Date: 12 January 2022
Swissmedic, Swiss Agency for Therapeutic Products

Swiss Public Assessment Report

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:
Marketing Authorisation Holder: Astellas Pharma AG
Marketing Authorisation No.: 68291
Decision and Decision date: approved on 09.11.2021

Note:

Assessment Report as adopted by Swissmedic with all information of a commercially confidential nature deleted.

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About Swissmedic

Swissmedic is the Swiss authority responsible for the authorisation and supervision of therapeutic products. Swissmedic's activities are based on the Federal Act of 15 December 2000 (Status as of 1 January 2020) on Medicinal Products and Medical Devices (TPA, SR 812.21). The agency ensures that only high-quality, safe and effective drugs are available in Switzerland, thus making an important contribution to the protection of human health.

About the Swiss Public Assessment Report (SwissPAR)

- The SwissPAR is referred to in Article 67 para. 1 of the Therapeutic Products Act and the implementing provisions of Art. 68 para. 1 let. e of the Ordinance of 21 September 2018 on Therapeutic Products (TPO, SR 812.212.21).
- The SwissPAR provides information about the evaluation of a prescription medicine and the considerations that led Swissmedic to approve or not approve a prescription medicine submission. The report focuses on the transparent presentation of the benefit-risk profile of the medicinal product.
- A SwissPAR is produced for all human medicinal products with a new active substance and transplant products for which a decision to approve or reject an authorisation application has been issued.
- A supplementary report will be published for approved or rejected applications for an additional indication for a human medicinal product for which a SwissPAR has been published following the initial authorisation.
- The SwissPAR is written by Swissmedic and is published on the Swissmedic website. Information from the application documentation is not published if publication would disclose commercial or manufacturing secrets.
- The SwissPAR is a “final” document, which provides information relating to a submission at a particular point in time and will not be updated after publication.
- In addition to the actual SwissPAR, a concise version of SwissPAR that is more comprehensible to lay persons (Public Summary SwissPAR) is also published.

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1 Terms, Definitions, Abbreviations

ADA	Anti-drug antibody
ADC	Antibody-drug conjugate
ADME	Absorption, Distribution, Metabolism, Elimination
AE	Adverse event
ALT	Alanine aminotransferase
API	Active pharmaceutical ingredient
AST	Aspartate transaminase
ATC	Anatomical Therapeutic Chemical Classification System
AUC	Area under the plasma concentration-time curve
AUC0-24h	Area under the plasma concentration-time curve for the 24-hour dosing interval
BCRP	Breast cancer resistance protein
CI95%	Confidence interval 95%
Cmax	Maximum observed plasma/serum concentration of drug
CPI	Checkpoint inhibitor
CrCl	Creatinine clearance
CYP	Cytochrome P450
DCR	Disease control rate
DCO	Data cut-off
ECOG	Eastern Cooperative Oncology Group
ERA	Environmental Risk Assessment
EV	Enfortumab vedotin
GLP	Good Laboratory Practice
HBV	Hepatitis B virus
HCV	Hepatitis C virus
HR	Hazard ratio
ICH	International Council for Harmonisation
Ig	Immunoglobulin
INN	International Nonproprietary Name
ITT	Intent-to-treat
LoQ	List of Questions
mAB	Monoclonal Antibody
MAH	Marketing Authorisation Holder
Max	Maximum
MHRA	Medicines and Healthcare products Regulatory Agency, United Kingdom
Min	Minimum
MMAE	Monomethyl auristatin E
MRP2	Multidrug resistance-associated protein 2
mUC	Metastatic urothelial carcinoma
N/A	Not applicable
NO(A)EL	No Observed (Adverse) Effect Level
NYHA	New York Heart Association
OATP1B1/3	Organic anion-transporting polypeptides 1B1/3
OAT1/3	Organic anion transporter 1/3
OCT2	Organic cation transporter 2
ORR	Overall response rate
PD	Pharmacodynamics
PD-1	Programmed cell death receptor-1
PD-L1	Programmed cell death-ligand 1
PFS	Progression-free survival
PIP	Paediatric Investigation Plan (EMA)
PK	Pharmacokinetics
PMDA	Pharmaceuticals and Medical Devices Agency, Japan

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PopPK	Population PK
PSP	Pediatric Study Plan (US-FDA)
RMP	Risk Management Plan
SwissPAR	Swiss Public Assessment Report
TEAE	Treatment emergent adverse event
TPA	Federal Act of 15 December 2000 (Status as of 1 January 2020) on Medicinal Products and Medical Devices (SR 812.21)
TPO	Ordinance of 21 September 2018 (Status as of 1 April 2020) on Therapeutic Products (SR 812.212.21)
UC	Urothelial carcinoma
ULN	Upper limit of normal
vcMMAE	MMAE with a protease-cleavable linker

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2 Background Information on the Procedure

2.1 Applicant's Request(s)

New Active Substance status
The applicant requested the status of a new active entity for the active substance enfortumab vedotin of the medicinal product mentioned above.

Fast-track authorisation procedure (FTP)
The applicant requested a fast-track authorisation procedure in accordance with Article 7 of the TPO.

