PADCEV® Dosing and Administration Guide

PADCEV J-code J9177

This information is provided for educational purposes only. This is not a guarantee of reimbursement. It is the provider's responsibility to determine the appropriate code and to submit true and correct claims.

BOXED 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.**

INDICATION

PADCEV, in combination with pembrolizumab, is indicated for the treatment of adult patients with locally advanced or metastatic urothelial cancer (mUC).

PADCEV, as a single agent, is indicated for the treatment of adult patients with locally advanced or 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.

Please see Important Safety Information and full Prescribing Information, including **BOXED WARNING.**

PADCEV®
enfortumab vedotin-ejfv
Injection for IV infusion 20 mg & 30 mg vials

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Introduction

PADCEV® is an FDA-approved treatment for locally advanced or metastatic urothelial cancer in the following clinical settings.[1]

In **combination with pembrolizumab** for[1]:

1. Patients with la/mUC

As a **single agent** for[1]:

2. Patients who previously received platinum-containing chemotherapy and a PD-(L)1 inhibitor
3. Cisplatin-ineligible patients who previously received one or more prior lines of therapy

FDA=US Food and Drug Administration; la/mUC=locally advanced or metastatic urothelial cancer; PD-(L)1=programmed death receptor-1 or programmed death-ligand 1.

Mechanism of action

PADCEV® is an ADC directed against Nectin-4[1]

- Nectin-4 is an adhesion protein located on the surface of cells

Nonclinical data suggest that the anticancer activity of PADCEV is a result of the following[1]:

1. Binding of the ADC to Nectin-4–expressing cells

2. Internalization of the ADC–Nectin-4 complex

3. Release of MMAE via proteolytic cleavage

4. Disruption of the microtubule network within the cell

5. Cell cycle arrest and apoptosis

In preclinical studies, the combination of PADCEV with a PD-1 blocking antibody resulted in upregulation of immune function and increased antitumor activity in tumor models expressing Nectin-4[1,2]

ADC=antibody-drug conjugate; MMAE=monomethyl auristatin E.

Recommended dosage and infusion schedule[1]

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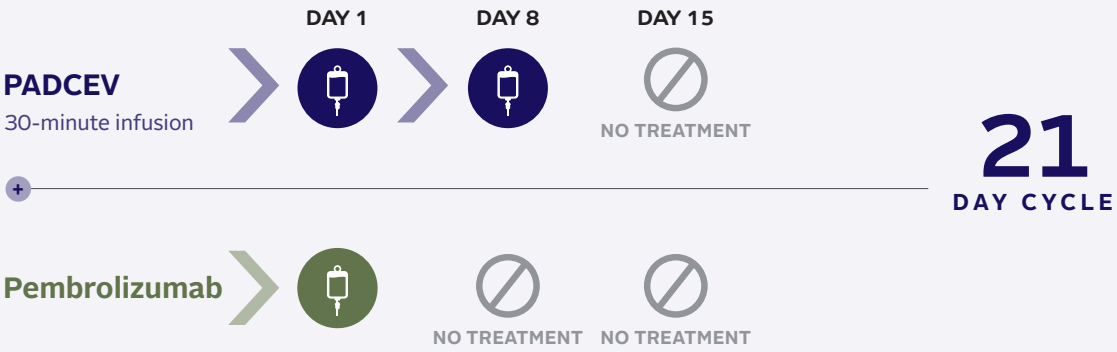
PADCEV® + pembrolizumab

When given in combination, the recommended dose of PADCEV is 1.25 mg/kg (up to a maximum of 125 mg for patients ≥100 kg) administered as an IV infusion over 30 minutes on **days 1 and 8 of every 21-day cycle until disease progression or unacceptable toxicity**.

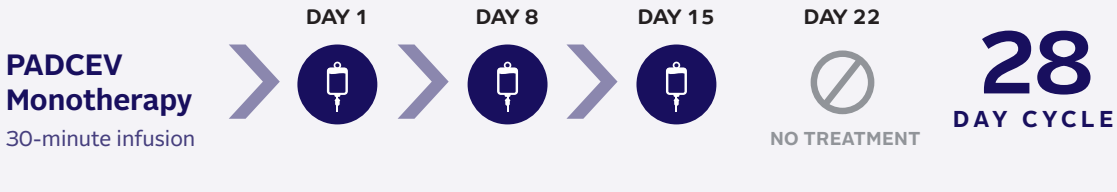
In the EV-302 trial, **day 1** PADCEV dosing of every 21-day dosing cycle was followed by pembrolizumab 200 mg IV, approximately 30 minutes after completion of PADCEV infusion.



