Genitourinary Masterclass

Workshop: Managing baseline comorbidities and staying ahead of AEs with EV

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Prescribing Information is available at the end of this presentation.

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EV, in combination with P, is indicated for the 1L treatment of adult patients with unresectable/mUC who are eligible for platinum-containing chemotherapy.[1]

Please note: This indication has received EMA approval; reimbursement in some EU countries is still pending.

EV as monotherapy is indicated for the treatment of adult patients with LA/mUC who have previously received a platinum-containing chemotherapy and a PD-1/L1 inhibitor.[1]

1L, first line; AE, adverse event; EMA, European Medicines Agency; EV, enfortumab vedotin; LA, locally advanced; mUC, metastatic urothelial carcinoma; P, pembrolizumab; PD-1/L1, programmed death-1/ligand-1.

1. PADCEV™ (enfortumab vedotin). Summary of Product Characteristics.

Date of preparation: June 2025 | Job code: MAT-NL-PAD-2025-00036

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PADCEV™ ▼
enfortumab vedotin
Injection for IV infusion 20 mg & 30 mg vials

astellas

Job code: MAT-NL-PAD-2025-00036

Genitourinary Masterclass

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Pre-initiation principles

Practical guidance on pre-initiation and monitoring considerations for treatment with EV+P for patients with comorbidities

Speaker disclosures

Disclosures of Dr Niedersüß-Beke

Honoraria for lectures or advisory boards

- Amgen, Astellas, Astra Zeneca, BMS, Janssen, Merck Serono, MSD, Servier

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- AstraZeneca, AvenCell, BMS, Lilly, MSD, Pfizer, Roche, Sanofi

Which baseline comorbidity would you like to explore further in this case?

- Impaired renal function
- Hyperglycaemia
- Peripheral neuropathy
- Skin reaction

Raise your hand to vote!

Job code: MAT-NL-PAD-2025-00036

Genitourinary Masterclass

Impaired renal function and peripheral neuropathy

Mr Z has **impaired renal function** and **baseline neuropathy**

Mr Z

Diagnosis: UTUC left with multiple LN metastases

- White male
- **Age:** 85 years
- **ECOG PS:** 1
- **GFR:** 44 mL/min
- **BMI:** 21.5 kg/m^2
- **HbA1c level**: 5.8%

Lifestyle: Widowed

Employment status/job: Retired, former IT expert

Family history of cancer: None

Relevant pre-existing comorbidities:

- Unsteady gait
- Downbeat nystagmus (2015)
- Vertrebrostenosis with claudication spinalis L3–S1 (decompensation surgery 2014) – repeated falls
- Axonal neuropathy suspected – not confirmed (2012)

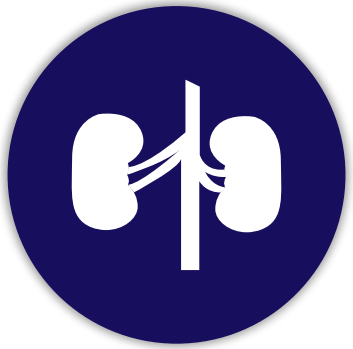
Habits: Enjoys spending time with friends

Priorities: Best treatment for his cancer, while preserving QoL

Fictious patient case created for illustrative purposes.

BMI, body mass index; ECOG PS, Eastern Cooperative Oncology Group performance status; GFR, glomerular filtration rate; HbA1C, haemoglobin A1c; IT, information technology; L, lumbar vertebra; LN, lymph node; QoL, quality of life; S, sacral vertebra; UTUC, upper tract urothelial carcinoma.

EV+P and renal function



Overview

The primary routes of elimination for EV and MMAE are not renal, and renal impairment does not seem to impact EV Pharmacokinetics[1]. EV is metabolised by the CYP3A4 liver enzyme, and excretion of MMAE occurs via faeces and urine[2]. Studies have shown that EV does not appear to affect renal function[1]

EV SmPC management guidance[3]

No dose adjustments are required for patients with mild (CrCL >60–90 mL/min), moderate (CrCL 30–60 mL/min) or severe (CrCL 15–<30 mL/min) renal impairment. EV has not been evaluated in patients with end-stage renal disease (CrCL <15 mL/min)

RWE[4]

Findings of an RWE study in Austria suggest that impaired renal function (eGFR<60) does not influence clinical outcomes in patients treated with EV+P (n=56)

CrCL, creatinine clearance; CYP, cytochrome P450; eGFR, estimated glomerular filtration rate; EV, enfortumab vedotin; MMAE, monomethyl auristatin E; P, pembrolizumab; RWE, real-world evidence; SmPC, Summary of Product Characteristics.

1. Furubayashi N et al. *Anticancer Res* 2024;44:3025–3032; 2. Maiorano BA et al. *Front Oncol* 2023;13:1254906; 3. PADCEV™ (enfortumab vedotin). Summary of Product Characteristics; 4. Niedersuess-Beke D et al. Presented at ASCO GU 2025. Abstract #736.

Managing patients with impaired renal function

Would you do anything for Mr Z *prior to* treatment with EV+P?[1]

- ✓ **Assess baseline renal function** via a GFR or serum creatinine test
- ✓ **Check if there is a postrenal cause** for the impaired renal function

Initiate treatment with EV+P

How would you monitor Mr Z *during treatment* with EV+P?[1]

- ✓ **Repeat assessment** of baseline renal function via a GFR or serum creatinine teat on Day 1 of each cycle prior to administering EV+P

For specific patients:

- ✓ For patients of concern, include an additional monitoring step on Day 8 of every cycle

For patients with mild, moderate or severe renal impairment, **no initial dose adjustments of EV+P are required.**
EV has not been evaluated in patients with end stage renal disease (CrCL <15mL/min)[2]

Fictious patient case created for illustrative purposes.
EV, enfortumab vedotin; GFR, glomerular filtration rate; P, pembrolizumab.
1. Speaker's own opinion; 2. PADCEV™ (enfortumab vedotin). Summary of Product Characteristics.

EV+P and peripheral neuropathy

Overview

Patients with pre-existing Grade ≥2 PN were excluded from clinical studies of EV[1]

PN was the second most common AE with EV+P, occurring in 67% of patients (Grade 3: 7%).[2] The majority of events reported were categorised as peripheral sensory neuropathy (any grade, 53.4%) and PN was the most common AESI leading to treatment discontinuation (12.2% of patients)[1]

Median time to onset

For EV+P, median time to onset Grade ≥2 is 6 months[2]

EV SmPC management guidance[1]

For patients who experience Grade 2 PN, EV should be withheld until Grade ≤1
For a first occurrence, treatment should resume at the same dose level
For a recurrence, withhold until Grade ≤1, then resume treatment reduced by one dose level
EV should be permanently discontinued for Grade ≥3 PN

Neurologist consultation

In cases where PN is unlikely to be caused by EV+P, a neurologist could be consulted;[3] however, where EV+P is likely to be the cause, follow SmPC guidance on management and dose modifications[1,4]

AE, adverse event; AESI, adverse event of special interest; EV, enfortumab vedotin; P, pembrolizumab; PN, peripheral neuropathy; SmPC, Summary of Product Characteristics.

1. PADCEV™ (enfortumab vedotin). Summary of Product Characteristics; 2. Brower B et al. *Front Oncol* 2024;14:1326715; 3. Speaker's own opinion; 4. Keytruda™ (pembrolizumab). Summary of Product Characteristics.

Managing patients with baseline peripheral neuropathy (1/2)

Would you do anything for Mr Z *prior to* treatment with EV+P?

Initiate treatment with EV+P

- ✓ **Assess PN at baseline**, with a focus on how PN impacts patients' daily activities, e.g. through assessment of **fine motor skills, gait and balance**[1–3]
- ✓ **Discuss and consider** the potential impact on QoL and daily activities on **an individual basis**, alongside the potential clinical benefits of EV+P[1]
- ✓ **Educate** on the signs, symptoms and potential management strategies for PN, as **patients may be reluctant to report PN** for fear of treatment interruption or discontinuation and should report any relevant symptoms or changes immediately[2]

Assessment should include a complete medical history exam and assessment of any risk factors that may impact PN, such as older age, spinal involvement of mUC, or diabetes[1,3,4]

Fictious patient case created for illustrative purposes.

EV, enfortumab vedotin; mUC, metastatic urothelial carcinoma; P, pembrolizumab; PN, peripheral neuropathy; QoL, quality of life.

1. Speaker's own opinion; 2. Brower B et al. *Front Oncol* 2024;14:1326715; 3. Pace A et al. *Clin J Oncol Nurs* 2021;25:E1–E9; 4. Jordan B et al. *Ann Oncol* 2020;31:1306–1319.

Managing patients with baseline peripheral neuropathy (2/2)

Initiate treatment with EV+P

How would you monitor Mr Z *during treatment* with EV+P?

The onset of PN may become **more likely over time** (median time to onset of Grade ≥2 PN is 6 months [range: 0.3–25 months])[3]

- ✓ **Monitor for symptoms** of PN at each visit by asking him for typical **changes in his daily life activities,** e.g.[1,2]
  - Problems with typing on the computer/mobile phone
  - Numbness on the fingertips
  - Problems buttoning a shirt
  - Burning sensations
  - Muscle weakness

Treatment with EV+P for patients with unresectable or mUC and baseline PN or who may be at risk of developing PN should be initiated per the SmPC guidance. **SmPC recommendations should also guide management** in the event of PN occurrence or worsening[1,4]

Fictious patient case created for illustrative purposes.

EV, enfortumab vedotin; mUC, metastatic urothelial carcinoma; P, pembrolizumab; PN, peripheral neuropathy; SmPC, Summary of Product Characteristics.

1. Speaker's own opinion; 2. Pace A et al. *Clin J Oncol Nurs* 2021;25:E1–E9; 3. Brower B et al. *Front Oncol* 2024;14:1326715; 4. PADCEV™ (enfortumab vedotin). Summary of Product Characteristics.

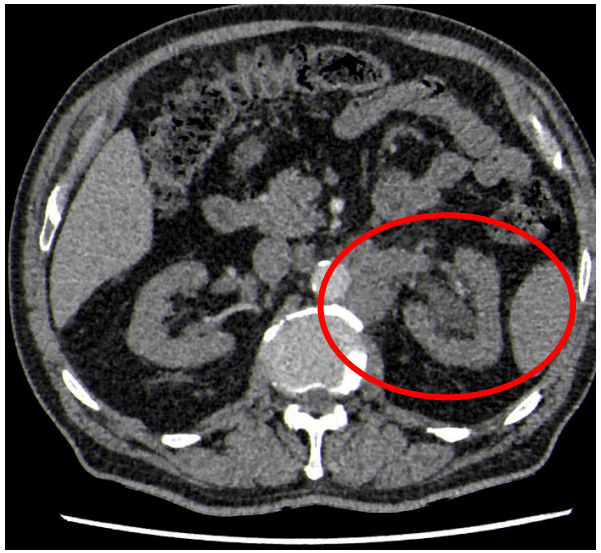
Mr Z had six cycles EV+P in total between January 2024 and May 2025

Cycle 6

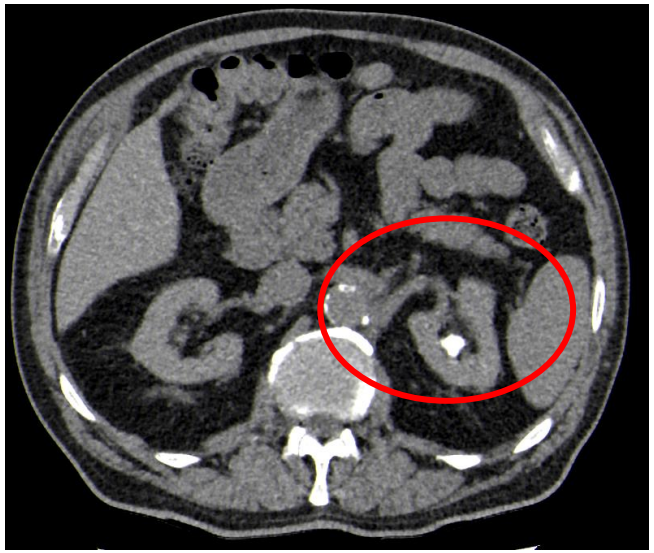
Six cycles were tolerated without serious AEs

