PADCEV® (ENFORTUMAB VEDOTIN) DOSING & ADMINISTRATION GUIDE

INDICATION

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 in the neoadjuvant/adjuvant, locally advanced or metastatic setting, or
- are ineligible for cisplatin-containing chemotherapy and have previously received a PD-1/PD-L1 inhibitor.

The following content does not constitute medical advice.
It should not replace professional judgment or clinical experience

WARNING: SERIOUS SKIN REACTIONS

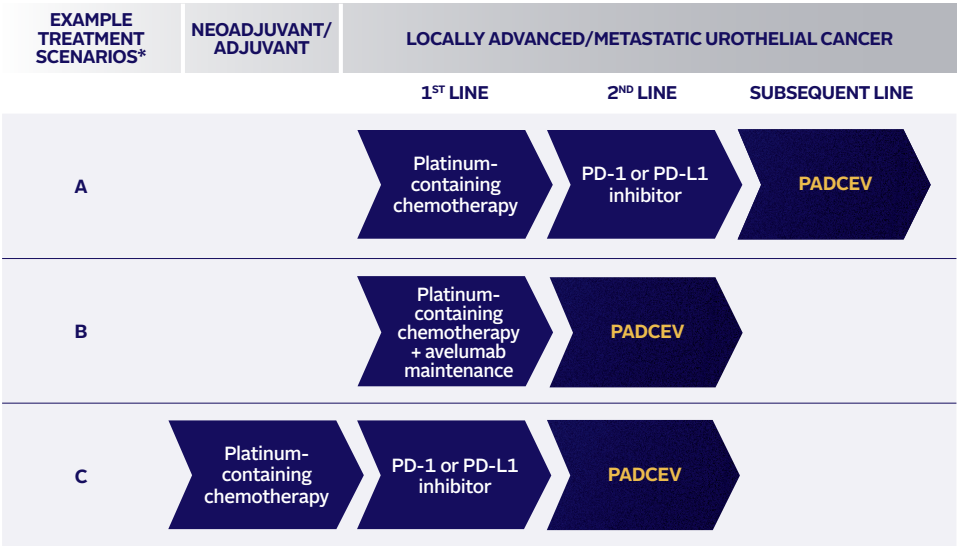
- PADCEV can cause severe and fatal cutaneous adverse reactions including Stevens-Johnson syndrome (SJS) and Toxic Epidermal Necrolysis (TEN), which occurred predominantly during the first cycle of treatment, but may occur later.
- Closely monitor patients for skin reactions.
- Immediately withhold PADCEV 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

For more information, please refer to physician leaflet

LA – locally advanced; mUC – metastatic urothelial carcinoma;

PD-1 – programmed death-1; PD-L1 – programmed death-ligand

Which of your patients could be eligible for PADCEV?[1]



* These are specific treatment scenarios for illustrative purposes only.

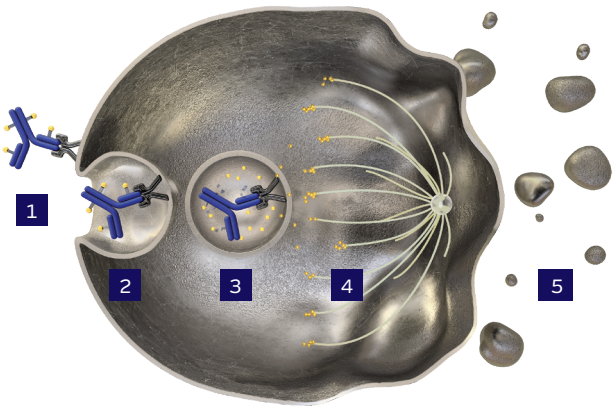
LA – locally advanced; PD-1 – programmed death-1; PD-L1 – programmed death-ligand [1]

PADCEV is an ADC targeted against Nectin-4[1]

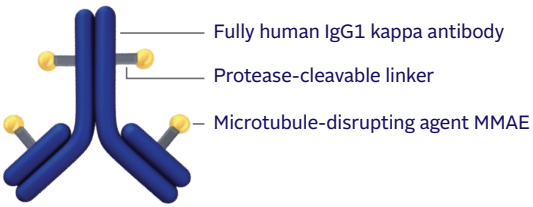
A Nectin-4–targeted treatment approved for LA/mUC in the post-platinum, post–PD-1/PD-L1 setting[1]

- Nectin-4 is an adhesion protein located on the surface of cells[1]
- Nectin-4 is highly expressed in bladder tumour specimens[5]
- Nonclinical data suggest that the main 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 apoptotic cell death



PADCEV is comprised of:



ADC – antibody-drug conjugate; IgG1 – immunoglobulin G1; LA – locally advanced; MMAE – monomethyl auristatin E; mUC – metastatic urothelial carcinoma; PD-1 – programmed death-1; PD-L1 – programmed death-ligand 1

PADCEV dosage & administration[1]

Recommended dosage[1]

The recommended dose of PADCEV is **1.25 mg/kg (up to a maximum of 125 mg for patients ≥100 kg)**

Aspects of PADCEV dosing and administration

Individual weight-based dosing[1]

30-minute infusion[1]

3 infusions every month (on Days 1, 8, and 15 of a 28-day cycle)[1]

Dosing calculations[1]

The table below presents the recommended PADCEV dosage by weight **(1.25 mg/kg, up to a maximum of 125 mg for patients ≥100 kg)** and does not account for dose modifications. This table should not replace professional judgement or clinical experience.