2.2 Indication and Dosage

2.2.1 Requested Indication

Padcev is indicated for treatment of adult patients with locally advanced or metastatic urothelial cancer who have previously received a programmed cell death receptor-1 (PD-1) or programmed cell death-ligand 1 (PD-L1) inhibitor, and who

- have received a platinum-containing chemotherapy in the neoadjuvant/adjuvant, locally advanced or metastatic setting, or
- are not eligible for cisplatin-containing chemotherapy.

2.2.2 Approved Indication

Padcev 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*").

2.2.3 Requested Dosage

1.25 mg/kg body weight (up to max. 125 mg for patients ≥ 100 kg body weight) as an intravenous infusion over 30 minutes on days 1, 8 and 15 of each 28-day cycle. Treatment is continued until disease progression or inacceptable toxicity.

2.2.4 Approved Dosage

(see appendix)

2.3 Regulatory History (Milestones)

Application	9 March 2021
Formal control completed	11 March 2021
List of Questions (LoQ)	12 May 2021
Answers to LoQ	8 August 2021
Predecision	23 September 2021
Answers to Predecision	21 October 2021
Final Decision	9 November 2021
Decision	approval

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3 Medical Context

Urothelial carcinoma (UC) is the ninth most common malignancy worldwide. Bladder tumours account for 90–95% of UCs and are the most common urinary tract malignancy.[1]

Systemic chemotherapy is recommended for first-line treatment of patients with inoperable locally advanced or metastatic urothelial carcinoma (mUC). The median overall survival with multi-agent chemotherapy is approximately 15 months (von der Maase et al., 2000 and 2005). A cisplatin-based combination chemotherapy regimen is the preferred initial therapy for patients with metastatic urothelial cancer of the bladder and urinary tract who are cisplatin-eligible.[2]

For patients who develop disease progression after prior platinum-based chemotherapy, PD-1 and PD-L1 inhibitors (checkpoint inhibitors (CPIs)) are an approved treatment option in Switzerland. However, disease progression after or during CPI therapy is common. No therapies are approved in Switzerland for this setting.

Enfortumab vedotin (EV) targets the cell surface protein Nectin-4, which is expressed in around 97% of all urothelial carcinoma histology samples.

4 Quality Aspects

4.1 Drug Substance

Enfortumab vedotin (AGS-22C3E) is an antibody-drug conjugate (ADC) composed of an anti-mitotic agent monomethyl auristatin E (MMAE) covalently conjugated to a fully human IgG1κ monoclonal antibody directed against Nectin-4. Enfortumab vedotin induces cytotoxicity in cancer cells by binding the Nectin-4 target on the cell surface and forming an ADC-Nectin-4 complex.
The intermediate drug substance, the antibody enfortumab, consists of two identical light chain (LC) polypeptides and two identical heavy chain (HC) polypeptides. Both HCs contain one oligosaccharide chain in the conserved Fc site (Asn297). The monoclonal antibody (mAb) is produced from a mammalian cell line (Chinese Hamster Ovary) using a fed-batch production process in a production bioreactor. The cell culture fluid is harvested and the antibody is purified by several chromatographic and filtration steps, including virus inactivation and virus removal steps. The other drug substance intermediate vedotin, also known as vcMMAE, is a synthetic small molecule and is manufactured by a six-step peptide synthesis process. It consists of MMAE and a protease-cleavable linker (vc). Satisfactory and consistent quality of vcMMAE, according to defined specifications was demonstrated.
The AGS-22C3E drug substance manufacturing process itself is performed by Lonza AG, Visp, Switzerland, and consists of reduction of the mAb, followed by introduction of vedotin for conjugation to reduced cysteine residues at the sites of the inter-chain disulfide bonds between LC and HC or between HCs. The target number of drug-linkers conjugated to each antibody molecule (drug-to-antibody ratio) is four. Impurities are removed by diafiltration and, finally, AGS-22C3E drug substance is concentrated by ultrafiltration.
The determination of the physicochemical and biological properties of the antibody-drug conjugate and its impurities were performed using state of the art methods.
The specifications for release include relevant tests and limits, e.g. for appearance, identity, pH, several purity tests (e.g. SE-HPLC, HIC, icIEF), protein concentration, and a potency assay. Specifications are based on clinical batch experience, batch analysis data (release and stability data) and are in conformance with current compendial or regulatory guidelines.

[1] Roupret et al. European Association of Urology Guidelines on Upper Urinary Tract Urothelial Carcinoma: 2020 Update. Eur Urol. 2021 Jan;79(1):62-79.
[2] Bellmunt et al., Treatment of metastatic urothelial cancer of the bladder and urinary tract, UpToDate, March 2021

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Batch analysis data from non-clinical batches, clinical batches, process performance qualification batches and commercial batches were provided. All specific analytical methods are described and were fully validated.
The drug substance is stored at ≤-60°C. No changes were observed within the proposed storage conditions. A shelf-life of 60 months has been accepted.

