# EUROPEAN UNION RISK MANAGEMENT PLAN

## Enfortumab vedotin (Padcev™)

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# European Union Risk Management Plan for Enfortumab vedotin (Padcev)

**RMP version to be assessed as part of this application:**

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| RMP Version number: | 4.0 |
| Data lock point for this RMP: | 08 Aug 2023 |
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| Rationale for submitting an updated RMP: | To update the RMP based on the changes in the approved RSI (within the variation EMA/VR/0000256819 in which the RMP was assessed) |
| Summary of significant changes in this RMP: | To update the "Indication(s)" and "Dosage in the EEA" in part I "Product overview"; moved from 'Proposed' to 'Current' section<br><br>To update the wordings from "clinical study report" to "final study report" in Part III.3 and Annex 2. |

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**List of Abbreviations**

| Abbreviation | Definition |
|---|---|
| ADC | Antibody Drug Conjugate |
| AE | Adverse Event |
| AESI | Adverse Events of Special Interest |
| AGEP | Acute Generalized Exanthematous Pustulosis |
| AIDS | Acquired Immuno Deficiency Syndrome |
| ALT | Alanine Transaminase |
| ANC | Absolute Neutrophil Count |
| AST | Aspartate aminotransferase |
| ATA | Anti-therapeutic Antibodies |
| ATC | Anatomical Therapeutic Classification |
| AUC | Area under the ROC curve |
| BMI | Body Mass Index |
| CHO | Chinese Hamster Ovary |
| CI | Confidence Interval |
| CNS | Central Nervous System |
| CPI | Checkpoint Inhibitor |
| CYP | Cytochrome P |
| DE | Dose Escalation |
| DRESS | Drug reaction with Eosinophilia and Systemic Symptoms |
| EAU | European Association of Urology |
| ECG | Electrocardiogram |
| ECOG | Eastern Cooperative Oncology Group |
| EEA | European Economic Area |
| EMA | European Medicines Agency |
| EPAR | European Public Assessment Report |
| EU | European Union |
| EU-SmPC | European Union Summary of Product Characteristics |
| EV | Enfortumab Vedotin |
| GC | Gemcitabine Plus Cisplatin |
| GLP | Good Laboratory Practice |
| HCV | Hepatitis C Virus |
| hERG | Human ether-à-go-go |
| HBsAg | Hepatitis B Surface Antigen |
| HD-MVAC | High Dose - Methotrexate, Vinblastine, Adriamycin Plus Cisplatin |
| HIV | Human Immunodeficiency Virus |
| HLT | High Level Term |
| ICH | International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use |
| ILD | Interstitial Lung Disease |
| INN | International Nonproprietary Name |
| irAE | immune-related Adverse Event |
| IRRs | Infusion-related reactions |
| ISS | Integrated Summary of Safety |
| IV | Intravenous |
| LA | Locally Advanced |
| MIBC | Muscle Invasive Bladder Cancer |
| MMAE | Monomethyl Auristatin E |

| | |
|---|---|
| mRCC | Metastatic Renal Cell Carcinoma |
| mTOR | Mechanistic Target of Rapamycin |
| mUC | Metastatic Urothelial cancer |
| MVAC | Methotrexate, Vinblastine, Adriamycin Plus Cisplatin |
| NCA | National Competent Authority |
| NCI-ODWG | National Cancer Institute- Organ Dysfunction Working Group |
| NYHA | New York Heart Association |
| NEC | Not Elsewhere Classified |
| NI-PASS | Non-Interventional Post Authorization Safety Study |
| NSAIDs | Non-Steroidal Anti-Inflammatory Drugs |
| NSCLC | Non-Small Cell Lung Carcinoma |
| PD-1 | Programmed Death Receptor-1 |
| PD-L1 | Programmed Cell Death-ligand 1 |
| PK | Pharmacokinetics |
| PL | Package Leaflet |
| PT | Preferred Term |
| QTcF | QTc corrected with Fridericia's formula |
| RC | Radical Cystectomy |
| RMP | Risk Management Plan |
| RNA | Ribonucleic Acid |
| RR | Reporting Rate |
| SAE | Serious Adverse Event |
| SCAR | Severe Cutaneous Adverse Reaction |
| SJS | Stevens Johnson Syndrome |
| SMQ | Standardized Medical Dictionary for Regulatory Activities Query |
| TEAEs | Treatment Emergent Adverse Events |
| TEN | Toxic Epidermal Necrolysis |
| UBC | Urinary bladder cancer |
| UC | Urothelial cancer |
| ULN | Upper Limit of Normal |
| US | United States |
| UTUC | Upper Tract Urothelial Carcinoma |

## Table of Contents

# PART I: PRODUCT OVERVIEW

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| Data-lock point for this Module | 08 Aug 2023 |
| Version when Module last updated | 4.0 |

**Table Part I.1: Product Overview**

| | |
|---|---|
| Active substance(s) {International Nonproprietary Name [INN] or common name} | Enfortumab vedotin |
| Pharmacotherapeutic group(s) Anatomical Therapeutic Classification (ATC) Code | L01FX13 |
| Marketing Authorization Applicant | Astellas Pharma Europe B. V |
| Medicinal products to which this RMP refers | 1 |
| Invented name(s) in the European Economic Area (EEA) | Padcev™ |
| Marketing authorization procedure | Centralized |
| Brief description of the product | Chemical class<br>Antibody-drug conjugate |
| | Enfortumab vedotin (ASG-22CE); hereafter enfortumab vedotin is an antibody-drug conjugate (ADC) comprising a fully human immunoglobulin (Ig) G1Kappa antibody conjugated to the microtubule-disrupting agent monomethyl auristatin E (MMAE) via a protease-cleavable valine-citrulline (vc) maleimidocaproyl linker. Enfortumab vedotin induces cytotoxicity in cancer cells by binding the Nectin-4 target on the cell surface and forming an ADC-Nectin-4 complex. This complex is internalized and traffics to lysosomes where MMAE is released by proteolytic cleavage of the vc-linker. Intracellular release of MMAE subsequently disrupts tubulin polymerization resulting in G2/M phase cell cycle arrest and apoptosis.<br>Based on in-vitro data, enfortumab vedotin undergoes catabolism into small peptides, amino acids, unconjugated MMAE, unconjugated MMAE-related catabolites, and MMAE is primarily metabolized by CYP3A4 in vitro. |
| | Drug product vials contain 20 mg or 30 mg of enfortumab vedotin, histine, histidine monohydrochloride monohydrate, trehalose dehydrate, and polysorbate 20 (E432)20. |
| Hyperlink to the product information | [Module 1.3.1; EU- Summary of Product Characteristics (EU-SmPC)] |

| | |
|---|---|
| Indication(s) in the EEA | Current (if applicable):<br>Padcev, in combination with pembrolizumab, is indicated for the first-line treatment of adult patients with unresectable or metastatic urothelial cancer who are eligible for platinum-containing chemotherapy.<br>Padcev as monotherapy is indicated for the treatment of adult patients with locally advanced or metastatic urothelial cancer who have previously received a platinum containing chemotherapy and a programmed death receptor-1 or programmed death-ligand 1 inhibitor. |
| | Proposed (if applicable):<br>Not applicable |
| Dosage in the EEA | Current (if applicable):<br>As monotherapy, the recommended dose of enfortumab vedotin is 1.25 mg/kg (up to a maximum dose of 125 mg for patients ≥100 kg) given as an intravenous infusion over 30 minutes on days 1, 8, and 15 of a 28-day cycle until disease progression or unacceptable toxicity.<br>When given in combination with pembrolizumab, the recommended dose of enfortumab vedotin is 1.25 mg/kg (up to a maximum of 125 mg for patients ≥100 kg) administered as an intravenous infusion over 30 minutes on Days 1 and 8 of every 3-week (21-day) cycle until disease progression or unacceptable toxicity. The recommended dose of pembrolizumab is either 200 mg every 3 weeks or 400 mg every 6 weeks administered as an intravenous infusion over 30 minutes. Patients should be administered pembrolizumab after enfortumab vedotin when given on the same day. Refer to the pembrolizumab SmPC for the recommended dosing information of pembrolizumab. |
| | Proposed (if applicable):<br>Not applicable |
| Pharmaceutical form(s) and strengths | Current (if applicable):<br>Enfortumab vedotin is supplied as single-dose vials containing sterile, preservative-free, white to off-white lyophilized powder for concentrate for reconstitution for intravenous infusion. Each vial contains either 20 mg or 30 mg enfortumab vedotin active ingredient that is reconstituted to a final concentration of 10 mg/mL. |
| | Proposed (if applicable):<br>Not applicable |
| Is/will the product be subject to additional monitoring in the EU? | Yes |

ADC: Antibody-drug Conjugate; ATC: Anatomical Therapeutic Classification; CYP3A4: Cytochrome P450 3A4; EEA: European Economic Area; EU: European Union; EU-SmPC: European Union-Summary of Product Characteristics; Ig: Immunoglobulin; INN: International Nonproprietary Name; MMAE: Monomethyl Auristatin E; RMP: Risk Management Plan; vc: Valine-Citrulline.

# PART II: SAFETY SPECIFICATION

# PART II: MODULE SI. EPIDEMIOLOGY OF THE INDICATION(S) AND TARGET POPULATION(S)

| | |
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**Indication:**

Padcev as monotherapy is indicated for the treatment of adult patients with locally advanced or metastatic urothelial cancer (UC) who have previously received a platinum-containing chemotherapy and a programmed death receptor-1 or programmed death-ligand 1 inhibitor.

Padcev, in combination with pembrolizumab, is indicated for the first-line treatment of adult patients with unresectable or metastatic urothelial cancer who are eligible for platinum-containing chemotherapy.

**Incidence:**

More than 90% of urothelial cancers occur in the bladder; 5%-10% occur in the renal pelvis or the ureters [Miyazaki and Nishiyama, 2017].

**I. Bladder cancer**

Urothelial cancers, based on histological assessments, constitute more than 90% of all bladder cancers [Miyazaki and Nishiyama, 2017].

Urinary bladder cancer (UBC) ranks 11$^{th}$ in absolute incidence worldwide, 7$^{th}$ in men, and 18$^{th}$ in women [Ferlay et al, 2023]. In 2020, 573,278 new UBC cases were diagnosed (440,864 in males and 132,414 in females), and the 5-year prevalence was 1,720,625 [Ferlay et al, 2023]. The annual age-standardized incidence rate is 9.5 per 100,000 in males and 2.4 per 100,000 in females, and approximately 664,605 new bladder cancer cases are projected for the year 2025 [Ferlay et al, 2023].

For the year 2020, the age-standardized incidence rate for bladder cancer was estimated at 11.3 per 100,000 for Europe, with 203,983 new cases [Ferlay et al, 2023]. The age-standardized bladder cancer incidence rate was estimated at 23.3 per 100,000 males and 5.7 per 100,000 females in the European Union (EU) in 2020 [Ferlay et al, 2023]. Slightly lower average rates were estimated over the entire European continent (20.0 per 100,000 among males and 4.6 per 100,000 among females). Within the EU, males in Greece had the highest rates (39.7 per 100,000) and males in Austria had the lowest rates (10.5 per 100,000). Among females, the highest rates were estimated in Hungary (9.1 per 100,000) and the lowest rates were estimated in Finland and Luxembourg (2.7 per 100,000) [Ferlay et al, 2023].

**II. Upper tract urothelial carcinoma: Renal pelvis cancer and Ureter cancer**

Approximately 90% of cancers occurring in the pelvis, ureter, and urethra are transitional cell carcinoma [Visser et al, 2012; Gatta et al, 2011] and at diagnosis the renal pelvis location is twice as likely the cancer site relative to the ureter [Soria et al, 2017].

The most recent estimates by the project Surveillance of Rare Cancers in Europe (RARECARE) estimated the number of new cases of transitional cell carcinoma of the pelvis and ureter at 8,144 in 2013 in the EU and the estimated number of new cases of transitional cell carcinoma of the urethra was 530 [RARECARENet, 2023]. The age-adjusted incidence rate in Europe for transitional cell carcinoma of the pelvis and ureter was estimated at 1.06 per 100,000 per year and the rate for transitional cell carcinoma of the urethra was 0.065 per 100,000 per year [RARECARENet, 2023]. Regionally, the age-adjusted incidence (per 100,000 per year) of transitional cell carcinoma of the pelvis and ureter was 0.950 in Northern Europe, 1.318 in Central Europe, 0.994 in Southern Europe and 0.777 in Eastern Europe. The incidence (per 100,000 per year) of transitional cell carcinoma of the urethra was 0.059 in Northern Europe, 0.092 in Central Europe, 0.047 in Southern Europe and 0.037 in Eastern Europe [RARECARENet, 2023].

