swissmedic

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Swiss Public Assessment Report

Extension of therapeutic indication

Padcev

International non-proprietary name: enfortumab vedotin
Pharmaceutical form: powder for concentrate for solution for infusion
Dosage strength(s): 20 mg, 30 mg
Route(s) of administration: intravenous
Marketing authorisation holder: Astellas Pharma AG
Marketing authorisation no.: 68291
Decision and decision date: approved on 17.09.2024

Note:

This assessment report is as adopted by Swissmedic with all information of a commercially confidential nature deleted.

SwissPARs are final documents that provide information on submissions at a particular point in time. They are not updated after publication.

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1 Terms, Definitions, Abbreviations

1L	First-line
AE	Adverse event
API	Active pharmaceutical ingredient
ATC	Anatomical Therapeutic Chemical Classification System
BICR	Blinded independent central review
CI	Confidence interval
ECOG	Eastern Cooperative Oncology Group
EMA	European Medicines Agency
ERA	Environmental risk assessment
EV	Enfortumab vedotin
FDA	Food and Drug Administration (US)
Gem	Gemcitabin
HR	Hazard ratio
ICH	International Council for Harmonisation
Ig	Immunoglobulin
INN	International non-proprietary name
LoQ	List of Questions
MAH	Marketing Authorisation Holder
Max	Maximum
Min	Minimum
MRHD	Maximum recommended human dose
MTD	Maximum tolerated dose
mUC	Unresectable locally advanced / metastatic UC
N/A	Not applicable
NCCN	National Comprehensive Cancer Network
ORR	Objective response rate
OS	Overall survival
PBPK	Physiology-based pharmacokinetics
PD	Pharmacodynamics
Pembro	Pembrolizumab
PFS	Progression-free survival
PIP	Paediatric Investigation Plan (EMA)
PK	Pharmacokinetics
Plat	Cisplatin or carboplatin
RMP	Risk management plan
SAE	Serious adverse event
SOC	Standard of care
SwissPAR	Swiss Public Assessment Report
TEAE	Treatment-emergent adverse event
TPA	Federal Act of 15 December 2000 on Medicinal Products and Medical Devices (SR 812.21)
TPO	Ordinance of 21 September 2018 on Therapeutic Products (SR 812.212.21)
UC	Urothelial cancer

2 Background information on the procedure

2.1 Applicant's request(s)

Extension(s) of the therapeutic indication(s)
The applicant requested the addition of a new therapeutic indication or modification of an approved one in accordance with Article 23 TPO.

Project Orbis
The applicant requested a marketing authorisation procedure within the framework of Project Orbis. Project Orbis is a programme for the assessment of promising cancer treatments coordinated by the US FDA. It provides a framework for concurrent submission and review of oncology products among international partners.

2.2 Indication and dosage

2.2.1 Requested indication

Padcev in combination with pembrolizumab is indicated for the treatment of adult patients with locally advanced or metastatic urothelial carcinoma.

2.2.2 Approved indication

Padcev, in combination with pembrolizumab, is indicated for the first-line treatment of adult patients with unresectable or metastatic urothelial cancer (mUC).

2.2.3 Requested dosage

Summary of the requested standard dosage:
The recommended dose of Padcev in combination with pembrolizumab is 1.25 mg/kg (up to a maximum dose of 125 mg for patients ≥100 kg) given as an intravenous infusion over 30 minutes on Days 1 and 8 of a 21-day cycle until disease progression or unacceptable toxicity.

2.2.4 Approved dosage

(see appendix)

2.3 Regulatory history (milestones)

Application	22 January 2024
Formal control completed	2 February 2024
List of Questions (LoQ)	14 May 2024
Response to LoQ	27 May 2024
Preliminary decision	12 July 2024
Response to preliminary decision	11 August 2024
Final decision	17 September 2024
Decision	approval

3 Medical context

Urothelial cancer (UC) is the sixth most common tumour in developed countries. The treatment of locally advanced / metastatic UC (mUC) had remained largely unchanged since pivotal trials published over 20 years ago set the standard of care for first-line (1L) treatment with cisplatin-based chemotherapy demonstrating an overall survival (OS) benefit. Because the median OS of 12 to 15 months achievable with standard-of-care (SOC) cisplatin-based chemotherapy[1] is still unsatisfactory, and due to the toxicity associated with cisplatin-based chemotherapy, there is a medical need for new therapeutic options with improved efficacy and safety for patients with mUC.

The evaluation of the clinical data of this application has been carried out in reliance on previous regulatory decisions by the US FDA. The available assessment reports and respective product information were used as a basis for the clinical (pharmacology) evaluation.

[1] Witjes JA et al. European Association of Urology (EAU) Guidelines on Muscle-invasive and Metastatic Bladder Cancer 2023.

4 Nonclinical aspects

The results of the submitted new nonclinical pharmacology studies support the combination treatment of enfortumab vedotin and immune checkpoint inhibitors such as anti-PD-1 antibodies for the treatment of Nectin-4 positive tumours. According to ICH S9, toxicology studies investigating the safety of combinations of pharmaceuticals intended to treat patients with advanced cancer are not warranted, particularly if the human toxicity profile of the pharmaceuticals has been characterised. Thus, no additional nonclinical studies are required to support the requested combination of enfortumab vedotin with pembrolizumab for the treatment for of advanced urothelial cancer, for which monotherapy with enfortumab vedotin is already authorised.
Since the requested change in the indication does not change the patient population (patients with bladder cancer), an updated ERA is not required.
From the nonclinical point of view, there are no objections to approval of the proposed extension of indication.

5 Clinical aspects

5.1 Clinical pharmacology

The available assessment reports and respective product information from the US FDA were used as a basis for the clinical pharmacology evaluation.

5.2 Dose finding and dose recommendation

No dedicated dose-finding data have been provided for enfortumab vedotin (EV) + pembrolizumab (EV + Pembro) in the proposed new indication. It therefore remains unknown whether lower dosages could result in an improved benefit-risk balance by capitalising on additive efficacy effects of the combination, which is of relevance given the substantial toxicity of the combination therapy. In light of the efficacy benefits and the overall manageable and acceptable safety profile in the context of the poor prognosis of the underlying condition, the dose finding was considered acceptable.

The evidence for the contribution of the single components to the overall efficacy of the combination is based on cross-study comparisons of the objective response rate (ORR). The confirmed ORR by blinded independent central review (BICR) for patients who had received EV in combination with pembrolizumab in study EV-302 was 68% (95% confidence interval (CI): 63, 72) as compared to 45% with EV monotherapy in study EV-103, and approximately 30% with pembrolizumab monotherapy in studies KEYNOTE-361 and 052. Despite the available level of evidence for the contribution of components being notably limited by cross-study comparisons and reliance on ORR, and a lack of reliable comparative information on relevant time-to-event endpoints including OS, this was accepted given the efficacy benefits and the overall manageable and acceptable safety profile in the context of the poor prognosis of the underlying condition.

5.3 Efficacy

The efficacy and safety of EV + Pembro vs SOC chemotherapy with cisplatin or carboplatin plus gemcitabine (Plat + Gem) were evaluated in the Phase 3, open-label, 1:1 randomised study EV-302, with inclusion of 886 patients with previously untreated mUC. For details regarding study design, study population, and treatment see the attached Information for healthcare professionals.

Study EV-302 met its primary endpoints showing statistically significant and clinically meaningful improvement of progression-free survival (PFS) and overall survival (OS). For PFS the hazard ratio (HR) was 0.45 (95% CI: 0.38, 0.54), with a median PFS of 12.5 months (95% CI: 10.4, 16.6) vs 6.3 months (95% CI: 6.2, 6.5). For OS the hazard ratio (HR) was 0.47 (95% CI: 0.38, 0.58), with a median OS of 31.5 months (95% CI: 25.4, -) vs 16.1 months (95% CI: 13.9, 18.3).

