PADCEV™ (ENFORTUMAB VEDOTIN)

Public Risk Management Plan (RMP) Summary

The Risk Management Plan (RMP) is a comprehensive document submitted as part of the application dossier for market approval of a medicine. The RMP summary contains information on the medicine's safety profile and explains the measures that are taken in order to further investigate and follow the risks as well as to prevent or minimise them. The RMP summary of Padcev is a concise document and does not claim to be exhaustive. As the RMP is an international document, the summary might differ from the "Arzneimittelinformation / Information sur le médicament" approved and published in Switzerland, e.g. by mentioning risks occurring in populations or indications not included in the Swiss authorization. Please note that the reference document which is valid and relevant for the effective and safe use of Padcev in Switzerland is the "Arzneimittelinformation/ Information sur le médicament" (see www.swissmedic.ch) approved and authorized by Swissmedic. Astellas Pharma AG is fully responsible for the accuracy and correctness of the content of the published summary RMP of Padcev.

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PART VI: SUMMARY OF THE RISK MANAGEMENT PLAN

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Summary of risk management plan for enfortumab vedotin

This is a summary of the RMP for Padcev. The RMP details important risks of enfortumab vedotin and how these risks can be minimized.

PADCEV's summary of product characteristics and its package leaflet give essential information to healthcare professionals and patients on how enfortumab vedotin should be used.

This summary of the RMP for Padcev should be read in the context of all this information including the assessment report of the evaluation and its plain-language summary, all which is part of the European Public Assessment Report (EPAR).

Important new concerns or changes to the current risks will be included in updates of enfortumab vedotin's RMP.

I. The medicine and what it is used for

Enfortumab vedotin as monotherapy is authorized for the treatment of adult patients with urinary tract cancer (locally advanced or metastatic urothelial cancer) who have previously received treatment for this (a PD-1 or PD-L1 inhibitor, and a platinum-containing chemotherapy) (see EU-SmPC for the full indication). The product contains enfortumab vedotin as the active substance and it is given by intravenous administration.

Further information about the evaluation of enfortumab vedotin's benefits can be found in enfortumab vedotin's EPAR, including in its plain-language summary, available on the European Medicines Agency website, under the medicine's webpage:

https://www.ema.europa.eu/en/medicines/human/EPAR/padcev

II. Risks associated with the medicine and activities to minimize or further characterize the risks

Important risks of Padcev, together with measures to minimize such risks and the proposed studies for learning more about Padcev 's risks, are outlined below.

Measures to minimize the risks identified for medicinal products can be:

- Specific information, such as warnings, precautions, and advice on correct use, in the package leaflet and EU-SmPC addressed to patients and healthcare professionals;
- Important advice on the medicine's packaging;
- The authorized pack size — the amount of medicine in a pack is chosen so to ensure that the medicine is used correctly;
- The medicine's legal status — the way a medicine is supplied to the patient (e.g., with or without prescription) can help to minimize its risks.

Together, these measures constitute *routine risk minimization* measures.

II.A List of important risks and missing information

Important risks of Padcev are risks that need special risk management activities to further investigate or minimize the risk, so that the medicinal product can be safely administered. Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of Padcev. Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this association has not been established yet and needs further evaluation. Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected (e.g., on the long-term use of the medicine).

List of important risks and missing information	
Important identified risks	• Skin reactions • Hyperglycemia • Pneumonitis/Interstitial lung disease
Important potential risks	• None
Missing information	• None

II.B Summary of important risks

Important identified risk: Skin reactions

Evidence for linking the risk to the medicine	The presence of Nectin-4 in skin may increase the risk of skin reactions as a result of Nectin-4 targeted microtubule-disrupting agent monomethyl auristatin E delivery. In EV-301, the overall incidence of skin reactions (including SCAR) in the enfortumab vedotin arm was 53.7% as compared to 19.9% in the standard chemotherapy groups, and the incidence of SCAR in the enfortumab vedotin arm was 26% as compared to 9.3% in the standard chemotherapy groups. When adjusted for events per patient-year, the event rates of skin reactions (including SCAR) and SCARs remained higher in the enfortumab-treated group (3.370 and 1.050 events per patient-year, respectively) compared with the chemotherapy groups (0.822 and 0.375 events per patient-year, respectively). The overall rate of skin reactions in the clinical trial of the ISS population (EV-203 ISS) is 55.6%, and the rate of SCARs was 24.1%. Of 793 patients treated with enfortumab vedotin (EV) 1.25 mg/kg, the incidence of skin reactions (including SCAR) was 56.7% and the incidence of SCAR was 24.3%. A review of postmarketing data up to 31 Aug 2022 showed 661 spontaneous cases of skin reactions, of which 48 cases were fatal. There were a total of 829 events in these 661 cases, of which 655 were non-serious, and the remaining 174 were serious events. The numbers and PTs identified by the SCAR SMQ (Broad) and 5 HLTs (Bullous conditions; Dermatitis and eczema; Rashes, eruptions and exanthemas NEC; Erythemas;