After Cycle 6, Mr Z experienced worsening of pre-existing neuropathy (categorised as Grade 2 *after* Cycle 6)

Management
EV+P was **withheld until Grade 1**, and resumed at the same dose following resolution



1/2024



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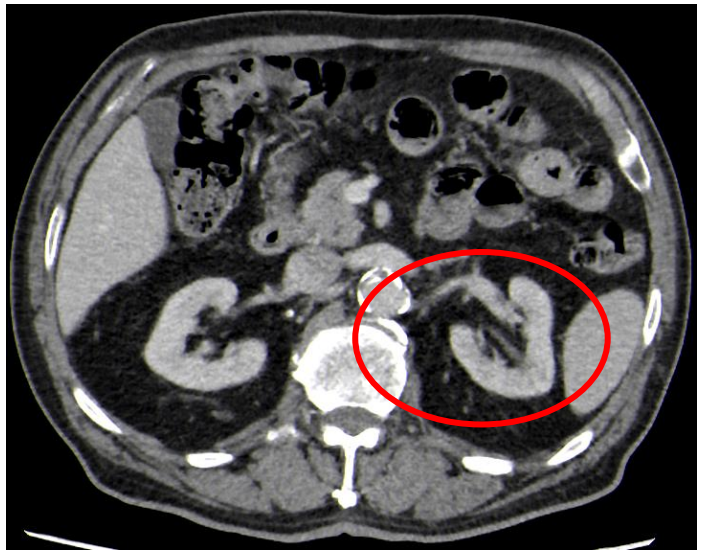
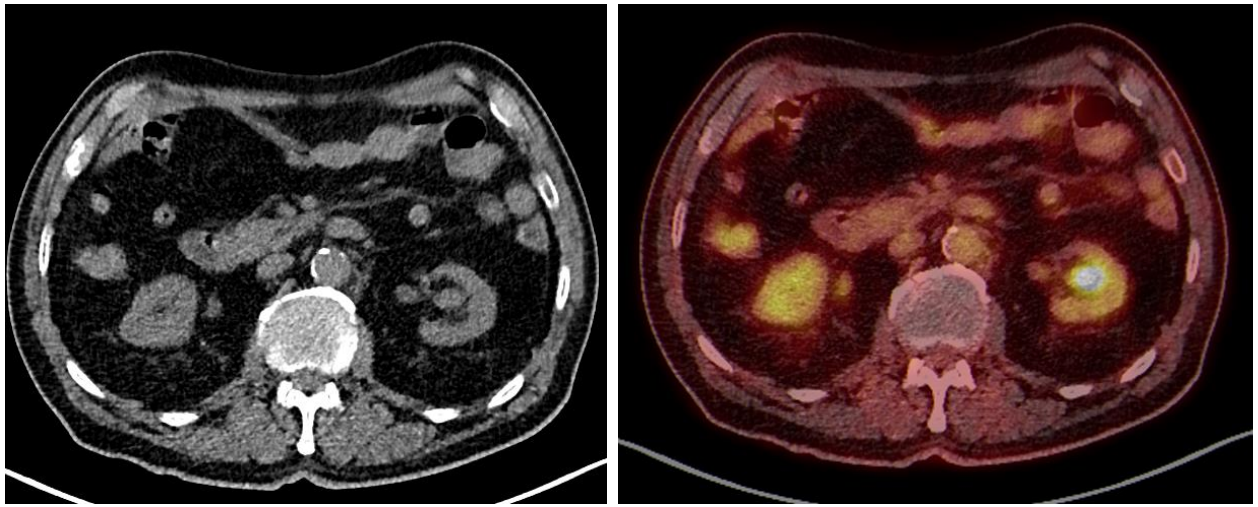


12/2024

Fictious patient case created for illustrative purposes.
Speaker's own images.
AE, adverse event; EV, enfortumab vedotin; P, pembrolizumab.

In March 2025, Mr Z experienced recurrent disease

- Recurrence of the primary tumour, lymph nodes stable
- Lap. tumour nephrectomy and ureterectomy sin. 5/2025
- Histology: Papillary UC high grade, pTa
- Kidney function slightly worsened, GFR 32 mL/min, CrCL 1.9 mg/dL
- PN stable, Grade 1–2, patient still walks with Nordic walking sticks



3/2025

Fictious patient case created for illustrative purposes.
Speaker's own images.
CrCL, creatinine clearance; GFR, glomerular filtration rate; Lap., laparoscopic; pTa, primary tumour is non-invasive papillary carcinoma; UC, urothelial carcinoma.

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Hyperglycaemia

Mr A has **baseline hyperglycaemia**

Mr A

Diagnosis: UTUC left with multiple LN metastases

- White male
- **Age:** 76 years
- **ECOG PS:** 1
- **GFR:** 60 mL/min
- **BMI:** 31 kg/m^2
- **HbA1c level**: 10.1%

Lifestyle: Widowed

Employment status/job: Retired, former IT expert

Family history of cancer: None

Relevant pre-existing comorbidities:
- Obese
- COPD II
- Uncontrolled diabetes mellitus

Clinical history:
- 2019: Prim rad CE pT4a, L1
- Adjuvant chemotherapy (CisGem)
- 2021: Progressive disease

Habits: Enjoys spending time with friends

Priorities: Best treatment for his cancer, while preserving QoL

Fictious patient case created for illustrative purposes.

BMI, body mass index; Cis, cisplatin; COPD, chronic obstructive pulmonary disease; ECOG PS, Eastern Cooperative Oncology Group performance status; GEM, gemcitabine; GFR, glomerular filtration rate; HbA1C, haemoglobin A1c; IT, information technology; L, lumbar vertebra; LN, lymph node; QoL, quality of life; UTUC, upper tract urothelial carcinoma.

EV+P and hyperglycaemia

Overview

Hyperglycaemia is an AESI associated with EV+P[1]

Patients with uncontrolled diabetes* were excluded from clinical studies of EV[1,2]

Median time to onset

For EV+P, median time to hyperglycaemia onset is 0.5 months[3]

EV SmPC management guidance[1]

If blood glucose levels are >13.9 mmol/l (>250 mg/dL), EV is to be withheld until blood glucose levels have improved to ≤13.9 mmol/l (≤250 mg/dL) when EV can resume at the same dose level

*Uncontrolled diabetes is defined as hemoglobin A1c (HbA1c) ≥8% or HbA1c 7%–<8% with associated diabetes symptoms (polyuria or polydipsia) that are not otherwise explained.[4]

AESI, adverse event of special interest; EV, enfortumab vedotin; HbA1c, haemaglobin A1c; P, pembrolizumab; SmPC, Summary of Product Characteristics.

1. PADCEV™ (enfortumab vedotin). Summary of Product Characteristics; 2. Powles T et al. *N Engl J Med* 2024;390:875–888; 3. Brower B et al. *Front Oncol* 2024;14:1326715; 4. Powles T et al. *N Engl J Med* 2024;390:875–888;Protocol.

Managing patients with baseline hyperglycaemia

Would you do anything for Mr A *prior to* treatment with EV+P?

- ✓ **Assess baseline** blood glucose levels,[1] HbA1c level, BMI, and renal and liver function[2,3]
- ✓ **Comprehensive education**, (including dietary advice) especially for patients at risk and their caregivers[2,3]

Initiate treatment with EV+P

How would you monitor Mr A *during treatment* with EV+P?

- ✓ **At each visit, assess blood glucose** levels[2,3]
- ✓ **Every 12 weeks**, assess HbA1c[2]

For specific patients:

- ✓ Patients at high risk for developing hyperglycaemia (e.g. high BMI, concomitant corticosteroids) should be monitored closely[2]

Hyperglycaemia or diabetes should be addressed in order to ensure treatment for mUC is not delayed.
Control of glucose levels can be achieved relatively quickly[2]

Fictious patient case created for illustrative purposes.

BMI, body mass index; EV, enfortumab vedotin; HbA1C, haemoglobin A1c; mUC, metastatic urothelial carcinoma; P, pembrolizumab.

1. PADCEV™ (enfortumab vedotin). Summary of Product Characteristics; 2. Speaker's own opinion; 3. Brower B et al. *Front Oncol* 2024;14:1326715.

Mr A initiated treatment with EV+P

Pre-initiation

- Mr A initiated blood glucose management and had bad compliance
  - Mr A had a blood sugar range of 200–340 mg/dL
  - Diabetic therapy was adapted

EV+P starting dose was 1.25 mg/kg. During treatment, EV+P dose **was reduced to 0.75 mg/kg** to manage his fluctuating blood glucose levels

Cycle 9

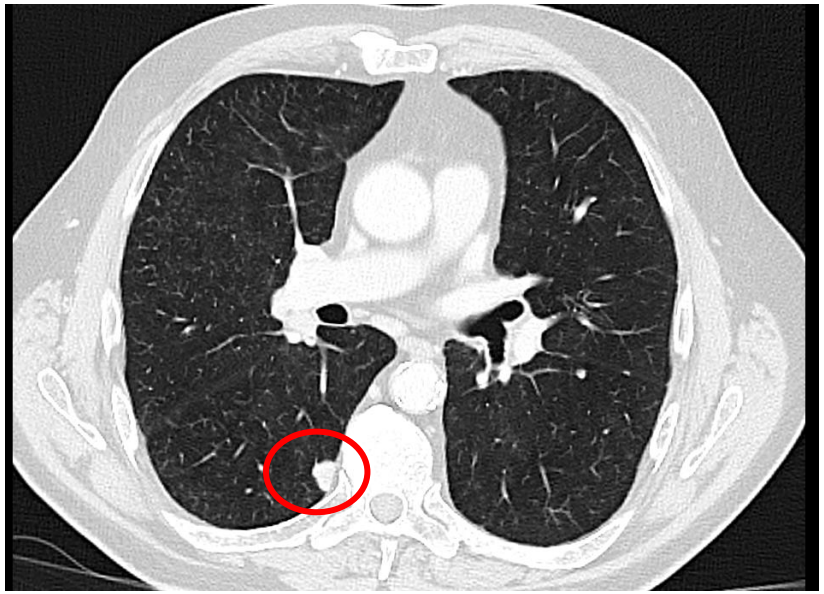
Treatment was discontinued after Cycle 9

HBA1c: 8.7% at the end of treatment

Fictious patient case created for illustrative purposes.

EV, enfortumab vedotin; HbA1C, haemoglobin A1c; P, pembrolizumab.