Refer to the pembrolizumab Prescribing Information for the recommended dosing information of pembrolizumab.

PADCEV monotherapy

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 IV infusion over 30 minutes on days 1, 8, and 15 of a 28-day cycle until disease progression or unacceptable toxicity.



IV=intravenous.

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PADCEV® dosage & administration

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Recommended starting dose calculation

The amounts shown in the dosing calculation below are based on the recommended dose of PADCEV (1.25 mg/kg [up to a maximum of 125 mg for patients ≥100 kg]) and do not include dose modifications. This calculation should not replace professional judgment or clinical experience.[1]

$$\left(\frac{\boxed{?}\ \text{Patient weight (lb)}}{2.2}\right) \times 1.25 = \text{DOSE (mg)}$$

Access the PADCEV dosing calculator for help determining your patient's recommended dose

ASPECTS OF PADCEV DOSING AND ADMINISTRATION

- **No biomarker testing required**[2-4]
- **Premedication is not required**[2-5*]
- **30-minute infusion time**[1]

*Premedication is not specified in the US Prescribing Information. In the EV-302, EV-301, and EV-201 trials, patients who experienced an infusion-related reaction may have been premedicated for subsequent infusions. Premedication may include pain medicine (eg, acetaminophen or equivalent), an antihistamine (eg, diphenhydramine hydrochloride), and a corticosteroid administered approximately 30 to 60 minutes prior to each infusion or according to institutional standards.[2-4]

Recommended dose reduction schedule[1]

STARTING DOSE LEVEL
DOSE LEVEL: 1.25 mg/kg up to 125 mg

1ST DOSE REDUCTION
DOSE LEVEL: 1.0 mg/kg up to 100 mg

2ND DOSE REDUCTION
DOSE LEVEL: 0.75 mg/kg up to 75 mg

3RD DOSE REDUCTION
DOSE LEVEL: 0.5 mg/kg up to 50 mg

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Drug interactions and use in specific populations[1]

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Drug interactions: 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, 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.

Specific populations

No clinically significant differences in the pharmacokinetics of the ADC or unconjugated MMAE were identified based on age (24 to 90 years), sex, race (Caucasian, Asian, or Black), renal impairment and mild hepatic impairment (total bilirubin of 1 to 1.5 x ULN and AST any, or total bilirubin ≤ULN and AST >ULN). The effect of end stage renal disease with or without dialysis and moderate or severe hepatic impairment (total bilirubin >1.5 x ULN and AST any) on the pharmacokinetics of the ADC or unconjugated MMAE is unknown.

PREGNANCY: Based on the mechanism of action and findings in animals, PADCEV can cause fetal harm when administered to a pregnant woman. Advise patients of the potential risk to the fetus.

LACTATION: Advise lactating women not to breastfeed during treatment with PADCEV and for 3 weeks after the last dose.

FEMALES AND MALES OF REPRODUCTIVE POTENTIAL: Verify pregnancy status in females of reproductive potential prior to initiating PADCEV treatment.

PADCEV can cause fetal harm when administered to a pregnant woman.

Advise females 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.

Based on findings in animal studies with MMAE-containing antibody-drug conjugates (ADCs), PADCEV may impair female fertility. The effect on fertility is reversible.

Based on findings from animal studies, PADCEV may also impair male fertility.

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

GERIATRIC USE: Of the 564 patients treated with PADCEV in combination with pembrolizumab, 44% (n=247) were 65-74 years and 26% (n=144) were 75 years or older. Of the 720 patients treated with PADCEV as a single agent in clinical trials, 39% (n=282) were 65-74 years and 24% (n=170) were 75 years or older.

No overall differences in effectiveness were observed between patients 65 years of age or older and younger patients.

Patients 75 years of age or older treated with PADCEV in combination with pembrolizumab and with PADCEV as a single agent experienced a higher incidence of fatal adverse reactions than younger patients.

No significant difference was observed in the pharmacokinetics of PADCEV between patients 65 years and older and younger patients.

HEPATIC IMPAIRMENT: Avoid the use of PADCEV in patients with moderate or severe hepatic impairment (total bilirubin >1.5 x ULN and AST any).

