Enfortumab vedotin (Padcev®) as monotherapy for the treatment of patients with locally advanced or metastatic urothelial cancer

General information [1]

Drug description	Indication
Enfortumab vedotin (Padcev®) is an antibody-drug conjugate that induces cytotoxicity in cancer cells by binding to the nectin-4 target on the cell surface and forming an ADC-nectin-4 complex. With the internalisation and release of the drug component, the cycle cell is interrupted and the cells die.	Enfortumab vedotin (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 (PD-1) or programmed death-ligand 1 (PD-L1) inhibitor.

Current treatment

- In the current NICE pathway for managing locally advanced metastatic bladder cancer, there are no recommended therapies in patients that have progressed after second-line treatment with chemotherapy and PD-1/L1 inhibitors [2].
- Prognosis of advanced urothelial carcinoma [3]:
  - Advances in the management of advanced urothelial (transitional cell) carcinoma using cisplatin-based combination chemotherapy have led to a substantial increase in survival.
  - Despite this progress, metastatic disease is associated with a limited life expectancy, and cures are infrequent.
- Treatment of chemotherapy and immunotherapy-relapsed disease, according to the ESMO [4]:
  - Enfortumab vedotin is recommended as standard treatment in this population.
  - Erdafitinib is an alternative in patients with FGFR alterations with a weaker level of evidence.
  - Chemotherapy can be considered instead of best supportive care, if clinically appropriate.
  - Retreatment with chemotherapy for those patients that relapse after all other treatment options can be considered.
  - Single-agent taxane therapy or vinflunine can be considered.

Regulatory status

EMA [1]

Approval status for this indication: On 24 February 2022, the CHMP adopted a positive opinion, recommending the granting of a marketing authorisation for Padcev®.

The CHMP had initially adopted an opinion on 16 December 2021. During the decision-making process further safety information was brought to the attention of the Committee. Following a request from the European Commission, the CHMP readopted its opinion on 24 February 2022, taking into account the latest information.

UPDATE: Date of issue of marketing authorisation valid throughout the European Union: 13/04/2022 [6]

<u>The full indication is:</u>

- Padcev® as monotherapy is indicated for the treatment of adult patients with locally advanced or metastatic urothelial cancer who have previously received platinum-containing chemotherapy and a PD-1 or PD-L1 inhibitor.

Other indications: none

FDA [5]

Approval status for this indication: On 9 July 2021, the FDA approved enfortumab vedotin-ejfv (Padcev®) for adult patients with locally advanced or metastatic urothelial cancer who:

- have previously received a PD-1 or PD-L1 inhibitor and platinum-containing chemotherapy, or
- are ineligible for cisplatin-containing chemotherapy and have previously received one or more prior lines of therapy.

✓ **Priority review**
✓ **Breakthrough therapy designation**

The FDA granted accelerated approval in December 2019 to enfortumab vedotin-ejfv for patients with locally advanced or metastatic urothelial cancer who have received a PD-1 or PD-L1 inhibitor and platinum-containing chemotherapy in the neoadjuvant/adjuvant, locally advanced, or metastatic setting.

Other indications: none

✓ **Medicine is under additional monitoring**	

Costs [7]

Padcev® powder for concentrate for solution for infusion 20 mg = € 710.41 (ex-factory price)
Padcev® powder for concentrate for solution for infusion 30 mg = € 1,065.62 (ex-factory price)

Warnings and precautions [8]