Mr A remains in complete remission



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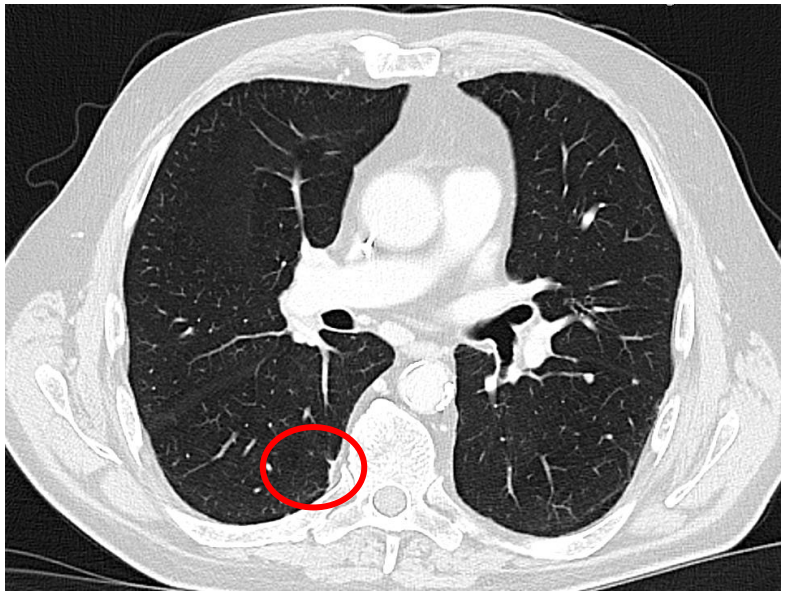

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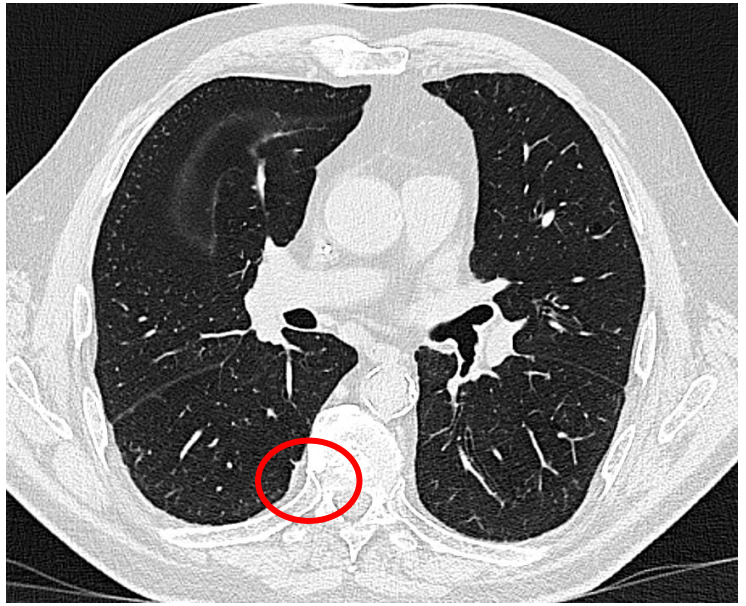

3/2025

Fictious patient case created for illustrative purposes.
Speaker's own images.
EV, enfortumab vedotin; P, pembrolizumab.

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Skin toxicity

Mr Y has **baseline rash maculo-papular**

Mr Y
Diagnosis: UTUC left with multiple LN metastases

- White male
- **Age:** 62 years
- **ECOG PS:** 1
- **GFR:** 60 mL/min
- **BMI:** 24 kg/m^2
- **HbA1c level**: 5.8%

Lifestyle: Married, two adult children

Employment status/job: Retired, former IT expert

Family history of cancer: None

Relevant pre-existing comorbidities:
- Psoriasis vulgaris

Clinical history:
- Neoadjuvant chemotherapy with dd MVAC, radical cystectomy
- Adjuvant nivolumab high risk ypT2, N1, M0 UC, high grade
- Progression with abdominal mainly parailiac LN metastases 1 year after adjuvant nivolumab (psoriasis worsened)

Habits: Enjoys spending time with friends

Priorities: Best treatment for his cancer, while preserving QoL

Disclaimer: PADCEV (enfortumab vedotin) can cause severe skin reactions, including SJS and TEN (predominantly during the first cycle of treatment).
Fictious patient case created for illustrative purposes.

BMI, body mass index; dd, dose-dense; ddMVAC, dose dense methotrexate, vinblastine, doxorubicin, cisplatin; ECOG PS, Eastern Cooperative Oncology Group performance status; GFR, glomerular filtration rate; HbA1C, haemoglobin A1c; IT, information technology; LN, lymph node; QoL, quality of life;
SJS, Stevens–Johnson syndrome; TEN, toxic epidermal necrolysis; UTUC, upper tract urothelial carcinoma.

EV+P and skin toxicities (1/2)

Overview

Skin reactions are an AESI associated with EV+P[1]

Mild-to-moderate skin reactions, predominantly maculopapular rash, have been reported with EV[1]

Severe cutaneous adverse reactions including SJS and TEN, with fatal outcome have also occurred in patients treated with EV[1]

Median time to onset

For EV+P, median time to onset of severe skin reactions is 1.7 months[1]

Red flag symptoms for severe cutaneous adverse reactions[1,2]

- Rash or itching that continues to get worse or comes back after treatment
- Skin blistering or peeling
- Mucosal involvement: Painful sores or ulcer in mouth or nose, throat or genital area
- Fever or flu-like symptoms
- Swollen lymph nodes

Disclaimer: PADCEV (enfortumab vedotin) can cause severe skin reactions, including SJS and TEN (predominantly during the first cycle of treatment).

AESI, adverse event of special interest; EV, enfortumab vedotin; P, pembrolizumab; SJS, Stevens–Johnson syndrome; TEN, toxic epidermal necrolysis.

1. PADCEV™ (enfortumab vedotin). Summary of Product Characteristics; 2. PADCEV™ (enfortumab vedotin). Summary of Product Characteristics (patient card).

EV+P and skin toxicities (2/2)

EV SmPC management guidance

Appropriate treatment such as topical corticosteroids and antihistamines can be considered for mild to moderate skin reactions

For Grade 2 worsening, Grade 2 with fever or Grade 3 skin reactions, treatment should be withheld until Grade ≤1 and referral for specialised care should be considered. Treatment should be resumed at the same dose level or consider dose reduction by one dose level

For suspected SJS or TEN, or in case of bullous lesions onset, withhold treatment immediately and refer to specialised care

Permanently discontinue EV for confirmed SJS or TEN, Grade 4 or recurrent Grade 3 skin reactions

Disclaimer: PADCEV (enfortumab vedotin) can cause severe skin reactions, including SJS and TEN (predominantly during the first cycle of treatment).

EV, enfortumab vedotin; P, pembrolizumab; SJS, Stevens–Johnson syndrome; SmPC, Summary of Product Characteristics; TEN, toxic epidermal necrolysis.

PADCEV™ (enfortumab vedotin). Summary of Product Characteristics.

Managing patients with a baseline skin toxicity

Would you do anything for Mr Y *prior to* treatment with EV+P?

- ✓ **Assess skin** including medical history, visual assessment and photographs irrespective of pre-existing skin conditions[1,2]
- ✓ **Take the time to perform a full-body examination[2]**
- ✓ **Educate** patients and caregivers to pay particular attention to any 'red flag' symptoms, which may be an early indication of severe skin reactions[1,4,5]

Initiate treatment with EV+P

How would you monitor Mr Y *during treatment* with EV+P?

- ✓ **For patient's pre-existing skin reaction due to prior immunotherapy,** closely monitored following initiation of EV+P[3]
- ✓ **For patient's excessive skin folds,** closely assess and monitor as it may be difficult to spot skin changes[3]
- ✓ **Closely monitor** the skin during subsequent treatment cycles and at each visit[1]
- ✓ **Take the time to perform a full-body examination[2]**

Well-controlled, mild skin conditions **should not delay treatment initiation**. Skin reactions that occur throughout treatment should be **managed per the SmPC guidance**[3,4]

Disclaimer: PADCEV (enfortumab vedotin) can cause severe skin reactions, including SJS and TEN (predominantly during the first cycle of treatment).

Fictious patient case created for illustrative purposes.

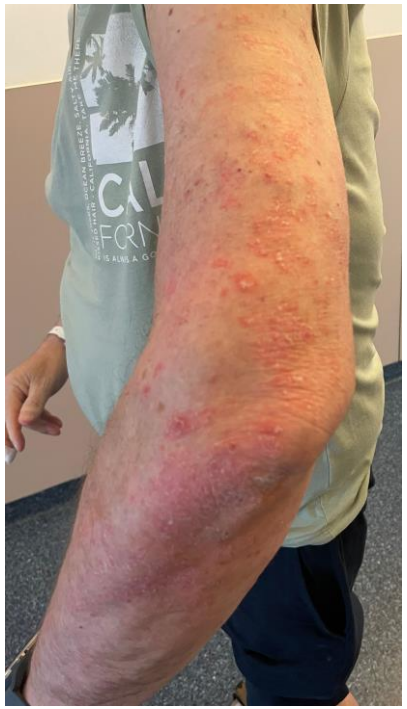
EV, enfortumab vedotin; P, pembrolizumab; SJS, Stevens–Johnson syndrome; SmPC, Summary of Product Characteristics; TEN, toxic epidermal necrolysis.

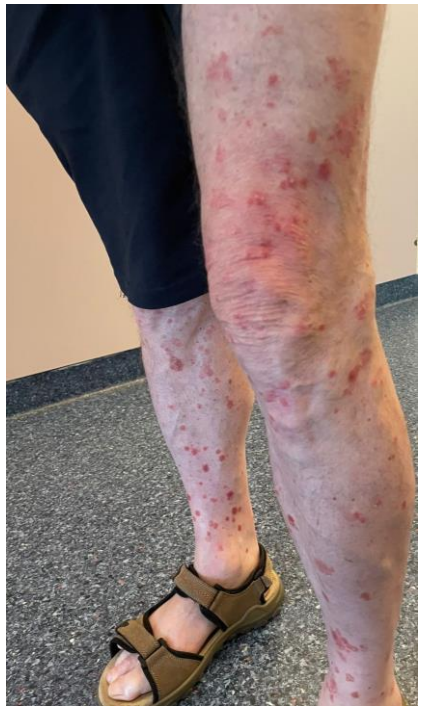
1. Brower B et al. *Front Oncol* 2024;14:1326715; 2. Barton-Burke M et al. *Nurs Clin North Am* 2017;52:83–113; 3. Speaker's own opinion; 4. PADCEV™ (enfortumab vedotin). Summary of Product Characteristics; 5. Kawsar A et al. *Br J Dermatol* 2023;189;3–10.

Mr Y initiated treatment with EV+P

Slight aggravation of his pre-existing psoriasis
Diagnosis: Grade 2 with no red flag symptoms