**Prevalence**:

**I. Bladder cancer**

The global annual prevalence of bladder cancer was estimated at 454,015 cases in 2020 (353,001 males and 101,014 females) and in Europe the annual was estimated at 172,263 cases (133,610 males and 38,653 females) [Ferlay et al,2023].

In 2020 the five-year prevalence of bladder cancer was estimated at 1,720,625 cases worldwide (1,343,119 males and 377,506 females), while the 5-year prevalence in Europe was estimated at 655,264 cases (510,178 males and 145,086 females) [Ferlay et al, 2023].

**II. Upper tract urothelial carcinoma: Renal pelvis cancer and Ureter cancer**

The annual prevalence of transitional cell carcinoma of the pelvis and of the ureter was estimated at 49,885 cases in 2013 in the EU and the prevalence of transitional cell carcinoma of the urethra was estimated at 3,095 cases [RARECARENet, 2023]. The 2013 estimates for Central Europe, Eastern Europe, Northern Europe, and Southern Europe were 1,218 cases, 356 cases, 61 cases, and 809 cases, respectively [RARECARENet, 2023].

**Demographics:**

**I. Bladder cancer**

Globally, the annual age-standardized incidence rate for bladder cancer among males is 4 times greater than that of females (9.5 per 100,000 vs. 2.4 per 100,000), and about 75% of all new bladder cancer cases occur in men (440,864 among males vs. 132,414 among females) [Ferlay et al, 2023; Richters et al, 2020; Fitzmaurice et al, 2019]. In Europe the gap may be slightly wider with an estimated age-standardized rate for men at 20.0 per 100,000 versus 4.6 per 100,000 for females [Ferlay et al, 2023]. In the EU the estimated age-standardized rate for

males is 23.3 per 100,000 versus 5.7 per 100,000 for females [Ferlay et al, 2023]. There were no race/ethnic bladder cancer incidence rates available for the European region, however, the following was observed in the United States (US). The male versus female UBC age standardized incidence rate was 39.0 versus 8.6 for non-Hispanic whites, 19.8 versus 6.7 for non-Hispanic blacks, and 15.2 versus 3.7 for non-Hispanic Asians and Pacific Islanders, 27.0 versus 6.5 for non-Hispanic American Indians and Alaskan Natives, and 18.8 versus 5.0 for Hispanics [Cronin et al, 2022]. The average age at the time of diagnosis was 73 years and the incidence rates of bladder cancer were noticeably higher in US Whites compared to other US race/ethnic groups [Henley et al, 2020].

**II. Upper tract urothelial carcinoma: Renal pelvis cancer and Ureter cancer**

Age-specific incidence rates for renal pelvis and ureter cancers increase with age [Soualhi et al, 2021; Bray et al, 2018; Visser et al, 2012]. Older age has been associated with advanced stage and grade at presentation, and the mean age at diagnosis is 73 years [Soualhi et al, 2021; Soria et al, 2017; Yap et al, 2011]. Less than 0.5% of ureter cancer cases occur in those under age 45, and over 95% occur in those age 55 and above [SEER Program, 2018]. UTUC is also more common (2:1 ratio) in men than in women [RARECARENet, 2023; Soria et al, 2017; Shariat et al, 2011]. There were no race/ethnic UTUC incidence rates available for the European region, however, the following is what we observed in the United States. African American and Hispanic patients were diagnosed at a younger age than Whites and Asians; Hispanics patients were more likely to be diagnosed with larger UTUC tumor sizes than Whites and Asians [Hosain et al, 2012]. Asian patients present with more advanced and higher-grade diseases compared to other race/ethnic groups [Soria et al, 2017]. Historical studies have shown mixed results when comparing UTUC incidence rates of American whites versus American blacks [Cronin et al, 2022].

**Risk Factors:**

**I. Bladder cancer**

Smoking is the most important risk factor for bladder cancer with an attributable risk of approximately 50% [Halaseh et al, 2022; Saginala et al, 2020; Cumberbatch et al, 2018]. Tobacco contains carcinogenic compounds which damage deoxyribonucleic acid. The risk of developing bladder cancer among smokers is 2 to 6 times higher than the risk for non-smokers [Saginala et al, 2020; American Cancer Society, 2018 (b); Cumberbatch et al, 2018;]. Smoking is responsible for 46% of bladder cancer deaths among males and 27% of deaths among females worldwide [Parkin, 2008]. Occupational exposure to carcinogens (e.g., 2-naphthylamine, benzidine, 4-aminobiphenyl, ortho-toluidine, and 4,4'-methylene-bis ([2-chloroaniline]) have also been estimated to increase the attributable risk of bladder cancer 5-7%. Other risk factors include environmental factors (e.g., arsenic and inorganic arsenic compounds). Some medical treatments and diseases such as radiotherapy, schistosomiasis, and cyclophosphamide are also risk factors for bladder cancer. Certain demographic factors such as older age, male sex, white race, industrialized regions, and a family history of bladder cancer are all risk factors for bladder cancer [ Halaseh et al, 2022; Saginala et al, 2020; Cumberbatch et al, 2018].

### II. Upper tract urothelial carcinoma

The most important risk factor for UTUC is smoking, which increases the relative risk for developing UTUC from 2.5 to 7 times compared to non-smokers [Roupret et al, 2023; Shvero et al, 2022; Soria et al, 2017]. Heavier smokers (40 cigarettes smoked per day versus 20 cigarettes smoked per day) and those who have smoked for a longer period have worse UTUC-related health outcomes. The second most important risk factor for UTUC is occupational exposure to diesel fumes and aromatic amines, which increases the relative risk to 8.3 times compared to non-exposure [Roupret et al, 2023; Shvero et al, 2022; Soria et al, 2017]. Aristolochic acid is a plant extract which is ingested as ingredients of traditional herbal remedies or ingested with bread contaminated by Aristolochia seeds [Roupret et al, 2023; Soria et al, 2017]. Aristolochic acid causes Balkan endemic nephropathy and Chinese herb nephropathy, and individuals with these disorders are at an increased risk for UTUC [Miyazaki and Nishiyama, 2017; Soria et al, 2017]. Familial or hereditary factors are also the risk factors for UTUC, accounting for 10 to 20% of all UTUCs. Lastly, patients with Lynch syndrome who have abnormalities in deoxyribonucleic acid mismatch repair, also have a 22-fold increased relative risk of developing UTUC [Shvero et al, 2022; Miyazaki and Nishiyama, 2017].

**Main existing treatment options:**

### I. Bladder cancer

Approximately 10-15% of patients with bladder cancer present with metastasis [Chin et al., 2017]. Patients with untreated metastatic urothelial cancer (UC) can be divided into three broad categories for treatment; (1) patients fit for cisplatin-based chemotherapy, (2) patients unfit for cisplatin, but fit for carboplatin-based chemotherapy, and (3) patients unfit for any platinum-based chemotherapy [Cathomas et al, 2022].

For first-line treatment of advanced or metastatic bladder cancer, the European Association of Urology (EAU) strongly recommends (a) cisplatin-containing combination chemotherapy with GC (gemcitabine plus cisplatin) or HD-MVAC (high-dose intensity methotrexate, vinblastine, adriamycin, and cisplatin) for platinum-fit patients, (b) the combination of carboplatin and gemcitabine for patients unfit for cisplatin, but fit for carboplatin, and (c) maintenance therapy with the PD-L1 inhibitor avelumab for patients achieving stable disease or better after first-line platinum-based chemotherapy [Witjes et al, 2023]. There are no strong recommendations for first-line treatment in patients unfit for platinum-based chemotherapy.

Regarding second-line treatment of metastatic cancer, the EAU strongly recommends pembrolizumab for patients experiencing disease progression during or after platinum-based combination chemotherapy. Concerning treatment after platinum chemotherapy and immunotherapy, enfortumab vedotin is strongly recommended as monotherapy for patients with advanced or metastatic UC pretreated with platinum chemotherapy and immunotherapy [Witjes et al, 2023]. The above recommendations by the EAU are based on the available evidence through 04 May 2022.

### II. Upper tract urothelial carcinoma (UTUC): Renal pelvis cancer and Ureter cancer

For first-line treatment of metastatic UTUC among platinum-eligible patients, the EAU strongly recommends (1) platinum combination chemotherapy, (2) cisplatin-based chemotherapy with gemcitabine/cisplatin or HD-MVAC, and (3) maintenance avelumab to patients who did not have disease progression after 4-6 cycles of gemcitabine plus cisplatin/carboplatin [Rouprêt et al, 2023]. Among patients ineligible for cisplatin, the EAU strongly recommends gemcitabine/carboplatin chemotherapy for first-line treatment.

Regarding the second-line treatment of metastatic UTUC, the EAU strongly recommends (1) a checkpoint inhibitor (pembrolizumab) for patients with disease progression during or after platinum-based combination chemotherapy, (2) enfortumab vedotin for patients previously treated with platinum-containing chemotherapy and who had disease progression during or after treatment with a PD-1 or PD-L1 inhibitor, and (3) vinflunine if immunotherapy or combination chemotherapy is not feasible (or vinflunine as a third- or subsequent-line treatment) [Rouprêt et al, 2023]. The above recommendations by the EAU are based on the available evidence through 04 May 2022.

**Natural history:**

### I. Bladder cancer

A local or pelvis recurrence is detected in 5-15% of bladder cancer patients, usually within 18 months after radial cystectomy [Witjes et al, 2023; Soukup et al, 2012]. Distant recurrences are seen in up to 50% of patients, depending on stage and nodal involvement. Median survival with platinum-based chemotherapy for recurrence is 1 to 2 years [Lehmann et al, 2009]. After radical cystectomy (RC), urethral tumors can be found in 1.5-6.0% of treated bladder cancer patients after a mean of 13.5-39.0 months, with a median survival of 28-38 months, of which >50% die from systemic disease. Risk factors for recurrence include RC for (recurrent) non-muscle-invasive bladder cancer and prostate involvement. UTUCs occur in 1.8-6.0% of patients undergoing RC and represent the most common sites of late recurrence. Median overall survival for these patients is 10-55 months, and 60-67% of patients die of the metastatic disease [Soukup et al, 2012].

Despite routine follow-up, more than half of metastases found in advanced bladder cancer patients after the appearance of symptoms [Witjes et al, 2023]. For the advanced or metastatic bladder cancer patient, performance status (Karnofsky performance status of 80% or less) and the presence of visceral metastases are independent poor prognostic factors for survival [Bellmunt et al, 2014; Bajorin et al, 1999].

Globally, approximately 212,536 patients died from bladder cancer in 2020 and the age-standardized mortality rate for males was estimated at 3.3 per 100,000 and 0.86 per 100,000 for females [Ferlay et al, 2023]. In Europe the age-standardized mortality rate was estimated at 5.5 per 100,000 for males and 1.2 per 100,000 for females in 2020 [Ferlay et al, 2023]. The cumulative risk of dying from bladder cancer between birth and age 74 is 2.58% for males and 0.54% for females and the overall 5-year survival is about 69% [Ferlay et al, 2023; Gerace et al, 2017].

**II. Upper tract urothelial carcinoma: Renal pelvis cancer and Ureter cancer**

Approximately 40% (range, 20-70%) of patients with UTUC, developed urothelial carcinoma of the lower urinary tract [Vikram et al, 2009]. Studies have cited stage, grade, carcinoma in situ, lymphovascular invasion, and lymph node involvement as important prognostic factors impacting survival after surgery [Colin et al, 2014; Lughezzani et al, 2012].

Survival from renal pelvis carcinoma depends on the stage of the disease, where 5-year survival rates are approximately 90% for pathologic stages (pTa/pT1) and less than 5% for stages involving lymph nodes or metastatic disease [Ehsani and Osunkoya, 2014]. In the EU the 5-year relative survival of cancer of the renal pelvis and ureter combined is 51% [Visser et al, 2012].

The one-, three-, and five-year relative survival for transitional cell carcinoma of the pelvis and ureter for males in Europe were 78%, 59%, and 53%, respectively [RARECARENet, 2023]. For females, the one-, three, and five-year relative survival were 75%, 56% and 49%, respectively. The one-, three-, and five-year relative survival for transitional cell carcinoma of the urethra for males in Europe were 77%, 52%, and 42%, respectively. For females the one-, three, and five-year relative survival were 75%, 55%, and 50%, respectively [RARECARENet, 2023].