Weight (kg)	Dose (mg)	Weight (kg)	Dose (mg)
40	50	46	57.5
41	51.25	47	58.75
42	52.5	48	60
43	53.75	49	61.25
44	55	50	62.5
45	56.25	51	63.75

Important information about the Dosing Table

This PADCEV dosing table is provided as additional information and is intended for use by a qualified healthcare provider. It should not replace professional judgement or clinical experience nor should it replace the need for medical examination. Please refer to the full SmPC for further information.

Dosing calculations[1] cont.

Weight (kg)	Dose (mg)	Weight (kg)	Dose (mg)
52	65	65	81.25
53	66.25	66	82.5
54	67.5	67	83.75
55	68.75	68	85
56	70	69	86.25
57	71.25	70	87.5
58	72.5	71	88.75
59	73.75	72	90
60	75	73	91.25
61	76.25	74	92.5
62	77.5	75	93.75
63	78.75	76	95
64	80	77	96.25

PADCEV dosage & administration[1]

Weight (kg)	Dose (mg)	Weight (kg)	Dose (mg)
78	97.5	91	113.75
79	98.75	92	115
80	100	93	116.25
81	101.25	94	117.5
82	102.5	95	118.75
83	103.75	96	120
84	105	97	121.5
85	106.25	98	122.5
86	107.5	99	123.75
87	108.75	100	125
88	110	101+	>125
89	111.25		
90	112.5		

Reconstitution is required. Please see page 14-15 of this brochure or the PADCEV full Prescribing Information for preparation and administration

Dose modification summary[1]

Recommended dose reduction schedule for adverse events[1]

Weight (kg)	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

Adverse reaction	Severity	Dose modification
Skin Reaction[1]	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
Pneumonitis[1]	Grade 2	Withhold until Grade ≤ 1 for persistent or recurrent Grade 2 pneumonitis, consider dose reduction by one dose level
	Grade≥3	Permanently discontinue
Hyperglycemia	Blood glucose >250 mg/dL.	Withhold until elevated blood glucose has improved to ≤ 250 mg/dL, then resume treatment at the same dose level

SJS – Stevens-Johnson syndrome; TEN – toxic epidermal necrolysis

Adverse reaction	Severity	Dose modification
Peripheral neuropathy	Grade 2	Withhold until Grade ≤ 1, then resume treatment at the same dose level (if first occurrence).For a recurrence, withhold until Grade ≤ 1 then, resume treatment reduced by one dose level
	Grade≥3	Permanently discontinue
Other 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

SJS – Stevens-Johnson syndrome; TEN – toxic epidermal necrolysis

Warning and Precautions[1]

Adverse reaction

SERIOUS SKIN REACTIONS[1]:

- 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.
- Monitor patients closely throughout treatment for skin reactions
- 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

MONITORING:

- Monitor patients for skin reactions.
- Consider appropriate treatment, such as topical corticosteroids and antihistamines for skin reactions, as clinically indicated

Pneumonitis[2]

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

MONITORING:

- Monitor patients for signs and symptoms indicative of pneumonitis such as hypoxia, cough, dyspnea or interstitial infiltrates on radiologic exams.
- 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

Hyperglycemia

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

MONITORING:

- 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
- Patients with HbA1C ≥ 8% were excluded from clinical trials

Peripheral neuropathy

- Peripheral neuropathy, predominantly peripheral sensory neuropathy, has occurred with PADCEV, including Grade ≥3 (severe) reactions.

Warning and Precautions

Peripheral neuropathy

- Monitoring:
- 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 that develop Grade ≥3 peripheral neuropathy

Ocular disorders

- Ocular disorders occurred in treated with PADCEV. The majority of these events involved the cornea and included keratitis, blurred vision, limbal stem cell deficiency and other events associated with dry eyes
- Monitoring:
  - 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.
- 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.

Embryo-fetal toxicity

- 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.
- 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

Adverse events in the EV-301 clinical trial[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	7
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

Adverse Reaction	PADCEV n=296		Chemotherapy n=291	
	All Grades %	Grade 3-4 %	All Grades %	Grade 3-4 %
Vascular disorders				
Hemorrhage[11]	17	3	13	2
Investigations				
Weight decreased	16	0.3	7	0

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

2 Includes: fatigue, asthenia

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

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

5 Includes: dysgeusia, ageusia, hypogeusia

6 Includes: diarrhea, colitis, enterocolitis

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

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

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

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

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

Laboratory abnormalities in the EV-301 clinical trial[2]

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	7
Chemistry				
Phosphate decreased	39	8	24	6
Glucose increased (non-fasting)	33	9	27	6
Creatinine increased	18	2	23	0
Potassium decreased	16	2	7	3
Lipase increased	13	8	7	4
Sodium decreased	8	8	5	5