Management
Additional local therapy



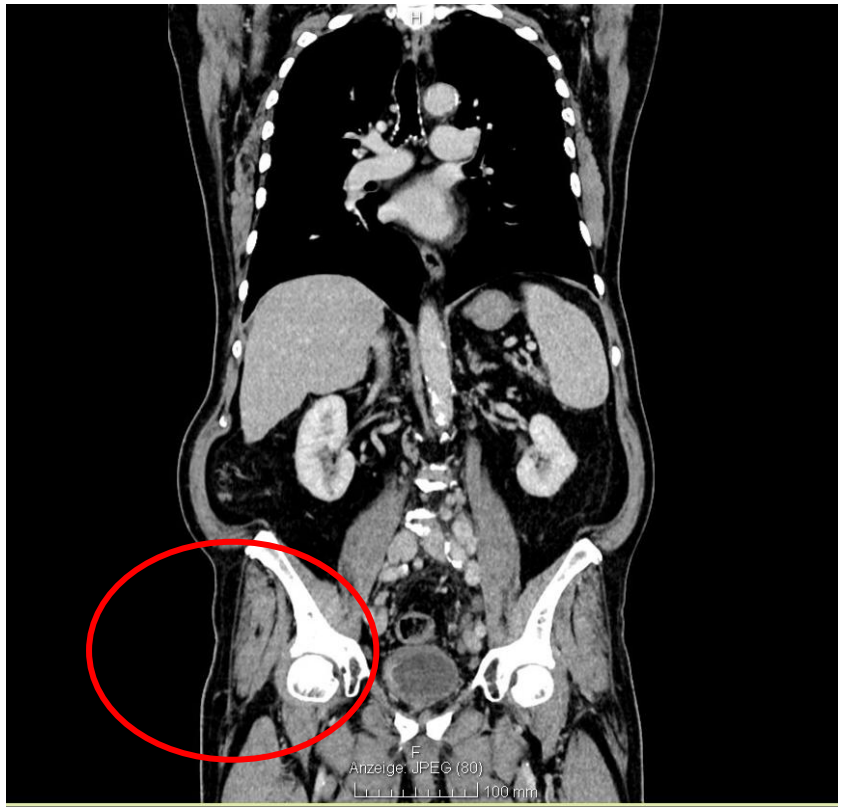


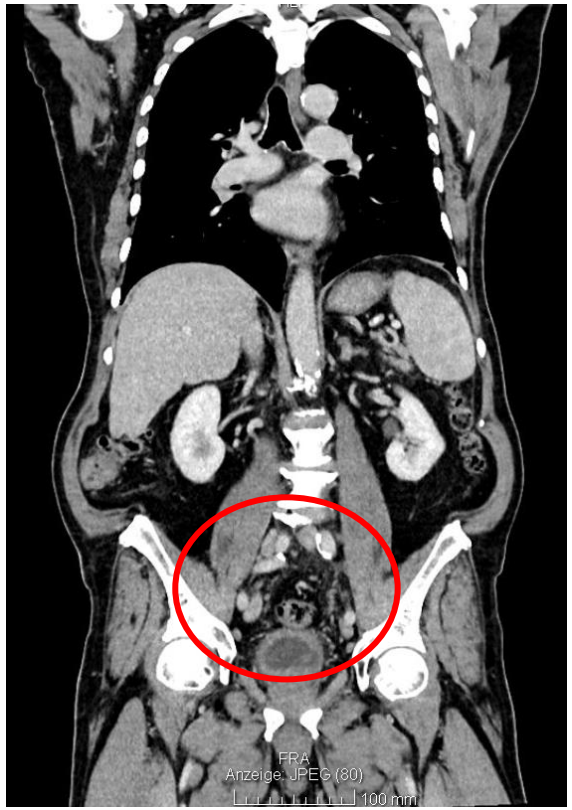
Dermatology consultations

Mr Y had regular consultations with his treating dermatologist

Disclaimer: PADCEV (enfortumab vedotin) can cause severe skin reactions, including SJS and TEN (predominantly during the first cycle of treatment).
Fictious patient case created for illustrative purposes.
Speaker's own images.
EV, enfortumab vedotin; P, pembrolizumab; SJS, Stevens–Johnson syndrome; TEN, toxic epidermal necrolysis.

Mr Y had no further EV+P-associated severe skin reactions during treatment





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Fictious patient case created for illustrative purposes.

Speaker's own images.

EV, enfortumab vedotin; P, pembrolizumab.

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Please refer to the EMA SmPC for PADCEV™ (enfortumab vedotin) via the following link: https://www.ema.europa.eu/en/documents/product-information/padcev-epar-product-information_en.pdf

Please scan the QR code to access the UK aPI for PADCEV

Please scan the QR code to access the NL SmPC for PADCEV

PADCEV is subject to medicinal prescription.
Astellas Pharma B.V., Sylviusweg 62, 2333 BE Leiden, The Netherlands

EMA, European Medicines Agency; aPI, abbreviated Prescribing Information; SmPC, Summary of Product Characteristics.

ABBREVIATED SUMMARY OF PRODUCT CHARACTERISTICS

For full prescribing information refer to the Summary of Product Characteristics (SPC).

▼This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. **NAME OF THE MEDICINAL PRODUCT:** Padcev 20 mg powder for concentrate for solution for infusion **&** Padcev 30 mg powder for concentrate for solution for infusion

QUALITATIVE AND QUANTITATIVE COMPOSITION: Padcev 20 mg powder for concentrate for solution for infusion: One vial of powder for concentrate for solution for infusion contains 20 mg enfortumab vedotin. Padcev 30 mg powder for concentrate for solution for infusion: One vial of powder for concentrate for solution for infusion contains 30 mg enfortumab vedotin. After reconstitution, each mL of solution contains 10 mg of enfortumab vedotin. Enfortumab vedotin is comprised of a fully human IgG1 kappa antibody, conjugated to the microtubule-disrupting agent monomethyl auristatin E (MMAE) via a protease-cleavable maleimidocaproyl valine-citrulline linker. For the full list of excipients, see section 6.1 of the SPC.

PHARMACEUTICAL FORM: Powder for concentrate for solution for infusion. White to off-white lyophilized powder.

CLINICAL PARTICULARS: Therapeutic indications: Padcev, in combination with pembrolizumab, is indicated for the first-line treatment of adult patients with unresectable or metastatic urothelial cancer who are eligible for platinum-containing chemotherapy. Padcev as monotherapy is indicated for the treatment of adult patients with locally advanced or metastatic urothelial cancer who have previously received a platinum-containing chemotherapy and a programmed death receptor-1 or programmed death-ligand 1 inhibitor (see section 5.1 of the SPC). **Posology and method of administration**: Treatment with Padcev should be initiated and supervised by a physician experienced in the use of anti-cancer therapies. Ensure good venous access prior to starting treatment (see section 4.4 of the SPC). Posology: As monotherapy, the recommended dose of enfortumab vedotin is 1.25 mg/kg (up to a maximum of 125 mg for patients ≥100 kg) administered as an intravenous infusion over 30 minutes on Days 1, 8 and 15 of a 28-day cycle until disease progression or unacceptable toxicity. When given in combination with pembrolizumab, the recommended dose of enfortumab vedotin is 1.25 mg/kg (up to a maximum of 125 mg for patients ≥100 kg) administered as an intravenous infusion over 30 minutes on Days 1 and 8 of every 3-week (21-day) cycle until disease progression or unacceptable toxicity. The recommended dose of pembrolizumab is either 200 mg every 3 weeks or 400 mg every 6 weeks administered as an intravenous infusion over 30 minutes. Patients should be administered pembrolizumab after enfortumab vedotin when given on the same day. Refer to the pembrolizumab SPC for additional dosing information of pembrolizumab.

Table 1. Recommended dose reductions of enfortumab vedotin for adverse reactions

	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

Dose modifications

Table 2. Dose interruption, reduction and discontinuation of enfortumab vedotin in patients with locally advanced or metastatic urothelial cancer

Adverse reaction	Severity*	Dose modification*
Skin reactions	Suspected Stevens-Johnson syndrome (SJS) or toxic epidermal necrolysis (TEN) or bullous lesions	Immediately withhold and refer to specialised care.
	Confirmed SJS or TEN; Grade 4 or recurrent Grade 3	Permanently discontinue.
	Grade 2 worsening Grade 2 with fever Grade 3	• Withhold until Grade ≤1. • Referral to specialised care should be considered. • Resume at the same dose level or consider dose reduction by one dose level (see Table 1).
Hyperglycaemia	Blood glucose >13.9 mmol/L (>250 mg/dL)	• Withhold until elevated blood glucose has improved to ≤13.9 mmol/L (≤250 mg/dL). • Resume treatment at the same dose level.
Pneumonitis/ interstitial lung disease (ILD)	Grade 2	• Withhold until Grade ≤1, then resume at the same dose or consider dose reduction by one dose level (see Table 1).
	Grade ≥3	Permanently discontinue.
Peripheral neuropathy	Grade 2	• Withhold until Grade ≤1. • For first occurrence, resume treatment at the same dose level. • For a recurrence, withhold until Grade ≤1, then resume treatment reduced by one dose level (see Table 1).
	Grade ≥3	Permanently discontinue.

*Toxicity was graded per National Cancer Institute Common Terminology Criteria for Adverse Events Version 5.0 (NCI-CTCAE v5.0) where Grade 1 is mild, Grade 2 is moderate, Grade 3 is severe and Grade 4 is life threatening.

Special populations: *Elderly*: No dose adjustment is necessary in patients ≥65 years of age. *Renal impairment*: No dose adjustment is necessary in patients with mild [creatinine clearance (CrCL) >60–90 mL/min], moderate (CrCL 30–60 mL/min) or severe (CrCL 15–<30 mL/min) renal impairment. Enfortumab vedotin has not been evaluated in patients with end stage renal disease (CrCL <15 mL/min) (see section 5.2 of the SPC). *Hepatic impairment*: No dose adjustment is necessary in patients with mild hepatic impairment [total bilirubin of 1 to 1.5 × upper limit of normal (ULN) and AST any, or total bilirubin ≤ ULN and AST > ULN]. Enfortumab vedotin has only been evaluated in a limited number of patients with moderate and severe hepatic impairment. Hepatic impairment is expected to increase the systemic exposure to MMAE (the cytotoxic drug); therefore, patients should be closely monitored for potential adverse events. Due to the sparsity of the data in patients with moderate and severe hepatic impairment, no specific dose recommendation can be given. *Paediatric population:* There is no relevant use of enfortumab vedotin in the paediatric population for the indication of locally advanced or metastatic urothelial cancer.