**Important co-morbidities:**

**I. Bladder cancer**

Comorbidities among bladder cancer patients have been identified as predictors of treatment choice and treatment outcomes [Goossens-Laan et al, 2014]. In a Danish population-based study, the comorbidities of 13,809 bladder cancer patients diagnosed between 1995 and 2011 were recorded [Ording et al, 2016]. The comorbidities among bladder cancer patients in this cohort with a prevalence greater than 5% include myocardial infarction, congestive heart failure, peripheral vascular disease, chronic obstructive pulmonary disease, ulcer disease, diabetes type I or II, and any tumor (except bladder). An 8.8% prevalence of major depressive disorder among bladder cancer patients had also been reported [Park et al, 2017]. Lastly, cancer cachexia has also been associated with UBC. The prevalence of cancer cachexia among UBC patients was reported as 0.6 per 100,000 in both the EU and the US [Anker et al, 2019].

**II. Upper tract urothelial carcinoma: Renal pelvis cancer and Ureter cancer**

UTUC patients are at an increased risk of developing colorectal cancer. Specifically, ureter cancer patients are at a 44% increased risk, and renal pelvis patients are at an 80% increased risk of developing colorectal cancer compared to the general population [Calderwood et al, 2008]. Secondary bladder cancer has also been associated with UTUC and is diagnosed approximately 2 years after the initial UTUC diagnosis [Kates et al, 2012].

# PART II: MODULE SII. NON-CLINICAL PART OF THE SAFETY SPECIFICATION

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|---|---|
| Data-lock point for this Module | 08 Aug 2023 |
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| Key safety findings from nonclinical studies | |
|---|---|
| **Key safety findings (from nonclinical studies)** | **Relevance to human usage** |
| ***Toxicity findings include:*** | |
| **Acute dose toxicity** | |
| Single-dose toxicity studies were not performed; acute toxicity (moribundity/mortality) was not observed in the repeat-dose studies prior to the second dose. | Not applicable |
| **Repeat-dose toxicity** | |
| **Mortality:** Deaths were observed at exposure levels that were at least 6-fold higher than the human exposure at the maximum recommended clinical dose. | High systemic exposures to enfortumab vedotin have been associated with mortality in rats and cynomolgus monkeys at least 6-fold higher than the human exposure at the clinically recommended dose. The rat and monkey deaths were preceded by clear and monitorable signs of toxicity. The recommended dose of enfortumab vedotin is 1.25 mg/kg (up to a maximum of 125 mg for patients ≥100 kg) and is communicated in the EU-SmPC. Appropriate clinical monitoring and care are warranted. |
| **Skin Findings:** In rats and cynomolgus monkeys, skin toxicity was dose limiting. The skin findings are consistent with a targeted toxicity based on the expression the target antigen, Nectin-4 by keratinocytes. In both species, abrasions and/or dry reddened skin were observed at approximately 1-fold the human systemic exposure. Microscopic changes typically associated with these observations included serocellular crusting, epidermal acanthosis, multifocal perivascular dermal and subcutaneous mononuclear cell infiltrates, increased mitotic figures, and erosion/ulceration. These skin-related findings were reversible. | Tissue cross reactivity studies showed that enfortumab vedotin binds to skin, and Nectin-4 is expressed by normal keratinocytes [Mollo et al, 2015; Fortugno et al, 2014]. As such, the skin findings are likely due to a target-dependent effect. The effect is dose-related and fully reversible upon discontinuation of dosing.<br><br>Skin reactions are considered an important identified risk for enfortumab vedotin and appropriate clinical monitoring is warranted. |
| **Injection Site Findings:** Injection site microscopic findings were generally similar to those in the skin and consisted of increased mitotic figures and single cell necrosis in the epidermis and/or adnexa including hair follicles and sebaceous glands, epidermal acanthosis, | Infusion site extravasation is a non-important identified risk for enfortumab vedotin and adequate venous access is to be ensured before infusion. |

| Key safety findings from nonclinical studies | |
|---|---|
| **Key safety findings (from nonclinical studies)** | **Relevance to human usage** |
| perivascular mononuclear infiltrates, and fibrosis. These minimal to mild findings were generally reversible. | |
| **Hematology/Bone Marrow Findings:** In both rats and cynomolgus monkeys, hematologic findings were consistent with bone marrow toxicity including changes in erythrocytic parameters indicative of altered erythropoiesis were noted. These changes were associated with histopathologic findings of hypocellularity in the rat (4-week repeat dose study; Study 20005662) and cynomolgus monkey (bridging study; Study 20021751) bone marrow following 4 weeks of weekly administration. In cynomolgus monkeys, there were also decreases in neutrophils and eosinophils. Hematologic findings were fully reversed by the end of a 6-week recovery period. | The hematological findings were monitorable, reversible, and expected with microtubule-disrupting agents; therefore, these effects are considered manageable with standard monitoring and clinical care. |
| **Ocular Findings:** There were no drug-related ophthalmologic findings in either rats (4-week and 13-week repeat dose studies) or cynomolgus monkeys (4-week repeat dose studies). Histologic findings of minimally increased mitotic figures in the corneal epithelium were noted only in the 13-week rat repeat dose study. | No preclinical findings of clinical significance. However, ocular findings have been reported in clinical trials, and dry eye is recognized as a non-important identified risk, and blurred vision and corneal disorders are non-important potential risks for enfortumab vedotin. Appropriate clinical monitoring is warranted. |
| **Reproductive and developmental toxicity** | |
| **Male Reproductive Organ Findings:** In rats, there were findings of decreased testes and epididymidis organ weights as well as gross pathological findings of small prostate and seminal vesicles. Histological findings included testicular tubular degeneration, hypospermia, and abnormal spermatids. These findings were partially reversible at the end of a 24-week recovery period. | Male reproductive findings have been observed with other microtubule disrupting agents such as vincristine and these chemotherapeutics have been reported to reduce sperm counts clinically [VINCASAR PFS prescribing information, 2018]. Other MMAE ADCs, including brentuximab vedotin [ADCETRIS SmPC, Dec 2020; Lin et al, 2015] have also induced testicular toxicity in rats. These male reproductive findings are considered acceptable in terms of the benefit-risk assessment in oncology treatment. |
| **Embryofetal Development:** Pregnant rats intravenously administered enfortumab vedotin on gestation days 6 and 13 at doses that resulted in systemic exposures ≥1-fold the human exposure, resulted in increases in post-implantation loss and decreases in the number of viable fetuses. The surviving fetuses had an increased incidence of skeletal | Enfortumab vedotin is not recommended during pregnancy and in women of childbearing potential not using contraception. Pregnancy testing is recommended for females of reproductive potential 7 days prior to initiating enfortumab vedotin treatment. Women of childbearing potential are recommended to use effective contraception during treatment and for at least 12 months after the last dose. Male patients with |

| Key safety findings from nonclinical studies | |
|---|---|
| **Key safety findings (from nonclinical studies)** | **Relevance to human usage** |
| variations, with structural malformations noted in one fetus.<br><br>**Fertility and Prenatal/Postnatal Development:** Consistent with ICH S9 for the development of oncology therapies, neither fertility nor prenatal and postnatal developmental studies were conducted for enfortumab vedotin. | female partners of reproductive potential should be advised to use effective contraception during treatment and for at least 9 months after the last dose.<br><br>Appropriate labeling and patient counseling should be used to mitigate this risk. Embryo-fetal toxicity is considered a non-important potential risk for enfortumab vedotin.<br><br>It is unknown whether enfortumab vedotin or its metabolites are excreted in human milk. A risk to nursing newborns/infants cannot be excluded. Breastfeeding should be discontinued during treatment with enfortumab vedotin and for at least 6 months after the last dose. |
| **Genotoxicity** | |
| An in vivo rat bone marrow micronucleus test was performed only on the cytotoxic agent, MMAE. The results revealed that MMAE was aneugenic in this model, which is consistent with the pharmacologic effects on tubulin polymerization. | Enfortumab vedotin is not recommended during pregnancy and in women of childbearing potential not using contraception. Females of reproductive potential are advised to use effective contraception during treatment with enfortumab vedotin and for at least 12 months after the last dose of enfortumab vedotin.<br>Males with female partners of reproductive potential are advised to use effective contraception during treatment with enfortumab vedotin and for at least 9 months after the last dose of enfortumab vedotin |
| **Carcinogenicity** | |
| In accordance with ICH S9, no carcinogenicity studies were conducted for enfortumab vedotin. | Carcinogenic potential of enfortumab vedotin has not been evaluated given the life expectancy in the indicated population. |
| ***General safety pharmacology findings:*** | |
| **In Vitro:** MMAE, at concentrations 19,405-fold higher than the clinically observed Cmax had limited (less than 50%) inhibition of potassium conductance via human ether-à-go-go (hERG) channel and at 10 µmol/L there was no significant inhibition of hERG channel activity. The ADC was not evaluated in these in vitro studies as the antibody portion of the ADC is too large to cross plasma membranes and therefore would be unable to access and block the promiscuous inner pore of the hERG channel.<br>**In Vivo:** In cynomolgus monkeys, AGS-22M6E had no effect on the QTcF and RR- | Findings noted at systemic exposures that are not achievable clinically suggesting enfortumab vedotin poses little or no safety risks clinically on ECG parameters, heart rate, blood pressure, respiratory or CNS safety pharmacology parameters. |

| Key safety findings from nonclinical studies | |
|---|---|
| **Key safety findings (from nonclinical studies)** | **Relevance to human usage** |
| interval at concentrations up to 6-fold higher than the clinically observed Cmax.<br><br>The anti-Nectin-4 monoclonal antibody, MMAE drug conjugate nor AGS-22M6E, had no effect on other ECG parameters, heart rate, blood pressure, respiratory or CNS safety pharmacology parameters. | |

ADC: Antibody-drug Conjugate; CNS: Central Nervous System; ECG: Electrocardiogram; hERG: human ether-à-go-go; ICH: International Council of Harmonization; MMAE: monomethyl auristatin E; QTcF: QTc corrected with Fridericia's formula; RR: Reporting Rate; SmPC: Summary of Product Characteristics.

# PART II: MODULE SIII. CLINICAL TRIAL EXPOSURE

| | |
|---|---|
| Data-lock point for this Module | 08 Aug 2023 |
| Version when Module last updated | 3.0 |

In this Risk Management Plan (RMP), the safety profile of enfortumab vedotin is derived from 7 clinical studies involving 793 EV Monotherapy patients and 564 EV + Pembro patients referred as EV Mono and EV + Pembro Combo respectively thereafter. These studies include:

- Study EV-301 (7465-CL-0301)
- Study EV-302 (SGN22E-003)
- Study EV-201 (SGN22E-001)
- Study EV-203 (7465-CL-1104)
- Study EV-101 (ASG-22CE-13-2)
- Study EV-102 (7465-CL-0101)
- Study EV-103 (SGN22E-002)

The studies included in the Integrated Safety Population for this RMP are summarized in [Table SIII 1].