4.2 Drug Product

The finished product Padcev is available as 20 mg or 30 mg of lyophilised product in a 10 mL vial. It is intended for intravenous infusion after reconstitution with sterile water for injection and dilution in sodium chloride solution, dextrose solution or lactated Ringer's solution. The reconstituted enfortumab vedotin is formulated in a histidine buffer solution, pH 6.0, containing trehalose and polysorbate 20. All excipients comply with the European Pharmacopoeia.
The finished product manufacturing process consists of thawing, pooling and mixing, sterile filtration, aseptic filling, lyophilisation, capping and inspection steps, and is conducted at Baxter Oncology GmbH, Halle/Westfalen, Germany. Process validation studies were executed at commercial scale using three validation batches, each with 20 mg and 30 mg strengths.
The specifications include relevant tests and limits, e.g. for appearance, identity, pH, water content, potency by cytotoxicity and drug-to-antibody ratio, osmolality, purity and impurity tests (SE-UHPLC, icIEF, RP-HPLC, HIC-HPLC), protein concentration, particles, sterility and bacterial endotoxins. All non-compendial methods are validated in accordance with ICH guidelines.
Batch analysis data from several batches, each with 20 mg and 30 mg strengths, including development batches, clinical batches, process performance qualification batches, and commercial batches were provided. All batch release data comply with the drug product specifications, which were valid at the time of batch release.
The drug product is stored at 2-8°C, protected from light. Due to its pharmaceutical form (lyophilisate), the product is quite stable. A shelf-life of 36 months has been accepted.

4.3 Quality Conclusions

The manufacturing processes (drug substance and drug product) are well described and demonstrate a consistent quality of drug substance and drug product. The shelf-life of drug substance and drug product is supported by data from studies with recommended storage conditions, as well as accelerated and stress studies. Safety concerns with regard to viral and non-viral contaminants were satisfactorily addressed.

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5 Nonclinical Aspects

Regarding the marketing authorisation application for Padcev (enfortumab vedotin), the Division Nonclinical Assessment conducted an abridged evaluation, which was based on the FDA assessment report (BLA 761137, dated 18 December 2019) provided by the applicant.

Overall, the submitted nonclinical documentation is considered appropriate to support the approval of Padcev in the proposed indication. The pharmaco-toxicological profile has been sufficiently characterised, and all nonclinical data that are relevant for safety are adequately mentioned in the information for healthcare professionals and in the RMP.

There is no safety concern regarding impurities and excipients.

According to the ERA, the risk of enfortumab vedotin to the environment is assumed to be low.

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6 Clinical and Clinical Pharmacology Aspects

6.1 Clinical Pharmacology

Enfortumab vedotin is an antibody-drug conjugate consisting of a human IgG1K monoclonal antibody conjugated to the microtubule-disrupting agent monomethyl auristatin E (MMAE).

ADME

Absorption

Enfortumab vedotin is administered by i.v. infusion over 30 min. Maximum concentrations of enfortumab vedotin and free MMAE were reached at the end of infusion and after ~2 days, respectively.

Upon administration of multiple doses (at 1.25 mg/kg), accumulation of enfortumab vedotin was limited (1.1 - 1.3-fold), while MMAE accumulated moderately (1.0 - 2.3-fold).

Enfortumab vedotin and MMAE exhibited dose proportional pharmacokinetics in patients with mUC at doses ranging from 0.5 mg/kg to 1.25 mg/kg.

Distribution

Based on a PopPK analysis, the mean total volume of distribution of enfortumab vedotin was 12.8 L, following a 1.25 mg/kg dose.

Based on in vitro studies, MMAE protein binding ranged from 67.9% to 82.2%. The apparent volume of distribution of free MMAE was estimated at 183.5 L in the PopPK analysis.

Metabolism and elimination

The metabolism of enfortumab vedotin has not been investigated in clinical studies. The antibody component of enfortumab vedotin is assumed to be degraded by endogenous protein catabolic pathways. Free MMAE is metabolised by CYP3A4, based on in vitro studies, and its metabolism in humans has been characterised in clinical studies conducted with a similar MMAE-containing ADC.

In the PopPK analysis, enfortumab vedotin CL was estimated to be 0.110 L/h, and the elimination half-life was calculated to be 87.2 h (3.6 d).
Free MMAE showed formation-limited elimination with a CL estimated to be 2.11 L/h, and the elimination half-life was calculated to be 61.2 h (2.6 d).

Special Populations / Intrinsic Factors

Impaired renal function

The effect of renal impairment on the PK of enfortumab vedotin and MMAE was assessed in patients with mild, moderate or severe renal impairment. In a PopPK analysis, no significant effect of CrCl was detected based on data from patients with mild (CrCl > 60 to < 90 mL/min; n = 272), moderate (CrCl 30 to < 60 mL/min; n = 315) or severe renal impairment (CrCl < 30 mL/min; n = 25), compared to patients with normal renal function (n=129). Only 1 patient with end stage renal disease (ESRD) was included in the PopPK dataset. Thus, the data in this subpopulation are too limited to allow conclusions to be drawn about the exposure.

Impaired hepatic function

The effect of mild hepatic impairment was assessed in a PopPK analysis, which indicated no significant differences in enfortumab vedotin or free MMAE exposures in patients with mild hepatic impairment (bilirubin of 1 to 1.5 × ULN and AST < ULN, or bilirubin ≤ ULN and AST > ULN, n=65 compared to patients with normal hepatic function (n=669). Data in patients with more severe hepatic impairment were too limited to allow any conclusions to be drawn.