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

SWFI – sterile water for injection

Instructions for preparation & administration[1]

Reconstitution in single-dose vial[1]

- Follow procedures for proper handling and disposal of anticancer drugs
- Use appropriate aseptic technique for reconstitution and preparation of dosing solutions
- Calculate the recommended dose based on the patient's weight to determine the number and strength (20 mg or 30 mg) of vials needed
- Reconstitute each vial with SWFI as follows, directing the stream of SWFI along the walls of the vial and not directly onto the lyophilised powder:

1

Reconstitution:

- **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

2

- 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**

3

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

- 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 ºC to 8 ºC
- **DO NOT FREEZE**. Discard unused vials with reconstituted solution beyond the recommended storage time

Dilution in infusion bag[1]

- 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**
- Visually inspect the infusion bag for any particulate matter or discolouration prior to use. The reconstituted solution should be clear to slightly opalescent, colourless to light yellow, and free of visible particles. DO NOT USE the infusion bag if particulate matter or discolouration is observed
- Discard any unused portion left in the single-dose vials
- The prepared infusion bag should not be stored longer than 8 hours under refrigeration 2 ºC to 8 ºC including infusion time. **DO NOT FREEZE**

SWFI – sterile water for injection

Administration[1]

Administer the infusion over 30 minutes through an intravenous line

DO NOT administer as an intravenous push or bolus

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

Prior to administration, the PADCEV vial is reconstituted with SWFI. The reconstituted solution is transferred to an intravenous infusion bag containing sterile 5% Dextrose injection, sterile 0.9% Sodium Chloride injection or sterile Lactated Ringer's injection for administration

Nature and contents of container[1]

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

Special precautions for disposal and other handling[1]

- PADCEV is an antineoplastic product. Any unused medicinal product or waste material should be disposed of in accordance with local requirements

Storage[1]

- Store in a refrigerator (dilution in infusion bag 2 ºC to 8 ºC). **DO NOT FREEZE**

Drug interactions, special populations and references[1]

Drug interactions:

- Strong CYP3A4 Inhibitors - Concomitant use with a strong CYP3A4 inhibitor may increase free MMAE which may increase the incidence or severity of PADCEV toxicities.
  - Closely monitor patients for signs of toxicity when PADCEV is given concomitantly with strong CYP3A4 inhibitors.

Special populations

No dose adjustment required:

- In patients ≥65 years of age
- In patients with mild hepatic impairment (bilirubin of 1 to 1.5x ULN and AST <ULN, or bilirubin ≤ULN and AST >ULN)
- In patients with mild CrCL (>60–90 mL/min), moderate (CrCL 30–60 mL/min) or severe (CrCL <30 mL/min) renal impairment

Not recommended:

- In patients with moderate or severe hepatic impairment (AST or ALT >2.5x ULN or total bilirubin >1.5x ULN) as there is limited to no safety and efficacy data in these patient populations

Please refer to the SmPC for contraindications.

For Padcev full prescribing information please refer to the approved physician leaflet
Padcev 20mg https://israeldrugs.health.gov.il/#!/medDetails/167%2037%2036604%2000
Padcev 30mg https://israeldrugs.health.gov.il/#!/medDetails/167%2038%2036605%2000
Padcev™ (Enfortumab Vedotin) 20mg and 30mg mg powder for concentrate for solution for infusion is available on medical prescription only.
Date of issue aPI: November 2021

References:

1. PADCEV™ Summary of Product Characteristics.
2. Powles T, Rosenberg JE, Sonpavde GP et al. Enfortumab vedotin in previously treated advanced urothelial carcinoma. N Engl J Med. 2021;384(12):1125-1135.
3. Challita-Eid PM, et al. Enfortumab vedotin antibody-drug conjugate targeting Nectin-4 Is a highly potent therapeutic agent in multiple preclinical cancer models. Cancer Res 2016;76(10):3003-3013.
4. NCCN guidelines Bladder cancer July 2021

ADC – antibody-drug conjugates; ALT – alanine aminotransferase; AST – aspartate aminotransferase; AUC – area under the curve; Cmax – maximum-observed concentration; CrCL – creatinine clearance; CYP3A4 – cytochrome P450 3A4; MMAE – monomethyl auristatin E; P-gp – P-glycoprotein; ULN – upper limit of normal

Reporting Safety Information

Any suspected adverse event should be reported to the Ministry of Health according to the National Regulation by using an online form https://sideeffects.health.gov.il/

Adverse events may also be reported to International B.V via an email Pharmacovigilance.IL@astellas.com

Further information available upon request from: Astellas Pharma International B.V., Israel

VV-PVG-007365

For printed copy of this "HCP Dosing and Administration Guide" please send email request to: **Pharmacovigilance.IL@astellas.com**

v.01: This "HCP Dosing and Administration Guide" format and content have been updated and approved by the Ministry of Health on 12.2022

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Astellas Pharma International B.V
Hamelacha 21, Rosh Haayn, Israel