## Table SIII 1: Clinical Studies Included in this RMP

| Study ID | Study phase | Study population (Study type) | Study design | Treatment regimen | Study Status | Subjects in Safety Analysis Set, total and by treatment group (as of 08 Aug 2023) |
|---|---|---|---|---|---|---|
| EV-302 (SGN22E-003) | 3 | Locally advanced or mUC previously untreated (Efficacy, safety) | Phase 3/randomized, open-label, enfortumab vedotin in combination with pembrolizumab vs chemotherapy | Arm A: IV infusion of enfortumab vedotin 1.25 mg/kg on Days 1, 8 and pembrolizumab 200 mg on Day 1 of each 21-day cycle. (Included)<br>Arm B: IV infusion of gemcitabine 1000 mg/m$^2$ on Days 1, and 8 and cisplatin 70 mg/m$^2$ or carboplatin at AUC 4.5 or 5 on Day 1 of each 21-day cycle. (Included)<br>Arm C: IV infusion of enfortumab vedotin 1.25 mg/kg on Days 1, 8 and pembrolizumab 200 mg on Day 1 and cisplatin 70 mg/m$^2$ or carboplatin at AUC 4.5 or 5 on Day 1 of each 21-day cycle.<br>Japan-specific safety run-in: IV infusion of enfortumab vedotin 1.25 mg/kg on Days 1, 8 and pembrolizumab 200 mg on Day 1 of each 21-day cycle. (Included). | Ongoing (enrollment closed) | Total: 876<br>EV + Pembro 443 (Arm A 440 and 3 Japan-specific safety run-in) |
| EV-301 (7465-CL-0301) | 3 | LA/mUC who have received a platinum-containing chemotherapy and have experienced disease progression or relapse during or following treatment with a PD-1 or PD-L1 inhibitor<br>(Efficacy, safety) | Phase 3 multinational, open-label, randomized trial of enfortumab vedotin vs. chemotherapy | Enfortumab vedotin: 1.25 mg/kg 30-min IV infusion on days 1, 8, and 15 of a 28-day cycle or Docetaxel 75 mg/m$^2$, paclitaxel 175 mg/m$^2$ or vinflunine 320 mg/m$^2$ on day 1 of a 21-day cycle | Ongoing (enrollment closed) | Total: 587<br>EV 1.25mg/kg: 296<br>Standard chemotherapy: 291 |

| Study ID | Study phase | Study population (Study type) | Study design | Treatment regimen | Study Status | Subjects in Safety Analysis Set, total and by treatment group (as of 08 Aug 2023) |
|---|---|---|---|---|---|---|
| EV-201 (SGN22E-001) | 2 | LA/mUC; previously treated with PD-1/PD-L1<br><br>(Efficacy, safety) | Open-label, multicenter trial of efficacy and safety as monotherapy/single-arm<br>Cohort 1: Prior PD-1/PD-L1 and platinum-based chemotherapy<br>Cohort 2: Prior PD-1/PD-L1, platinum naïve in the LA/mUC setting, cisplatin-ineligible | 1.25 mg/kg on days 1, 8, and 15 of a 28-day cycle | Ongoing<br>(enrollment closed) | EV 1.25mg/kg: 214 |
| EV-101 (ASG-22CE-13-2) | 1 | mUC and other Nectin-4-expressing malignant solid tumors<br><br>(Safety, PK) | Open-label, nonrandomized, multicenter study of the safety and PK of escalating doses of enfortumab vedotin as monotherapy followed by expansion Part A: dose escalation<br>Part B: expansion (including renal insufficiency, NSCLC, and ovarian cancer expansion cohorts)<br>Part C: in subjects previously treated with PD-1/PD-L1 inhibitors | 0.5 to 1.25 mg/kg on days 1, 8, and 15 of a 28-day cycle | Completed | All Enfortumab vedotin: 213<br>[EV 1.25 mg/kg: 162] |
| EV-102 (7465-CL-0101) | 1 | Japanese subjects with LA/mUC<br><br>(Safety, PK) | Open-label, randomized, multicenter study of the safety, tolerability, and PK of 2 doses of enfortumab vedotin in Japanese subjects | 1.0 or 1.25 mg/kg on days 1, 8, and 15 of a 28-day cycle | Completed | All Enfortumab vedotin: 17<br>[EV 1.25 mg/kg: 8] |

| Study ID | Study phase | Study population (Study type) | Study design | Treatment regimen | Study Status | Subjects in Safety Analysis Set, total and by treatment group (as of 08 Aug 2023) |
|---|---|---|---|---|---|---|
| EV-103 / SGN22E-002 (Global) | 1b/2 | Subjects with la/mUC who must be either ineligible for first-line cisplatin-based chemotherapy and have not received prior systemic treatment for la/mUC or must have disease progression during or following treatment with at least 1 platinum-containing regimen.<br>Subjects with muscle invasive bladder cancer (MIBC) who must be ineligible for cisplatin-based chemotherapy and must not have received prior systemic treatment, chemoradiation, or radiation therapy for MIBC. | Monotherapy or combination with other anticancer therapies, open-label | All cohorts receive on Days 1, 8 of each 21-day cycle.<br>For EV + Pembro, subjects: Pembrolizumab 200 mg on Day 1 of each 21-day cycle approximately 30 minutes after completion of enfortumab vedotin infusion<br>• **la/mUC**<br>Dose Escalation:<br>EV 1.0 mg/kg + Pembro<br>EV 1.25 mg/kg + Pembro<br>Expansion Cohort A: EV 1.25 mg/kg + Pembro<br>Expansion Cohort D: EV 1.25mg/kg + Cisplatin<br>Expansion Cohort E: EV 1.25 mg/kg + Carboplatin<br>Expansion Cohort G: EV 1.25 mg/kg + Cisplatin/Carboplatin + Pembro<br>Randomized Cohort K:<br>EV mono arm: EV 1.25 mg/kg (Included)<br>EV + Pembro arm: EV 1.25 mg/kg + Pembro<br>• **MIBC**<br>Cohort H: EV 1.25 mg/kg in neoadjuvant setting<br>Cohort L : EV 1.25 mg/kg in perioperative setting | Ongoing<br>(Enrollment closed) | [EV-103 Cohort K EV monotherapy1.25 mg/kg: 73]<br>[EV-103 EV + Pembro: DE/Cohort A + Cohort K combo arm: 121] |
| EV-203/7465-CL-1104 (China) | 2 | Chinese subjects with locally advanced or metastatic urothelial carcinoma (mUC) | Monotherapy, single-arm, open-label | 1.25 mg/kg on Days 1, 8 and 15 of each 28-day cycle | Ongoing (enrollment closed) | All Enfortumab vedotin: 40<br>[EV 1.25 mg/kg: 40] |

DE: Dose Escalation; EV: Enfortumab vedotin; LA: Locally Advanced; MIBC: Muscle Invasive Bladder Cancer; mUC: metastatic urothelial cancer; NSCLC: Non-Small Cell Lung Carcinoma; PD-1: Programmed Cell Death Receptor-1; PD-L1: Programmed Cell Death-ligand 1; PK: Pharmacokinetics.
EV-302 data cutoff date is 08 Aug 2023.
EV-201, EV-301, EV-103, EV-203, data cutoff date is 13 Mar 2023.
EV-101 data cutoff date is 16 Dec 2022.
EV-102 data cutoff date is 25 Feb 2019.

**Table SIII.2: Duration of Exposure**

| EV Mono | | |
|---|---|---|
| **Duration of exposure** | **Patients** | **Person time (months)** |
| <1 month | 109 | 92.7 |
| 1 to 6 months | 382 | 1381.9 |
| 6 to 12 months | 190 | 1539.4 |
| ≥12 months | 112 | 2270.2 |
| Total | 793 | 5284.2 |
| | | |
| **EV + Pembro Combo** | | |
| **Duration of exposure** | **Patients** | **Person time (months)** |
| <1 month | 34 | 22.1 |
| 1 to 6 months | 196 | 742.0 |
| 6 to 12 months | 198 | 1701.7 |
| ≥12 months | 136 | 2313.0 |
| Total | 564 | 4778.9 |

EV: Enfortumab vedotin; Source: EV-302 ISS Adhoc RMP Table 12.2.1.3

**Table SIII.3: Exposure by Age Group and Gender**

| EV Mono | | | | |
|---|---|---|---|---|
| | **Patients** | | **Person time (months)** | |
| **Age group** | **M** | **F** | **M** | **F** |
| <65 years | 195 | 84 | 1462.4 | 516.8 |
| 65-74 years | 229 | 81 | 1606.7 | 574.5 |
| >=75 years | 160 | 44 | 872.8 | 251.1 |
| Total | 584 | 209 | 3941.9 | 1342.4 |
| | | | | |
| **EV + Pembro Combo** | | | | |
| | **Patients** | | **Person time (months)** | |
| **Age group** | **M** | **F** | **M** | **F** |
| <65 years | 141 | 32 | 1328.5 | 354.1 |
| 65-74 years | 195 | 52 | 1493.9 | 512.5 |
| >=75 years | 96 | 48 | 740.7 | 349.1 |
| Total | 432 | 132 | 3563.2 | 1215.7 |

EV: Enfortumab vedotin; Pembro: Pembrolizumab; F: female; M: male. Source: EV-302 ISS Adhoc RMP Table 12.2.1.3

**Table SIII.4: Exposure by Dose**

| Dose of exposure | Patients | Person time (months) |
|---|---|---|
| EV Mono | 793 | 5284.2 |
| EV + Pembro Combo | 564 | 4778.9 |

EV: Enfortumab vedotin; Source: EV-302 ISS Adhoc RMP Table 12.2.1.3

**Table SIII.5: Exposure by Race**

| **EV Mono (person time)** | | |
|---|---|---|
| **Race** | **Patients** | **Person time (months)** |
| White | 527 | 3399.9 |
| Black or African American | 12 | 106.0 |
| Asian | 191 | 1359.1 |
| American Indian or Alaska Native | 0 | 0 |
| Other | 62 | 405.3 |
| Missing | 1 | 13.9 |
| Total | 793 | 5284.2 |
| | | |
| **EV + Pembro Combo** | | |
| **Race** | **Patients** | **Person time (months)** |
| White | 410 | 3292.5 |
| Black or African American | 9 | 90.3 |
| Asian | 107 | 1094.3 |
| American Indian or Alaska Native | 2 | 20.5 |
| Other | 36 | 281.3 |
| Missing | 0 | 0 |
| Total | 564 | 4778.9 |

EV: Enfortumab vedotin; Source: EV-302 ISS Adhoc RMP Table 12.2.1.3

# PART II: MODULE SIV. POPULATIONS NOT STUDIED IN CLINICAL TRIALS

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|---|---|
| Data-lock point for this Module | 08 Aug 2023 |
| Version when Module last updated | 3.1 |

## SIV.1 Exclusion criteria in pivotal clinical studies within the development program

EV-301 is the pivotal clinical study within the enfortumab vedotin clinical development program. The majority of exclusion criteria in the trials within the clinical development program were established in order to avoid confounding the assessment of safety and efficacy or to prevent enrollment of subjects with conditions for whom participation in a clinical trial would not be in their best interest. Important exclusion criteria in the clinical development program are discussed in [Table SIV 1].

EV-302 is an ongoing, global phase 3, open-label, 2-arm randomized multicenter study to evaluate the combination of enfortumab vedotin + pembrolizumab vs standard of care gemcitabine + platinum-containing chemotherapy in subjects with previously untreated locally advanced or metastatic urothelial cancer. The exclusion criteria included in EV-302 for enfortumab vedotin were generally consistent with the important exclusion criteria included in the enfortumab vedotin monotherapy clinical development program. Any differences or additional exclusion criteria included in EV-302 were updated in [Table SIV 1].

**Table SIV 1: Important Exclusion Criteria in Pivotal Clinical Trials Across the Development Program**

| **Criterion 1** | **Subjects <18 years of age or not considered an adult according to local regulation** |
|---|---|
| Reason for being an exclusion criterion | There are currently no safety or efficacy data to support the use of enfortumab vedotin in the pediatric population. The safety and efficacy of enfortumab vedotin in pediatric subjects aged 18 years and younger have not been established. |
| Is it considered to be included as missing information? | No |
| Rationale (if not included as missing information) | A pediatric waiver was granted for enfortumab vedotin on 23 Feb 2018 by the European Medicines Agency (EMA). The waiver was granted on the grounds that the disease or condition for which the specific medicinal product is intended does not occur in the specified pediatric subset(s), children aged 0-18. |
| **Criterion 2** | **Subjects with cancers other than histologically or cytologically confirmed urothelial carcinoma** |
| Reason for being an exclusion criterion | The safety and efficacy of enfortumab vedotin in subjects with cancers other than urothelial carcinoma have not been established. |
| Is it considered to be included as missing information? | No |