	Dermatitis ascribed to specific agent) consisted of Rash (408), Erythema (68), Drug eruption (34), Blister (29), Stevens-Johnson syndrome (28), Rash pruritis and Rash erythematous (26 each) and Skin exfoliation, Stomatitis and Toxic epidermal necrolysis (22 each).
Risk factors and risk groups	Risk factors for SCAR include both drug dosage and inherent patient factors. There appears to be an increased risk of SCAR with higher drug dosages [Mustafa et al, 2018]. Antiepileptic agents, along with baseline conditions such as systemic lupus erythematous, tuberculosis and HIV (human immunodeficiency virus) increase the risk of SCAR [Mustafa et al, 2018]. Drugs commonly associated with SCAR include antimicrobial agents (cotrimoxazole, vancomycin, aminopenicillin, minocycline, sulfasalazine and dapsone) and NSAIDs (nonsteroidal anti-inflammatory drugs). Genetic predisposition and individual drug metabolism or drug clearance also affect the risk of SCAR [Chung et al, 2016]. Many subjects who experienced SCAR events during the enfortumab vedotin clinical trials had risk factors for development of a skin reaction, including a past medical history of rash or initiation of new concomitant medications frequently implicated as a cause of rash within 30 days prior to SCAR onset. To date, there are no specific product related risk factors for development of SCAR detected.
Risk minimization measures	Routine risk communication: • EU-SmPC sections 4.2, 4.4 and 4.8; • PL sections 2 and 4 Routine risk minimization activities recommending specific clinical measures to address the risk: • Recommendations are provided in the EU-SmPC Section 4.4 to monitor for severe skin reactions starting with the first cycle and throughout enfortumab vedotin treatment. Fever or flu-like symptoms may be the first sign of a severe skin reaction, and patients should be observed, if this occurs. - For Grade 2 worsening, Grade 2 with Fever or Grade 3 skin reactions, treatment should be withheld until Grade ≤1 and referral for specialized care should be considered. Treatment should be resumed at the same dose level or consider dose reduction by one dose level. - For suspected SJS or TEN, or in case of bullous lesions onset, withhold treatment immediately and refer to specialised care; histologic confirmation, including consideration of multiple biopsies, is critical to early recognition, as diagnosis and intervention can improve prognosis. - Permanently discontinue enfortumab vedotin for confirmed SJS or TEN, Grade 4 or recurrent severe skin reactions.

	• Recommendations are provided in the EU-SmPC Section 4.2 for treatment interruption, dose reduction and treatment discontinuation of enfortumab vedotin. Additional risk minimization measures: • Patient card
Additional pharmacovigilance activities	Patient survey study

NSAIDs: Nonsteroidal Anti-Inflammatory Drugs; HIV: Human Immunodeficiency Virus; HLT: High Level Term; PL: Package Leaflet; PT: Preferred Term; SCAR: Severe Cutaneous Adverse Reaction; SJS: Stevens Johnson Syndrome; EU-SmPC: European Union-Summary of Product Characteristics; SMQ: Standardized MedDRA Query; TEN: Toxic Epidermal Necrolysis.

Important identified risk: Hyperglycemia

Evidence for linking the risk to the medicine	The overall rate of hyperglycemia in the 7 clinical trials in the EV-203 ISS population was 16.2% (140/862 subjects). Of 793 patients treated with EV 1.25 mg/kg, the incidence of hyperglycemia was 16.6% (132/793 subjects). The most frequently reported PTs in the EV 1.25 mg/kg group were Hyperglycemia (14.9%), Blood glucose increased and Diabetes mellitus (0.9%). Most hyperglycemia events in the EV 1.25 mg/kg group were Grade 3 (52/132; 39.4%), followed by Grade 2 (41/132; 31.1%) and Grade 1(31/132; 23.5%). Six subjects experienced Grade 4 events (4.5%) and 2 subjects experienced Grade 5 event (1.5%). SAEs were reported in 20 subjects (20/793; 2.5%). In the enfortumab vedotin clinical program testing for fasting glucose was not included. The rate of any hyperglycemia event in subjects without risk factors (BMI <30 and no pre-existing hyperglycemia or diabetes) was 5.6% in the EV 1.25 mg/kg group. A review of post-marketing data up to 31 Aug 2022 showed 153 spontaneous cases of the Hyperglycaemia/new onset diabetes mellitus SMQ (Narrow). There were a total of 166 events in these 153 cases, of which 125 were non serious, and the remaining 41 were serious events. The most frequently reported PTs were Hyperglycaemia (99), Blood glucose increased (45), and diabetic ketoacidosis (8). Three cases reported a fatal outcome. Two fatal cases lacked sufficient information for a meaningful medical assessment. In the remaining fatal case, the patient had concurrent SCAR event.
Risk factors and risk groups	Literature shows that diabetes was reported in approximately 20% of subjects in the few urothelial cancer trials where pre-existing comorbidities are documented [Galsky et al, 2018; Niegisch et al, 2018], consistent with rates reported in the general population of older adults [Centers for Disease Control and Prevention, 2017]. The major risk factors for hyperglycemia include a family history of type 2 diabetes, being overweight or obese, low birth weight, older age, gestational diabetes (in women), and socioeconomic