5.4 Safety

Patients who received EV + Pembro in pivotal study EV-302 had lower rates of treatment-emergent adverse events (TEAEs) ≥ Grade 3 vs patients who received Plat + Gem (73.0% vs 78.8%) but higher rates of serious TEAEs (50.0% vs 39.0%) and TEAEs leading to treatment discontinuation (39.8% vs 21.5%) and dose interruption (78.9% vs 64.4%). Patients who received EV + Pembro experienced more skin disorders, peripheral neuropathy, pneumonitis/interstitial lung disease, hyperglycaemia, increased transaminases, ocular disorders, and immune-related TEAEs compared to patients who received Plat + Gem (see Information for healthcare professionals of Padcev® and Keytruda® for details).

Although the safety profile of EV + Pembro was consistent with the monotherapies, the combination showed generally increased rates of TEAEs when compared with the pooled safety data of the monotherapies. Known adverse events of special interest associated with EV and observed in study EV-302 included skin reactions, hyperglycaemia, pneumonitis/ILD, peripheral neuropathy, ocular disorders, and infusion site extravasation. These adverse events are labelled in the “Warnings and Precautions” section of the Information for healthcare professionals.

5.5 Final clinical benefit-risk assessment

Based on the statistically significant and clinically meaningful improvement in OS and PFS, along with an overall manageable and acceptable safety profile – despite significant toxicity – combined EV + Pembro was considered to have a positive benefit-risk balance. In light of the poor prognosis of the underlying condition, the combination was approved for the 1L treatment of mUC.

6 Risk management plan summary

The RMP summaries contain information on the medicinal products' safety profiles and explain the measures that are taken to further investigate and monitor the risks, as well as to prevent or minimise them.
The RMP summaries are published separately on the Swissmedic website. It is the responsibility of the marketing authorisation holder to ensure that the content of the published RMP summaries is accurate and correct. As the RMPs are international documents, their summaries might differ from the content in the Information for healthcare professionals / product information approved and published in Switzerland, e.g. by mentioning risks that occur in populations or indications not included in the Swiss authorisations.

7 Appendix

Approved Information for healthcare professionals

Please be aware that the following version of the Information for healthcare professionals for Padcev was approved with the submission described in the SwissPAR. This Information for healthcare professionals may have been updated since the SwissPAR was published.

Please note that the valid and relevant reference document for the effective and safe use of medicinal products in Switzerland is the Information for healthcare professionals currently authorised by Swissmedic (see www.swissmedicinfo.ch).

Note:
The following Information for healthcare professionals has been translated by the MAH. It is the responsibility of the authorisation holder to ensure the translation is correct. The only binding and legally valid text is the Information for healthcare professionals approved in one of the official Swiss languages.

▼ 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 new or serious adverse reactions. See "*Undesirable effects*" for advice on the reporting of adverse reactions.

PADCEV™

Composition

Active substances

Enfortumab vedotin (enfortumab is genetically engineered using CHO [Chinese Hamster Ovary]-cells).

Excipients

Histidine, Histidine hydrochloride monohydrate, Trehalose dehydrate, Polysorbate 20.

Pharmaceutical form and active substance quantity per unit

Powder for concentrate for solution for infusion. White to off-white lyophilized powder. Vials contain 20 mg or 30 mg of enfortumab vedotin.

Indications/Uses

PADCEV, in combination with pembrolizumab, is indicated for the first-line treatment of adult patients with unresectable or metastatic urothelial cancer (mUC).

PADCEV as monotherapy is indicated for the treatment of adults with locally advanced or metastatic urothelial cancer (mUC) who have received a platinum containing chemotherapy in the neoadjuvant/adjuvant locally advanced, or metastatic setting and who have progressed or relapsed during or after treatment with a programmed death receptor-1 (PD-1) or programmed death-ligand 1 (PD-L1) inhibitor (see "*Clinical Efficacy"*).

Dosage/Administration

Treatment with PADCEV should be initiated and supervised by a physician experienced in the use of anti-cancer therapies.
In order to improve the traceability of biological medicinal products, the name and the batch number of the administered product should be clearly recorded.

Combination therapy with pembrolizumab / 21-day cycle, 2 doses

When given in combination with pembrolizumab, the recommended dose of PADCEV is 1.25 mg/kg (up to a maximum of 125 mg for patients ≥100 kg) administered as an intravenous infusion over 30 minutes on Days 1 and 8 of a 21-day cycle until disease progression or unacceptable toxicity. In patients treated with the combination, PADCEV will be administered before pembrolizumab. Refer to the pembrolizumab Prescribing Information for the recommended dosing information of pembrolizumab.

Monotherapy / 28-day cycle, 3 doses

As monotherapy, the recommended dose of PADCEV is 1.25 mg/kg (up to a maximum of 125 mg for patients ≥ 100 kg) administered as an intravenous infusion over 30 minutes on Days 1, 8 and 15 of a 28-day cycle until disease progression or unacceptable toxicity.

Dose Modifications

Dose adjustment following undesirable effects/interactions

Table 1: Dose Modifications of PADCEV

Adverse Reaction	**Severity**[1]	**Dose Modification**[1]
Skin Reactions	For persistent or recurrent Grade 2 skin reactions Grade 2 with fever Grade 3 (severe skin reaction)	• Withhold until Grade ≤ 1. • Referral to specialized care should be considered. • Resume at the same dose level or consider dose reduction by one dose level (see Table 2).
	Suspected Stevens-Johnson syndrome (SJS) or toxic epidermal necrolysis (TEN) or bullous lesions	Immediately withhold and refer to specialized care.
	Confirmed SJS or TEN; Grade 4 or recurrent Grade 3	Permanently discontinue.

Adverse Reaction	Severity[1]	Dose Modification[1]
Hyperglycemia	Blood glucose > 250 mg/dL	Withhold until elevated blood glucose has improved to ≤ 250 mg/dL, then resume treatment at the same dose level.
Pneumonitis/interstitial lung disease (ILD)	Grade 2	Withhold until Grade ≤ 1, then resume at the same dose level or consider dose reduction by one dose level.
	Grade ≥ 3	Permanently discontinue.
Peripheral Neuropathy	Grade 2	Withhold until Grade ≤ 1, then resume treatment at the same dose level (if first occurrence). For a recurrence, withhold until Grade ≤ 1, then resume treatment reduced by one dose level.
	Grade ≥ 3	Permanently discontinue.
Other nonhematologic toxicity	Grade 3	Withhold until Grade ≤ 1, then resume treatment at the same dose level or consider dose reduction by one dose level.
	Grade 4	Permanently discontinue.
Hematologic toxicity	Grade 3, or Grade 2 thrombocytopenia	Withhold until Grade ≤ 1, then resume treatment at the same dose level or consider dose reduction by one dose level.
	Grade 4	Withhold until Grade ≤ 1, then reduce dose by one dose level or discontinue treatment.

[1]Grade 1 is mild, Grade 2 is moderate, Grade 3 is severe, Grade 4 is life-threatening.

Dose adjustment/titration

Table 2: Recommended Dose Reduction Schedule of PADCEV 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

Patients with impaired hepatic function

No dose adjustment is required in patients with mild hepatic impairment. PADCEV has only been evaluated in a limited number of patients with moderate hepatic impairment and has not been evaluated in patients with severe hepatic impairment. Use of PADCEV in patients with moderate and severe hepatic insufficiency should therefore be avoided. Patients with impaired liver function should be monitored closely for occurrence of adverse reactions (see "*Pharmacokinetics"*).