| | |
|---|---|
| Rationale (if not included as missing information) | EV-202 study is currently ongoing. The EV-202 study is an open-label, multicenter, multicohort, phase 2 study to evaluate enfortumab vedotin in subjects with previously treated locally advanced or metastatic malignant solid tumors. |
| **Criterion 3** | **Subjects with ECOG Performance Score of ≥2** |
| Reason for being an exclusion criterion | Only subjects with ECOG performance status of 0 or 1 were included in Studies EV-101, EV-102, EV-201 Cohort 1, EV-203 and EV-301. Subjects with ECOG performance status 0 to 2 were allowed to participate in Study EV-103 and EV-201 Cohort 2, as ECOG performance status 2 is considered a reason for cisplatin ineligibility and these studies/cohorts were designed to evaluate efficacy and safety in cisplatin ineligible subjects. In Study EV-302, subjects who were both cisplatin eligible and ineligible were allowed to participate, and therefore subjects with ECOG performance status of 0 to 2 were allowed to participate. Subjects with ECOG 2 or higher performance status were excluded from the other trials in order to reduce potential confounding of the assessment of efficacy or safety. |
| Is it considered to be included as missing information? | No |
| Rationale (if not included as missing information) | Subjects with ECOG of greater than 2 were excluded for clinical trial purposes only to allow clear assessment of efficacy and safety. Subjects with poor performance status due to locally advanced or metastatic urothelial carcinoma are not expected to have a different risk-benefit ratio. |
| **Criterion 4** | **Subjects with baseline neutropenia (ANC ≤1500/mm$^3$)** |
| Reason for being an exclusion criterion | Subjects with an ANC ≥ 1.0 x $10^9$/L were included in studies EV-101, EV-102, EV-201, and EV-203. Subjects in EV-301 and EV-302 were required to have a higher ANC of ≥ 1500/mm$^3$ since the comparator chemotherapy agents in this study are associated with neutropenia. Subjects with an ANC ≥ 1.5 x $10^9$/L were included in Study EV-103. The safety and efficacy of enfortumab vedotin has not been established in subjects with an ANC < 1.0 x $10^9$/L. Neutropenia is considered a non-important identified risk for enfortumab vedotin. Among hematological changes, neutropenia is frequently observed in enfortumab vedotin clinical trials. Of the 793 subjects in the EV Mono Integrated Safety Population, 134 (16.9%) had any neutropenia reported, including 60 (7.6%) subjects with TEAE of Neutropenia, 69 (8.7%) subjects with TEAE of Neutrophil count decreased and 12 (1.5%) with Febrile neutropenia (EV-302 ISS Table 12.6.1.5.7.1). Subjects with neutropenia were excluded in order to reduce potential confounding of the assessment of safety. |
| Is it considered to be included as missing information? | No |
| Rationale (if not included as missing information) | Neutropenia is a non-important identified risk for enfortumab vedotin. Subjects should have adequate neutrophil counts prior to starting therapy with enfortumab vedotin to minimize any potential neutropenia that may occur while on treatment. |

| **Criterion 5** | **Subjects with baseline creatinine clearance <30 mL/min** |
|---|---|
| Reason for being an exclusion criterion | Study EV-102 included subjects with a measured 24-hour creatinine clearance of ≥ 45 mL/min. Studies EV-101, EV-103, EV-201, EV-203, EV-301 and EV-302 included subjects with creatinine clearance of ≥ 30 mL/min.<br><br>An additional renal insufficiency cohort was included in the EV-101 study and included subjects with creatinine clearance ≥ 15 mL/min and < 30 mL/min.<br>Subjects with severe renal insufficiency were excluded from other enfortumab vedotin clinical trials in order to reduce potential confounding of the assessment of safety. Of the 793 subjects who participated in EV Mono clinical trials, there was only 1 subject with end-stage renal disease. |
| Is it considered to be included as missing information? | No |
| Rationale (if not included as missing information) | The population pharmacokinetics analysis of enfortumab vedotin and unconjugated MMAE were conducted after the administration of enfortumab vedotin as monotherapy 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 significant differences in exposure (AUC) of ADC and unconjugated MMAE were observed in patients with mild, moderate or severe renal impairment compared to patients with normal renal function. The effect of end stage renal disease with or without dialysis on the pharmacokinetics of ADC or unconjugated MMAE is unknown. Data from the EV-101 study renal impairment cohort also confirms that subjects with severe renal impairment have the same benefit-risk ratio as subjects with normal renal function. No dose adjustment is required in subjects with mild, moderate or severe renal impairment.<br>Similar results were observed from studies of enfortumab vedotin in combination with pembrolizumab. |

| | |
|---|---|
| **Criterion 6** | **Subjects with baseline hepatic dysfunction (alanine aminotransferase (ALT) and aspartate aminotransferase (AST) > 2.5 × upper limit of normal (ULN) or > 3 x ULN for subjects with liver metastases or serum total bilirubin > 1.5 × ULN or > 3 × ULN for subjects with Gilbert's disease)** |
| Reason for being an exclusion criterion | Subjects with baseline moderate and severe hepatic dysfunction were excluded from enfortumab vedotin clinical trials in order to reduce potential confounding of the assessment of safety. However, there were 2 subjects with moderate hepatic impairment (National Cancer Institute- Organ Dysfunction Working Group [NCI-ODWG criteria]) included in study EV-301 and 1 subject with moderate hepatic impairment included in Cohort 2 of EV-201. Studies EV-101 Renal Impairment Cohort and EV-102 included subjects with ALT and AST of ≤ 1.5 x ULN. Studies EV-101 dose escalation and NSCLC, Ovarian, and CPI-Treated Expansion Cohorts, EV-103, EV-201, and EV-203 included subjects with ALT and AST ≤ 3.0 x ULN. EV-301 included subjects with ALT and AST ≤ 2.5 × ULN or ≤ 3 x ULN for subjects with liver metastases. EV-302 included subjects with ALT and AST ≤ 2.5 × ULN or ≤ 5 x ULN for subjects with liver metastases. Studies EV-101, EV-102, EV-103, EV-201, EV-301 and EV-302 included subjects with a Total bilirubin of ≤ 1.5 x ULN; however, EV-103, EV-201, EV-301 and EV-302 included a provision for subjects with Gilbert's disease with a Total bilirubin of ≤3 × ULN. |
| Is it considered to be included as missing information? | No |
| Rationale (if not included as missing information) | Based on population pharmacokinetics analysis using data from enfortumab vedotin monotherapy clinical trials in subjects with metastatic UC, no significant differences in ADC exposure and a 37% and 16% increase in unconjugated MMAE average concentrations in patients with previously treated and previously untreated locally advanced or metastatic urothelial cancer, respectively, with mild hepatic impairment (total bilirubin of 1 to 1.5 × ULN and AST any, total bilirubin ≤ ULN and AST > ULN, n=65) compared to subjects with normal hepatic function (n=669). Enfortumab vedotin has only been evaluated in a limited number of patients with moderate and severe hepatic impairment. Hepatic impairment is expected to increase systemic exposure to MMAE (the cytotoxic drug); therefore, patients should be closely monitored for potential adverse events. Due to the sparsity of the data in patients with moderate and severe hepatic impairment, no specific dose recommendation can be given.<br>Similar results were observed from studies of enfortumab vedotin in combination with pembrolizumab. |
| **Criterion 7** | **Subjects who are pregnant or breastfeeding** |

| | |
|---|---|
| Reason for being an exclusion criterion | The effect of enfortumab vedotin on human embryo-fetal development is unknown. In an animal reproduction study, the administration of enfortumab vedotin to pregnant rats during organogenesis at clinically relevant systemic exposures was associated with an increased rate of embryo-fetal mortality, structural malformations, and skeletal anomalies.<br>There is no information regarding the presence of enfortumab vedotin in human milk, the effects on the breastfed infant, or the effects on milk production. |
| Is it considered to be included as missing information? | No |
| Rationale (if not included as missing information) | As described in the EU-SmPC (Section 4.6), Pregnancy testing is recommended for females of reproductive potential within 7 days prior to initiating enfortumab vedotin treatment. Females of reproductive potential are advised to use effective contraception during treatment with enfortumab vedotin and for at least 12 months after the last dose of enfortumab vedotin. Males with female partners of reproductive potential are advised to use effective contraception during treatment with enfortumab vedotin and for at least 9 months after the last dose of enfortumab vedotin.<br>There is no information regarding the presence of enfortumab vedotin in human milk. A risk to breast-fed children cannot be excluded. Breastfeeding is not recommended during enfortumab vedotin treatment and for at least 6 months after the last dose. |
| **Criterion 8** | **Subject has preexisting sensory or motor neuropathy Grade ≥ 2** |
| Reason for being an exclusion criterion | Subjects with preexisting sensory or motor neuropathy Grade ≥ 2 were excluded from enfortumab vedotin clinical trials in order to reduce potential confounding of the assessment of safety. The cytotoxic component of enfortumab vedotin, MMAE, is a microtubule-disrupting agent, which is known to be associated with peripheral neuropathy. Peripheral neuropathy is commonly observed in subjects treated with enfortumab vedotin. Of the 793 subjects in the EV Mono Integrated Safety Population, 422 (53.2%) had a treatment-emergent peripheral motor or sensory neuropathy event (EV-302 ISS Table 12.6.1.5.1.1). |
| Is it considered to be included as missing information? | No |

| | |
|---|---|
| Rationale (if not included as missing information) | Subjects with Grade ≥ 2 peripheral neuropathy were excluded to reduce the potential for confounding the interpretation of the safety data in clinical trials.<br>Per the Jul 2020 ESMO-EONS-EANO Clinical Practice Guidelines for diagnosis, prevention, treatment, and follow-up of systemic anticancer therapy-induced neurotoxicity, concurrent exposure to other neurotoxic agents and pre-existing neuropathy should be considered as a potential risk factor for the development of peripheral neuropathy. However, in the EV Mono Integrated Safety Population, the incidence of peripheral neuropathy events was not higher in subjects with a history of peripheral neuropathy (114/231 [49.4%] in all subjects treated with enfortumab vedotin monotherapy with a history of peripheral neuropathy vs. 308/562 [54.8%] in all subjects treated with enfortumab vedotin monotherapy without a history of peripheral neuropathy) [EV-302 ISS Table 12.6.1.5.1.11].<br>Peripheral neuropathy is a non-important identified risk for enfortumab vedotin. Dose modification guidelines are presented in the EU-SmPC to mitigate this risk. In clinical practice, given the severity of the disease being treated with enfortumab vedotin and given that there was not an increase in peripheral neuropathy events in clinical trials for subjects with a history of peripheral neuropathy, patients with pre-existing peripheral neuropathy will likely be treated with enfortumab vedotin. Therefore, prescribers and patients will need to evaluate the benefits and risks associated with enfortumab vedotin, including the risk for worsening neuropathy in individual patients with pre-existing peripheral neuropathy when making treatment decisions. |
| **Criterion 9** | **Subject has active central nervous system (CNS) metastases.** |
| Reason for being an exclusion criterion | CNS metastases from urothelial carcinoma are rare [Yao et al, 2019; Dong et al, 2017] and when present, represent advanced disease with poor prognosis. If a subject chooses to have treatment for CNS metastases, treatment may include radiation, surgery or stereotactic radiosurgery.<br>These subjects were excluded from enfortumab vedotin clinical trials in order to reduce potential confounding of the assessment of efficacy and safety. |
| Is it considered to be included as missing information? | No |
| Rationale (if not included as missing information) | This exclusion criterion was implemented to create a controlled clinical trial environment, and not for a specific safety concern. |
| **Criterion 10** | **Subject has ongoing clinically significant toxicity (Grade 2 or higher with the exception of alopecia) associated with prior treatment (including systemic therapy, radiotherapy or surgery).** |
| Reason for being an exclusion criterion | These subjects were excluded from enfortumab vedotin pivotal trials in order to reduce potential confounding of the assessment of safety. |
| Is it considered to be included as missing information? | No |

| | |
|---|---|
| Rationale (if not included as missing information) | Not applicable. This exclusion criterion was implemented to create a controlled clinical trial environment, and not for a specific safety concern. |
| **Criterion 11** | **Subject has prior treatment with EV or other MMAE-based ADCs.** |
| Reason for being an exclusion criterion | Subjects previously treated with EV or other MMAE-based ADCs were excluded from enfortumab vedotin clinical trials in order to reduce potential confounding of the assessment of efficacy and safety. |
| Is it considered to be included as missing information? | No |
| Rationale (if not included as missing information) | Not applicable. This exclusion criterion was implemented to create a controlled clinical trial environment, and not for a specific safety concern. |
| **Criterion 12** | **Subject has received more than 1 prior chemotherapy regimen for locally advanced or metastatic urothelial cancer, including chemotherapy for adjuvant or neo-adjuvant disease if recurrence occurred within 12 months of completing therapy.** |
| Reason for being an exclusion criterion | This was an exclusion criterion only in study EV-301. These subjects were excluded from EV-301 for clinical trial purposes only in order to reduce potential confounding of the assessment of efficacy and safety. |
| Is it considered to be included as missing information? | No |
| Rationale (if not included as missing information) | Not applicable. This exclusion criterion was implemented to create a controlled clinical trial environment, and not for a specific safety concern. |
| **Criterion 13** | **Subjects must not have received prior systemic therapy for locally advanced or metastatic urothelial carcinoma including adjuvant or neo-adjuvant chemotherapy if recurrence occurred within 12 months of completing therapy.** |
| Reason for being an exclusion criterion | This was an exclusion criterion only in study EV-302/EV-103 (Cohort A, Cohort D, Cohort E, Cohort G and Cohort K). |
| Is it considered to be included as missing information? | No |
| Rationale (if not included as missing information) | Not applicable. This exclusion criterion was implemented to create a controlled clinical trial environment, and not for a specific safety concern. |
| **Criterion 14** | **Subject has history of another malignancy within 3 years before the first dose of study drug, or any evidence of residual disease from a previously diagnosed malignancy. Subjects with nonmelanoma skin cancer, localized prostate cancer treated with curative intent with no evidence of progression, low-risk or very low-risk (per standard guidelines) localized prostate cancer under active surveillance/watchful waiting without intent to treat, or carcinoma in situ of any type (if complete resection was performed) are allowed.** |
| Reason for being an exclusion criterion | These subjects were excluded from enfortumab vedotin clinical trials in order to reduce potential confounding of the assessment of efficacy and safety. |