AST=aspartate aminotransferase; CYP3A4=cytochrome P450 3A4; P-gp=permeability glycoprotein; ULN=upper limit of normal.

PADCEV® dose modifications due to adverse reactions[1]

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ADVERSE REACTION	SEVERITY*	DOSE MODIFICATION*†
SKIN REACTIONS	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	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)	Grade 2	Withhold until Grade ≤1, then resume treatment at the same dose level or consider dose reduction by one dose level.
	Grade ≥3	Permanently discontinue.
PERIPHERAL NEUROPATHY	Grade 2	Withhold until Grade ≤1, then resume treatment at the same dose level (if first occurrence). For a recurrence, withhold until Grade ≤1, then resume treatment reduced by one dose level.
	Grade ≥3	Permanently discontinue.

SJS=Stevens-Johnson syndrome; TEN=toxic epidermal necrolysis.
*Grade 1 is mild; Grade 2 is moderate; Grade 3 is severe; Grade 4 is life-threatening.
†Recommended dose reduction schedule: starting dose (dose level: 1.25 mg/kg up to 125 mg), first dose reduction (dose level: 1.0 mg/kg up to 100 mg), second dose reduction (dose level: 0.75 mg/kg up to 75 mg), third dose reduction (dose level: 0.5 mg/kg up to 50 mg).[1]

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PADCEV® dose modifications due to adverse reactions[1]

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ADVERSE REACTION	SEVERITY*	DOSE MODIFICATION*†
OCULAR DISORDERS	N/A	Consider dose interruption or dose reduction of PADCEV for symptomatic ocular disorders.
INFUSION SITE EXTRAVASATION	N/A	Stop the infusion and monitor for adverse reactions.
OTHER NONHEMATOLOGIC TOXICITY	Grade 3	Withhold until Grade ≤1, then resume treatment at the same dose level or consider dose reduction by one dose level.
	Grade 4	Permanently discontinue.
HEMATOLOGIC TOXICITY	Grade 3, or Grade 2 thrombocytopenia	Withhold until Grade ≤1, then resume treatment at the same dose level or consider dose reduction by one dose level.
	Grade 4	Withhold until Grade ≤1, then reduce dose by one dose level or discontinue treatment.

*Grade 1 is mild; Grade 2 is moderate; Grade 3 is severe; Grade 4 is life-threatening.
†Recommended dose reduction schedule: starting dose (dose level: 1.25 mg/kg up to 125 mg), first dose reduction (dose level: 1.0 mg/kg up to 100 mg), second dose reduction (dose level: 0.75 mg/kg up to 75 mg), third dose reduction (dose level: 0.5 mg/kg up to 50 mg).[1]

It is important to proactively monitor, identify, and treat adverse reactions that may arise during treatment.

Please see Important Safety Information and full Prescribing Information, including **BOXED WARNING.**

PADCEV® preparation, administration, storage, and handling information[1]

PADCEV
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Injection for IV infusion 20 mg & 30 mg vials

- Administer PADCEV as an IV infusion only
- PADCEV is a hazardous drug. Follow applicable special handling and disposal procedures

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:
   - 20 mg vial: Add 2.3 mL of SWFI, resulting in 10 mg/mL PADCEV
   - 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)
8. DO NOT FREEZE. Discard unused vials with reconstituted solution beyond the recommended storage time

PADCEV® preparation, administration, storage, and handling information[1]

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Injection for IV infusion 20 mg & 30 mg vials

Dilution in infusion bag

- Withdraw the calculated dose amount of reconstituted solution from the vial(s) and transfer into an infusion bag
- 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
- Mix diluted solution by gentle inversion. DO NOT SHAKE THE BAG. Do not expose to direct sunlight
- 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
- Discard any unused portion left in the single-dose vials

Administration

- Immediately administer the infusion over 30 minutes through an IV line
- 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.