For another MMAE-containing antibody drug conjugate, a study in subjects with hepatic impairment indicated a higher frequency of adverse events (AEs) in subjects with moderate or severe hepatic

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impairment. Due to a comparable exposure of free MMAE following therapeutic doses of enfortumab vedotin, a similar effect is expected, and the use of enfortumab vedotin should be avoided in these subpopulations.

Other demographic factors
Based on a PopPK analysis, body weight, age or gender had no clinically significant influence on the exposure of enfortumab vedotin and free MMAE. No dose adjustments are required based on these demographic factors.

Interactions
No clinical drug-drug interaction studies were conducted with enfortumab vedotin. However, the interaction potential for enfortumab vedotin is considered to be low.
Free MMAE is a substrate of CYP3A4 and P-gp. Consequently, concomitant use of CYP3A4 / P-gp inhibitors or inducers are expected to affect the levels of free MMAE. Concerning the strength of potential interactions, a physiologically based pharmacokinetic (PBPK) model-based approach was applied for the simulation of drug-drug interaction (DDI) effects:

Effects of other drugs on enfortumab vedotin
Based on these simulations, concomitant use of enfortumab vedotin with ketoconazole (a combined P-gp and strong CYP3A inhibitor) is predicted to increase free MMAE C_{max} by 15% and AUC by 38%, with no change in enfortumab vedotin exposure. While there is no limitation on the concomitant use of CYP3A and P-gp inhibitors, close monitoring of patients for signs of toxicity is recommended.

Concomitant use of enfortumab vedotin with rifampicin (a combined P-gp and CYP3A inducer) is predicted to decrease free MMAE C_{max} by 28% and AUC by 53%, with no change in enfortumab vedotin exposure. Concomitant use with CYP3A and P-gp inducers is not restricted.

Effects of enfortumab vedotin on other drugs
The PBPK model-based simulations indicated no interaction effects of free MMAE on the CYP3A4 substrate midazolam or the P-gp substrate digoxin.

In vitro DDI data
CYPs: MMAE is not an inducer of CYP1A2, 2B6 and 3A4/5
MMAE caused little or no inhibition of CYP1A2, 2B6, 2C8, 2C9, 2C19 or 2D6, but exhibited inhibition of CYP3A4/5

Transporter Systems: MMAE is a substrate of P-glycoprotein (P-gp), but not an inhibitor of P-gp.
MMAE is not a substrate or inhibitor of BCRP, MRP2, OATP1B1, OATP1B3, OCT2, OAT1 and OAT3.

Pharmacodynamics
Mechanism of Action and primary Pharmacology
Enfortumab vedotin is an antibody-drug conjugate. The antibody is a human IgG1 directed against Nectin-4, an adhesion protein located on the surface of cells. MMAE is a microtubule-disrupting agent attached to the antibody via a protease-cleavable linker.
Nonclinical data suggest that the anticancer activity of enfortumab vedotin-ejfv is due to the binding of the ADC to Nectin-4-expressing cells, followed by internalisation 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 apoptotic cell death.

Secondary Pharmacology (Safety)
At the proposed therapeutic dose (1.25 mg/kg), enfortumab vedotin caused no large QTc prolongation (>20 msec). No supratherapeutic doses were assessed.

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6.2 Dose Finding and Dose Recommendation

EV-101 is an open-label, phase 1 study that was designed to assess the safety and pharmacokinetics of EV, including determination of the maximum tolerated dose (MTD) and/or recommended phase 2 dose (RP2D) in subjects with mUC and other solid tumours. In study EV-101, EV was evaluated in 89 patients with mUC and prior CPI treatment.

The weekly (Q1W) dose of 1.25 mg/kg was considered as acceptable for further testing in mUC due to longer progression-free survival (PFS) and overall survival (OS) for EV 1.25 mg/kg Q1W compared to <1.25 mg/kg, and a similar safety profile for 1.25 mg/kg Q1W compared to lower doses. Further dose escalation was not pursued due to dose reductions and drug-related rash and diarrhoea, which occurred at higher dose levels. The applicant reported no dose-limiting toxicities for the EV dose of 1.25mg/kg.

6.3 Efficacy

The applicant submitted one pivotal study (EV-301) and one supportive study (EV-201).

Pivotal study EV-301

Study EV-301 is an open-label, 1:1 randomised, multicentre phase 3 study to evaluate EV versus (vs) single agent chemotherapy in subjects with previously treated locally advanced or metastatic urothelial carcinoma (mUC) after platinum (cisplatin or carboplatin) and CPI-based therapy. Subjects were stratified according to the Eastern Cooperative Oncology Group (ECOG) Performance Status score (0 vs 1), regions of the world (Western EU vs US vs Rest of the World) and liver metastasis status (yes vs no).