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| Is it considered to be included as missing information? | No |
| Rationale (if not included as missing information) | Not applicable. This exclusion criterion was implemented to create a controlled clinical trial environment, and not for a specific safety concern. The safety and efficacy profile for such subjects is not expected to be different. |
| **Criterion 15** | **Subject is currently receiving systemic antimicrobial treatment for viral, bacterial, or fungal infection at the time of first dose of EV. Routine antimicrobial prophylaxis is permitted.** |
| Reason for being an exclusion criterion | These subjects were excluded from enfortumab vedotin clinical trials in order to reduce potential confounding of the assessment of safety. |
| Is it considered to be included as missing information? | No |
| Rationale (if not included as missing information) | Not applicable. This exclusion criterion was implemented to create a controlled clinical trial environment, and not for a specific safety concern. |
| **Criterion 16** | **Subject has known active Hepatitis B (e.g., HBsAg reactive) or active Hepatitis C (e.g., HCV RNA [qualitative] is detected).** |
| Reason for being an exclusion criterion | These subjects were excluded from enfortumab vedotin clinical trials in order to reduce potential confounding of the assessment of safety. |
| Is it considered to be included as missing information? | No |
| Rationale (if not included as missing information) | This exclusion criterion was implemented to create a controlled clinical trial environment and minimize confounding of safety from either Hepatitis infection or the antiviral therapies used to treat Hepatitis B or C. |
| **Criterion 17** | **Subject has known history of human immunodeficiency virus (HIV) infection (HIV 1 or 2).** |
| Reason for being an exclusion criterion | As subjects with HIV can have impaired immune function, these subjects were excluded from enfortumab vedotin clinical trials in order to reduce potential confounding of the assessment of efficacy and safety. |
| Is it considered to be included as missing information? | No |
| Rationale (if not included as missing information) | Not applicable. This exclusion criterion was implemented to create a controlled clinical trial environment, and not for a specific safety concern. |
| **Criterion 18** | **Subject has documented history of a cerebral vascular event (stroke or transient ischemic attack), unstable angina, myocardial infarction, or cardiac symptoms (including congestive heart failure) consistent with New York Heart Association (NYHA) Class III-IV within 6 months prior to the first dose of study drug.** |

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| Reason for being an exclusion criterion | Subjects with significant cardiovascular or cerebrovascular disease were excluded from clinical trials to reduce potential confounding of the assessment of safety and not because of a specific safety concern. Subjects with NYHA Class III heart failure were allowed to participate in studies EV-103 (Cohort H, Cohort K and Cohort L) and EV-302, as NYHA Class III heart failure is considered a reason for cisplatin ineligibility and these studies evaluated efficacy and safety in cisplatin-ineligible subjects. Enfortumab vedotin has not been studied in subjects with a history of congestive heart failure consistent with NYHA Class IV within 6 months of the first dose of enfortumab vedotin. |
| Is it considered to be included as missing information? | No |
| Rationale (if not included as missing information) | This exclusion criterion was implemented to ensure that patients were clinically stable prior to enrolling in clinical trials. |
| **Criterion 19** | **Subject has radiotherapy or major surgery within 4 weeks prior to first dose of study drug.** |
| Reason for being an exclusion criterion | This exclusion criterion was implemented to create a controlled clinical trial environment and reduce potential confounding of the assessment of safety and not for a specific safety concern. Subjects who have received radiotherapy within 2 weeks prior to randomization or received major surgery within 4 weeks prior to randomization were excluded in study EV-302. Subjects with locally advanced or metastatic urothelial cancer who had received radiotherapy or major surgery within 2 weeks prior to first dose of study drug were excluded in study EV-103. |
| Is it considered to be included as missing information? | No |
| Rationale (if not included as missing information) | Not relevant because the exclusion criterion was implemented to create a controlled clinical trial environment, and not for a specific safety concern. Prescribers will have to use clinical judgement to determine the timing of starting enfortumab vedotin after a subject completes radiotherapy or undergoes major surgery. |
| **Criterion 20** | **Subject has had chemotherapy, biologics, investigational agents, and/or antitumor treatment with immunotherapy that is not completed 2 weeks prior to first dose of study drug.** |
| Reason for being an exclusion criterion | This exclusion criterion was implemented to create a controlled clinical trial environment and reduce potential confounding of the assessment of efficacy and safety and not for a specific safety concern. Subjects with locally advanced or metastatic urothelial cancer who had received anti-cancer treatment with chemotherapy, biologics, or investigational agents that was not completed 4 weeks prior to first dose of study treatment were excluded in studies EV-103 and EV-302. |
| Is it considered to be included as missing information? | No |

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| Rationale (if not included as missing information) | Not relevant because the exclusion criterion was implemented to create a controlled clinical trial environment, and not for a specific safety concern. Prescribers will have to use clinical judgement to determine the timing of starting enfortumab vedotin after a subject stops prior anticancer therapy. |
| **Criterion 21** | **Subject has known hypersensitivity to EV or to any excipient contained in the drug formulation of EV (including histidine, histidine monohydrochloride monohydrate, trehalose dihydrate, and polysorbate 20 (E432)); OR subject has known hypersensitivity to biopharmaceuticals produced in Chinese hamster ovary (CHO) cells.** |
| Reason for being an exclusion criterion | Subjects with a known hypersensitivity to enfortumab vedotin or to any excipient contained in the drug formulation of enfortumab vedotin (including histidine, histidine monohydrochloride monohydrate, trehalose dihydrate, and polysorbate 20); OR subject has known hypersensitivity to biopharmaceuticals produced in Chinese hamster ovary (CHO) cells were excluded for patient safety.<br><br>Subjects in study EV-103 with a known severe (≥ Grade 3) hypersensitivity to enfortumab vedotin or to any excipient contained in the drug formulation of enfortumab vedotin (including histidine, trehalose dihydrate, and polysorbate 20); OR subject has known severe (≥ Grade 3) hypersensitivity to pembrolizumab or to any excipient contained in the drug formulations of pembrolizumab were excluded for patient safety.<br><br>Subjects in study EV-302 with a known severe (≥ Grade 3) hypersensitivity to any enfortumab vedotin excipient contained in the drug formulation of enfortumab vedotin (including histidine, trehalose dihydrate, and polysorbate 20); OR subject has known severe (≥ Grade 3) hypersensitivity to any pembrolizumab excipient contained in the drug formulations of pembrolizumab; OR subject has known severe (≥ Grade 3) hypersensitivity to the platinum agent selected by the investigator for study treatment, OR subject has known severe (≥ Grade 3) hypersensitivity to the gemcitabine were excluded for patient safety. |
| Is it considered to be included as missing information? | No |
| Rationale (if not included as missing information) | Section 4.3 of the EU-SmPC informs prescribers about hypersensitivity to the active substance(s) to any of the excipients. Given the contraindication in the label, it is unlikely that additional information will become available regarding the population of patients who have a known hypersensitivity to EV or any other excipient contained in the drug formulation. |
| **Criterion 22** | **Subject has known active keratitis or corneal ulcerations. Subject with superficial punctate keratitis is allowed if the disorder is being adequately treated in the opinion of the investigator.** |

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| Reason for being an exclusion criterion | Subjects with known active keratitis or corneal ulcerations were excluded from clinical trials to reduce potential confounding of the assessment of safety. Keratitis or other corneal epithelial changes have been reported with several ADCs containing anti-tubulin cytotoxic moieties. Although MMAE ADCs, however, are not typically associated with corneal events [Eaton, et al, 2015], Nectin-4 was noted to be present on corneal tissue. Corneal events were carefully monitored in the clinical trial program and were considered to be adverse events of interest. |
| Is it considered to be included as missing information? | No |
| Rationale (if not included as missing information) | Subjects with known active keratitis or corneal ulcerations were excluded to reduce the potential for confounding of the interpretation of the safety data in clinical trials.<br>In clinical practice, prescribers, in collaboration with patients who have active keratitis or corneal ulcerations, will need to discuss the potential risk of ocular adverse events. Prescribers and patients will need to evaluate the benefits and risks associated with enfortumab vedotin applicable to each individual patient. Ocular toxicity is a potential risk for enfortumab vedotin and patients should be monitored for symptoms associated with dry eye and treated accordingly. |
| **Criterion 23** | **History of uncontrolled diabetes mellitus within 3 months of the first dose of study drug. Uncontrolled diabetes is defined as hemoglobin A1C (HbA1c) ≥ 8% or HbA1c between 7 and < 8% with associated diabetes symptoms (polyuria or polydipsia) that are not otherwise explained.** |
| Reason for being an exclusion criterion | Subjects with a history of uncontrolled diabetes were excluded from clinical trials to reduce potential confounding of the assessment of safety.<br>Events of diabetic ketoacidosis, including those with a fatal outcome, have occurred in the development program in subjects with and without preexisting diabetes mellitus. During the execution of study EV-101, three drug-related deaths in obese subjects occurred. These events were associated with hyperglycemia, including 1 event of diabetic ketoacidosis. Each subject had pre-existing comorbidities that placed them at increased risk. Subsequent to these events, clinical protocols were amended to exclude subjects with a history of uncontrolled diabetes mellitus within 3 months of the first dose of study drug. Subjects with uncontrolled diabetes mellitus were excluded from studies EV-103 and EV-302 without the 3 month provision prior to first dose of study drug. |
| Is it considered to be included as missing information? | No |

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| Rationale (if not included as missing information) | Subjects with uncontrolled diabetes were excluded to reduce the potential for confounding of the interpretation of the safety data in clinical trials.<br>Hyperglycemia is an important identified risk for enfortumab vedotin. The EU-SmPC informs prescribers about monitoring of 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 hyperglycemia. Dose modification guidelines are presented in the EU-SmPC to mitigate this risk. |

ADC: Antibody-drug Conjugate; ALT: Alanine Aminotransferase; ANC: Absolute Neutrophil Count; AST: Aspartate Aminotransferase; CHO: Chinese Hamster Ovary; CNS: Central Nervous System; CPI: Checkpoint Inhibitor; CrCL: Creatinine Clearance; ECOG: Eastern Cooperative Oncology Group; EMA: European Medicines Agency; EU-SmPC: European Union-Summary of Product Characteristics; EV: Enfortumab vedotin; Hb: Hemoglobin; HbA1c: Hemoglobin A1C; HBsAg: Hepatitis B Surface Antigen; HCV: Hepatitis C Virus; HIV: Human Immunodeficiency Virus; ISS: Integrated Summary of Safety; MMAE: Monomethyl Auristatin E; NCI-ODWG: National Cancer Institute- Organ Dysfunction Working Group; NSCLC: Non-Small Cell Lung Carcinoma; NYHA: New York Heart Association; RNA: Ribonucleic acid; TEAE: Treatment Emergent Adverse Events; UC: Urothelial cancer; ULN: Upper limit of normal.

## SIV.2 Limitations to detect adverse reactions in clinical trial development program

The clinical development program for enfortumab vedotin is unlikely to detect certain types of adverse reactions such as rare adverse reactions (occurring in < 1/2250 subjects), adverse reactions with a long latency, or adverse reactions caused by prolonged or cumulative exposure.