Method of administration

Padcev is for intravenous use. The recommended dose must be administered by intravenous infusion over 30 minutes. Enfortumab vedotin must not be administered as an intravenous push or bolus injection. For instructions on reconstitution and dilution of the medicinal product before administration, see section 6.6 of the SPC. **Contraindications**: Hypersensitivity to the active substance or to any of the excipients listed in section 6.1 of the SPC. **Special warnings and precautions for use**: Traceability: In order to improve the traceability of biological medicinal products, the name and the batch number of the administered product should be clearly recorded. Skin reactions: Skin reactions are associated with enfortumab vedotin as a result of enfortumab vedotin binding to Nectin-4 expressed in the skin. Fever or flu-like symptoms may be the first sign of a severe skin reaction, and patients should be observed, if this occurs. Mild to moderate skin reactions, predominantly rash maculo-papular, have been reported with enfortumab vedotin. The incidence of skin reactions occurred at a higher rate when enfortumab vedotin was given in combination with pembrolizumab compared to enfortumab vedotin as monotherapy (see section 4.8 of the SPC). Severe cutaneous adverse reactions, including SJS and TEN, with fatal outcome have also occurred in patients treated with enfortumab vedotin, predominantly during the first cycle of treatment. Patients should be monitored starting with the first cycle and throughout treatment for skin reactions. Appropriate treatment such as topical corticosteroids and antihistamines can be considered for mild to moderate skin reactions. For suspected SJS or TEN, or in case of bullous lesions onset, withhold treatment immediately and refer to specialised care; histologic confirmation, including consideration of multiple biopsies, is critical to early recognition, as diagnosis and intervention can improve prognosis. Permanently discontinue Padcev for confirmed SJS or TEN, Grade 4 or recurrent Grade 3 skin reactions. For Grade 2 worsening, Grade 2 with fever or Grade 3 skin reactions, treatment should be withheld until Grade ≤1 and referral for specialised care should be considered. Treatment should be resumed at the same dose level or consider dose reduction by one dose level (see section 4.2 of the SPC). Pneumonitis/ILD: Severe, life-threatening or fatal pneumonitis/ILD have occurred in patients treated with enfortumab vedotin. The incidence of pneumonitis/ILD, including severe events occurred at a higher rate when enfortumab vedotin was given in combination with pembrolizumab compared to enfortumab vedotin as monotherapy (see section 4.8 of the SPC). Monitor patients for signs and symptoms indicative of pneumonitis/ILD such as hypoxia, cough, dyspnoea or interstitial infiltrates on radiologic exams. Corticosteroids should be administered for Grade ≥ 2 events (e.g., initial dose of 1-2 mg/kg/day prednisone or equivalent followed by a taper). Withhold Padcev for Grade 2 pneumonitis/ILD and consider dose reduction. Permanently discontinue Padcev for Grade ≥3 pneumonitis/ILD (see section 4.2 of the SPC). Hyperglycaemia: Hyperglycaemia and diabetic ketoacidosis (DKA), including fatal events, occurred in patients with and without pre-existing diabetes mellitus, treated with enfortumab vedotin (see section 4.8 of the SPC). Hyperglycaemia occurred more frequently in patients with pre-existing hyperglycaemia or a high body mass index (≥30 kg/m²). Patients with baseline HbA1c ≥8% were excluded from clinical studies. Blood glucose levels should be monitored prior to dosing and periodically throughout the course of treatment as clinically indicated in patients with or at risk for diabetes mellitus or hyperglycaemia. If blood glucose is elevated >13.9 mmol/L (>250 mg/dL), Padcev should be withheld until blood glucose is ≤13.9 mmol/L (≤250 mg/dL) and treat as appropriate (see section 4.2 of the SPC). Serious infections: Serious infections such as sepsis (including fatal outcomes) have been reported in patients treated with Padcev. Patients should be carefully monitored during treatment for the emergence of possible serious infections. Peripheral neuropathy: Peripheral neuropathy, predominantly peripheral sensory neuropathy, has occurred with enfortumab vedotin, including Grade ≥3 reactions (see section 4.8 of the SPC). Patients with preexisting peripheral neuropathy Grade ≥2 were excluded from clinical studies. Patients should be monitored for symptoms of new or worsening peripheral neuropathy as these patients may require a delay, dose reduction or discontinuation of enfortumab vedotin (see Table 1). Padcev should be permanently discontinued for Grade ≥3 peripheral neuropathy (see section 4.2 of the SPC). Ocular disorders: Ocular disorders, predominantly dry eye, have occurred in patients treated with enfortumab vedotin (see section 4.8 of the SPC). Patients should be monitored for ocular disorders. Consider artificial tears for prophylaxis of dry eye and referral for ophthalmologic evaluation if ocular symptoms do not resolve or worsen. Infusion site extravasation: Skin and soft tissue injury following enfortumab vedotin administration has been observed when extravasation occurred (see section 4.8 of the SPC). Ensure good venous access prior to starting Padcev and monitor for possible infusion site extravasation during administration. If extravasation occurs, stop the infusion and monitor for adverse reactions. Embryo-foetal toxicity and contraception: Pregnant women should be informed of the potential risk to a foetus (see sections 4.6 and 5.3 of the SPC). Females of reproductive potential should be advised to have a pregnancy test within 7 days prior to starting treatment with enfortumab vedotin, to use effective contraception during treatment and for at least 6 months after stopping treatment. Men being treated with enfortumab vedotin are advised not to father a child during treatment and for at least 4 months following the last dose of Padcev. Patient information pack: The prescriber must discuss the risks of Padcev therapy, including combination therapy with pembrolizumab, with the patient. The patient should be provided with the patient information leaflet and patient card with each prescription. **Interactions:** Formal drug–drug interaction studies with enfortumab vedotin have not been conducted. Caution is advised in case of concomitant treatment with CYP3A4 inhibitors. Patients receiving concomitant strong CYP3A4 inhibitors should be monitored more closely for signs of toxicities. Strong CYP3A4 inducers may decrease the exposure of unconjugated MMAE with moderate effect (see section 5.2 of the SPC). **Undesirable effects**: Summary of the safety profile: *Enfortumab vedotin as monotherapy*: The safety of enfortumab vedotin was evaluated as monotherapy in 793 patients who received at least one dose of enfortumab vedotin 1.25 mg/kg in two phase 1 studies (EV-101 and EV-102), three phase 2 studies (EV-103, EV-201 and EV-203) and one phase 3 study (EV-301) (see Table 3). Patients were exposed to enfortumab vedotin for a median duration of 4.7 months (range: 0.3 to 55.7 months). The most common adverse reactions with enfortumab vedotin were alopecia (47.7%), decreased appetite (47.2%), fatigue (46.8%), diarrhoea (39.1%), peripheral sensory neuropathy (38.5%), nausea (37.8%), pruritus (33.4%), dysgeusia (30.4%), anaemia (29.1%), weight decreased (25.2%), rash maculo-papular (23.6%), dry skin (21.8%), vomiting (18.7%), aspartate aminotransferase increased (17%), hyperglycaemia (14.9%), dry eye (12.7%), alanine aminotransferase increased (12.7%) and rash (11.6%). The most common serious adverse reactions (≥2%) were diarrhoea (2.1%) and hyperglycaemia (2.1%). Twenty-one percent of patients permanently discontinued enfortumab vedotin for adverse reactions; the most common adverse reaction (≥2%) leading to dose discontinuation was peripheral sensory neuropathy (4.8%). Adverse reactions leading to dose interruption occurred in 62% of patients; the most common adverse reactions (≥2%) leading to dose interruption were peripheral sensory neuropathy (14.8%), fatigue (7.4%), rash maculo-papular (4%), aspartate aminotransferase increased (3.4%), alanine aminotransferase increased (3.2%), anaemia (3.2%), hyperglycaemia (3.2%), neutrophil count decreased (3%), diarrhoea (2.8%), rash (2.4%) and peripheral motor neuropathy (2.1%). Thirty-eight percent of patients required a dose reduction due to an adverse reaction; the most common adverse reactions (≥2%) leading to a dose reduction were peripheral sensory neuropathy (10.3%), fatigue (5.3%), rash maculo-papular (4.2%) and decreased appetite (2.1%). *Enfortumab vedotin in combination with pembrolizumab*: When enfortumab vedotin is administered in combination with pembrolizumab, refer to the SmPC for pembrolizumab prior to initiation of treatment. The safety of enfortumab vedotin was evaluated in combination with pembrolizumab in 564 patients who received at least one dose of enfortumab vedotin 1.25 mg/kg in combination with pembrolizumab in one phase 2 study (EV-103) and one phase 3 study (EV-302) (see Table 3). Patients were exposed to enfortumab vedotin in combination with pembrolizumab for a median duration of 9.4 months (range: 0.3 to 34.4 months). The most common adverse reactions with enfortumab vedotin in combination with pembrolizumab were peripheral sensory neuropathy (53.4%), pruritus (41.1%), fatigue (40.4%), diarrhoea (39.2%), alopecia (38.5%), rash maculo-papular (36%), weight decreased (36%), decreased appetite (33.9%), nausea (28.4%), anaemia (25.7%), dysgeusia (24.3%), dry skin (18.1%), alanine aminotransferase increased (16.8%), hyperglycaemia (16.7%), aspartate aminotransferase increased (15.4%), dry eye (14.4%), vomiting (13.3%), rash macular (11.3%), hypothyroidism (10.5%) and neutropenia (10.1%). The most common serious adverse reactions (≥2%) were diarrhoea (3%) and pneumonitis (2.3%). Thirty-six percent of patients permanently discontinued enfortumab vedotin for adverse reactions; the most common adverse reactions (≥2%) leading to discontinuation were peripheral sensory neuropathy (12.2%) and rash maculo-papular (2%). Adverse reactions leading to dose interruption of enfortumab vedotin occurred in 72% of patients. The most common adverse reactions (≥2%) leading to dose interruption were peripheral sensory neuropathy (17%), rash maculo-papular (6.9%), diarrhoea (4.8%), fatigue (3.7%), pneumonitis (3.7%), hyperglycaemia (3.4%), neutropenia (3.2%), alanine aminotransferase increased (3%), pruritus (2.3%) and anaemia (2%). Adverse reactions leading to dose reduction of enfortumab vedotin occurred in 42.4% of patients. The most common adverse reactions (≥2%) leading to dose reduction were peripheral sensory neuropathy (9.9%), rash maculo-papular (6.4%), fatigue (3.2%), diarrhoea (2.3%) and neutropenia (2.1%). Tabulated summary of adverse reactions: Adverse reactions observed during clinical studies of enfortumab vedotin as monotherapy or in combination with pembrolizumab, or reported from post-marketing use of enfortumab vedotin are listed in this section by frequency category. Frequency categories are defined as follows: very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000); very rare (<1/10,000); not known (cannot be estimated from the available data). Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

Table 3. Adverse reactions in patients treated with enfortumab vedotin

	Monotherapy	In combination with pembrolizumab
Infections and infestations		
Common	Sepsis	Sepsis
Blood and lymphatic system disorders		
Very common	Anaemia	Anaemia
Not known[1]	Neutropenia, febrile neutropenia, neutrophil count decreased	Neutropenia, febrile neutropenia, neutrophil count decreased
Endocrine disorders		
Very common		Hypothyroidism
Metabolism and nutrition disorders		
Very common	Hyperglycaemia, decreased appetite	Hyperglycaemia, decreased appetite
Not known[1]	Diabetic ketoacidosis	Diabetic ketoacidosis
Nervous system disorders		
Very common	Peripheral sensory neuropathy, dysgeusia	Peripheral sensory neuropathy, dysgeusia
Common	Neuropathy peripheral, peripheral motor neuropathy, peripheral sensorimotor neuropathy, paraesthesia, hypoaesthesia, gait disturbance, muscular weakness	Peripheral motor neuropathy, peripheral sensorimotor neuropathy, paraesthesia, hypoaesthesia, gait disturbance, muscular weakness
Uncommon	Demyelinating polyneuropathy, polyneuropathy, neurotoxicity, motor dysfunction, dysaesthesia, muscle atrophy, neuralgia, peroneal nerve palsy, sensory loss, skin burning sensation, burning sensation	Neurotoxicity, dysaesthesia, myasthenia gravis, neuralgia, peroneal nerve palsy, skin burning sensation
Eye disorders		
Very common	Dry eye	Dry eye
Respiratory, thoracic, and mediastinal disorders		
Very common		Pneumonitis/ILD[2]
Common	Pneumonitis/ILD[2]	
Gastrointestinal disorders		
Very common	Diarrhoea, vomiting, nausea	Diarrhoea, vomiting, nausea
Skin and subcutaneous tissue disorders		
Very common	Alopecia, pruritus, rash, rash maculo-papular, dry skin	Alopecia, pruritus, rash maculo-papular, dry skin, rash macular
Common	Drug eruption, skin exfoliation, conjunctivitis, dermatitis bullous, blister, stomatitis, palmar-plantar erythrodysesthesia syndrome, eczema, erythaema, rash erythaematous, rash macular, rash papular, rash pruritic, rash vesicular	Rash, skin exfoliation, conjunctivitis, dermatitis bullous, blister, stomatitis, palmar-plantar erythrodysesthesia syndrome, eczema, erythaema, rash erythaematous, rash papular, rash pruritic, rash vesicular, erythaema multiforme, dermatitis
Uncommon	Dermatitis exfoliative generalised, erythaema multiforme, exfoliative rash, pemphigoid, rash maculovesicular, dermatitis, dermatitis allergic, dermatitis contact, intertrigo, skin irritation, stasis dermatitis, blood blister	Drug eruption, dermatitis exfoliative generalised, exfoliative rash, pemphigoid, dermatitis contact, intertrigo, skin irritation, stasis dermatitis
Not known[1]	Toxic epidermal necrolysis, skin hyperpigmentation, skin discoloration, pigmentation disorder, Stevens Johnson syndrome, epidermal necrosis, symmetrical drug-related intertriginous and flexural exanthaema	Toxic epidermal necrolysis, skin hyperpigmentation, skin discoloration, pigmentation disorder, Stevens Johnson syndrome, epidermal necrosis, symmetrical drug-related intertriginous and flexural exanthaema
Musculoskeletal and connective tissue disorders		
Common		Myositis
General disorders and administration site conditions		
Very common	Fatigue	Fatigue
Common	Infusion site extravasation	Infusion site extravasation
Investigations		
Very common	Alanine aminotransferase increased, aspartate aminotransferase increased, weight decreased	Alanine aminotransferase increased, aspartate aminotransferase increased, weight decreased
Common		Lipase increased
Injury, poisoning and procedural complications		
Common	Infusion related reaction	Infusion related reaction

[1]Based on global post-marketing experience.

[2]Includes: acute respiratory distress syndrome, autoimmune lung disease, immune-mediated lung disease, interstitial lung disease, lung opacity, organising pneumonia, pneumonitis, pulmonary fibrosis, pulmonary toxicity and sarcoidosis.