In the experimental arm, EV was administered at the dose of 1.25 mg/kg as an intravenous infusion over 30 minutes on days 1, 8, and 15 of each 28-day cycle. The active control arm consisted of the investigator's pre-selected choice of single agent chemotherapy with either docetaxel 75 mg/m^2 every three weeks (Q3W), paclitaxel 175 mg/m^2 Q3W or vinflunine 320 mg/m^2 Q3W. These therapies are not approved in Switzerland for the treatment of mUC. However, these therapies are recommended by international guidelines and are therefore acceptable as controls[3]. Patients were treated until radiological disease progression or unacceptable toxicity.

Disease was assessed at baseline and every 2 months (± 7 days) from the first dose of study treatment throughout the study until radiological disease progression, loss to follow-up, withdrawal of study consent, or start of a subsequent anticancer therapy.

The study was conducted at 158 contracted sites in a total of 19 countries in Europe, North America, South America, Australia and Asia. Ten study sites were audited, which covered 19% of the population. Four inspections were performed (one by MHRA and three by PMDA). No critical findings were reported.

The study included subjects with histologically or cytologically confirmed mUC. Only patients treated with prior platinum-containing therapy (patients with prior adjuvant/neoadjuvant therapy must have progressed within 12 months of completion) and progression/relapse during or after CPI therapy were allowed to enter the study. Patients also had to present an ECOG performance status of 0-1, have adequate bone marrow and hepatic function as well as a creatinine clearance of ≥ 30 mL/min.

The study excluded patients with peripheral neuropathy grade ≥ 2, active CNS metastases, significant toxicity from prior tumour treatment, HIV or active HBV, HCV infections, more than one prior chemotherapy for mUC, cerebrovascular event, unstable angina, myocardial infarction, or cardiac

[3] J. Bellmunt et al., “Bladder cancer: ESMO Practice Guidelines for diagnosis, treatment and follow-up”, Annals of Oncology Volume 25, Supplement 3, September 2014, Pages iii40-iii48

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symptoms consistent with NYHA class III-IV, active keratitis, corneal ulcerations and uncontrolled diabetes mellitus.

The primary endpoint of the study was overall survival (OS). Relevant secondary endpoints were progression-free survival (PFS), overall response rate (ORR) and disease control rate (DCR). The statistical analysis plan was acceptable. Formal hypothesis tests were to be performed hierarchically in the order OS→PFS→ ORR→DCR.

Evaluation of efficacy and safety was based on an interim analysis with a data cut-off (DCO) of July 2020.

Overall, 745 patients were screened and 608 patients were randomised, 301 to the EV arm and 307 to the control arm. In the control arm, 109 subjects were treated with docetaxel, 107 with paclitaxel and 75 with vinflunine. At the submitted DCO, treatment was ongoing in 56 patients in the EV arm versus 22 patients in the control arm.

In the intent-to-treat (ITT) population (n=608), the median age was 68 years, 77% were male, 52% were Caucasian and 33% Asian. According to tumour localisation, 66% of all tumours were located in the bladder and 34% were located in the upper urinary tract. Overall, 63% of patients had received prior cisplatin, 26% had received carboplatin, and 11% had received both cisplatin and carboplatin. Baseline demographic and disease characteristics were balanced.

At the submitted DCO, the median follow-up time was 11.1 months. At DCO, 45% of patients in the EV arm and 54% in the control arm had an OS event. The OS in the ITT population for patients treated with EV was statistically significantly prolonged in comparison to the control arm: HR 0.702 CI95% 0.556, 0.886, median OS 12.88 months vs 8.97 months, one-sided p-value 0.00142 (boundary 0.00679). The OS rates at 6, 12 and 18 months in the EV arm compared to the control arm were 78% vs 70%, 52% vs 39% and 28% vs 23%, respectively. Patients who were treated in the locally advanced/metastatic setting with platinum-based chemotherapy followed by CPI presented consistent results irrespective of the applied platinum-agent (carboplatin or cisplatin). Subgroup analyses of female patients demonstrated no OS benefit in the EV arm compared to the control arm (HR of 1.171, CI95% 0.724, 1.894).

PFS in the ITT population was statistically significant for EV versus the control arm: HR of 0.615 CI95% 0.505, 0.748, median PFS 5.55 vs 3.71 months. The ORR in the EV arm was 41% and in the control arm 18%.

Supportive study EV-201
The results of the supportive study EV-201 for patients who received prior platinum and prior CPI therapy were consistent with the results of the pivotal study EV-301.

6.4 Safety

The safety database consists of 680 patients who were treated with EV 1.25 mg/kg, including 296 patients from the study EV-301, 125 patients from the study EV-201 with mUC after prior platinum and prior CPI-based therapy, as well as 89 patients from the study EV-201 who received prior CPI but were platinum-naïve. The safety analyses are from the December 2020 data cut-off. The treatment duration for the pooled safety population was 4.67 months. Safety results from the control arm of the study EV-301 are provided for comparison.

The frequencies of treatment-related adverse events of any grade (all EV 1.25mg/kg treated patients 94% vs. control arm of the study EV-301 92%), serious adverse events (45% vs. 45%), treatment emergent adverse events (TEAEs) of grade ≥3 (69% vs. 67%), TEAEs leading to drug discontinuation (19% vs 18%) and TEAEs leading to death (7% vs 6%) were similar for EV 1.25mg/kg compared to

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the control arm. TEAEs leading to dose reduction (35% vs 28%) and TEAEs leading to dose interruption (63% vs 30%) were more frequent in EV treated patients.