# SIV.3 Limitations in respect to populations typically under-represented in clinical trial development programs

**Table SIV.3: Exposure of special populations included or not in clinical trial development programs**

| Type of special population | Exposure |
|---|---|
| Pregnant women | Pregnant and breastfeeding women were not included in the clinical development program |
| Breastfeeding women | |
| Subjects with relevant comorbidities: | |
| Subjects with hepatic impairment | In general, subjects with moderate or severe hepatic impairment (NCI-ODWG criteria) were excluded from enfortumab vedotin clinical trials in order to reduce potential confounding of the assessment of safety. However, there were 2 subjects with moderate hepatic impairment included in EV-301 and 1 subject in EV-201, Cohort 2 who received at least 1 dose of 1.25mg/kg of enfortumab vedotin. Applying NCI-ODWG criteria based on total bilirubin and ALT or AST, of the 793 subjects in the EV Mono Integrated Safety Population, 74 (9.3%) had mild hepatic impairment, 4 (0.5%) had moderate hepatic impairment, none had severe hepatic impairment and 11 (1.4%) had unknown hepatic impairment [EV-302 ISS Table 12.1.2.3].<br>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 (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. ). Enfortumab vedotin has only been evaluated in a limited number of patients with moderate and severe hepatic impairment. Hepatic impairment is expected to increase systemic exposure to MMAE (the cytotoxic drug); therefore, patients should be closely monitored for potential adverse events. Due to the sparsity of the data in patients with moderate and severe hepatic impairment, no specific dose recommendation can be given. |
| Subjects with renal impairment | Subjects with serum creatinine > 2.0 mg/dL or creatinine clearance < 30mL/min (as calculated by the Cockcroft-Gault method) were not included in the studies comprising the Integrated Safety Population except in the Renal Insufficiency Expansion Cohort of EV-101. This cohort included patients with a creatinine clearance ≥ 15 mL/min and < 30 mL/min. |

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| | Of the 793 subjects in the EV Mono Integrated Safety Population, 121 (15.4%) had baseline normal creatinine clearance of ≥ 90 mL/min, 276 (35.1%) had baseline mild renal impairment with a creatinine clearance of 60 to < 90 mL/min, 365 (46.4%) had baseline moderate renal impairment with a creatinine clearance of ≥30 to < 60 mL/min, 24 (3.0%) had baseline severe renal impairment with creatinine clearance of ≥15 to <30 mL/min (EV-302 ISS Table 12.1.2.2).<br>Nonclinical and clinical data indicate renal excretion is a minor elimination route with <15% of a single intravenous dose of an MMAE conjugated ADC (cAC10-vc-3H-MMAE) or 3H-MMAE.<br>The effect of renal impairment on ADC and MMAE exposure after monotherapy was assessed using the population pharmacokinetic model (Study 7465-PK-0009) which included subjects with normal (n=129), mild (n=272), moderate (n=315), and severe (n= 25) renal impairment. Serum creatinine and CrCl appeared to have no effect on exposures of enfortumab vedotin and free MMAE in a covariate assessment. These results were in accord with the expected exposures simulated from individual pharmacokinetic parameters of subjects with different renal function (mild, moderate, and severe impaired renal function): no effect on exposures ($C_{max}$, $C_{trough}$ and AUC) of enfortumab vedotin or free MMAE was observed, which is expected given that the primary routes of elimination of both ADC and MMAE are not renal. Therefore, dose adjustment is not warranted in subjects with mild, moderate or severe renal impairment. Enfortumab vedotin has not been evaluated in patients with end stage renal disease (CrCL <15 mL/min). |
| Subjects with cardiovascular impairment | Subjects with congestive heart failure NYHA class III or IV were not included in the studies comprising the EV Mono Integrated Safety Population with the exception of EV-103 Cohort K where subjects with NYHA class III were allowed to participate. Subjects with unstable angina, or myocardial infarction within 6 months of their first dose of enfortumab vedotin were also excluded from the trials included in the Integrated Safety Population. Study EV-102 excluded subjects with Grade 2 or greater peripheral vascular disease, uncontrolled hypertension, or arrhythmias not controlled by medication within 12 months from the first dose of enfortumab vedotin. EV-102 further excluded subjects with a congenital long QT syndrome or family history of unexpected cardiac death, or QTc corrected with Fridericia's formula (QTcF) > 450 milliseconds for males and > 470 milliseconds for females on screening ECG. |

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| | Of the 793 subjects in the EV Mono Integrated Safety Population, 5 (0.6%) had a history of cardiac failure congestive and 2 (0.3%) cardiac failure (EV-302 ISS Table 12.1.3). |
| Subjects with Neutropenia | Subjects with an ANC ≥ 1.0 x $10^9$/L were included in Studies EV-101, EV-102, and EV-201. Subjects in EV-301 were required to have a higher ANC of ≥ 1500/$mm^3$, since the comparator chemotherapy agents in this study are associated with neutropenia. Subjects with an ANC ≥ 1.5 x $10^9$/L were included in Study EV-103. The safety and efficacy of enfortumab vedotin has not been established in subjects with an ANC < 1.0 x $10^9$/L.<br>Of the 793 subjects in the EV Mono Integrated Safety Population, 4 (0.5%) had a history of neutropenia (EV-302 ISS Table 12.1.3). |
| Subjects with Anemia | In 4 of the 6 studies included in the EV Mono Integrated Safety Population, subjects were required to have a baseline hemoglobin ≥ 9 g/dL.<br>Of the 793 subjects in the EV Mono Integrated Safety Population, 169 (21.6%) had baseline hemoglobin values <10 mg/dL (EV-302 ISS Table 12.1.2.2). |
| Subjects with a disease severity different from inclusion criteria in clinical trials | Subjects with urothelial carcinoma who were eligible for definitive therapy with curative intent were not included in clinical trials. Only subjects with ECOG performance status of ≤1 were included in studies, EV-101, EV-102, EV-201 Cohort 1 and EV-301. EV-103 and EV-201, Cohort 2 included subjects with ECOG performance status of ≤2. Of the 793 subjects in the EV Mono Integrated Safety Population, 284 (35.8%) had a baseline ECOG performance status of 0, 485 (61.2%) had a baseline ECOG performance status of 1, 24 (3.0%) had a baseline ECOG performance status of 2, and no subjects had a baseline ECOG performance status of >2 (EV-302 ISS Table 12.1.2.1). |
| Subjects with pre-existing peripheral neuropathy | Subjects with pre-existing peripheral motor or sensory neuropathy Grade ≥2 were excluded from the studies included in the Integrated Safety Population. Of the 793 subjects in the EV Mono Integrated Safety Population, 231 (29.1%) had a medical history of peripheral neuropathy and 562 (70.9%) had no history of neuropathy (EV-302 ISS Table 12.1.2.3). Of the 231 subjects with pre-existing peripheral neuropathy, 114 (49.4%) had a TEAE of any peripheral neuropathy event. Of these 114 subjects, 43 (18.6%) had any peripheral motor neuropathy event and 102 (44.2%) had any peripheral sensory neuropathy event.<br>Of the 562 subjects without pre-existing peripheral neuropathy, 308 (54.8%) had a TEAE of any peripheral neuropathy event. Of these 308 subjects, 80 (14.2%) had any peripheral motor neuropathy event and 284 (50.5%) |

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| | had any peripheral sensory neuropathy event (EV-302 ISS Table 12.6.1.5.1.11). |
| Subjects with diabetes and hyperglycemia | In 4 of the 6 studies included in the EV Mono Integrated Safety Population, subjects with a history of uncontrolled diabetes mellitus were excluded. Uncontrolled diabetes was defined as hemoglobin A1C (HbA1c) ≥ 8% or HbA1c > 7 to < 8% with associated diabetes symptoms (polyuria or polydipsia) that are not otherwise explained.<br>Of the 793 subjects in the EV Mono Integrated Safety Population, baseline hemoglobin A1c values were available for 619 subjects; 272 (43.9%) had a normal Hemoglobin A1c, 264 (42.6%) had a baseline Hemoglobin A1c of 5.7 to <6.5% (prediabetes), and 83 (13.4%) had a baseline Hemoglobin A1c of > 6.5% (diabetes) (EV-302 ISS Table 12.1.2.3).<br>Of the 793 subjects in the EV Mono Integrated Safety Population, 186 (23.5%) had a medical history of diabetes/ hyperglycemia (EV-302 ISS Table 12.1.2.3). Of the 186 subjects with pre-existing diabetes/ hyperglycemia, 69 (37.1%) had a TEAE of any diabetes/ hyperglycemia event. Of the 607 subjects without pre-existing diabetes/ hyperglycemia, 64 (10.5%) had a TEAE of any diabetes/ hyperglycemia event (EV-302 ISS Table 12.6.1.5.4.12). |
| Subjects with active keratitis | In 2 of the 6 studies included in the EV Mono Integrated Safety Population (EV-101 and EV-102), subjects with ocular conditions such as active infection or corneal ulcer (e.g., keratitis), monocularity, history of corneal transplantation, wet macular degeneration, uveitis, papilledema, or optic disc disorder were excluded. In addition, subjects who were contact lens dependent and unable to switch to glasses during the entire study duration, had uncontrolled glaucoma despite topical medications, uncontrolled or evolving retinopathy were excluded. In EV-103, EV-201 and EV-301, subjects with active keratitis or corneal ulcerations were excluded but subjects with superficial punctate keratitis were allowed if the disorder was being adequately treated in the opinion of the investigator. Of the 793 subjects in the EV Mono Integrated Safety Population, 372 (46.9%) had a medical history of an eye disorder including 70 (8.8%) with Dry eye, 15 (1.9%) with Punctate keratitis and 2 (0.3%) with Keratitis (EV-302 ISS Table 12.1.3). |
| Subjects with Hepatitis B or Hepatitis C | Subjects with positive Hepatitis B surface antigen and active Hepatitis C infection were excluded from trials included in the Integrated Safety Population. Of the 793 subjects in the EV Mono Integrated Safety Population, 12 (1.5%) had a medical history of Hepatitis B, 1 (0.1%) had a medical history of Hepatitis B core antigen positive, and |

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| | 2 (0.3%) had a history of Hepatitis C (EV-302 ISS Table 12.1.3). |
| Subjects with HIV | Subjects with HIV were excluded from trials included in the Integrated Safety Population. Of the 793 subjects in the EV Mono Integrated Safety Population, there were no subjects with a history of HIV or AIDS (EV-302 ISS Table 12.1.3). |
| Population with relevant different ethnic origin | The multi-ethnic population reflects the target population as described in the Epidemiology Demographics section (Module SI) [Henley et al, 2020; American Cancer Society, 2018 (a); Antoni et al, 2017; Soria et al, 2017; Hosain et al, 2012]. Of the 793 subjects in the EV Mono Integrated Safety Population, 527 (66.5%) were white, 191 (24.1%) were Asian, 12 (1.5%) were black or African American, 62 (7.8%) were of other race or ethnic origin (1 was missing information). |
| Pediatric subjects | Subjects <18 years of age were not included in the studies comprising the Integrated Safety Population. |
| Elderly subjects | The relative proportion of the different age groups is representative of the target population as described in the Epidemiology Demographics section (Module SI). Of the 793 subjects in the EV Mono Integrated Safety Population, 310 (39.1%) were ≥ 65 years of age and <75 years of age, and 204 (25.7%) were ≥ 75 years of age (EV-302 ISS Table 12.1.2.1). |

ADC: Antibody-Drug Conjugate; AIDS: Acquired Immuno Deficiency Syndrome; ANC: absolute neutrophil count; ALT: Alanine Aminotransferase; AST: Aspartate Aminotransferase; AUC: Area under curve; ECG: Electrocardiogram; ECOG: Eastern Cooperative Oncology Group; EV: Eudravigilance; HbA1c: Hemoglobin A1C; HIV: Human Immunodeficiency Virus; ISS: Integrated Summary of Safety; MMAE: monomethyl auristatin E; NCI ODWG: National Cancer Institute- Organ Dysfunction Working Group; NYHA: New York Heart Association; PK: Pharmacokinetics; QTcF: QTc corrected with Fridericia's formula; EU-SmPC: European Union-Summary of Product Characteristics; TEAE: Treatment Emergent Adverse Events; UC: Urothelial cancer ULN: Upper Limit of Normal.

# PART II: MODULE SV. POSTAUTHORIZATION EXPERIENCE

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| Data-lock point for this Module | 08 Aug 2023 |
| Version when Module last updated | 3.0 |

## SV.1 Postauthorization exposure

Enfortumab vedotin as monotherapy has received first marketing authorization on 18 Dec 2019 in the US for the treatment of adult patients with locally advanced or metastatic urothelial cancer who have previously received a Programmed Death Receptor-1(PD-1) or Programmed Cell Death-ligand 1 (PD-L1) inhibitor, and a platinum-containing chemotherapy. A second indication to include patients ineligible for cisplatin-containing chemotherapy and have previously received one or more prior lines of therapy was approved on 09 Jul 2021.

The recommended dose of enfortumab vedotin is 1.25 mg/kg (up to a maximum dose of 125 mg) given as an intravenous infusion over 30 minutes on Days 1, 8, and 15 of a 28-day cycle until disease progression or unacceptable toxicity.

### SV.1.1 Method used to calculate exposure

The worldwide estimated patient exposure from marketing experience is based on internal company sales data and/or audited pharmacy or wholesale sales of enfortumab vedotin received from IQVIA or similar syndicated sources. This estimate is based on standard units sold during 18 Dec 2019 to 08 Aug 2023.