Patients with impaired renal function

No dose adjustment is required in patients with mild, moderate or severe renal impairment (see "*Pharmacokinetics"* and "*Undesirable Effects"*). PADCEV has not been evaluated in patients with end stage renal disease.

Elderly patients

No dose adjustment is required in patients ≥ 65 years of age (see "*Pharmacokinetics"* and "*Undesirable Effects"*).

Paediatric Population

PADCEV is not approved for use in the paediatric population.

Mode of administration

The recommended dose of enfortumab vedotin 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 "*Instructions for handling"*).

Administration

1. Administer the infusion over 30 minutes through an intravenous line. DO NOT administer as an IV push or bolus.
2. DO NOT co-administer other drugs through the same infusion line.

Contraindications

Hypersensitivity to the active substance or to any of the excipients.

Warnings and precautions

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.
Severe cutaneous adverse reactions, including SJS and TEN, with fatal outcome have occurred in patients treated with enfortumab vedotin, predominantly during the first cycle of treatment. Mild to moderate skin reactions, predominantly rash maculo-papular, have been reported with PADCEV. The incidence of skin reactions, including severe reactions, occurred at a higher rate when PADCEV was given in combination with pembrolizumab compared to PADCEV as monotherapy (see "*Undesirable effects*").

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, withhold treatment immediately and refer to specialised care: histological evidence, including performing multiple biopsies, is essential for early detection, as the diagnosis and treatment can improve prognosis. Permanently discontinue PADCEV for confirmed SJS or TEN, Grade 4 or recurrent Grade 3 skin reactions. For persistent or recurrent Grade 2 skin reactions, Grade 2 skin reactions 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 "*Dosage/Administration*").

Hyperglycaemia

Hyperglycaemia and diabetic ketoacidosis (DKA) including fatal events, occurred in patients with and without pre-existing diabetes mellitus, treated with PADCEV. Hyperglycaemia occurred more frequently in patients with pre-existing hyperglycaemia or a high body mass index (≥ 30 kg/m^2). Blood glucose levels should be monitored regularly in patients with or at risk for diabetes mellitus

or hyperglycaemia. If blood glucose is elevated (> 13.9 mmol/L; > 250 mg/dL), withhold PADCEV (see "*Dosage/Administration",* "*Properties/Effects"* and "*Undesirable Effects"*).

Pneumonitis/ILD

Severe, life-threatening or fatal pneumonitis/ILD occurred in patients treated with PADCEV. The incidence of pneumonitis/ILD, including severe events occurred at a higher rate when PADCEV was given in combination with pembrolizumab compared to PADCEV as monotherapy (see "*Undesirable effects*").
Monitor patients for signs and symptoms indicative of pneumonitis/ILD such as hypoxia, cough, dyspnoea or interstitial infiltrates on radiologic exams. Evaluate and exclude infectious, neoplastic and other causes for such signs and symptoms through appropriate investigations.

Withhold PADCEV for patients who develop Grade 2 pneumonitis/ILD and consider dose reduction. Permanently discontinue PADCEV in all patients with Grade 3 or 4 pneumonitis/ILD (see "*Dosage/Administration*").

Peripheral neuropathy

Peripheral sensory neuropathy (38.5%) and motor neuropathy (6.7%), have occurred with PADCEV, including Grade ≥ 3 reactions. The incidence of peripheral neuropathy occurred at a higher rate when PADCEV was given in combination with pembrolizumab compared to PADCEV as monotherapy. Monitor patients for symptoms of new or worsening peripheral neuropathy as these patients may require a delay, dose reduction or discontinuation of PADCEV (see "*Dosage/Administration"*, "*Properties/Effects"* and "*Undesirable Effects"*).

Ocular disorders

Ocular disorders, predominantly dry eye, occurred in patients treated with PADCEV. The majority of these events involved the cornea and included keratitis, blurred vision, limbal stem cell deficiency, and other events associated with dry eyes. Severe (Grade 3) ocular disorders occurred in 3 patients (0.4%). Monitor patients for ocular disorders such as dry eye. Consider artificial tears for prophylaxis of dry eye and refer patient for ophthalmologic evaluation if ocular symptoms do not resolve or worsen (see "*Undesirable Effects"*).

Infusion Site Extravasation

Skin and soft tissue injury following PADCEV administration has been observed when extravasation occurred. 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 (see "*Undesirable Effects"*).

Embryo-foetal Toxicity and effects on spermatogenesis

Based on its mechanism of action, PADCEV can cause teratogenic effects and/or embryo-fetal lethality when administered to pregnant women. Since monomethyl auristatin E (MMAE) has aneugenic properties, men treated with this medicinal product should be advised to have sperm samples frozen before treatment (see "*Pregnancy, lactation"* and *"Preclinical data").*

Interactions

Formal drug-drug interaction studies with enfortumab vedotin have not been conducted. To evaluate the drug-drug interaction potential of unconjugated MMAE, physiologically-based pharmacokinetic (PBPK) modeling was conducted to predict the drug-drug interaction potential of enfortumab vedotin following coadministration with other drugs.

Effect of other medicinal products on PADCEV

CYP3A4 and P-gp Inhibitors

Concomitant use of enfortumab vedotin with ketoconazole (a combined P-gp and strong CYP3A4 inhibitor) is predicted to increase unconjugated MMAE C_{max} by 15% and AUC by 38%. Closely monitor for adverse reactions when enfortumab vedotin is given concomitantly with strong CYP3A4 and P-gp inhibitors.

CYP3A4 and P-gp Inducers

Concomitant use of enfortumab vedotin with rifampicin (a combined P-gp and strong CYP3A4 inducer) is predicted to decrease unconjugated MMAE C_{max} by 28% and AUC by 53%.

Effect of PADCEV on other medicinal products

CYP Substrates

Concomitant use of enfortumab vedotin is predicted not to affect exposure to midazolam (a sensitive CYP3A4 substrate) or digoxin (a P-gp substrate). *In vitro* studies using human liver microsomes indicate that unconjugated MMAE inhibits CYP3A4/5 but not CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, and CYP2D6. Unconjugated MMAE did not induce CYP1A2, CYP2B6, and CYP3A4/5 in human hepatocytes.

Transporter

In vitro studies indicate that unconjugated MMAE is a substrate of the efflux transporter P-gp. *In vitro* studies determined that unconjugated MMAE was not a substrate of breast cancer resistance protein (BCRP), multidrug resistance-associated protein 2 (MRP2), organic anion transporting polypeptide 1B1 or 1B3 (OATP1B1 or OATP1B3), organic cation transporter 2 (OCT2), or organic anion transporter 1 or 3 (OAT1 or OAT3). Unconjugated MMAE was not an inhibitor of the bile salt export pump (BSEP), P-gp, BCRP, MRP2, OCT1, OCT2, OAT1, OAT3, OATP1B1, or OATP1B3 at clinically relevant concentrations.

Pregnancy, lactation

Women of childbearing age or their partners

Verify pregnancy status in women of childbearing age prior to initiating PADCEV treatment. Women of childbearing potential should be advised of the need to use effective contraception during treatment with PADCEV and for at least 6 months after the last dose. Due to the genotoxic potential, male patients with partners of childbearing potential should be advised of the need for effective contraception during treatment with PADCEV and for at least 4 months after the last dose.