The most common TEAEs of any grade in all EV 1.25m/kg patients were alopecia, fatigue, decreased appetite, peripheral sensory neuropathy, diarrhoea, nausea, pruritus, dysgeusia, anaemia, constipation, maculopapular rash, decreased weight and dry skin.

The most frequent grade 3-4 TEAEs in all EV 1.25m/kg patients were anaemia, hyperglycaemia, fatigue, maculopapular rash, neutropenia and hyponatraemia.

The most common serious adverse events in all EV 1.25 mg/kg patients were acute kidney injury, pneumonia, urinary tract infection, sepsis, hyperglycaemia, and diarrhoea.

The following TEAEs leading to death (grade 5) were observed in at least 2 subjects treated with EV 1.25mg/kg: malignant neoplasm progression (n=10), urothelial cell carcinoma (n=5), multiple organ dysfunction (n=5), sepsis (n=3), cardiac arrest (n=2), pneumonia (n=2), diabetic ketoacidosis or hyperglycaemia (n=2), acute kidney injury (n=2), acute respiratory failure (n=2), dyspnoea (n=2).

Adverse events of special clinical interest were rash, peripheral neuropathy, hyperglycaemia, gastrointestinal toxicity, ocular disorders, interstitial lung disease (including pneumonitis), haematological toxicities, infections and increase of lipase, AST and/or ALT. These adverse events are adequately addressed in the product information in the “Warning and precautions” and “Undesirable effects” sections (see attached appendix “Information for Healthcare Professionals” for further details).

6.5 Final Clinical and Clinical Pharmacology Benefit Risk Assessment

Urothelial carcinoma is the most common cancer of the urinary system, accounting for approximately 90% of all bladder cancers in Western countries. Patients with mUC who develop disease progression after prior platinum-based chemotherapy followed by CPI treatment have a poor prognosis, and limited treatments options are available. Therefore, there is an unmet medical need for these patients.

Overall, the pharmacokinetics of enfortumab vedotin and MMAE have been sufficiently characterised. Remaining uncertainties due to lack of data are addressed by restrictive wording in the product information.

The pivotal study demonstrated a statistically significant and clinically meaningful OS benefit for EV compared to control in patients with prior platinum and CPI treatment.

Overall, the toxicity of EV is manageable in the clinical practice. Relevant safety concerns are adequately addressed in the product information.

Considering the prolongation by 3.9 months of the median overall survival in pretreated patients with no alternative approved treatment options and the manageable safety profile of enfortumab-vedotin, the benefit-risk is favourable for adult patients who have a locally advanced or metastatic UC with prior platinum-based chemotherapy and progression or relapse during or after treatment with a CPI.

6.6 Approved Indication and Dosage

See information for healthcare professionals in the Appendix.

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7 Risk Management Plan Summary

The RMP summaries contain information on the medicinal products' safety profiles and explain the measures that are taken in order 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. Marketing Authorisation Holders are responsible for the accuracy and correctness of the content of the published RMP summaries. 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 occurring in populations or indications not included in the Swiss authorisations.

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8 Appendix

8.1 Approved Information for Healthcare Professionals

Please be aware that the following version of the information for healthcare professionals relating to 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 reference document, which is valid and relevant for the effective and safe use of medicinal products in Switzerland, is the information for healthcare professionals approved and authorised by Swissmedic (see www.swissmedicinfo.ch).

Note:
The following information for healthcare professionals has been translated by the MAH. The Authorisation Holder is responsible for the correct translation of the text. Only the information for healthcare professionals approved in one of the official Swiss languages is binding and legally valid.

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▼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 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.

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

Adverse Reaction	Severity[1]	Dose Modification[1]
Skin Reactions	Suspected SJS or TEN	Immediately withhold, consult a specialist to confirm the diagnosis. If not SJS/TEN, see Grade 3 skin reactions.
	Confirmed SJS or TEN; Grade 4 or recurrent Grade 3 skin reactions	Permanently discontinue.
	Grade 3 (severe) skin reactions	Withhold until Grade ≤ 1, then resume treatment at the same dose level or consider dose reduction by one dose level.
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	Grade 2	Withhold until Grade < 1 for persistent or recurrent Grade 2 pneumonitis, 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

Adverse Reaction	Severity[1]	Dose Modification[1]
		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 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 requiring a dose reduction may have been re-escalated by 1 dose level provided the toxicity did not require drug discontinuation and had returned to baseline or ≤ Grade 1. If the toxicity recurred, re-escalation was not permitted. Patients with ≥ Grade 2 cornea adverse reactions were not permitted to dose re-escalate in phase 3 study (EV-301) (see *"Warnings and precautions"*).

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"*).

Children and adolescents

The safety and efficacy of Padcev in children aged below 18 years have not been established.

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.

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 anticipated on-target events, as Nectin-4 is expressed in the skin.

Severe cutaneous adverse reactions, including Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN), with fatal outcome have occurred in patients treated with Padcev, predominantly during the first cycle of treatment. These can also occur at a later time.