How supplied

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

Special handling

- PADCEV is a hazardous drug. Follow applicable special handling and disposal procedures

Adverse reactions in the EV-302 clinical trial (previously untreated patients)[1]

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Talk with your patients about adverse reactions that may occur during treatment with PADCEV® and pembrolizumab

ADVERSE REACTIONS ≥15% (ALL GRADES) IN PATIENTS TREATED WITH PADCEV IN COMBINATION WITH PEMBROLIZUMAB[1]

	PADCEV IN COMBINATION WITH PEMBROLIZUMAB n=440		CHEMOTHERAPY n=433	
ADVERSE REACTION, %	**ALL GRADES**	**GRADES 3-4**	**ALL GRADES**	**GRADES 3-4**
Skin and subcutaneous tissue disorders				
Rash*	68	15	15	0
Pruritus	41	1.1	7	0
Alopecia	35	0.5	8	0.2
Dry skin	17	0.2	1	0
General disorders and administration site conditions				
Fatigue*	51	6	57	7
Pyrexia	18	0.7	16	1.2
Nervous system disorders				
Peripheral neuropathy*	67	8	14	0
Dysgeusia	21	0	9	0
Metabolism and nutrition disorders				
Decreased appetite	33	1.8	26	1.8
Gastrointestinal disorders				
Diarrhea	38	4.5	16	1.4
Nausea	26	1.6	41	2.8
Constipation	26	0	34	0.7
Investigations				
Decreased weight	33	3.6	9	0.2
Eye disorders				
Dry eye*	24	0	2.1	0
Infections and infestations				
Urinary tract infection	21	5	19	8

*Includes: multiple terms.

Please see Important Safety Information and full Prescribing Information, including **BOXED WARNING.**

Laboratory abnormalities in the EV-302 clinical trial[1]

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SELECTED LABORATORY ABNORMALITIES REPORTED IN ≥15% (ALL GRADES) OF PATIENTS TREATED WITH PADCEV® IN COMBINATION WITH PEMBROLIZUMAB[1]

	PADCEV IN COMBINATION WITH PEMBROLIZUMAB*		CHEMOTHERAPY*	
LABORATORY ABNORMALITY, %	**ALL GRADES**	**GRADES 3-4**	**ALL GRADES**	**GRADES 3-4**
Chemistry				
Increased aspartate aminotransferase	75	5	39	3
Increased creatinine	71	3	68	3
Increased glucose	66	14	54	5
Increased alanine aminotransferase	59	5	49	3
Decreased sodium	46	13	47	13
Decreased phosphate	44	9	36	9
Decreased albumin	39	2	35	0.5
Decreased potassium	26	5	16	3
Increased potassium	24	1	36	4
Increased calcium	21	1	14	0.2
Hematology				
Decreased lymphocytes	58	15	59	17
Decreased hemoglobin	53	7	89	33
Decreased neutrophils	30	9	80	50

- Median duration of exposure to PADCEV was 7 months (range: 0.3 to 31.9 months)[1]
- Serious adverse reactions occurred in 50% of patients treated with PADCEV in combination with pembrolizumab. The most common serious adverse reactions (≥2%) were rash (6%), acute kidney injury (5%), pneumonitis/ILD (4.5%), urinary tract infection (3.6%), diarrhea (3.2%), pneumonia (2.3%), pyrexia (2%), and hyperglycemia (2%)[1]
- Fatal adverse reactions occurred in 3.9% of patients treated with PADCEV in combination with pembrolizumab including acute respiratory failure (0.7%), pneumonia (0.5%), and pneumonitis/ILD (0.2%)[1]

- **Adverse reactions leading to discontinuation** of PADCEV occurred in 35% of patients. The most common adverse reactions (≥2%) leading to discontinuation of PADCEV were peripheral neuropathy (15%), rash (4.1%), and pneumonitis/ILD (2.3%)[1]
- **Adverse reactions leading to dose interruption** of PADCEV occurred in 73% of patients. The most common adverse reactions (≥2%) leading to dose interruption of PADCEV were peripheral neuropathy (22%), rash (16%), COVID-19 (10%), diarrhea (5%), pneumonitis/ILD (4.8%), fatigue (3.9%), hyperglycemia (3.6%), increased alanine aminotransferase (3%), and pruritus (2.5%)[1]
- **Adverse reactions leading to dose reduction** of PADCEV occurred in 42% of patients. The most common adverse reactions (≥2%) leading to dose reduction of PADCEV were rash (16%), peripheral neuropathy (13%), and fatigue (2.7%)[1]

*The denominator used to calculate the rate varied from 407 to 439 based on the number of patients with a baseline value and at least one post-treatment value.