Pregnancy

Based on its mechanism of action, PADCEV can cause teratogenic effects and/or embryo-fetal lethality when administered to pregnant women. No data are available on use in pregnant patients to assess the risk associated with this medicinal product. Animal studies showed reproductive toxicity (see "*Preclinical data"*). The potential risk for humans is not known. The medicine should not be administered during pregnancy unless absolutely necessary. Pregnant women and women of childbearing age must be informed of the potential risk to the foetus.

Lactation

There are no data available on excretion of enfortumab-vedotin into human breast milk. A risk to breast-fed children cannot be excluded. Because of the potential for serious adverse reactions in a breastfed child, advise lactating women not to breastfeed during treatment with PADCEV and for at least 3 weeks after the last dose.

Fertility

There are no data on the effect of PADCEV on human fertility. Animal studies with enfortumab vedotin indicate that male fertility may be impaired (see "*Preclinical data"*).

Effects on ability to drive and use machines

Dry eye, blurred vision, fatigue, nausea and peripheral neuropathy have been reported in patients taking PADCEV and should be considered when assessing a patient's ability to drive or use machines. No corresponding studies have been performed.

Undesirable effects

Enfortumab vedotin as monotherapy

The safety of PADCEV was evaluated as monotherapy in 793 patients with locally advanced or metastatic urothelial cancer who received at least one dose of PADCEV 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 (≥ 10%) 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%), dry eye (30.1%), anaemia (29.1%), weight decreased (25.2%), rash maculo-papular (23.6%), dry skin (21.8%), vomiting (18.7%), aspartate aminotransferase increased (17%), hyperglycaemia (16.8%), alanine aminotransferase increased (12.7%) and rash (11.6%).

Serious adverse reactions occurred in 46% of patients; the most common serious adverse reactions (≥ 2%) were acute kidney injury (8.6%), pneumonia (4%), urinary tract infection (4%), sepsis (3%), diarrhoea (2%) and hyperglycaemia (2%). Two patients (0.3%) experienced a fatal event of acute respiratory failure. Permanent discontinuation occurred in 21% of patients; the most common adverse reaction (≥ 2%) leading to dose discontinuation was peripheral sensory neuropathy (5%). Dose interruption occurred in 62% of patients; the most common adverse reactions (≥ 2%) leading to dose interruption were peripheral sensory neuropathy (15%), fatigue (7%), rash maculo-papular (4%), aspartate aminotransferase increased (3%), alanine aminotransferase increased (3%), anaemia (3%), diarrhoea (3%), hyperglycaemia (3%), neutrophil count decreased (3%), rash (2%), and peripheral motor neuropathy (2%).

Dose reduction occurred in 38% of patients; the most common adverse reactions (≥ 2%) leading to a dose reduction were peripheral sensory neuropathy (10%), fatigue (5%), rash maculo-papular (4%), and decreased appetite (2%).

Enfortumab vedotin in combination with pembrolizumab

When PADCEV is administered in combination with pembrolizumab, refer to the Prescribing Information for pembrolizumab prior to initiation of treatment.

The safety of PADCEV was evaluated in combination with pembrolizumab in 564 patients who received at least one dose of PADCEV 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 PADCEV 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 PADCEV 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%), dry eye (27.7%), anaemia (25.7%), dysgeusia (24.3%), hyperglycaemia (19.0%), dry skin (18.1%), alanine aminotransferase increased (16.8%), aspartate aminotransferase increased (15.4%), vomiting (13.3%), rash macular (11.3%), hypothyroidism (10.5%) and neutropenia (10.1%).

Compared to enfortumab vedotin as monotherapy, an increase in the incidence of skin reactions, pneumonitis/ILD and peripheral neuropathy was observed during therapy with enfortumab vedotin in combination with pembrolizumab (see "*Description of specific adverse reactions and additional information*" and "*Warnings and precautions*").

The most common serious adverse reactions (≥2%) were pneumonitis/ILD (4.3%) and diarrhoea (3%). Two patients (0.4%) experienced a fatal event of acute respiratory failure. Thirty-six percent of patients permanently discontinued PADCEV 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 PADCEV 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%), pneumonitis/ILD (4.4%), fatigue (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 PADCEV 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%).

Adverse reactions observed during clinical studies of PADCEV as monotherapy or in combination with pembrolizumab, or reported from post-marketing use of PADCEV 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).

Table 3: Adverse Reactions in patients with PADCEV

	Monotherapy[1]	**In combination with pembrolizumab**[2]
Blood and lymphatic system disorders		
Very common	Anaemia (29.1%)	Anaemia (25.7%), Neutropenia (10.1%)
Common	Neutropenia, febrile neutropenia, neutrophil count decreased	Neutrophil count decreased
Uncommon		Febrile neutropenia
Endocrine disorders		
Very common		Hypothyroidism (10.5%)
Infections and infestations		
Common	Pneumonia, urinary tract infection	Pneumonia, urinary tract infection
Respiratory, thoracic, and mediastinal disorders		
Common	Pneumonitis/ILD[3]	Pneumonitis/ILD[3]
Uncommon	Acute respiratory failure	Acute respiratory failure
Gastrointestinal disorders		
Very common	Diarrhoea (39.1%), nausea (37.8%), vomiting (18.7%)	Diarrhoea (39.2%), nausea (28.4%), vomiting (13.3%)
General disorders and administration site conditions		
Very common	Fatigue (46.8%)	Fatigue (40.4%)
Common	Infusion site extravasation	Infusion site extravasation
Hepatobiliary disorders		
Very common	Aspartate aminotransferase increased (17%), alanine aminotransferase increased (12.7%)	Alanine aminotransferase increased (16.8%), aspartate aminotransferase increased (15.4%)
Metabolism and nutrition disorders		
Very common	Decreased appetite (47.2%), hyperglycaemia (16.8%)	Decreased appetite (33.9%), hyperglycaemia (19.0%)
Nervous system disorders		
Very common	Peripheral sensory neuropathy (38.5%), dysgeusia (30.4%)	Peripheral sensory neuropathy (53.4%), dysgeusia (24.3%)
Common	Gait disturbance, hypoaesthesia, neuropathy peripheral, muscular weakness, paraesthesia,	Peripheral motor neuropathy, peripheral sensorimotor neuropathy, paraesthesia,

	Monotherapy[1]	In combination with pembrolizumab[2]
	peripheral motor neuropathy, peripheral sensorimotor neuropathy	hypoaesthesia, gait disturbance, muscular weakness
Uncommon	Burning sensation, demyelinating polyneuropathy, dysaesthesia, motor dysfunction, muscle atrophy, neuralgia, neurotoxicity, peroneal nerve palsy, polyneuropathy, skin burning sensation, sensory loss	Neurotoxicity, dysaesthesia, myasthenia gravis, neuralgia, peroneal nerve palsy, skin burning sensation
Eye disorders		
Very common	Dry eye[4] (30.1%)	Dry eye[4] (27.7%)
Skin and subcutaneous tissue disorders		
Very common	Alopecia (47.7%), pruritus (33.4%), rash maculo-papular (23.6%), dry skin (21.8%), rash (11.6%)	Pruritus (41.1%), alopecia (38.5%), rash maculo-papular (36.0%), dry skin (18.1%), rash macular (11.3%)
Common	Blister, conjunctivitis, drug eruption, erythaema, eczema, dermatitis bullous, palmar-plantar erythrodysesthesia syndrome, rash erythaematous, rash macular, rash papular, rash pruritic, rash vesicular, skin exfoliation, stomatitis	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	Blood blister, dermatitis, dermatitis allergic, dermatitis contact, dermatitis exfoliative generalised, erythaema multiforme, exfoliative rash, intertrigo, pemphigoid, rash maculovesicular, skin irritation, stasis dermatitis, Stevens-Johnson syndrome	Drug eruption, dermatitis exfoliative generalised, exfoliative rash, pemphigoid, dermatitis contact, intertrigo, skin irritation, stasis dermatitis, toxic epidermal necrolysis, symmetrical drug-related intertriginous and flexural exanthaema
Not known	Epidermal necrosis, symmetrical drug-related intertriginous and flexural exanthaema, toxic epidermal necrolysis	Stevens-Johnson syndrome, epidermal necrosis
Musculoskeletal and connective tissue disorders		
Common		Myositis
Renal and urinary disorders		
Common	Acute kidney injury	Acute kidney injury
Investigations		
Very common	Increased creatinine[5] (58.0%), decreased albumin[5] (50.3%), decreased sodium[5] (40.7%), decreased phosphate[5] (39.9%),	Increased creatinine[5] (70.1%), increased lipase[5] (59.6%), decreased sodium[5] (48.8%), decreased phosphate[5] (45.5%), decreased albumin[5] (43.1%),