- **Serious skin reactions**
  - Padcev® can cause severe and fatal cutaneous adverse reactions, including Stevens-Johnson syndrome (SJS) and Toxic Epidermal Necrolysis (TEN).
  - Immediately withhold Padcev® and consider referral for specialised 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.
- **Hyperglycemia:**
  - Diabetic ketoacidosis may occur in patients with and without pre-existing diabetes mellitus, which may be fatal.
  - Closely monitor blood glucose levels in patients with, or at risk for, diabetes mellitus or hyperglycemia.
  - Withhold Padcev® if blood glucose is >250 mg/dL.
- **Pneumonitis:**
  - Severe, life-threatening, or fatal pneumonitis may occur.
  - Withhold Padcev® for persistent or recurrent Grade 2 pneumonitis and consider dose reduction.
  - Permanently discontinue Padcev® for Grade 3 or 4 pneumonitis.
- **Peripheral neuropathy:**
  - Monitor patients for new or worsening peripheral neuropathy and consider dose interruption, dose reduction, or discontinuation of Padcev®.
- **Ocular disorders:**
  - Ocular disorders, including vision changes, may occur.
  - Monitor patients for signs or symptoms of ocular disorders.
  - Consider prophylactic artificial tears for dry eyes and treatment with ophthalmic topical steroids after an ophthalmic exam.
  - Consider dose interruption or dose reduction of Padcev® when symptomatic ocular disorders occur.
- **Infusion site extravasation**:
  - Ensure adequate venous access prior to administration.
  - Monitor the infusion site during Padcev® administration and stop the infusion immediately for suspected extravasation.
- **Embryo-foetal toxicity:**
  - Padcev® can cause foetal harm.
  - Advise of the potential risk to a foetus and to use effective contraception.

Study characteristics [9-13]

Trial name	*n*	Intervention (I)	Comparator (C)	PE	Characteristics	Biomarker	Funding	Publication(s)
EV-301 NCT03474107	608 (301 vs. 307)	Enfortumab vedotin at a dose of 1.25 mg/kg of body weight	Chemotherapy[1] (selected by the investigator	OS	**ongoing**, global, open-label, randomised, phase 3 trial	-	Astellas Pharma US and Seagen	[12]

[1] Chemotherapy and was one of the following: docetaxel at a dose of 75 mg/m^2 of BSA, administered IV over 60 minutes; paclitaxel at a dose of 175 mg/m^2, administered IV over 3 hours; or vinflunine (in regions where it is approved for treatment of urothelial carcinoma) at a dose of 320 mg/m^2, administered IV over 20 minutes. The use of vinflunine was capped at 35% of the patients in this trial. The chemotherapy treatments were administered on day 1 of a 21-day cycle.

		by means of IV infusion over 30 minutes on days 1, 8, and 15 of a 28-day cycle	before randomisation)[2]					