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Adverse reactions in the EV-301 clinical trial (post-platinum, post–PD-(L)1 patients)[1]

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Talk with your patients about adverse reactions that may occur during treatment with PADCEV®

ADVERSE REACTIONS REPORTED IN ≥15% (ALL GRADES) OF PATIENTS TREATED WITH PADCEV[1]				
	PADCEV (n=296)		CHEMOTHERAPY (n=291)	
ADVERSE REACTION, %	**ALL GRADES**	**GRADES 3-4**	**ALL GRADES**	**GRADES 3-4**
Skin and subcutaneous tissue disorders				
Rash*	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*	50	9	40	7
Pyrexia*	22	2	14	0
Nervous system disorders				
Peripheral neuropathy*	50	5	34	3
Dysgeusia*	26	0	8	0
Metabolism and nutrition disorders				
Decreased appetite	41	5	27	2
Gastrointestinal disorders				
Diarrhea*	35	4	23	2
Nausea	30	1	25	2
Constipation	28	1	25	2
Abdominal pain*	20	1	14	3
Musculoskeletal and connective tissue disorders				
Musculoskeletal pain*	25	2	35	5
Eye disorders				
Dry eye*	24	0.7	6	0.3
Infections and infestations				
Urinary tract infection*	17	6	13	3
Vascular disorders				
Hemorrhage*	17	3	13	2
Investigations				
Decreased weight	16	0.3	7	0

*Includes: multiple terms.

Please see Important Safety Information and full Prescribing Information, including **BOXED WARNING.**

Laboratory abnormalities in the EV-301 clinical trial[1]

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SELECTED LABORATORY ABNORMALITIES REPORTED IN ≥15% (GRADES 2-4) OR ≥5% (GRADES 3-4) OF PATIENTS TREATED WITH PADCEV®[1]

	PADCEV*		CHEMOTHERAPY*	
LABORATORY ABNORMALITY, %	**GRADES 2-4**	**GRADES 3-4**	**GRADES 2-4**	**GRADES 3-4**
Hematology				
Decreased lymphocytes	41	14	34	18
Decreased hemoglobin	28	4	42	14
Decreased neutrophils	27	12	25	17
Chemistry				
Decreased phosphate	39	8	24	6
Increased glucose (non-fasting)	33	9	27	6
Increased creatinine	18	2	13	0
Decreased potassium	16	2	7	3
Increased lipase	13	8	7	4
Decreased sodium	8	8	5	5

- Median duration of exposure was 5 months (range: 0.5-19 months) with PADCEV[1]
- 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%), hepatic dysfunction, septic shock, hyperglycemia, pneumonitis/ILD, and pelvic abscess (0.3% each)[1]

- **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%)[1]
- **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%)[1]
- **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%)[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.

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Adverse reactions in the EV-201 Cohort 2 trial (cisplatin-ineligible, post–PD-(L)1 patients)[1]

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Talk with your patients about adverse reactions that may occur during treatment with PADCEV®

ADVERSE REACTIONS REPORTED IN ≥15% (ALL GRADES) OR ≥5% (GRADES 3-4) OF PATIENTS TREATED WITH PADCEV[1]		
	PADCEV (n=89)	
ADVERSE REACTION, %	**ALL GRADES**	**GRADES 3-4**
Skin and subcutaneous tissue disorders		
Rash*	66	17
Alopecia	53	0
Pruritus	35	3
Dry skin	19	1
Nervous system disorders		
Peripheral neuropathy*	58	8
Dysgeusia*	29	0
General disorders and administration site conditions		
Fatigue*	48	11
Metabolism and nutrition disorders		
Decreased appetite	40	6
Hyperglycemia	16	9
Gastrointestinal disorders		
Diarrhea*	36	8
Nausea	30	1
Investigations		
Decreased weight	35	1
Eye disorders		
Dry eye*	30	0

*Includes: multiple terms.

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Laboratory abnormalities in the EV-201 Cohort 2 trial[1]

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SELECTED LABORATORY ABNORMALITIES REPORTED IN ≥15% (GRADES 2-4) OR ≥5% (GRADES 3-4) OF PATIENTS TREATED WITH PADCEV®[1]

	PADCEV (n=88)*	
LABORATORY ABNORMALITY, %	**GRADES 2-4**	**GRADES 3-4**
Hematology		
Decreased lymphocytes	43	15
Decreased hemoglobin	34	5
Decreased neutrophils	20	9
Chemistry		
Increased glucose (non-fasting)	36	13
Decreased phosphate	25	7
Increased creatinine	23	3
Increased lipase	18	11
Increased urate	9	9
Increased potassium	8	6
Decreased sodium	7	7