	Monotherapy[1]	In combination with pembrolizumab[2]
	increased lipase[5] (29.3%), weight decreased (25.2%), decreased potassium[5] (21.6%), increased potassium[5] (18.3%)	weight decreased (36%), decreased potassium[5] (27.8%), increased potassium[5] (24.6%), increased calcium[5] (22.1%)
Common	Increased calcium	

1. Preferred terms in MedDRA (v26.0). The above-mentioned listed adverse reactions have been observed during clinical studies (EV-101, EV-102, EV-103 cohort K EV monotherapy arm, EV-201, EV-203 and EV-301).
2. Preferred terms in MedDRA (v26.0). The above-mentioned listed adverse reactions have been observed during clinical studies EV-103 dose escalation cohort + cohort A+ cohort K, and EV-302 global portion and Japan-specific safety run-in.
3. Includes: acute respiratory distress syndrome, alveolitis, autoimmune lung disease, immune-mediated lung disease, interstitial lung disease, lung opacity, organising pneumonia, pneumonitis, pulmonary fibrosis, pulmonary toxicity, sarcoidosis.
4. Includes: blepharitis, conjunctivitis, conjunctivitis allergic, corneal disorder, dry eye, eye irritation, keratitis, keratopathy, lacrimation decreased, lacrimation increased, limbal stem cell deficiency, Meibomian gland dysfunction, ocular discomfort, punctate keratitis, tear break up time decreased.
5. Frequency is based on central laboratory values.

Description of specific adverse reactions and additional information

Skin Reactions

In clinical studies of PADCEV as monotherapy, skin reactions occurred in 57% (452) of the 793 patients treated with PADCEV 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). 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 PADCEV 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.

Hyperglycaemia

In clinical studies of PADCEV as monotherapy, hyperglycaemia occurred in 16.8% (133) of the 793 patients treated with PADCEV 1.25 mg/kg. Severe (Grade 3 or 4) hyperglycaemia occurred in 58 patients (Grade 3: 6.6%, Grade 4: 0.8%). Two 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 A1C. The median time to onset of hyperglycaemia was 0.5 months (range: 0 to 20.3) (see "*Warnings and precautions"*). 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.

In clinical studies of PADCEV in combination with pembrolizumab, hyperglycaemia occurred in 19% (107) of the 564 patients. Severe (Grade 3 or 4) hyperglycaemia occurred in 52 patients (Grade 3: 8.0%, Grade 4: 1.2%). The median time to onset of hyperglycaemia reactions was 0.7 months (range: 0 to 16.8 months). Patients with baseline haemoglobin A1C ≥ 8% were excluded from clinical studies.

Pneumonitis/ILD

In clinical studies of PADCEV as monotherapy, pneumonitis/ILD occurred in 26 (3.3%) of the 793 patients treated with enfortumab vedotin 1.25 mg/kg. Severe (Grade 3 or 4) pneumonitis/ILD occurred in 6 patients (Grade 3: 0.5%, Grade 4: 0.3%). The median time to onset of any grade pneumonitis/ILD was 2.7 months (range: 0.6 to 6.0 months).
In clinical studies of PADCEV in combination with pembrolizumab, pneumonitis/ILD of any grade 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%). Two patients (0.4%) experienced a fatal event of pneumonitis/ILD. The median time to onset of any grade pneumonitis/ILD was 4.0 months (range 0.3 to 26.2 months).

Peripheral Neuropathy

In clinical studies of PADCEV as monotherapy, peripheral neuropathy occurred in 422 (53.2%) of the 793 patients treated with PADCEV 1.25 mg/kg. Severe (Grade 3 or 4) peripheral neuropathy including sensory and motor events occurred in 41 patients (Grade 3: 5.0%, Grade 4: 0.1%). 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.

In clinical studies of PADCEV in combination with pembrolizumab, peripheral neuropathy occurred in 376 (66.7%) of the 564 patients. Severe (Grade 3) peripheral neuropathy including sensory and motor events occurred in 38 patients (Grade 3: 6.7%). The median time to onset of Grade ≥ 2 peripheral neuropathy was 5.8 months (range: 0.3 to 25.3). Patients with pre-existing peripheral neuropathy Grade ≥ 2 were excluded from clinical studies.

Ocular Disorders

In clinical studies of PADCEV as monotherapy, 30.1% (239) of patients experienced dry eye disorders and 9.7% (77) of patients experienced blurred vision during treatment with PADCEV 1.25 mg/kg. Treatment was interrupted in 1.5% of patients and 0.1% of patients permanently discontinued treatment due to dry eye disorders. The median time to onset of dry eye disorders was 1.7 months (range: 0 to 30.6 months).

Infusion Site Extravasation

Of the 793 patients, 2% of patients experienced skin and soft tissue reactions, including 0.3% who experienced Grade 3-4 reactions. Reactions may be delayed. Erythema, swelling, increased temperature, and pain worsened until 2-7 days after extravasation and resolved within 1-4 weeks of peak. Two patients (0.3%) developed extravasation reactions with secondary cellulitis, bullae, or exfoliation.

Elderly Patients

Of the 793 patients treated with PADCEV 1.25 mg/kg in clinical studies, 514 (65%) were 65 years or older and 204 (26%) were 75 years or older. Based on the data from all patients treated with PADCEV 1.25 mg/kg in the clinical studies, the toxicity in older patients (≥ 65 years) was higher compared to younger patients (< 65 years, N = 279): serious adverse events 242 (47%) vs 121 (43%), adverse events leading to death 42 (8%) vs 14 (5%) and adverse events of grade ≥ 3 376 (73%) vs 188 (67%).

Severe Renal Impairment

Of the 793 patients treated with PADCEV 1.25 mg/kg in clinical studies, 276 (35%) had mild renal impairment, 365 (46%) had moderate renal impairment and 24 (3%) had severe renal impairment. Based on the data from all patients treated with PADCEV 1.25 mg/kg in the clinical studies, 21/24 (88%) patients with severe renal impairment experienced grade ≥ 3 adverse events.

Immunogenicity

The observed incidence of anti-drug antibody (ADA) is highly dependent on the sensitivity and specificity of the assay. Differences in assay methods preclude meaningful comparisons of the incidence of ADA in the studies described below with the incidence of ADA in other studies, including those of PADCEV or of other enfortumab vedotin products.
A total of 697 patients were tested for immunogenicity to PADCEV 1.25 mg/kg as monotherapy; 16 patients were confirmed to be positive at baseline for anti-therapeutic antibody (ATA), 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 PADCEV following PADCEV in combination with pembrolizumab; 24 patients were confirmed to be positive at baseline for ATA, and in patients that were negative at baseline (N = 466), a total of 14 (3.0%) were positive post baseline. The incidence of treatment-emergent anti-enfortumab vedotin antibody formation was consistent when assessed following PADCEV 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, pharmacodynamics, or pharmacokinetics.
Reporting suspected adverse reactions after authorisation of the medicinal product is very important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions online via the ElViS portal (Electronic Vigilance System). You can obtain information about this at www.swissmedic.ch.