	disadvantage [WHO, 2020; IDF, 2020]. Race/ethnicity is also a major risk factor for hyperglycemia. Higher rates are seen in people of South Asian descent and people of African and African-Caribbean origin [WHO, 2020]. In the enfortumab vedotin clinical development program, hyperglycemia events were more common in subjects with a baseline BMI ≥ 30 kg/m^2, or with a prior medical history of hyperglycemia, or in subjects with an elevated baseline HbA1c.
Risk minimization measures	Routine risk communication: • EU-SmPC sections 4.2, 4.4 and 4.8; • PL sections 2 and 4. Routine risk minimization activities recommending specific clinical measures to address the risk: • Recommendations are provided in EU-SmPC Section 4.4 to monitor blood glucose levels prior to dosing and periodically throughout the course of treatment as clinically indicated in patients with or at risk for diabetes mellitus or hyperglycaemia. If blood glucose is elevated >13.9 mmol/L (>250 mg/dL), enfortumab vedotin should be withheld until blood glucose is ≤13.9 mmol/L (≤250 mg/dL) and treat as appropriate. • Recommendations are provided in EU-SmPC Section 4.2 for treatment interruption and when to resume treatment of enfortumab vedotin.
Additional pharmacovigilance activities	None

BMI: body mass index; EV: Enfortumab vedotin; HbA1c: hemoglobin A1C; HIV: Human Immunodeficiency Virus; PL: Package Leaflet; SAE: serious adverse event; SMQ: Standardized MedDRA Query; EU-SmPC: European Union-Summary of Product Characteristics; WHO: World Health Organization.

Important identified risk: Pneumonitis/Interstitial lung disease

Evidence for linking the risk to the medicine	The overall rate of Pneumonitis/Interstitial lung disease in the clinical trials of the EV-203 ISS population was 3.3% (29/862). Of 793 patients treated with enfortumab vedotin 1.25 mg/kg, Pneumonitis/Interstitial lung disease occurred in 3.1% of subjects. The most common PTs reported were Pneumonitis (2.1%), followed by Interstitial lung disease (0.6%). Of the 793 patients treated with enfortumab vedotin 1.25 mg/kg, majority of the events were Grade 1 and 2. No Grade 5 events were observed. A review of post-marketing data up to 31 Aug 2022 showed 51 spontaneous cases of pneumonitis/interstitial lung disease. There were a total of 53 events in these 51 cases, of which 4 were non serious, and the remaining 49 were serious events. The most frequently reported PT was Interstitial lung disease (n = 37), followed by Pneumonitis (n = 7). Seven cases reported a fatal outcome. The 7 fatal cases concerned patients from Japan (n = 6) and Germany (n = 1) and all were elderly. The reported cause of death was Interstitial lung disease (n = 5); pneumonia and acute respiratory distress syndrome (n = 1); and pneumonitis and

	respiratory insufficiency (n = 1). The time to onset ranged from 1 to 3 months in 5 cases and was not provided in the remaining 2 cases. Three of these cases reported a prior episode of interstitial pneumonia and 1 case reported an immune-related adverse event due to pembrolizumab. Pembrolizumab was reported as a concomitant/co-suspect drug in 4 of these cases.
Risk factors and risk groups	Interstitial lung disease is a heterogeneous group of disorders characterized by fibrosis (scarring) of the lungs which are classified based on histopathological, radiologic, and clinical parameters. Interstitial lung disease, where there is damage to tissues between the alveoli, is one of the major patterns of lung injury following systemic cancer therapies. This pattern of lung injury may arise from direct cytotoxicity, oxidative stress, and immune-mediated mechanisms.
Risk minimization measures	Routine risk communication: • EU-SmPC sections 4.2, 4.4 and 4.8; • PL sections 2 and 4. Routine risk minimization activities recommending specific clinical measures to address the risk: • For Grade 2 pneumonitis/interstitial lung disease, withhold enfortumab vedotin until Grade ≤1, then resume at the same dose level or consider dose reduction by one dose level. Permanently discontinue enfortumab vedotin for Grade ≥3 pneumonitis/interstitial lung disease.
Additional pharmacovigilance activities	None

ISS: Integrated Summary of Safety; EU: European Union, PL: Package Leaflet; PT: Preferred Term; SmPC: Summary of Product Characteristics

II.C Postauthorization development plan

II.C.1 Studies which are conditions of the marketing authorization

There are no studies that are conditions of the marketing authorization or specific obligation of Padcev.

II.C.2 Other studies in postauthorization development plan

Patient survey study

Purpose of the study: To evaluate patients' understanding and awareness of the content of the patient card related to risks of skin reactions and patient behaviours to minimize the risk.