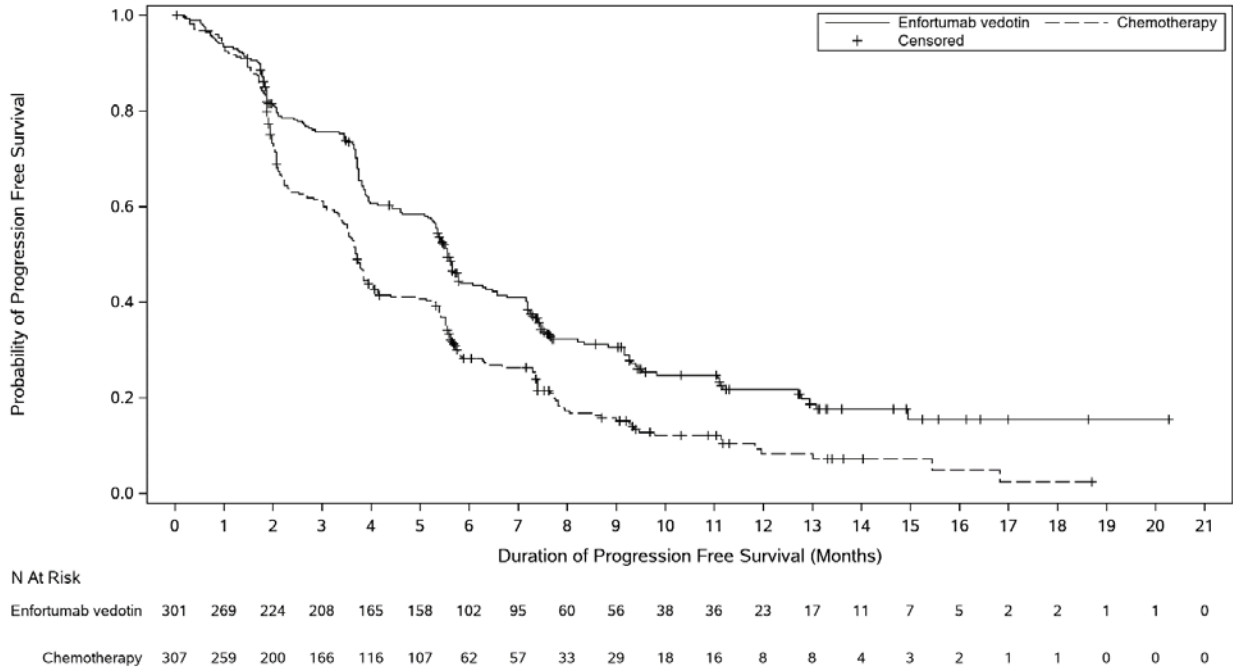


Figure 3. Kaplan Meier Plot of Progression Free Survival



EV-201, Cohort 1

The efficacy of PADCEV was also investigated in Cohort 1 of EV-201, 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 \geq Grade 2, heart failure, or uncontrolled diabetes defined as hemoglobin A1C (HbA1c) \geq 8% or HbA1c \geq 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 11.

Table 11. 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

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

Cisplatin Ineligible Patients with Locally Advanced or Metastatic Urothelial Carcinoma

The efficacy of PADCEV 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 \geq Grade 2, heart failure, or uncontrolled diabetes defined as hemoglobin A1C (HbA1c) \geq 8% or HbA1c \geq 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 12 below.

Table 12. 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

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

15 REFERENCES

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

16 HOW SUPPLIED/STORAGE AND HANDLING

16.1 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)

16.2 Storage

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.

16.3 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

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

Manufactured and Marketed by:

Astellas Pharma US, Inc.
Northbrook, Illinois 60062

Distributed and Marketed by:

Seagen Inc.
Bothell, WA 98021
1-855-4SEAGEN

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PATIENT INFORMATION

PADCEV® (PAD-sev)
(enfortumab vedotin-ejfv)
for injection

What is the most important information I should know about PADCEV?

PADCEV may cause serious side effects, including:

Skin reactions. Severe skin reactions have happened in people treated with PADCEV, in some cases severe skin reactions have caused death. Most severe skin reactions occurred during the first cycle (28 days) of treatment but may happen later. Your healthcare provider will monitor you during treatment 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 if you:

- have received an immunotherapy medicine **and** chemotherapy that contains platinum, **or**
- you are not able to receive a chemotherapy that contains the medicine cisplatin and you have received one or more prior therapy.

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.
- You will receive your PADCEV over periods of time called cycles.
 - Each PADCEV cycle is 28 days.
 - You will receive PADCEV on days 1, 8 and 15 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).** You can develop high blood sugar during treatment with PADCEV. 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. Tell your healthcare provider right away if you get new or worsening symptoms, including trouble breathing, shortness of breath, or cough.
- **Peripheral neuropathy.** You may develop nerve problems called peripheral neuropathy during treatment with PADCEV. 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.** You can develop certain eye problems during treatment with PADCEV. Tell your healthcare provider right away if you have dry eyes, 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, or discomfort at the infusion site.

The most common side effects of PADCEV include:

- | | | |
|---|--|---|
| • skin rash | • hair loss | • itching |
| • changes in liver and kidney function tests | • decreased appetite | • change in sense of taste |
| • increased sugar (glucose) in the blood | • diarrhea | • increased uric acid in the blood |
| • tiredness | • decreased sodium, phosphate and protein (albumin) in the blood | • increased lipase (a blood test done to check your pancreas) |
| • numbness or tingling in your hands or feet, or muscle weakness | • nausea | • decreased weight |
| • decreased white blood cell, red blood cell, and platelet counts | | • dry skin |

If you have certain side effects, your healthcare provider may decrease your dose or stop your treatment with PADCEV for a period of time (temporarily) or completely.

PADCEV may cause fertility problems in males, which may affect the ability to father 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. If you would like more information about PADCEV, talk with your healthcare provider. 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 dehydrate.

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For more information, go to www.padcev.com or call 1-888-4-PADCEV