Overdose

No cases of overdose have been reported. 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).

Properties/Effects

Enfortumab vedotin is a Nectin-4 targeted antibody-drug conjugate (ADC) comprised of a fully human IgG1 kappa antibody, conjugated to the microtubule-disrupting agent MMAE via a protease-cleavable vc maleimidocaproyl linker.

The clinical pharmacology of enfortumab vedotin was evaluated in patients with solid tumours who received enfortumab vedotin administered by intravenous infusion.

ATC code

L01FX13

Mechanism of action

Enfortumab vedotin is an ADC targeting Nectin-4, an adhesion protein located on the surface of the urothelial cancer cells. It is comprised of a fully human IgG1-kappa antibody conjugated to the microtubule-disrupting agent MMAE via a protease-cleavable linker. Nonclinical data suggest that the anticancer activity of enfortumab vedotin is due to the binding of the ADC to Nectin-4-expressing cells, followed by internalization of the ADC-Nectin-4 complex, and the release of MMAE via proteolytic cleavage. Release of MMAE disrupts the microtubule network within the cell, subsequently inducing cell cycle arrest and apoptosis, and immunogenic cell death. The combination of enfortumab vedotin with a PD-1 blocking antibody resulted in up-regulation of immune function and increased anti-tumor activity in syngeneic mouse tumor models expressing Nectin.

Pharmacodynamics

In an exposure-response analysis for safety, a higher exposure was associated with higher incidence of some adverse reactions (e.g., Grade ≥ 2 peripheral neuropathy, Grade ≥ 3 hyperglycaemia). The exposure-response relationship for efficacy has not been fully characterized.

Cardiac Electrophysiology

At the recommended dose of 1.25 mg/kg, enfortumab vedotin had no large effect on QTc prolongation (> 20 msec).

Clinical efficacy

Enfortumab vedotin in combination with pembrolizumab

Previously untreated unresectable or metastatic urothelial cancer

EV-302

The efficacy of PADCEV in combination with pembrolizumab was evaluated in study EV-302, an open-label, randomised, phase 3, multicentre study that enrolled 886 patients with unresectable or metastatic urothelial cancer who received no prior systemic therapy for locally advanced or metastatic disease.

Patients were randomised 1:1 to receive either enfortumab vedotin in combination with pembrolizumab or gemcitabine and platinum-based chemotherapy (cisplatin or carboplatin). Patients in arm A received enfortumab vedotin 1.25 mg/kg as an intravenous infusion over 30 minutes on Days 1 and 8 of a 21-day cycle followed by pembrolizumab 200 mg on Day 1 of a 21-day cycle approximately 30 minutes after enfortumab vedotin. Therapy should be continued until progression or unacceptable toxicity, with pembrolizumab being administered for a maximum duration of 2 years (35 cycles). Patients in arm B received a maximum of 6 cycles of gemcitabine 1000 mg/m^2 administered on Days 1 and 8 of a 21-day cycle with cisplatin 70 mg/m^2 or carboplatin (AUC = 4.5 or 5 mg/mL/min according to local guidelines) administered on Day 1 of a 21-day cycle. Randomisation was stratified by cisplatin eligibility, PD-L1 expression, and presence of liver metastases.

Patients were excluded from the study if they had active CNS metastases, ongoing sensory or motor neuropathy Grade ≥2, or uncontrolled diabetes defined as haemoglobin A1C (HbA1c) ≥8% or HbA1c ≥7% with associated diabetes symptoms.

The median age was 69 years (range: 22 to 91); 77% were male; and most were White (67%) or Asian (22%). Patients had a baseline Eastern Cooperative Oncology Group (ECOG) performance status of 0 (49%), 1 (47%) or 2 (3%). Forty-seven percent of patients had a documented baseline HbA1c of <5.7%. At baseline, 95% of patients had metastatic urothelial cancer and 5% of patients had unresectable locally advanced urothelial cancer. Seventy-two percent of patients had visceral metastasis at baseline including 22% with liver metastases. Eighty-five percent of patients had urothelial carcinoma (UC) histology, 6% had UC mixed squamous differentiation and 2% had UC mixed other histologic variants. Forty-six percent of patients were cisplatin-ineligible and 54% were

cisplatin-eligible at time of randomisation. The median follow-up time for this study was 17.2 months (range: 0.1 to 37.2).

At the time of the primary analysis, 33% of patients in the enfortumab vedotin in combination with pembrolizumab arm and no patients in the gemcitabine and platinum-based chemotherapy arm remained on treatment. Thirty-two percent of patients in the enfortumab vedotin in combination with pembrolizumab arm received subsequent therapy; 25% of patients received gemcitabine and platinum-based chemotherapy as first subsequent therapy. Seventy-one percent of patients in the gemcitabine and platinum-based chemotherapy arm received subsequent therapy; 59% of patients received a PD-1 or PD-L1 inhibitor, including 30% of patients who received avelumab maintenance therapy, and 26% of patients who received a PD-1 or PD-L1 inhibitor post-progression as first subsequent therapy; 13% of patients received enfortumab vedotin monotherapy as subsequent therapy.

Patients randomised to the enfortumab vedotin in combination with pembrolizumab arm had a significant improvement in OS compared to the gemcitabine and platinum-based chemotherapy arm with a median OS of 31.5 months (95% CI: 25.4, not estimable) versus 16.1 months (95% CI: 13.9, 18.3), respectively (HR 0.47; 95% CI: 0.38, 0.58; 2-sided p-value: <0.00001). Patients randomised to receive enfortumab vedotin in combination with pembrolizumab arm experienced longer PFS compared to those randomised to receive gemcitabine and platinum-based chemotherapy with a median PFS of 12.5 months (95% CI: 10.4, 16.6; 2-sided p-value: <0.00001) versus 6.3 months (95% CI: 6.2, 6.5), respectively (HR 0.450; 95% CI: 0.38, 0.54). Among the 437 patients randomised who received enfortumab vedotin in combination with pembrolizumab with measurable disease at baseline, the confirmed ORR was 67.7% (95% CI: 63.1, 72.1) compared with gemcitabine and platinum-based chemotherapy with a confirmed ORR of 44.4% (95% CI: 39.7, 49.2). Efficacy results were consistent across all stratified patient subgroups.

Enfortumab vedotin as monotherapy

Previously treated locally advanced or metastatic urothelial cancer

EV-301

The efficacy of enfortumab vedotin as monotherapy was evaluated in study EV-301, an open-label, randomized, phase 3, multicenter study that enrolled 608 patients with locally advanced or metastatic urothelial cancer who received prior treatment with a platinum containing chemotherapy and who have progressed or relapsed during or after prior treatment with a PD-1 or PD-L1 inhibitor. If platinum was administered in the adjuvant/neoadjuvant setting, the patient must have progressed within 12 months of completion. One hundred and eighty-three patients received

cisplatin and 130 received carboplatin as initial systemic therapy for the treatment of metastatic or locally advanced urothelial carcinoma followed by CPI therapy. One hundred and fifty-eight received a platinum-containing chemotherapy for UC in the (neo-) adjuvant setting followed by disease progression/relapse within 12 months and were subsequently treated with CPI. The requirement for creatinine clearance was ≥ 30 mL/min for patients to enter the study.