Description of selected adverse reactions: *Immunogenicity:* A total of 697 patients were tested for immunogenicity to enfortumab vedotin 1.25 mg/kg as monotherapy; 16 patients were confirmed to be positive at baseline for anti-drug antibody (ADA), and in patients that were negative at baseline (N=681), a total of 24 (3.5%) were positive post baseline. A total of 490 patients were tested for immunogenicity against enfortumab vedotin following enfortumab vedotin in combination with pembrolizumab; 24 patients were confirmed to be positive at baseline for ADA, and in patients that were negative at baseline (N=466), a total of 14 (3%) were positive post baseline. The incidence of treatment-emergent anti-enfortumab vedotin antibody formation was consistent when assessed following enfortumab vedotin administration as monotherapy and in combination with pembrolizumab. Due to the limited number of patients with antibodies against Padcev, no conclusions can be drawn concerning a potential effect of immunogenicity on efficacy, safety or pharmacokinetics. *Skin reactions*: In clinical studies of enfortumab vedotin as monotherapy, skin reactions occurred in 57% (452) of the 793 patients treated with enfortumab vedotin 1.25 mg/kg. Severe (Grade 3 or 4) skin reactions occurred in 14% (108) of patients and a majority of these reactions included rash maculo-papular, stomatitis, rash erythematous, rash or drug eruption. The median time to onset of severe skin reactions was 0.7 months (range: 0.1 to 8.2 months). Serious skin reactions occurred in 4.3% (34) of patients. Of the patients who experienced skin reactions and had data regarding resolution (N=366), 61% had complete resolution, 24% had partial improvement, and 15% had no improvement at the time of their last evaluation. Of the 39% of patients with residual skin reactions at last evaluation, 38% had Grade ≥2 events. In clinical studies of enfortumab vedotin in combination with pembrolizumab, skin reactions occurred in 70% (392) of the 564 patients and a majority of these skin reactions included rash maculo-papular, rash macular and rash papular. Severe (Grade 3 or 4) skin reactions occurred in 17% (97) of patients (Grade 3: 16%, Grade 4: 1%). The median time to onset of severe skin reactions was 1.7 months (range: 0.1 to 17.2 months). Of the patients who experienced skin reactions and had data regarding resolution (N=391), 59% had complete resolution, 30% had partial improvement, and 10% had no improvement at the time of their last evaluation. Of the 41% of patients with residual skin reactions at last evaluation, 27% had Grade ≥2 events. *Pneumonitis/ILD*: In clinical studies of enfortumab vedotin as monotherapy, pneumonitis/ILD occurred in 26 (3.3%) of the 793 patients treated with enfortumab vedotin 1.25 mg/kg. Less than 1% of patients experienced severe (Grade 3 or 4) pneumonitis/ILD (Grade 3: 0.5%, Grade 4: 0.3%). Pneumonitis/ILD led to discontinuation of enfortumab vedotin in 0.5% of patients. There were no deaths from pneumonitis/ILD. The median time to onset of any grade pneumonitis/ILD was 2.7 months (range: 0.6 to 6.0 months) and the median duration for pneumonitis/ILD was 1.6 months (range: 0.1 to 43.0 months). Of the 26 patients who experienced pneumonitis/ILD, 8 (30.8%) had resolution of symptoms. In clinical studies of enfortumab vedotin in combination with pembrolizumab, pneumonitis/ILD occurred in 58 (10.3%) of the 564 patients. Severe (Grade 3 or 4) pneumonitis/ILD occurred in 20 patients (Grade 3: 3.0%, Grade 4: 0.5%). Pneumonitis/ILD led to discontinuation of enfortumab vedotin in 2.1% of patients. Two patients experienced a fatal event of pneumonitis/ILD. The median time to onset of any grade pneumonitis/ILD was 4 months (range: 0.3 to 26.2 months). *Hyperglycaemia*: In clinical studies of enfortumab vedotin as monotherapy, hyperglycaemia (blood glucose >13.9 mmol/L) occurred in 17% (133) of the 793 patients treated with enfortumab vedotin 1.25 mg/kg. Serious events of hyperglycaemia occurred in 2.5% of patients, 7% of patients developed severe (Grade 3 or 4) hyperglycaemia and 0.3% of patients experienced fatal events, one event each of hyperglycaemia and diabetic ketoacidosis. The incidence of Grade 3-4 hyperglycaemia increased consistently in patients with higher body mass index and in patients with higher baseline haemoglobin A1C (HbA1c). The median time to onset of hyperglycaemia was 0.5 months (range: 0 to 20.3). Of the patients who experienced hyperglycaemia and had data regarding resolution (N=106), 66% had complete resolution, 19% had partial improvement, and 15% had no improvement at the time of their last evaluation. Of the 34% of patients with residual hyperglycaemia at last evaluation, 64% had Grade ≥2 events. *Peripheral neuropathy*: In clinical studies of enfortumab vedotin as monotherapy, peripheral neuropathy occurred in 53% (422) of the 793 patients treated with enfortumab vedotin 1.25 mg/kg. Five percent of patients experienced severe (Grade 3 or 4) peripheral neuropathy including sensory and motor events. The median time to onset of Grade ≥2 peripheral neuropathy was 5 months (range: 0.1 to 20.2). Of the patients who experienced neuropathy and had data regarding resolution (N=340), 14% had complete resolution, 46% had partial improvement, and 41% had no improvement at the time of their last evaluation. Of the 86% of patients with residual neuropathy at last evaluation, 51% had Grade ≥2 events. *Ocular disorders*: In clinical studies of enfortumab vedotin as monotherapy, 30% of patients experienced dry eye during treatment with enfortumab vedotin 1.25 mg/kg. Treatment was interrupted in 1.5% of patients and 0.1% of patients permanently discontinued treatment due to dry eye. Severe (Grade 3) dry eye only occurred in 3 patients (0.4%). The median time to onset of dry eye was 1.7 months (range: 0 to 30.6 months). Special populations: *Elderly*: Enfortumab vedotin in combination with pembrolizumab has been studied in 173 patients <65 years and 391 patients ≥65 years. Generally, adverse event frequencies were higher in patients ≥65 years of age compared to <65 years of age, particularly for serious adverse events (56.3%, and 35.3%, respectively) and Grade ≥3 events (80.3% and 64.2%, respectively), similar to observations with the chemotherapy comparator. **Overdose:** There is no known antidote for overdosage with enfortumab vedotin. In case of overdosage, the patient should be closely monitored for adverse reactions, and supportive treatment should be administered as appropriate taking into consideration the half-life of 3.6 days (ADC) and 2.6 days (MMAE).

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system.

België/Belgique: Federaal Agentschap voor Geneesmiddelen en Gezondheidsproducten / Agence fédérale des médicaments et des produits de santé; www.fagg.be / www.afmps.be; Afdeling Vigilantie / Division Vigilance: Website/Site internet: www.eenbijwerkingmelden.be / www.notifierunneffetindesirable.be; e-mail: adr@fagg-afmps.be

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Luxembourg/Luxemburg : Centre Régional de Pharmacovigilance de Nancy ou Division de la pharmacie et des médicaments de la Direction de la santé ; Site internet : www.guichet.lu/pharmacovigilance

MARKETING AUTHORISATION HOLDER:
Astellas Pharma Europe B.V. Sylviusweg 62, 2333 BE Leiden, The Netherlands

MARKETING AUTHORISATION NUMBERS: EU/1/21/1615/001 & EU/1/21/1615/002

DATE OF REVISION OF THE TEXT: December 2024
Job Bag Number: MAT-BX-PAD-2025-00004

Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu.
Ireland: Astellas Pharma Co. Ltd., Tel.: +353 1 467 1555. SPC may be found at www.medicines.ie.
Delivery Status: subject to medical prescription.
Astellas Pharma B.V.,
NL: Sylviusweg 62, 2333BE Leiden, Netherlands
BE/LU: Medialaan 50, 1800 Vilvoorde, Belgium
IE: Legal classification: S1A.

Prescribing Information: PADCEV™▼ (enfortumab vedotin) 20 mg and 30 mg powder for concentrate for solution for infusion

For full prescribing information refer to the Summary of Product Characteristics (SPC).

Presentation: One vial of PADCEV powder for concentrate for solution for infusion contains either 20 mg or 30 mg enfortumab vedotin. After reconstitution, each ml of solution contains 10 mg of enfortumab vedotin. Enfortumab vedotin is comprised of a fully human IgG1 kappa antibody, conjugated to the microtubule-disrupting agent monomethyl auristatin E (MMAE) via a protease-cleavable maleimidocaproyl valine-citrulline linker.

Indications: PADCEV, in combination with pembrolizumab, is indicated for the first-line treatment of adult patients with unresectable or metastatic urothelial cancer who are eligible for platinum-containing chemotherapy. PADCEV as monotherapy is indicated for the treatment of adult patients with locally advanced or metastatic urothelial cancer who have previously received a platinum-containing chemotherapy and a programmed death receptor-1 or programmed death-ligand 1 inhibitor (see section 5.1 of the SPC).

Posology and method of administration: Treatment with PADCEV should be initiated and supervised by a physician experienced in the use of anti-cancer therapies. PADCEV is for intravenous use. It must not be administered as an intravenous push or bolus injection. Good venous access prior to starting treatment should be ensured (see section 4.4 of the SPC). As monotherapy, the recommended dose of enfortumab vedotin is 1.25 mg/kg (up to a maximum of 125 mg for patients ≥100 kg). It must be administered as an intravenous infusion over 30 minutes on Days 1, 8 and 15 of a 28-day cycle until disease progression or unacceptable toxicity. When given in combination with pembrolizumab, the recommended dose of enfortumab vedotin is 1.25 mg/kg (up to a maximum of 125 mg for patients ≥100 kg) administered as an intravenous infusion over 30 minutes on Days 1 and 8 of every 3-week (21-day) cycle until disease progression or unacceptable toxicity. The recommended dose of pembrolizumab is either 200 mg every 3 weeks or 400 mg every 6 weeks administered as an intravenous infusion over 30 minutes. Patients should be administered pembrolizumab after enfortumab vedotin when given on the same day. Refer to the pembrolizumab SmPC for additional dosing information of pembrolizumab. For information on recommended dose reductions of enfortumab vedotin for adverse reactions as well as instructions on dose modifications (interruption, reduction and discontinuation) in patients experiencing adverse reactions refer to section 4.2 of the SPC. Special Populations: *Elderly:* No dose adjustment is necessary in patients ≥65 years of age (see section 5.2 of the SPC). *Renal impairment:* No dose adjustment is necessary in patients with mild [creatinine clearance (CrCL) >60-90 mL/min], moderate (CrCL 30–60 mL/min) or severe (CrCL 15–<30 mL/min) renal impairment. Enfortumab vedotin has not been evaluated in patients with end stage renal disease (CrCL <15 mL/min) (see section 5.2 of the SPC). *Hepatic impairment:* No dose adjustment is necessary in patients with mild hepatic impairment [total bilirubin of 1 to 1.5 × upper limit of normal (ULN) and aspartate transaminase (AST) any, or total bilirubin ≤ ULN and AST > ULN]. Enfortumab vedotin has only been evaluated in a limited number of patients with moderate and severe hepatic impairment. Hepatic impairment is expected to increase the systemic exposure to MMAE (the cytotoxic drug); therefore, patients should be closely monitored for potential adverse events. Due to the sparsity of the data in patients with moderate and severe hepatic impairment, no specific dose recommendation can be given (see section 5.2 of the SPC). *Paediatric population:* There is no relevant use of enfortumab vedotin in the paediatric population for the indication of locally advanced or metastatic urothelial cancer.

Contraindications: Hypersensitivity to the active substance or to any of the excipients listed in section 6.1 of the SPC.