Starting with the first cycle and throughout treatment, monitor patients for skin reactions. Consider appropriate treatment such as topical corticosteroids and antihistamines for mild to moderate skin reactions. For severe (Grade 3) skin reactions, suspected SJS or TEN, withhold Padcev and consider referral for specialized care. Permanently discontinue Padcev for confirmed SJS or TEN; Grade 4 or recurrent Grade 3 skin reactions (see "*Dosage/Administration"* and "*Undesirable Effects"*).

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

Severe, life-threatening or fatal pneumonitis occurred in patients treated with Padcev. In clinical trials, 3.1% of the 680 patients treated with Padcev had pneumonitis of any grade and 0.7% had Grade 3-4. In clinical trials, the median time to onset of pneumonitis was 2.9 months (range: 0.6 to 6 months).
Monitor patients for signs and symptoms indicative of pneumonitis such as hypoxia, cough, dyspnea or interstitial infiltrates on radiologic exams. Evaluate and exclude infectious, neoplastic and other causes for such signs and symptoms through appropriate investigations.

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

Peripheral neuropathy

Peripheral sensory neuropathy (38.7%) and motor neuropathy (6%), have occurred with Padcev, including Grade ≥ 3 reactions. 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 rifampin (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 MMAE inhibits CYP3A4/5 but not CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, and CYP2D6. MMAE did not induce CYP1A2, CYP2B6, and CYP3A4/5 in human hepatocytes.

Transporter

In vitro studies indicate that MMAE is a substrate of the efflux transporter P-gp. *In vitro* studies determined that 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). 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 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

The safety of Padcev was evaluated as monotherapy in 680 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), one phase 2 study (EV-201) and one phase 3 study (EV-301) (see Table 3).

The most common undesirable effects (≥ 10%) were alopecia (48.8%), fatigue (46.8%), decreased appetite (44.9%), peripheral sensory neuropathy (38.7%), diarrhoea (37.6%), nausea (36.0%), pruritus (33.4%), dysgeusia (29.9%), anaemia (26.5%), weight decreased (23.4%), rash maculo-papular (22.9%), dry skin (21.6%), vomiting (18.4%), aspartate aminotransferase increased (15.3%), hyperglycaemia (13.1%), dry eye (12.8%), alanine aminotransferase increased (12.1%) and rash (10.4%).

Serious adverse reactions occurred in 45% of patients. The most common serious adverse reactions (≥ 2%) were acute kidney injury (7%), pneumonia (4%), urinary infection (4%), sepsis (3%), diarrhoea (2%) and hyperglycaemia (2%). Nineteen percent of patients permanently discontinued Padcev for adverse events; the most common adverse reaction (≥ 2%) leading to dose discontinuation was peripheral sensory neuropathy (4%). Adverse events leading to 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 (4%), alanine aminotransferase increased (4%), anemia (3%), diarrhoea (3%), and hyperglycaemia (3%). Thirty-five percent of patients required a dose reduction due to an adverse event; 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%).

Adverse reactions observed during clinical studies 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

Enfortumab vedotin monotherapy[1]	
Blood and lymphatic system disorders	
Very common	Anaemia (26.5%)
Common	Neutropenia, febrile neutropenia, neutrophil count decreased
Infections and infestations	
Common	Pneumonia, urinary tract infection
Gastrointestinal disorders	
Very common	Diarrhoea (37.6%), nausea (36.0%), vomiting (18.4%)
General disorders and administration site conditions	
Very common	Fatigue (46.8%)
Common	Infusion site extravasation
Hepatobiliary disorders	
Very common	Aspartate aminotransferase increased (15.3%), alanine aminotransferase increased (12.1%)
Metabolism and nutrition disorders	
Very common	Decreased appetite (44.9%), weight decreased (23.4%), hyperglycaemia (13.1%)
Common	Lipase increased
Nervous system disorders	
Very common	Dysgeusia (29.9%), peripheral sensory neuropathy (38.7%)
Common	Gait disturbance, hypoaesthesia, neuropathy peripheral, muscular weakness, paraesthesia, peripheral motor neuropathy, peripheral sensorimotor neuropathy
Uncommon	Burning sensation, demyelinating polyneuropathy, dysaesthesia, motor dysfunction, muscle atrophy, neuralgia, neurotoxicity, peroneal nerve palsy, polyneuropathy, skin burning sensation, sensory

	loss
Eye disorders	
Very common	Dry eye (12.8%)
Skin and subcutaneous tissue disorders	
Very common	Alopecia (48.8%), pruritus (33.4%), rash maculo-papular (22.9%), dry skin (21.6%), rash (10.4%)
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
Uncommon	Blood blister, dermatitis, dermatitis allergic, dermatitis contact, dermatitis exfoliative generalised, erythaema multiforme, exfoliative rash, intertrigo, pemphigoid, rash maculovesicular, skin irritation, stasis dermatitis
Not known	Epidermal necrosis, Stevens-Johnson syndrome, symmetrical drug-related intertriginous and flexural exanthaema, toxic epidermal necrolysis[2]

[1]Preferred term in MedDRA (v23.0). The above-mentioned listed adverse reactions have been observed during clinical studies (EV-101, EV-102, EV-201 and EV-301).