- Median duration of exposure was 5.98 months (range: 0.3-24.6 months)[1]
- 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/ILD (1.1% each)[1]

- **Adverse reactions leading to discontinuation** occurred in 20% of patients; the most common adverse reaction (≥2%) leading to discontinuation was peripheral neuropathy (7%)[1]
- **Adverse reactions leading to dose interruption** occurred in 60% of patients; the most common adverse reactions (≥3%) leading to dose interruption were peripheral neuropathy (19%), rash (9%), fatigue (8%), diarrhea (5%), increased aspartate aminotransferase (3%), and hyperglycemia (3%)[1]
- **Adverse reactions leading to dose reduction** occurred in 49% of patients; the most common adverse reactions (≥3%) leading to dose reduction were peripheral neuropathy (19%), rash (11%), and fatigue (7%)[1]

*Based on the number of patients with a baseline value and at least one post-treatment value.

Important Safety Information

BOXED 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.**

IMPORTANT SAFETY INFORMATION

WARNINGS AND PRECAUTIONS

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 70% (all grades) of the 564 patients treated with PADCEV in combination with pembrolizumab in clinical trials. When PADCEV was given in combination with pembrolizumab, the incidence of skin reactions, including severe events, occurred at a higher rate compared to PADCEV as a single agent. 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 17% of patients (Grade 3: 16%, Grade 4: 1%), 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 (0.2%). The median time to onset of severe skin reactions was 1.7 months (range: 0.1 to 17.2 months). Skin reactions led to discontinuation of PADCEV in 6% of patients.

Skin reactions occurred in 58% (all grades) of the 720 patients treated with PADCEV as a single agent in clinical trials. Twenty-three percent (23%) of patients had maculo-papular rash and 34% had pruritus. Grade 3-4 skin reactions occurred in 14% 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 0.6 months (range: 0.1 to 8 months). Among patients experiencing a skin reaction leading to dose interruption who then restarted PADCEV (n=75), 24% of patients restarting at the same dose and 24% of patients restarting at a reduced dose experienced recurrent severe skin reactions. Skin reactions led to discontinuation of PADCEV in 3.1% of patients.

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.

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, 17% of the 720 patients treated with PADCEV developed hyperglycemia of any grade; 7% of patients developed Grade 3-4 hyperglycemia (Grade 3: 6.5%, Grade 4: 0.6%). Fatal events of hyperglycemia and DKA 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. The median time to onset of hyperglycemia was 0.5 months (range: 0 to 20 months). Hyperglycemia led to discontinuation of PADCEV in 0.7% of patients. Five percent (5%) of patients required initiation of insulin therapy for treatment of hyperglycemia. Of the patients who initiated insulin therapy for treatment of hyperglycemia, 66% (23/35) discontinued insulin at the time of last evaluation. 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.

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Important Safety Information (cont'd)

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Pneumonitis/Interstitial Lung Disease (ILD) Severe, life-threatening or fatal pneumonitis/ILD occurred in patients treated with PADCEV®. When PADCEV was given in combination with pembrolizumab, 10% of the 564 patients treated with combination therapy had pneumonitis/ILD of any grade and 4% had Grade 3-4. A fatal event of pneumonitis/ILD occurred in two patients (0.4%). The incidence of pneumonitis/ILD, including severe events, occurred at a higher rate when PADCEV was given in combination with pembrolizumab compared to PADCEV as a single agent. The median time to onset of any grade pneumonitis/ILD was 4 months (range: 0.3 to 26 months).

In clinical trials of PADCEV as a single agent, 3% of the 720 patients treated with PADCEV had pneumonitis/ILD of any grade and 0.8% had Grade 3-4. The median time to onset of any grade pneumonitis/ILD was 2.9 months (range: 0.6 to 6 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.

Peripheral neuropathy (PN) When PADCEV was given in combination with pembrolizumab, 67% of the 564 patients treated with combination therapy had PN of any grade, 36% had Grade 2 neuropathy, and 7% had Grade 3 neuropathy. The incidence of PN occurred at a higher rate when PADCEV was given in combination with pembrolizumab compared to PADCEV as a single agent. The median time to onset of Grade ≥2 PN was 6 months (range: 0.3 to 25 months).