Patients were randomized 1:1 to receive either PADCEV 1.25 mg/kg on Days 1, 8 and 15 of a 28-day cycle or one of the following chemotherapies as decided by the investigator: docetaxel (38%), paclitaxel (36%), or vinflunine (25%).

Patients were excluded from the study if they had:

- active CNS metastases, ongoing sensory or motor neuropathy ≥ Grade 2, or uncontrolled diabetes defined as haemoglobin A1C (HbA1c) ≥ 8% or HbA1c ≥ 7% with associated diabetes symptoms.
- received more than 1 prior chemotherapy regimen for mUC (the substitution of carboplatin for cisplatin does not constitute a new regimen).
- cerebral vascular event, unstable angina, myocardial infarction, or cardiac symptoms consistent with New York Heart Association Class III-IV.
- active keratitis or corneal ulcerations.

The median age was 68 years (range: 30 to 88 years), 77% were male, and most patients were White (52%) or Asian (33%). All patients had a baseline ECOG performance status of 0 (40%) or 1 (60%). Eighty percent of patients had visceral metastases including 31% with liver metastases. Seventy-six percent of patients had urothelial carcinoma/transitional cell carcinoma (TCC) histology and 14% had urothelial carcinoma mixed. A total of 13% of patients received ≥ 3 lines of prior systemic therapy. Fifty-two percent of patients received prior PD-1 inhibitor, 47% received prior PD-L1 inhibitor, and an additional 1% received both PD-1 and PD-L1 inhibitors. Sixty-nine percent of patients did not respond to prior therapy with a PD-1 or PD-L1 inhibitor. All patients had received prior platinum-based chemotherapy: sixty-three percent received prior cisplatin-based regimens, 26% received prior carboplatin-based regimens, and an additional 11% received both cisplatin and carboplatin-based regimens.

The study demonstrated statistically significant improvements in the primary endpoint OS, and the secondary endpoints PFS and ORR for patients randomized to PADCEV as compared to chemotherapy. Formal statistical hypothesis tests on the selected secondary endpoints were performed hierarchically per the order of PFS followed by ORR only when the OS testing result was rejected. The median follow-up time for this study was 11.1 months (95% CI: 10.6 to 11.6). Patients randomized to the PADCEV arm had a statistically significant improvement in OS

compared to the chemotherapy arm with a median OS of 12.9 months versus 9 months, respectively (HR 0.702; 95% CI: 0.556, 0.886; 1-sided p-value: 0.00142). Patients randomized to receive PADCEV experienced longer PFS compared to those randomized to receive chemotherapy with a median PFS of 5.6 months versus 3.7 months, respectively (HR 0.615; 95% CI: 0.505, 0.748) and ORR was 40.6% versus 17.9%. The OS hazard ratio (95% CI) was 1.171 (0.724, 1,894) in female subgroup (n = 63/301). Median PFS in female population was 5.39 months for enfortumab vedotin versus 3.84 months for chemotherapy arm and Hazard Ratio (95% CI) was 0.997 (0.667, 1.490). ORR in females was 45% in enfortumab vedotin arm versus 22% in chemotherapy arm.

Pharmacokinetics

Enfortumab vedotin pharmacokinetics were characterized after single and multiple doses in patients with locally advanced or metastatic urothelial carcinoma and other solid tumors in the course of a population pharmacokinetic analysis. This analysis included data of 748 patients treated with enfortumab vedotin as monotherapy from five studies.

The pharmacokinetics of ADC and unconjugated MMAE were consistent when assessed following enfortumab vedotin as monotherapy and in combination with pembrolizumab in Cycle 1.

The exposure parameters of ADC and unconjugated MMAE (the cytotoxic component of enfortumab vedotin) are summarised in Table 4 below. Peak ADC concentrations were observed near the end of intravenous infusion while peak unconjugated MMAE concentrations were observed approximately 2 days after enfortumab vedotin dosing. Minimal accumulation of the ADC and unconjugated MMAE was observed following repeat administration of enfortumab vedotin. Steady-state concentrations of ADC concentrations were reached after 1 treatment cycle for enfortumab vedotin as monotherapy and in combination with pembrolizumab.

Table 4: Exposure parameters of ADC and unconjugated MMAE after first treatment cycle of 1.25 mg/kg of enfortumab vedotin dose of Days 1, 8 and 15

	ADC Mean (± SD)	**Unconjugated MMAE Mean (± SD)**
C_{max}	28 (6.1) µg/mL	5.5 (3.0) ng/mL
$AUC_{0\text{-}28d}$	110 (26) µg·d/mL	85 (50) ng·d/mL
$C_{trough,0\text{-}28d}$	0.31 (0.18) µg/mL	0.81 (0.88) ng/mL

C_{max} = maximum concentration, $AUC_{0\text{-}28d}$ = area under the concentration-time curve from time zero to 28 days, $C_{trough,0\text{-}28d}$ = pre-dose concentration on day 28.

Distribution

The mean estimate of steady-state volume of distribution of ADC was 12.8 L following 1.25 mg/kg of enfortumab vedotin.

In vitro, the binding of unconjugated MMAE to human plasma proteins ranged from 68% to 82%. Unconjugated MMAE is not likely to displace or to be displaced by highly protein-bound drugs. *In vitro* studies indicate that unconjugated MMAE is a substrate of P-glycoprotein.

Metabolism

The metabolism of enfortumab vedotin has not been studied in clinical studies. However, it can be assumed that enfortumab vedotin is broken down into small peptides, amino acids, free MMAE and its metabolites. Unconjugated MMAE is released from enfortumab vedotin through proteolysis and based on *in vitro* data metabolism of unconjugated MMAE occurs primarily via oxidation by CYP3A4.

Elimination

The mean clearance (CL) of ADC and unconjugated MMAE in patients was 0.11 L/h and 2.11 L/h, respectively. ADC elimination exhibited a multi-exponential decline with a half-life of 3.6 days. Elimination of unconjugated MMAE appeared to be limited by its rate of release from enfortumab vedotin. Unconjugated MMAE elimination exhibited a multi-exponential decline with a half-life of 2.6 days.

Hepatic impairment

Based on population pharmacokinetics analysis using data from clinical studies in patients with metastatic UC, there was no significant differences in ADC exposure and a 37% and 16% increase in unconjugated MMAE average concentrations in patients with previously treated and previously untreated locally advanced or mUC, respectively, with mild hepatic impairment (total bilirubin 1 to 1.5 × ULN and AST of any level, or total bilirubin ≤ ULN and AST > ULN, n= 65) compared to patients with normal hepatic function. Enfortumab vedotin has only been studied in a limited number of patients with moderate hepatic impairment (n = 3) , and has not been evaluated in patients with severe hepatic impairment (total bilirubin > 1.5 x ULN and AST of any level). A clinical study was conducted with another ADC that contains MMAE to evaluate the PK of brentuximab vedotin and MMAE after the administration of 1.2 mg/kg dose to patients with mild (Child-Pugh A; n = 1), moderate (Child-Pugh B; n = 5) and severe (Child-Pugh C; n = 1) hepatic impairment. Compared to patients with normal hepatic function, MMAE exposure increased approximately 1.77 to 3.51-fold in patients with mild to moderate hepatic impairment. A higher exposition of MMAE

was associated with a higher toxicity. Similarly, administration of PADCEV to patients with moderate or severe hepatic impairment may result in higher MMAE exposure and higher toxicity.