[2]Based on global postmarketing experience.

Description of specific adverse reactions and additional information

Skin Reactions

In clinical studies, skin reactions occurred in 55% (375) of the 680 patients treated with Padcev 1.25 mg/kg. Severe (Grade 3 or 4) skin reactions occurred in 13% (85) of patients and a majority of these reactions included maculo-papular rash, rash erythematous, rash or drug eruption. The median time to onset of severe skin reactions was 0.62 months (range: 0.1 to 6.4).

In the EV-201 clinical study, of the patients who experienced skin reactions, 75% had complete resolution and 14% had partial improvement (see "*Warnings and precautions"*).

Hyperglycaemia

In clinical studies, hyperglycaemia occurred in 14% (98) of the 680 patients treated with Padcev 1.25 mg/kg. Seven percent of patients who received Padcev developed severe (Grade 3-4) hyperglycaemia. 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 0.6 months (range: 0.1 to 20.3). Patients with baseline haemoglobin A1C ≥ 8% were excluded from clinical studies (see "*Warnings and precautions"*).

In the EV-201 clinical study, at the time of their last evaluation, 61% of patients had complete resolution, and 19% of patients had partial improvement (see "*Warnings and precautions"*).

Peripheral Neuropathy

In clinical studies peripheral neuropathy occurred in 52% (352) of the 680 patients treated with Padcev 1.25 mg/kg. Four percent of patients experienced severe (Grade 3-4) peripheral neuropathy including sensory and motor events. The median time to onset of Grade ≥ 2 was 4.6 months (range: 0.1 to 15.8). Patients with pre-existing peripheral neuropathy Grade ≥ 2 were excluded from clinical studies.

In the EV-201 clinical study, at the time of their last evaluation, 19% of patients had complete resolution, and 39% of patients had partial improvement (see "*Warnings and precautions"*).

Ocular Disorders

Ocular disorders were reported in 40% of the 384 patients treated with Padcev in clinical trials in which ophthalmologic exams were scheduled. Dry eye symptoms occurred in 34% of patients, and blurred vision occurred in 13% of patients, during treatment with Padcev. The median time to onset to symptomatic ocular disorder was 1.6 months (range: 0 to 19.1 months). In clinical studies, 14 (2.1%) patients interrupted, and 1 (0.1%) patient permanently discontinued treatment for ocular disorders (see "*Warnings and precautions"*).

Infusion Site Extravasation

Of the 680 patients, 1.6% 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 680 patients treated with Padcev 1.25 mg/kg in clinical trials, 440 (65%) were 65 years or older and 168 (25%) were 75 years or older. Based on the data from all patients treated with Padcev 1.25 mg/kg in the clinical trials, the toxicity in older patients (≥ 65 years) was higher compared to younger patients (< 65 years, N = 240): serious adverse events 208 (47%) vs 98 (41%), adverse events leading to death 37 (8%) vs 10 (4%) and adverse events of grade ≥ 3 315 (72%) vs 153 (64%).

Severe Renal Impairment

Of the 680 patients treated with Padcev 1.25 mg/kg in clinical trials, 245 (36%) had mild renal impairment, 295 (43%) had moderate renal impairment and 21 (3%) had severe renal impairment. Based on the data from all patients treated with Padcev 1.25 mg/kg in the clinical trials, 19/21 (91%) patients with severe renal impairment experienced grade ≥ 3 adverse events.

Immunogenicity

A total of 590 patients were tested for immunogenicity to Padcev 1.25 mg/kg; 15 patients were confirmed to be positive at baseline for anti-therapeutic antibody (ATA), and in patients that were negative at baseline (N = 575), a total of 16 (2.8%) were positive postbaseline (13 transiently and 3 persistently). 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.

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 EIViS 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 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

L01XC36

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 apoptotic cell death.

Pharmacodynamics

In an exposure-response analysis, a higher exposure was associated with higher incidence of some adverse reactions (e.g., Grade ≥ 2 peripheral neuropathy, Grade ≥ 3 hyperglycaemia).

Cardiac Electrophysiology

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

Clinical efficacy

Metastatic Urothelial Cancer

EV-301

The efficacy of enfortumab vedotin 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 Eastern Cooperative Oncology Group (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 Overall Survival (OS), and the secondary endpoints Progression Free Survival (PFS) and Objective Response Rate (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 from five studies.

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

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

Metabolism

The metabolism of enfortumab vedotin has not been studied in clinical trials. However, it can be assumed that enfortumab vedotin is broken down into small peptides, amino acids, free MMAE and its metabolites. MMAE is released from enfortumab vedotin through proteolysis and based on *in vitro* data metabolism of 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 MMAE appeared to be limited by its rate of release from enfortumab vedotin. 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% increase in unconjugated MMAE AUC were observed in patients with mild hepatic impairment (total bilirubin 1 to 1.5 × ULN and AST any, 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 any). 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 < 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.

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 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 sterile 5% Dextrose injection, sterile 0.9% Sodium Chloride injection or sterile Lactated Ringer's injection.

Instructions for preparation and administration

Reconstitution in single-dose vial

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