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
Important potential risks	• None
Missing information	• Long-term safety

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. The overall rate of skin reactions in the clinical trial of the ISS population is 53.9%, and the rate of SCARs was 23.5%. Of 680 patients treated with enfortumab vedotin (EV) 1.25 mg/kg, the incidence of skin reactions (including SCAR) was 55.1% and the incidence of SCAR was 23.7%. 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 most frequently reported PTs within the 5 HLTs in the EV 1.25 mg/kg group were rash maculo-papular (22.9%), rash (10.4%), followed by rash erythematous (> 5% of the subjects). The most frequently reported PTs in the SCAR SMQ in the EV 1.25 mg/kg group were stomatitis (> 5% of the subjects), followed by conjunctivitis, drug eruption, blister, skin exfoliation and dermatitis bullous (> 2% of the subjects). The majority of skin reaction events (including SCAR) were Grade 1 or 2 in severity (78.5%, 317/404); Grade 3 or 4 events were

	reported in 21.5% (87/404) of patients, and no Grade 5 events were reported. A review of postmarketing data up to 15 Sep 2020 showed 47 spontaneous cases, of which 7 cases were fatal. There were a total of 55 events in these 47 cases, of which 34 were non serious, and the remaining 21 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 (26), Rash erythematous (4), SJS (4), Rash pruritic (3), Palmar-plantar erythrodysesthesia syndrome (2), Blister (2), Dermatitis Bullous (2), Toxic erythema of chemotherapy (2), Symmetrical Drug-Related Intertriginous and Flexural Exanthema (2), Toxic Epidermal Necrolysis (2), Dermatitis allergic (1), Rash maculo-papular (1), Rash papular (1), Exfoliative Rash (1), Epidermal Necrosis (1), and Stomatitis (1).
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; 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	Of 680 patients treated with enfortumab vedotin 1.25 mg/kg, hyperglycemia occurred in 14.4% of subjects. The most common PT reported was Hyperglycemia (13.1%), followed by Glucose tolerance impaired (0.6%). In EV-301, the incidence of hyperglycemia in the enfortumab vedotin arm was 11.8% as compared to 2.7% in the other standard chemotherapy groups. When adjusted for the duration of the exposure, the event rates of hyperglycemia remained higher in the enfortumab-treated group (0.589 events per patient-year) compared with the chemotherapy arms (0.104 events per patient-year). Majority of the events were grade 3 (43/98, 43.9%) of which SAEs were (15/98, 15.3%) There was a higher incidence of treatment emergent hyperglycemia reported in obese subjects (BMI >/= 30 kg/m2), subjects who had preexisting hyperglycemia and subjects with HbA1C in the pre diabetic/diabetic range. A fatal outcome was reported in 2 (0.3%) patients who experienced SAEs of hyperglycemia and diabetic ketoacidosis (related), respectively. A review of post-marketing data up to 08 Oct 2020 showed 11 spontaneous cases of the Hyperglycaemia/new onset diabetes SMQ (Narrow). There were 7 serious caseas and 4 non-serious cases. Of the 7 serious cases, 4 cases reported a fatal outcome. The cause of death was not reported in 3 out of 4 cases. The remaining case reported multi-organ failure as cause of death. The frequencies and PTs reported from the Hyperglycaemia/new onset diabetes SMQ (Narrow): Hyperglycemia (7), Blood glucose increased (3), and Diabetes mellitus inadequate control (1).

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/m2, 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 SmPC Section 4.2 for treatment interruption and when to resume treatment of enfortumab vedotin.
Additional pharmacovigilance activities	None

Missing Information: Long-term safety

Risk minimization measures	Routine risk minimization activities recommending specific clinical measures to address the risk: • None Other routine risk minimization measures beyond the Product Information: • None

Missing Information: Long-term safety

Additional pharmacovigilance activities	• Final overall survival report based on the prespecified final number of events for the clinical trial EV-301, titled "An Open-label, Randomized Phase 3 Study to Evaluate Enfortumab Vedotin vs Chemotherapy in Subjects with Previously Treated Locally Advanced or Metastatic Urothelial Cancer." • See section II.C of this summary for an overview of the post-authorization development plan

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.

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

Final overall survival report based on the prespecified final number of events for the clinical trial EV-301, titled “An Open-label, Randomized Phase 3 Study to Evaluate Enfortumab Vedotin vs Chemotherapy in Subjects with Previously Treated Locally Advanced or Metastatic Urothelial Cancer.”

Purpose of the study: Updated exploratory overall survival analysis to provide additional data on the efficacy and safety of treatment with enfortumab vedotin in patients enrolled in EV-301. Analysis will also include data for patients who have received treatment with enfortumab for 1 year or more.

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.