Special warnings and precautions for use: Traceability: In order to improve the traceability of biological medicinal products, the name and the batch number of the administered product should be clearly recorded. Skin reactions: Skin reactions are associated with enfortumab vedotin as a result of enfortumab vedotin binding to Nectin-4 expressed in the skin. Fever or flu-like symptoms may be the first sign of a severe skin reaction, and patients should be observed, if this occurs. Mild to moderate skin reactions, predominantly rash maculo-papular, have been reported with enfortumab vedotin. The incidence of skin reactions occurred at a higher rate when enfortumab vedotin was given in combination with pembrolizumab compared to enfortumab vedotin as monotherapy (see section 4.8 of the SPC). Severe cutaneous adverse reactions, including Stevens-Johnson syndrome (SJS) and Toxic Epidermal Necrolysis (TEN), with fatal outcome have also occurred in patients treated with enfortumab vedotin, predominantly during the first cycle of treatment. Patients should be monitored starting with the first cycle and throughout treatment for skin reactions. Appropriate treatment such as topical corticosteroids and antihistamines can be considered for mild to moderate skin reactions. For suspected SJS or TEN, or in case of bullous lesions onset, withhold treatment immediately and refer to specialised care; histologic confirmation, including consideration of multiple biopsies, is critical to early recognition, as diagnosis and intervention can improve prognosis. Permanently discontinue PADCEV for confirmed SJS or TEN, Grade 4 or recurrent Grade 3 skin reactions. For Grade 2 worsening, Grade 2 with fever or Grade 3 skin reactions, treatment should be withheld until Grade ≤1 and referral for specialised care should be considered. Treatment should be resumed at the same dose level or consider dose reduction by one dose level (see section 4.2 of the SPC). Pneumonitis/Interstitial Lung Disease (ILD): Severe, life-threatening or fatal pneumonitis/ILD have occurred in patients treated with enfortumab vedotin. The incidence of pneumonitis/ILD, including severe events occurred at a higher rate when enfortumab vedotin was given in combination with pembrolizumab compared to enfortumab vedotin as monotherapy (see section 4.8 of the SPC). Monitor patients for signs and symptoms indicative of pneumonitis/ILD such as hypoxia, cough, dyspnoea or interstitial infiltrates on radiologic exams. Corticosteroids should be administered for Grade ≥ 2 events (e.g., initial dose of 1-2 mg/kg/day prednisone or equivalent followed by a taper). Withhold PADCEV for Grade 2 pneumonitis/ILD and consider dose reduction. Permanently discontinue PADCEV for Grade ≥3 pneumonitis/ILD (see section 4.2 of the SPC). Hyperglycaemia: Hyperglycaemia and diabetic ketoacidosis (DKA), including fatal events, occurred in patients with and without pre- existing diabetes mellitus, treated with enfortumab vedotin (see section 4.8 of the SPC). Hyperglycaemia occurred more frequently in patients with pre-existing hyperglycaemia or a high body mass index (≥30 kg/m^2). Patients with baseline HbA1c ≥8% were excluded from clinical studies. Blood glucose levels should be monitored prior to dosing and periodically throughout the course of treatment as clinically indicated in patients with or at risk for diabetes mellitus or hyperglycaemia. If blood glucose is elevated >13.9 mmol/L (>250 mg/dL), PADCEV should be withheld until blood glucose is ≤13.9 mmol/L (≤250 mg/dL) and treat as appropriate (see section 4.2 of the SPC). Serious infections: Serious infections such as sepsis (including fatal outcomes) have been reported in patients treated with PADCEV. Patients should be carefully monitored during treatment for the emergence of possible serious infections. Peripheral neuropathy: Peripheral neuropathy, predominantly peripheral sensory neuropathy, has occurred with enfortumab vedotin, including Grade ≥3 reactions (see section 4.8 of the SPC). Patients with pre-existing peripheral neuropathy Grade ≥2 were excluded from clinical studies. Patients should be monitored for symptoms of new or worsening peripheral neuropathy as these patients may require a delay, dose reduction or discontinuation of enfortumab vedotin. PADCEV should be permanently discontinued for Grade ≥3 peripheral neuropathy (see section 4.2 of the SPC). Ocular disorders: Ocular disorders, predominantly dry eye, have occurred in patients treated with enfortumab vedotin (see section 4.8 of the SPC). Patients should be monitored for ocular disorders. Consider artificial tears for prophylaxis of dry eye and referral for ophthalmologic evaluation if ocular symptoms do not resolve or worsen. Infusion site extravasation: Skin and soft tissue injury following enfortumab vedotin administration has been observed when extravasation occurred (see section 4.8 of the SPC). Ensure good venous access prior to starting PADCEV and monitor for possible infusion site extravasation during administration. If extravasation occurs, stop the infusion and monitor for adverse reactions. Embryo-foetal toxicity and contraception: Pregnant women should be informed of the potential risk to a foetus (see sections 4.6 and 5.3 of the SPC). Females of reproductive potential should be advised to have a pregnancy test within 7 days prior to starting treatment with enfortumab vedotin, to use effective contraception during treatment and for at least 6 months after stopping treatment. Men being treated with enfortumab vedotin are advised not to father a child during treatment and for at least 4 months following the last dose of PADCEV. Patient information pack: The prescriber must discuss the risks of PADCEV therapy, including combination therapy with pembrolizumab, with the patient. The patient should be provided with the patient information leaflet and patient card with each prescription.

Effects on ability to drive and use machines: PADCEV has no or negligible influence on the ability to drive and use machines.

Interactions: Formal drug–drug interaction studies with enfortumab vedotin have not been conducted. Caution is advised in case of concomitant treatment with CYP3A4 inhibitors. Patients receiving concomitant strong CYP3A4 inhibitors (e.g. boceprevir, clarithromycin, cobicistat, indinavir, itraconazole, nefazodone, nelfinavir, posaconazole, ritonavir, saquinavir, telaprevir, telithromycin, voriconazole) should be monitored more closely for signs of toxicities. Strong CYP3A4 inducers (e.g. rifampicin, carbamazepine, phenobarbital, phenytoin, St John's wort [*Hypericum perforatum*]) may decrease the exposure of unconjugated MMAE with moderate effect (see section 5.2 of the SPC).

Fertility, pregnancy and lactation: Women of childbearing potential/ Contraception in males and females: Refer to 'Special warnings and precautions for use' section above. Pregnancy: PADCEV can cause foetal harm when administered to pregnant women based upon findings from animal studies. PADCEV is not recommended during pregnancy and in women of childbearing potential not using effective contraception. Breast-feeding: Breast-feeding should be discontinued during PADCEV treatment and for at least 6 months after the last dose. Fertility: Men being treated with this medicinal product are advised to have sperm samples frozen and stored before treatment. There are no data on the effect of PADCEV on human fertility.

Undesirable effects: Summary of the safety profile: *Enfortumab vedotin as monotherapy*: The safety of enfortumab vedotin was evaluated as monotherapy in 793 patients who received at least one dose of enfortumab vedotin 1.25 mg/kg in two phase 1 studies (EV-101 and EV-102), three phase 2 studies (EV-103, EV-201 and EV-203) and one phase 3 study (EV-301) (see Table 3 in section 4.8 of the SPC). Patients were exposed to enfortumab vedotin for a median duration of 4.7 months (range: 0.3 to 55.7 months). The most common adverse reactions with enfortumab vedotin were alopecia (47.7%), decreased appetite (47.2%), fatigue (46.8%), diarrhoea (39.1%), peripheral sensory neuropathy (38.5%), nausea (37.8%), pruritus (33.4%), dysgeusia (30.4%), anaemia (29.1%), weight decreased (25.2%), rash maculo-papular (23.6%), dry skin (21.8%), vomiting (18.7%), aspartate aminotransferase increased (17%), hyperglycaemia, (14.9%), dry eye (12.7%), alanine aminotransferase increased (12.7%) and rash (11.6%). The most common serious adverse reactions (≥2%) were diarrhoea (2.1%) and hyperglycaemia (2.1%). Twenty-one percent of patients permanently discontinued enfortumab vedotin for adverse reactions; the most common adverse reaction (≥2%) leading to dose discontinuation was peripheral sensory neuropathy (4.8%). Adverse reactions leading to dose interruption occurred in 62% of patients; the most common adverse reactions (≥2%) leading to dose interruption were peripheral sensory neuropathy (14.8%), fatigue (7.4%), rash maculo-papular (4%), aspartate aminotransferase increased (3.4%), alanine aminotransferase increased (3.2%), anaemia (3.2%), hyperglycaemia (3.2%), neutrophil count decreased (3%), diarrhoea (2.8%), rash (2.4%) and peripheral motor neuropathy (2.1%). Thirty-eight percent of patients required a dose reduction due to an adverse reaction; the most common adverse reactions (≥2%) leading to a dose reduction were peripheral sensory neuropathy (10.3%), fatigue (5.3%), rash maculo-papular (4.2%) and decreased appetite (2.1%). *Enfortumab vedotin in combination with pembrolizumab:* When enfortumab vedotin is administered in combination with pembrolizumab, refer to the SPC for pembrolizumab prior to initiation of treatment. The safety of enfortumab vedotin was evaluated in combination with pembrolizumab in 564 patients who received at least one dose of enfortumab vedotin 1.25 mg/kg in combination with pembrolizumab in one phase 2 study (EV-103) and one phase 3 study (EV-302) (see Table 3). Patients were exposed to enfortumab vedotin in combination with pembrolizumab for a median duration of 9.4 months (range: 0.3 to 34.4 months). The most common adverse reactions with enfortumab vedotin in combination with pembrolizumab were peripheral sensory neuropathy (53.4%), pruritus (41.1%), fatigue (40.4%), diarrhoea (39.2%), alopecia (38.5%), rash maculo-papular (36%), weight decreased (36%), decreased appetite (33.9%), nausea (28.4%), anaemia (25.7%), dysgeusia (24.3%), dry skin (18.1%), alanine aminotransferase increased (16.8%), hyperglycaemia (16.7%), aspartate aminotransferase increased (15.4%), dry eye (14.4%), vomiting (13.3%), rash macular (11.3%), hypothyroidism (10.5%) and neutropenia (10.1%). The most common serious adverse reactions (≥2%) were diarrhoea (3%) and pneumonitis (2.3%). Thirty-six percent of patients permanently discontinued enfortumab vedotin for adverse reactions; the most common adverse reactions (≥2%) leading to discontinuation were peripheral sensory neuropathy (12.2%) and rash maculo-papular (2%). Adverse reactions leading to dose interruption of enfortumab vedotin occurred in 72% of patients. The most common adverse reactions (≥2%) leading to dose interruption were peripheral sensory neuropathy (17%), rash maculo-papular (6.9%), diarrhoea (4.8%), fatigue (3.7%), pneumonitis (3.7%), hyperglycaemia (3.4%), neutropenia (3.2%), alanine aminotransferase increased (3%), pruritus (2.3%) and anaemia (2%). Adverse reactions leading to dose reduction of enfortumab vedotin occurred in 42.4% of patients. The most common adverse reactions (≥2%) leading to dose reduction were peripheral sensory neuropathy (9.9%), rash maculo-papular (6.4%), fatigue (3.2%), diarrhoea (2.3%) and neutropenia (2.1%). Summary of adverse reactions: Adverse reactions observed during clinical studies of enfortumab vedotin as monotherapy or in combination with pembrolizumab, or reported from post-marketing use of enfortumab vedotin are listed in this section according to Medical Dictionary for Regulatory Activities (MedDRA) system organ classification by frequency category. Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness. Frequency categories are defined as follows: very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000); very rare (<1/10,000); not known (cannot be estimated from the available data). *Infections and infestations:* (monotherapy and in combination with pembrolizumab) Common: Sepsis. *Blood and lymphatic system disorders:* (monotherapy and in combination with pembrolizumab) Very common: Anaemia. Not known[1]: Neutropenia, febrile neutropenia, neutrophil count decreased. *Endocrine disorders:* (in combination with pembrolizumab) Very common: Hypothyroidism. *Metabolism and nutrition disorders:* (monotherapy and in combination with pembrolizumab) Very common: Hyperglycaemia, decreased appetite. Not known[1]: Diabetic ketoacidosis. *Nervous system disorders:* (monotherapy and in combination with pembrolizumab) Very common: Peripheral sensory neuropathy, dysgeusia. (monotherapy) Common: Neuropathy peripheral, peripheral motor neuropathy, peripheral sensorimotor neuropathy, paraesthesia, hypoaesthesia, gait disturbance, muscular weakness. (in combination with pembrolizumab) Common: Peripheral motor neuropathy, peripheral sensorimotor neuropathy, paraesthesia, hypoaesthesia, gait disturbance, muscular weakness. (monotherapy) Uncommon: Demyelinating polyneuropathy, polyneuropathy, neurotoxicity, motor dysfunction, dysaesthesia, muscle atrophy, neuralgia, peroneal nerve palsy, sensory loss, skin burning sensation, burning sensation. (in combination with pembrolizumab) Uncommon: Neurotoxicity, dysaesthesia, myasthenia gravis, neuralgia, peroneal nerve palsy, skin burning sensation. *Eye disorders:* (monotherapy and in combination with pembrolizumab) Very common: Dry eye. *Respiratory, thoracic, and mediastinal disorders:* (in combination with pembrolizumab) Very common: Pneumonitis/ILD[2]. (monotherapy) Common: Pneumonitis/ILD[2]. *Gastrointestinal disorders:* (monotherapy and in combination with pembrolizumab) Very common: Diarrhoea, vomiting, nausea. *Skin and subcutaneous tissue disorders:* (monotherapy) Very common: Alopecia, pruritus, rash, rash maculo-papular, dry skin. (in combination with pembrolizumab) Very common: Alopecia, pruritus, rash maculo-papular, dry skin, rash macular. (monotherapy) Common: Drug eruption, skin exfoliation, conjunctivitis, dermatitis bullous, blister, stomatitis, palmar-plantar erythrodysesthesia syndrome, eczema, erythaema, rash erythaematous, rash macular, rash papular, rash pruritic, rash vesicular. (in combination with pembrolizumab) Common: Rash, skin exfoliation, conjunctivitis, dermatitis bullous, blister, stomatitis, palmar-plantar erythrodysesthesia syndrome, eczema, erythaema, rash erythaematous, rash papular, rash pruritic, rash vesicular, erythaema multiforme, dermatitis. (monotherapy) Uncommon: Dermatitis exfoliative generalised, erythaema multiforme, exfoliative rash, pemphigoid, rash maculovesicular, dermatitis, dermatitis allergic, dermatitis contact, intertrigo, skin irritation, stasis dermatitis, blood blister. (in combination with pembrolizumab) Uncommon: Drug eruption, dermatitis exfoliative generalised, exfoliative rash, pemphigoid, dermatitis contact, intertrigo, skin irritation, stasis dermatitis. (monotherapy and in combination with pembrolizumab) Not known[1]: TEN, SJS, epidermal necrosis, skin hyperpigmentation, skin discoloration, pigmentation disorder, symmetrical drug-related intertriginous and flexural exanthaema. *Musculoskeletal and connective tissue disorders:* (in combination with pembrolizumab) Common: Myositis. *General disorders and administration site conditions:* (monotherapy and in combination with pembrolizumab) Very common: Fatigue. (monotherapy and in combination with pembrolizumab) Common: Infusion site extravasation. *Investigations:* (monotherapy and in combination with pembrolizumab) Very common: Alanine aminotransferase increased, aspartate aminotransferase increased, weight decreased. (in combination with pembrolizumab) Common: Lipase increased. *Injury, poisoning and procedural complications:* (monotherapy and in combination with pembrolizumab) Common: Infusion related reaction.