Renal impairment

The pharmacokinetics of ADC and unconjugated MMAE were evaluated after the administration of 1.25 mg/kg of enfortumab vedotin to patients with mild (creatinine clearance; CrCL > 60-90 mL/min; n = 272), moderate (CrCL 30–60 mL/min; n = 315) and severe (CrCL 15-<30 mL/min; n = 25) renal impairment. No relevant differences in AUC exposure of ADC or unconjugated MMAE were observed in patients with mild, moderate or severe renal impairment compared to patients with normal renal function. Enfortumab vedotin has not been evaluated in patients with end stage renal disease (CrCL < 15 mL/min). Data on exposure in patients with end-stage renal impairment are too limited to allow a statement to be made regarding exposure in this patient group.

Elderly patients

Population pharmacokinetic analysis indicates that age [range: 24 to 90 years; 60% (450/748) > 65 years, 19% (143/748) > 75 years] does not have a clinically meaningful effect on the pharmacokinetics of enfortumab vedotin.

Children and adolescents

The pharmacokinetics of enfortumab vedotin in paediatric patients has not been evaluated.

Ethnicity

Based on population pharmacokinetic analysis, race [69% (519/748) White, 21% (158/748) Asian, 1% (10/748) Black and 8% (61/748) others or unknown] and gender [73% (544/748) male] do not have a clinically meaningful effect on the pharmacokinetics of enfortumab vedotin. Body weight is a significant covariate on the pharmacokinetics of enfortumab vedotin and MMAE. Weight-based dosing (recommended dose of 1.25 mg/kg [up to a maximum of 125 mg for patients ≥ 100 kg]) should maintain similar exposure across all patients.

Preclinical data

Long-term toxicity (or repeat dose toxicity)

Skin lesions were noted in conventional repeat dose animal studies in rats (≥ 5 mg/kg; 2-fold the human systemic exposure) and in cynomolgus monkeys (≥ 1 mg/kg; 0.7-fold the human systemic exposure). The skin changes were fully reversible at the end of a 6-week recovery period.

Hyperglycaemia and histopathological findings in the pancreas were not observed in animal studies on rats and cynomolgus monkeys.

Genotoxicity

No mutagenic potential of MMAE was detected in the reverse mutation assay on bacteria (Ames test) or L5178Y TK+/- mouse lymphoma assay. MMAE did induce chromosomal aberrations in the *in vivo* micronucleus test in rats which is consistent with the pharmacological action of microtubule-disrupting agents.

Carcinogenicity

Carcinogenicity studies with enfortumab vedotin or the small molecule cytotoxic agent (MMAE) have not been conducted.

Reproductive toxicity

Fertility studies with enfortumab vedotin or MMAE have not been conducted.

However, results of repeat-dose toxicity studies in rats indicate the potential for enfortumab vedotin to impair male reproductive function and fertility. In repeat-dose toxicology studies conducted in rats for up to 13 weeks, doses ≥ 2 mg/kg enfortumab vedotin (at exposures similar to the exposures at the recommended human dose) resulted in decreases in testes and epididymis weights, seminiferous tubule degeneration, spermatid/spermatocyte depletion in the testes and cell debris, sperm granuloma and hypospermia/abnormal spermatids in the epididymis. Findings in the testes and epididymis were partially reversible by the end of the recovery period.
Intravenous administration of MMAE (0.2 mg/kg; C_{max} 1.1-fold the human C_{max} at the recommended clinical dose) on Gestation Day 6 and 13 resulted in embryo-foetal lethality and foetal external malformations (protruding tongue, malrotated hindlimbs, gastroschisis, and agnathia).
A dose of 2 mg/kg (approximately similar to the exposure at the recommended human dose) resulted in maternal toxicity, embryo-fetal lethality and structural malformations that included gastroschisis, malrotated hindlimb, absent forepaw, malpositioned internal organs and fused cervical arch. Additionally, skeletal anomalies (asymmetric, fused, incompletely ossified, and misshapen sternebrae, misshapen cervical arch, and unilateral ossification of the thoracic centra) and decreased fetal weight were observed.
No dedicated preclinical safety studies were conducted with enfortumab vedotin in combination with pembrolizumab.

Other information

Incompatibilities

Do not co-administer other drugs through the same infusion line.

Shelf life

36 months, lyophilized, unopened, clear glass vial.

Shelf life after opening

Reconstituted vial: 24 hours in refrigeration at 2°C to 8°C. DO NOT FREEZE.
Reconstituted bag: 16 hours under refrigeration at 2°C to 8°C including infusion time. DO NOT FREEZE.

Special precautions for storage

Store and transport at 2ºC to 8ºC, refrigerated and protected from light. DO NOT FREEZE.
Store in the original packaging.
Keep out of the reach of children.

Instructions for handling

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

Prior to administration, the PADCEV vial is reconstituted with Sterile Water for Injection (SWFI). The reconstituted solution is subsequently diluted in an intravenous infusion bag containing either sterile 5% Dextrose injection, sterile 0.9% Sodium Chloride injection or sterile Lactated Ringer's injection.

Instructions for preparation and administration

<u>Reconstitution in single-dose vial</u>

1. Follow procedures for proper handling and disposal of anticancer drugs.
2. Use appropriate aseptic technique for reconstitution and preparation of dosing solutions.
3. Calculate the recommended dose based on the patient's weight to determine the number and strength (20 mg or 30 mg) of vials needed.
4. Reconstitute each vial as follows and, if possible, direct the stream of SWFI along the walls of the vial and not directly onto the lyophilized powder:
   a. 20 mg vial: Add 2.3 mL of SWFI, resulting in 10 mg/mL PADCEV.
   b. 30 mg vial: Add 3.3 mL of SWFI, resulting in 10 mg/mL PADCEV.

5. Slowly swirl each vial until the contents are completely dissolved. Allow the reconstituted vial(s) to settle for at least 1 minute until the bubbles are gone. DO NOT SHAKE THE VIAL. Do not expose to direct sunlight.
6. Visually inspect the solution for particulate matter and discolouration. The reconstituted solution should be clear to slightly opalescent, colourless to light yellow and free of visible particles. Discard any vial with visible particles or discolouration.
7. Based upon the calculated dose amount, the reconstituted solution from the vial(s) should be added to the infusion bag immediately. This product does not contain a preservative. If not used immediately, reconstituted vials may be stored for up to 24 hours in refrigeration at 2°C to 8°C. DO NOT FREEZE. Discard unused vials with reconstituted solution beyond the recommended storage time.

Dilution in infusion bag

8. Withdraw the calculated dose amount of reconstituted solution from the vial(s) and transfer into an infusion bag.
9. Dilute PADCEV with either 5% Dextrose Injection or 0.9% Sodium Chloride Injection or Lactated Ringer's Injection. The infusion bag size should allow enough diluent to achieve a final concentration of 0.3 mg/mL to 4 mg/mL PADCEV.
10. Mix diluted solution by gentle inversion. DO NOT SHAKE THE BAG. Do not expose to direct sunlight.
11. Visually inspect the infusion bag for any particulate matter or discolouration prior to use. The reconstituted solution should be clear to slightly opalescent, colourless to light yellow and free of visible particles. DO NOT USE the infusion bag if particulate matter or discolouration is observed.
12. Discard any unused portion left in the single-dose vials.
13. The prepared infusion bag should not be stored longer than 16 hours under refrigeration at 2°C to 8°C including infusion time. DO NOT FREEZE.

Authorisation number

68291 (Swissmedic)

Packs

20 mg vial, 20 mm aluminium seal with a green ring and green cap [A].
30 mg vial, 20 mm aluminium seal with a silver ring and yellow cap [A].

Marketing authorisation holder

Astellas Pharma AG, 8304 Wallisellen

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