PN occurred in 53% of the 720 patients treated with PADCEV as a single agent in clinical trials including 38% with sensory neuropathy, 8% with muscular weakness and 7% with motor neuropathy. Thirty percent of patients experienced Grade 2 reactions and 5% experienced Grade 3-4 reactions. PN occurred in patients treated with PADCEV with or without preexisting PN. The median time to onset of Grade ≥2 PN was 4.9 months (range: 0.1 to 20 months). Neuropathy led to treatment discontinuation in 6% of patients.

Monitor patients for symptoms of new or worsening PN and consider dose interruption or dose reduction of PADCEV when PN occurs. Permanently discontinue PADCEV in patients who develop Grade ≥3 PN.

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 30% of patients, and blurred vision occurred in 10% of patients, during treatment with PADCEV. The median time to onset to symptomatic ocular disorder was 1.7 months (range: 0 to 30.6 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.

Infusion site extravasation Skin and soft tissue reactions secondary to extravasation have been observed after administration of PADCEV. Of the 720 patients treated with PADCEV as a single agent in clinical trials, 1% 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.

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Embryo-fetal toxicity PADCEV® can cause fetal harm when administered to a pregnant woman. Advise patients of the potential risk to the fetus. Advise female patients of reproductive potential to use effective contraception during PADCEV treatment 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.

ADVERSE REACTIONS

Most common adverse reactions, including laboratory abnormalities (≥20%) (PADCEV in combination with pembrolizumab)

Increased aspartate aminotransferase (AST), increased creatinine, rash, increased glucose, PN, increased lipase, decreased lymphocytes, increased alanine aminotransferase (ALT), decreased hemoglobin, fatigue, decreased sodium, decreased phosphate, decreased albumin, pruritus, diarrhea, alopecia, decreased weight, decreased appetite, increased urate, decreased neutrophils, decreased potassium, dry eye, nausea, constipation, increased potassium, dysgeusia, urinary tract infection and decreased platelets.

Most common adverse reactions, including laboratory abnormalities (≥20%) (PADCEV monotherapy)

Increased glucose, increased AST, decreased lymphocytes, increased creatinine, rash, fatigue, PN, decreased albumin, decreased hemoglobin, alopecia, decreased appetite, decreased neutrophils, decreased sodium, increased ALT, decreased phosphate, diarrhea, nausea, pruritus, increased urate, dry eye, dysgeusia, constipation, increased lipase, decreased weight, decreased platelets, abdominal pain, dry skin.

EV-302 Study: 440 patients with previously untreated la/mUC (PADCEV in combination with pembrolizumab)

Serious adverse reactions occurred in 50% of patients treated with PADCEV in combination with pembrolizumab. The most common serious adverse reactions (≥2%) were rash (6%), acute kidney injury (5%), pneumonitis/ILD (4.5%), urinary tract infection (3.6%), diarrhea (3.2%), pneumonia (2.3%), pyrexia (2%), and hyperglycemia (2%). **Fatal adverse reactions** occurred in 3.9% of patients treated with PADCEV in combination with pembrolizumab including acute respiratory failure (0.7%), pneumonia (0.5%), and pneumonitis/ILD (0.2%).

Adverse reactions leading to discontinuation of PADCEV occurred in 35% of patients. The **most common adverse reactions (≥2%) leading to discontinuation** of PADCEV were PN (15%), rash (4.1%) and pneumonitis/ILD (2.3%). Adverse reactions leading to dose interruption of PADCEV occurred in 73% of patients. The **most common adverse reactions (≥2%) leading to dose interruption** of PADCEV were PN (22%), rash (16%), COVID-19 (10%), diarrhea (5%), pneumonitis/ILD (4.8%), fatigue (3.9%), hyperglycemia (3.6%), increased ALT (3%) and pruritus (2.5%). Adverse reactions leading to dose reduction of PADCEV occurred in 42% of patients. The **most common adverse reactions (≥2%) leading to dose reduction** of PADCEV were rash (16%), PN (13%) and fatigue (2.7%).