Efficacy (I vs. C)	Safety (I vs. C)
OS: After a median follow-up of 11.1 months, the risk of death was 30% lower with Enfortumab vedotin than with chemotherapy. **Median OS:** 12.88 months (95% CI, 10.58-15.21) vs. 8.97 months (95% CI, 8.05-10.74), HR for death 0.70; 95% CI, 0.56-0.89; p=0.001 **Estimated percentage of patients alive at 12 months:** 51.5% (95% CI, 44.6-58.0) vs. 39.2% (95% CI, 32.6-45.6) **PFS:** Treatment with enfortumab vedotin resulted in significantly longer PFS than chemotherapy and a 38% lower risk of progression or death. **Median PFS**: 5.55 months (95% CI, 5.32-5.82) vs. 3.71 months (95% CI, 3.52-3.94), HR for progression or death 0.62; 95% CI, 0.51-0.75; p<0.001 **Clinical Response:** Confirmed overall response was higher in the enfortumab vedotin group than in the chemotherapy group: 40.6% (95% CI, 34.9-46.5 vs. 17.9% (95% CI, 13.7-22.8; p<0.001) Complete response: 4.9% vs. 2.7% Disease control: 71.9% (95% CI, 66.3-77.0) vs. 53.4% (95% CI, 47.5-59.2), p<0.001 Median duration of response in patients who had a complete or partial response: 7.39 months vs. 8.11 months **QoL**: ❖ Questionnaire compliance rates at baseline were 90% in both groups; during the study, average rates were 70.2% (I) and 66.9% (C). ❖ Baseline QLQ-C30 scores were similar between groups. ❖ At week 12, scores on the global health status (GHS) scale were similar between groups (I: -2.8, C: -5.0; p=.2429), but chemotherapy was associated with numerically greater deterioration and more variability in QoL over the first 12 weeks. ❖ Patients receiving Enfortumab vedotin had significant reduction in pain symptoms (I: -5.62, C: +0.11; adjusted difference: -5.73, p<.05), but significant worsening of appetite loss (I: +8.55, C: +1.26; adjusted difference: 7.29, p<.05) compared with chemotherapy. ❖ Other symptom scores were not significantly different between groups. ❖ Higher proportions of patients on I vs. C had significant confirmed improvements across all functioning domains (role, physical, emotional, social, cognitive), GHS, and several symptom scales (pain, fatigue, dyspnea, constipation). The greatest difference in improvement was reported for pain (I: 51.6%, C: 28.8%; OR = 2.76,1.81, 4.22). ❖ Conclusions: Compared with chemotherapy, patients receiving enfortumab vedotin had numerically less deterioration and variability in QoL during the first 12 weeks of treatment. More patients in I had improvements over C in 10 of 15 QLQ-C30 domains; improvement in pain showed the largest benefit.	**Treatment-related AEs:** n=278/296 (93.9%) vs. n=267/291 (91.8%) **Treatment-related AEs grade ≥3:** 152/296 (51.4%) vs. 145/291 (49.8%) **Treatment-related AEs leading to withdrawal**: n=40/296 (13.5%) vs. n=33/291 (11.3%) **Investigator-assessed treatment-related AEs that resulted in death**: n=7/296 (2.4%) vs. n=3/291 (1.0%) **Overall treatment-emergent AEs:** n=290/296 (98.0%) vs. n=288/291 (99.0%) **Serious treatment-emergent AEs:** n=138/296 (46.6%) vs. n=128/291 (44.0%) **Treatment-emergent grade ≥3 AEs:** n=210/296 (70.9%) vs. n=193/291 (66.3%) **Treatment-emergent AEs leading to treatment withdrawal:** n=51/296 (17.2%) vs. n=51/291 (17.5%) **Treatment-emergent AEs leading to death:** n=21/296 (7.1%) vs. n=16/291 (5.5%) **Treatment-emergent AEs leading to death, excluding disease progression:** n=11/296 (3.7%) vs. n=11/291 (3.8%)

ESMOMCBS version 1.1 [14]

Scale	Int.	Form	MG ST	MG	HR (95% CI)	Score calculation	PM	Toxicity	QoL	AJ	FM

[2] All patients who received paclitaxel or docetaxel received premedication to prevent hypersensitivity reactions or fluid retention.

Original	NC	2a	≤12 months	OS: +3.91 months	0.70 (0.56-0.89)	HR≤0.65 AND gain ≥3 months	4	x	NSD	x	4
Adapted	NC	2a	≤12 months	OS: +3.91 months	0.70 (0.56-0.89)	HR >0.65-0.70 AND gain ≥1.5 months	2	x	NSD	x	2

Risk of bias (RCT) [15]					
Adequate generation of randomisation sequence	Adequate allocation concealment	Blinding	Selective outcome reporting unlikely	Other aspects which increase the risk of bias	**Risk of bias**
yes	-	No, open-label	unclear[3]	yes[4]	unclear

First published: 01/2022
Last updated: 06/2022

Abbreviations: AE=adverse event, AJ=adjustment, BSA=body-surface area, C=comparator, CHMP=Committee for Medicinal Products for Human Use, CI=confidence interval, EMA=European Medicines Agency, ESMO-MCBS= European Society of Medical Oncology – Magnitude of Clinical Benefit Scale, FDA=Food and Drug Administration, GHS=global health status, FGFR= fibroblast growth factor receptor, FM=final magnitude of clinical benefit grade, HR=hazard ratio, I=intervention, Int.=intention, IV=intravenous(ly), NSD=no significant difference, MG=median gain, n=number of patients, OS=overall survival, PD-1=programmed death receptor-1, PD-L1=programmed death-ligand, PE=primary endpoint, PFS=progression-free survival, PM=preliminary grade, QoL=quality of life, SAE=serious adverse event, SJS= Stevens-Johnson syndrome, ST=standard treatment, TEN=Toxic Epidermal Necrolysis

References:

1. European Medicines Agency (EMA). Medicines. Padcev. [Available from: https://www.ema.europa.eu/en/medicines/human/summaries-opinion/padcev].
2. National Institute for Health Research (NIHR). Enfortumab vedotin for locally advanced or metastatic urothelial cancer. [Available from: https://www.io.nihr.ac.uk/wp-content/uploads/2020/07/13663-Enfortumab-Vedotin-for-Urothelial-Cancer-V1.0-JUL2020.-Non-CONF.pdf].
3. UpToDate, Bellmunt J. Treatment of metastatic urothelial cancer of the bladder and urinary tract. [Available from: https://www.uptodate.com/contents/treatment-of-metastatic-urothelial-cancer-of-the-bladder-and-urinary-tract#H24].
4. Powles T, Bellmunt J, Comperat E, et al., on behalf of the ESMO Guidelines Committee. Bladder Cancer: ESMO Clinical Practice Guideline for diagnosis, treatment and follow-up. [Available from: https://www.esmo.org/guidelines/genitourinary-cancers/bladder-cancer].
5. U.S. Food and Drug Administration (FDA). FDA grants regular approval to enfortumab vedotin-ejfv for locally advanced or metastatic urothelial cancer. [Available from: https://www.fda.gov/drugs/resources-information-approved-drugs/fda-grants-regular-approval-enfortumab-vedotin-ejfv-locally-advanced-or-metastatic-urothelial-cancer].
6. European Medicines Agency (EMA). Medicine. EPAR. Padcev. [Available from: https://www.ema.europa.eu/en/medicines/human/EPAR/padcev].
7. Österreichischer Apotheker-Verlag. Warenverzeichnis Online. [Available from: https://warenverzeichnis.apoverlag.at/].
8. U.S. Food and Drug Administration (FDA). Padcev. Label information. [Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/761137s006s008lbl.pdf].
9. Supplement to: Powles T, Rosenberg JE, Sonpavde GP, et al. Enfortumab vedotin in previously treated advanced urothelial carcinoma. N Engl J Med 2021;384:1125-35.
10. Protocol for: Powles T, Rosenberg JE, Sonpavde GP, et al. Enfortumab vedotin in previously treated advanced urothelial carcinoma. N Engl J Med 2021;384:1125-35.
11. Mamtani R, et al. Quality of life, functioning, and symptoms in patients with previously treated locally advanced or metastatic urothelial carcinoma from EV-301: A randomized phase 3 trial of enfortumab vedotin versus chemotherapy. [Available from: https://ascopubs.org/doi/abs/10.1200/JCO.2021.39.15_suppl.4539].
12. Powles T, Rosenberg JE, Sonpavde GP, Loriot Y, et al. Enfortumab Vedotin in Previously Treated Advanced Urothelial Carcinoma. N Engl J Med 2021;384:1125-35. [Available from: https://www.nejm.org/doi/full/10.1056/NEJMoa2035807].
13. U.S. National Library of Medicine, ClinicalTrials.gov. A Study to Evaluate Enfortumab Vedotin Versus (vs) Chemotherapy in Subjects With Previously Treated Locally Advanced or Metastatic Urothelial Cancer (EV-301). [Available from: https://clinicaltrials.gov/ct2/show/NCT03474107].
14. Cherny NI, Dafni U, Bogaerts J., et al. ESMO-Magnitude of Clinical Benefit Scale version 1.1. Annals of Oncology 28: 2340–2366, 2017.

[3] EV-301 is currently ongoing; estimated study completion date is 02/2022.

[4] The trial was designed by the sponsors in collaboration with an advisory committee. Data were collected by the trial investigators, analysed by statisticians employed by the sponsor, and interpreted by all authors. The authors, with writing and editorial support funded by the trial sponsors, developed and approved the manuscript.

15. European Network for Health Technology Assessment (EUnetHTA). Levels of evidence. Internal validity of randomised controlled trials. Adapted version (2015). [Available from: https://www.eunethta.eu/wp-content/uploads/2018/01/Internal-validity-of-randomised-controlled-trials.pdf].