[1]Based on global post-marketing experience.

[2]Includes: acute respiratory distress syndrome, autoimmune lung disease, immune-mediated lung disease, interstitial lung disease, lung opacity, organizing pneumonia, pneumonitis, pulmonary fibrosis, pulmonary toxicity and sarcoidosis.

Description of selected adverse reactions. *Immunogenicity:* A total of 697 patients were tested for immunogenicity to enfortumab vedotin1.25 mg/kg as monotherapy; 16 patients were confirmed to be positive at baseline for anti-drug antibody (ADA), and in patients that were negative at baseline (N=681), a total of 24 (3.5%) were positive post baseline. A total of 490 patients were tested for immunogenicity against enfortumab vedotin following enfortumab vedotin in combination with pembrolizumab; 24 patients were confirmed to be positive at baseline for ADA, and in patients that were negative at baseline (N=466), a total of 14 (3%) were positive post baseline. The incidence of treatment-emergent anti-enfortumab vedotin antibody formation was consistent when assessed following enfortumab vedotin administration as monotherapy and in combination with pembrolizumab. Due to the limited number of patients with antibodies against PADCEV, no conclusions can be drawn concerning a potential effect of immunogenicity on efficacy, safety or pharmacokinetics. *Skin reactions:* In clinical studies of enfortumab vedotin as monotherapy, skin reactions occurred in 57% (452) of the 793 patients treated with enfortumab vedotin 1.25 mg/kg. Severe (Grade 3 or 4) skin reactions occurred in 14% (108) of patients and a majority of these reactions included rash maculo-papular, stomatitis, rash erythematous, rash or drug eruption. The median time to onset of severe skin reactions was 0.7 months (range: 0.1 to 8.2 months). Serious skin reactions occurred in 4.3% (34) of patients. Of the patients who experienced skin reactions and had data regarding resolution (N=366), 61% had complete resolution, 24% had partial improvement, and 15% had no improvement at the time of their last evaluation. Of the 39% of patients with residual skin reactions at last evaluation, 38% had Grade ≥2 events. In clinical studies of enfortumab vedotin in combination with pembrolizumab, skin reactions occurred in 70% (392) of the 564 patients and a majority of these skin reactions included rash maculo-papular, rash macular and rash papular. Severe (Grade 3 or 4) skin reactions occurred in 17% (97) of patients (Grade 3: 16%, Grade 4: 1%). The median time to onset of severe skin reactions was 1.7 months (range: 0.1 to 17.2 months). Of the patients who experienced skin reactions and had data regarding resolution (N=391), 59% had complete resolution, 30% had partial improvement, and 10% had no improvement at the time of their last evaluation. Of the 41% of patients with residual skin reactions at last evaluation, 27% had Grade ≥2 events. *Pneumonitis/ILD:* In clinical studies of enfortumab vedotin as monotherapy, pneumonitis/ILD occurred in 26 (3.3%) of the 793 patients treated with enfortumab vedotin 1.25 mg/kg. Less than 1% of patients experienced severe (Grade 3 or 4) pneumonitis/ILD (Grade 3: 0.5%, Grade 4: 0.3%). Pneumonitis/ILD led to discontinuation of enfortumab vedotin in 0.5% of patients. There were no deaths from pneumonitis/ILD. The median time to onset of any grade pneumonitis/ILD was 2.7 months (range: 0.6 to 6.0 months) and the median duration for pneumonitis/ILD was 1.6 months (range: 0.1 to 43.0 months). Of the 26 patients who experienced pneumonitis/ILD, 8 (30.8%) had resolution of symptoms. In clinical studies of enfortumab vedotin in combination with pembrolizumab, pneumonitis/ILD occurred in 58 (10.3%) of the 564 patients. Severe (Grade 3 or 4) pneumonitis/ILD occurred in 20 patients (Grade 3: 3.0%, Grade 4: 0.5%). Pneumonitis/ILD led to discontinuation of enfortumab vedotin in 2.1% of patients. Two patients experienced a fatal event of pneumonitis/ILD. The median time to onset of any grade pneumonitis/ILD was 4 months (range: 0.3 to 26.2 months). *Hyperglycaemia:* In clinical studies of enfortumab vedotin as monotherapy, hyperglycaemia (blood glucose >13.9 mmol/L) occurred in 17% (133) of the 793 patients treated with enfortumab vedotin 1.25 mg/kg. Serious events of hyperglycaemia occurred in 2.5% of patients, 7% of patients developed severe (Grade 3 or 4) hyperglycaemia and 0.3% of patients experienced fatal events, one event each of hyperglycaemia and diabetic ketoacidosis. The incidence of Grade 3-4 hyperglycaemia increased consistently in patients with higher body mass index and in patients with higher baseline haemoglobin A1C (HbA1c). The median time to onset of hyperglycaemia was 0.5 months (range: 0 to 20.3). Of the patients who experienced hyperglycaemia and had data regarding resolution (N=106), 66% had complete resolution, 19% had partial improvement, and 15% had no improvement at the time of their last evaluation. Of the 34% of patients with residual hyperglycaemia at last evaluation, 64% had Grade ≥2 events. *Peripheral neuropathy:* In clinical studies of enfortumab vedotin as monotherapy, peripheral neuropathy occurred in 53% (422) of the 793 patients treated with enfortumab vedotin 1.25 mg/kg. Five percent of patients experienced severe (Grade 3 or 4) peripheral neuropathy including sensory and motor events. The median time to onset of Grade ≥2 peripheral neuropathy was 5 months (range: 0.1 to 20.2). Of the patients who experienced neuropathy and had data regarding resolution (N=340), 14% had complete resolution, 46% had partial improvement, and 41% had no improvement at the time of their last evaluation. Of the 86% of patients with residual neuropathy at last evaluation, 51% had Grade ≥2 events. *Ocular disorders:* In clinical studies of enfortumab vedotin as monotherapy, 30% of patients experienced dry eye during treatment with enfortumab vedotin 1.25 mg/kg. Treatment was interrupted in 1.5% of patients and 0.1% of patients permanently discontinued treatment due to dry eye. Severe (Grade 3) dry eye only occurred in 3 patients (0.4%). The median time to onset of dry eye was 1.7 months (range: 0 to 30.6 months). *Special populations:* Elderly: Enfortumab vedotin in combination with pembrolizumab has been studied in 173 patients <65 years and 391 patients ≥65 years. Generally, adverse event frequencies were higher in patients ≥65 years of age compared to <65 years of age, particularly for serious adverse events (56.3%, and 35.3%, respectively) and Grade ≥3 events (80.3% and 64.2%, respectively), similar to observations with the chemotherapy comparator. Prescribers should consult the full SPC in relation to other adverse reactions.

Overdose: There is no known antidote for overdosage with enfortumab vedotin. In case of overdosage, the patient should be closely monitored for adverse reactions, and supportive treatment should be administered as appropriate taking into consideration the half-life of 3.6 days (ADC) and 2.6 days (MMAE).

Cost (excluding VAT): PADCEV 20 mg powder for concentrate for solution for infusion x 1 vial: £578
PADCEV 30 mg powder for concentrate for solution for infusion x 1 vial: £867

Legal classification: POM

Marketing Authorisation numbers:

PADCEV 20 mg powder for concentrate for solution for infusion PLGB 00166/0432.
PADCEV 30 mg powder for concentrate for solution for infusion PLGB 00166/0433.

Marketing Authorisation Holder:

Astellas Pharma Ltd. 300 Dashwood Lang Road, Bourne Business Park, Addlestone, United Kingdom, KT15 2NX.

Date of Preparation of Prescribing Information: February 2025

Job Bag Number: MAT-GB-PAD-2025-00017

Further information available from: Astellas Pharma Ltd, Medical Information 0800 783 5018. For full prescribing information, refer to the SPC, which may be found at: https://www.medicines.org.uk/emc.

Adverse events should be reported. Reporting forms and information can be found at www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store. Adverse events should also be reported to Astellas Pharma Ltd. on 0800 783 5018.