EV-103 Study: 121 patients with previously untreated la/mUC who were not eligible for cisplatin-containing chemotherapy (PADCEV in combination with pembrolizumab)

Serious adverse reactions occurred in 50% of patients treated with PADCEV in combination with pembrolizumab; the most common (≥2%) were acute kidney injury (7%), urinary tract infection (7%), urosepsis (5%), sepsis (3.3%), pneumonia (3.3%), hematuria (3.3%), pneumonitis/ILD (3.3%), urinary retention (2.5%), diarrhea (2.5%), myasthenia gravis (2.5%), myositis (2.5%), anemia (2.5%), and hypotension (2.5%). **Fatal adverse reactions** occurred in 5% of patients treated with PADCEV in combination with pembrolizumab, including sepsis (1.6%), bullous dermatitis (0.8%), myasthenia gravis (0.8%), and pneumonitis/ILD (0.8%). **Adverse reactions leading to discontinuation** of PADCEV occurred in 36% of patients; the most common (≥2%) were PN (20%) and rash (6%). **Adverse reactions leading to dose interruption** of PADCEV occurred in 69% of patients; the most common (≥2%) were PN (18%), rash (12%), increased lipase (6%), pneumonitis/ILD (6%), diarrhea (4.1%), acute

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kidney injury (3.3%), increased ALT (3.3%), fatigue (3.3%), neutropenia (3.3%), urinary tract infection (3.3%), increased amylase (2.5%), anemia (2.5%), COVID-19 (2.5%), hyperglycemia (2.5%), and hypotension (2.5%). **Adverse reactions leading to dose reduction** of PADCEV® occurred in 45% of patients; the most common (≥2%) were PN (17%), rash (12%), fatigue (5%), neutropenia (5%), and diarrhea (4.1%).

EV-301 Study: 296 patients previously treated with a PD-1/L1 inhibitor and platinum-based chemotherapy (PADCEV monotherapy)

Serious adverse reactions occurred in 47% of patients treated with PADCEV; the most common (≥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%), hepatic dysfunction, septic shock, hyperglycemia, pneumonitis/ILD, and pelvic abscess (0.3% each). **Adverse reactions leading to discontinuation** occurred in 17% of patients; the most common (≥2%) were PN (5%) and rash (4%). **Adverse reactions leading to dose interruption** occurred in 61% of patients; the most common (≥4%) were PN (23%), rash (11%), and fatigue (9%). **Adverse reactions leading to dose reduction** occurred in 34% of patients; the most common (≥2%) were PN (10%), rash (8%), decreased appetite, and fatigue (3% each).

EV-201, Cohort 2 Study: 89 patients previously treated with a PD-1/L1 inhibitor and not eligible for cisplatin-based chemotherapy (PADCEV monotherapy)

Serious adverse reactions occurred in 39% of patients treated with PADCEV; the most common (≥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/ILD (1.1% each). **Adverse reactions leading to discontinuation** occurred in 20% of patients; the most common (≥2%) was PN (7%). **Adverse reactions leading to dose interruption** occurred in 60% of patients; the most common (≥3%) were PN (19%), rash (9%), fatigue (8%), diarrhea (5%), increased AST, and hyperglycemia (3% each).

Adverse reactions leading to dose reduction occurred in 49% of patients; the most common (≥3%) were PN (19%), rash (11%), and fatigue (7%).

DRUG INTERACTIONS

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 monomethyl auristatin E exposure, 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.

SPECIFIC POPULATIONS

Lactation Advise lactating women not to breastfeed during treatment with PADCEV and for 3 weeks after the last dose.

Hepatic impairment Avoid the use of PADCEV in patients with moderate or severe hepatic impairment.

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If you have any questions or would like more information about PADCEV® dosing and administration:

Call **1-888-4PADCEV** (1-888-472-3238) or visit **PADCEVhcp.com**

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References: 1. PADCEV [package insert]. Northbrook, IL: Astellas Pharma US, Inc. **2.** Pfizer Inc. and Astellas. PADCEV. Data on File. **3.** Protocol for: Powles T, Rosenberg JE, Sonpavde GP, et al. Enfortumab vedotin in previously treated advanced urothelial carcinoma. N Engl J Med 2021;384(12):1125-35. **4.** Supplement to: Rosenberg JE, O'Donnell PH, Balar AV, et al. Pivotal trial of enfortumab vedotin in urothelial carcinoma after platinum and anti-programmed death 1/programmed death ligand 1 therapy. J Clin Oncol 2019;37(29):2592-600. **5.** Powles T, Rosenberg JE, Sonpavde GP, et al. Enfortumab vedotin in previously treated advanced urothelial carcinoma. N Engl J Med 2021;384(12):1125-35.

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