Given the uncertainty of the therapy duration, types of treatment, and compliance, market experience is calculated in number of patients. The numbers must be interpreted with care. The market experience has been calculated using data from available sales volume and assumes that on an average thirty units of enfortumab vedotin sold account for 1 patient. It is estimated that the worldwide exposure during the period of this report, 18 Dec 2019 – 08 Aug 2023, is equivalent to 33,527 patients.

Calculation:

Number of Patients = Number of units sold / 30 units per patient

**Table SV.1: Cumulative exposure from marketing experience**

| Region | No. of Patients Cumulative interval (Launch – 08 Aug 2023) |
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| **Total** | **33,527** |

Note: Values were calculated from estimated patient exposure and rounded to the nearest whole number.

# PART II: MODULE SVI. ADDITIONAL EU REQUIREMENTS FOR THE SAFETY SPECIFICATION

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| Data-lock point for this Module | 15 Sep 2020 |
| Version when Module last updated | 0.1 |

**Potential for misuse for illegal purposes**

The potential for enfortumab vedotin drug abuse and dependence is unknown. The proposed indication makes it unlikely that enfortumab vedotin has abuse potential. In clinical studies, there were no signals suggestive of abuse such as increased incidence of events of euphoria, excessive use of study drug, and refusal to return unused study drug after study termination. Specific clinical studies evaluating for misuse potential have not been conducted.

# PART II: MODULE SVII. IDENTIFIED AND POTENTIAL RISKS

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| Data-lock point for this Module | 08 Aug 2023 |
| Version when Module last updated | 3.0 |

## SVII.1 Identification of safety concerns in the initial RMP submission

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| Data-lock point for this Module | 15 Sep 2020 |

### SVII.1.1 Risks not considered important for inclusion in the list of safety concerns in the RMP

**Risks not Included in the List of Safety Concerns in the RMP**

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| **Identified risks that are ADRs with minimal clinical impact on patients (in relation to the severity of the indication treated):** |
| Anemia |
| Nausea, Vomiting, Diarrhea |
| Fatigue, Decreased appetite, Decreased weight |
| Alopecia, Dry skin, Pruritus |
| Aspartate aminotransferase increased, Alanine aminotransferase increased |
| Neutropenia |
| **Adverse reactions with clinical consequences, even serious, but occurring with a low frequency and considered to be acceptable in relation to the severity of the indication treated:** |
| Infusion site extravasation |
| **Identified risks that are well-established in the class of MMAEs and micro-tubulin inhibitor agents and require no further characterization, are followed up via routine pharmacovigilance, and for which the risk minimization messages in the product information are adhered by prescribers (e.g., actions being part of standard clinical practice in each EU Member state where the product is authorized):** |
| Peripheral sensory neuropathy, Dysgeusia, Burning sensation, Demyelinating polyneuropathy, Dysesthesia, Gait disturbance, Hypoesthesia, Motor dysfunction, Muscle atrophy, Muscular weakness, Neuralgia, Neuropathy peripheral, Neurotoxicity, Paresthesia, Peripheral motor neuropathy<br>Peroneal nerve palsy, Peripheral sensorimotor neuropathy, Polyneuropathy, Skin burning sensation, Sensory loss |
| **Identified risks that do not impact the benefit-risk profile:** |
| Dry eye |

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| **Potential risks that are well-established in the class of MMAEs and micro-tubulin inhibitor agents and require no further characterization, are followed up via routine pharmacovigilance, and for which the risk minimization messages in the product information are adhered by prescribers (e.g., actions being part of standard clinical practice in each EU Member state where the product is authorized):** |
| Embryo-fetal toxicity |
| **Potential risks that are findings from non-clinical studies which have not been observed in clinical studies and are not considered important due to the low reproductive potential in the target population** |
| Testicular toxicity |
| **Potential risks that will be followed up via routine pharmacovigilance and if confirmed would be considered to be acceptable in relation to the severity of the indication treated or would not impact the overall benefit-risk profile (metastatic urothelial carcinoma which is a life-threatening disease with limited treatment options)** |
| Corneal disorders |
| Blurred vision |
| Infusion-related reactions (IRRs) (other than extravasation site reactions) |
| Anti-therapeutic antibodies (ATA) |

ADRs: Adverse Drug Reactions; ATA: Anti-therapeutic Antibodies; EU: European Union; IRRs: Infusion-related Reactions; MMAE: Monomethyl Auristatin E; RMP: Risk Management Plan.

## SVII.1.2 Risk considered important for inclusion in the list of safety concerns in the RMP

| Safety Concerns for Inclusion in RMP | Benefit-risk Impact |
|---|---|
| **Important identified risks** | |
| Skin reactions | Skin reactions are commonly associated with enfortumab vedotin treatment. As Nectin-4 is expressed in the skin, the risk of skin reactions could be due to Nectin-4-targeted MMAE delivery.<br>A search strategy comprised of the 5 HLTs of "Bullous conditions", "Dermatitis and eczema", "Rashes, eruptions, and exanthemas NEC", Erythemas", and "Dermatitis" ascribed to specific agent" has been used to define rash events. Additionally, the Severe Cutaneous Adverse Reactions (SCAR) SMQ has been used to define severe cutaneous events. Together, these search strategies have been used to define events consistent with the medical concept of skin reactions. The overall rate of skin reactions (including SCAR) in the clinical trials of the ISS population (all EV group) 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%.<br>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. Across the ISS population, the onset of the majority of skin reaction events occurred within the first 2 treatment cycles and the majority were Grades 1 or 2 (78.5%, 317/404). There were no fatal (Grade 5) events in the 5 clinical trials of the ISS population. In these clinical trials, the median time to onset of the first event for all grades was 0.49 months and ≥ Grade 3 skin reactions was 0.62 months. The median time to onset of the first event of SCAR for all grades (1.23 months) and ≥ Grade 3 SCAR (0.59 months) occurred within the first 2 months of enfortumab vedotin treatment suggesting that monitoring for new or worsening symptoms may be needed for patients shortly after initiating treatment with enfortumab vedotin. Furthermore, among all enfortumab vedotin patients in the ISS population, dose modifications were frequently used for ≥ Grade 3 SCAR (17/24 subjects [70.8%]), with dose interruptions in 7/24 subjects (29.1%), discontinuations in 6/24 (25%) subjects and dose reductions in 4/24 (16.6%) subjects), indicating the importance of dose interruptions, reductions and discontinuations in the management of these cases. When adjusted for events per patient-year, the event rates of skin reactions (including SCAR) and SCAR 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).<br>A review of postmarketing data up to 15 Sep 2020 showed 47 spontaneous cases of skin reactions, 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).<br>Patients should be monitored starting with the first cycle and throughout treatment for skin reactions, early detection is recommended to mitigate the development of serious outcomes. Fever or flu-like symptoms may be the first sign of a severe skin reaction, and patients should be observed, if this occurs. Appropriate treatment such as topical corticosteroids and antihistamines can be considered for mild to moderate skin reactions. 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 specialized care; histologic confirmation, including consideration of multiple biopsies, is critical to early recognition, as diagnosis and intervention can improve prognosis. Permanently discontinue enfortumab vedotin treatment for confirmed SJS or TEN, Grade 4 or recurrent severe skin reactions. Along with the communication of the risk in the EU-SmPC and PL, the overall benefits outweigh the risk in the treatment of metastatic urothelial carcinoma. |
| **Important identified risks** | |
| Hyperglycemia | Hyperglycemia was defined by all adverse events within Hyperglycemia/new onset diabetes mellitus SMQ (Narrow), and also the 2 PTs of Blood glucose abnormal and Blood glucose fluctuation.<br><br>The overall rate of hyperglycemia in the clinical trials of the ISS population is 14.2% (106/749). 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). Of the 680 patients treated with enfortumab vedotin 1.25 mg/kg, majority of the events were Grade 1 and 2 (50/98, 51%) and Grade 3 events were 43/98, 44%. There was a higher incidence of treatment-emergent hyperglycemia reported in obese subjects (BMI $\geq$ 30 kg/m$^2$), 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 (related) and diabetic ketoacidosis (related). Both patients were obese, and 1 patient had pre-existing diabetes mellitus type 2.<br><br>A review of post-marketing data up to 08 Oct 2020 showed 11 spontaneous cases of the Hyperglycemia/new onset diabetes mellitus SMQ (Narrow). Seven cases were serious, and 4 cases were non-serious. Of the 7 serious cases, 4 cases reported a fatal outcome. In 3 of 4 fatal cases, the patient had concurrent SCAR events (2 cases of SJS and 1 case of TEN). The remaining fatal case had multiple other concurrent laboratory abnormalities. The numbers and PTs identified by the Hyperglycemia/new onset diabetes mellitus SMQ (Narrow): Hyperglycemia (7), Blood glucose increased (3), and Diabetes mellitus inadequate control (1).<br><br>Blood glucose levels should be monitored prior to dosing and periodically throughout the course of treatment as clinically indicated in patients with or at risk for diabetes mellitus or hyperglycemia. Appropriate treatment and interruption of enfortumab vedotin in patients whose blood glucose is elevated >13.9 mmol/L (>250 mg/dL); until blood glucose is ≤13.9 mmol/L (≤250 mg/dL) is recommended. Given the severity of the indication being treated and the effective management strategies established for hyperglycemia, the impact on the benefit-risk balance is considered low. Along with the communication of the risk in the EU-SmPC and PL, the overall benefits outweigh the risk in the treatment of metastatic urothelial carcinoma. |
| **Missing Information** | |
| Long-term safety | Long-term safety data for enfortumab vedotin are limited and additional analysis of data from the ongoing development program is planned. The overall impact on the benefit-risk balance of the product is considered low. |

BMI: Body Mass Index; EU-SmPC: European Union-Summary of Product Characteristics; EV: Eudravigilance; HbA1c: Hemoglobin A1C; HLT: High Level Term; ISS: Integrated Summary of Safety;

MMAE: Monomethyl Auristatin E; NEC: Not Elsewhere Classified; PL: Package Leaflet; PT: Preferred term; RMP: Risk Management Plan; SAE: Serious Adverse Events; SCAR: Severe Cutaneous Adverse Reaction; SJS: Stevens Johnson Syndrome; SMQ: Standard MedDRA Query; TEN: Toxic Epidermal Necrolysis

## SVII.2 New safety concerns and reclassification with a submission of an updated Risk Management Plan

Not applicable.

## SVII.3 Details of important identified risks, important potential risks, and missing information

### SVII3.1 Presentation of important identified risks and important potential risks

**Important Identified Risk: Skin reactions**

**Potential mechanisms**

The target of enfortumab vedotin, Nectin-4, is expressed in the skin. Due to the mechanism of action of monomethyl auristatin E (MMAE), actively and rapidly dividing cells are particularly sensitive to its ability to arrest the cell cycle. As the epidermis is in a state of constant turnover to fulfill its biological function, these dividing cells are susceptible to the antimitotic effects of localized MMAE delivery and suggest that skin reactions result from Nectin-4-targeted MMAE delivery.

**Evidence source(s) and strength of evidence**

The safety population includes all patients who received at least 1 dose of study drug in studies EV-101, EV-102, EV-103, EV-201, EV-203, EV-301, and EV-302.

In study EV-302, the proportion of subjects experiencing skin reactions adverse events of special interest (AESI) is 69.5 % in EV + Pembro Combo ISS group as compared to 57.0% in the EV Mono ISS group [EV-302 ISS Table 12.6.1.5.3.1].

The most common skin reaction PTs observed in the EV + Pembro Combo ISS analysis group were rash maculo-papular (36.0%), rash macular (11.3%), and rash papular (7.6%); In EV Mono ISS analysis group, most common PTs observed were rash maculo-papular (23.6%), rash (11.6%) and rash erythematous (4.7%) [EV-302 ISS Table 12.6.1.5.3.1]. The proportion of subjects with severe cutaneous adverse reaction events in the EV + Pembro Combo ISS analysis group (27.5%) was similar to that in the EV Mono ISS analysis group (24.8%) [EV-302 ISS Table 12.6.1.5.3.1].

The higher frequency of skin reactions between these analysis groups was likely due to a contribution of both drugs and a longer duration of exposure during combination therapy (9.43 months) than in previous experience with enfortumab vedotin monotherapy (4.70 months) [EV-302 ISS Table 12.2.1.1]. In study EV-302, the frequency of serious skin reactions was also similar between the EV + Pembro Combo ISS and EV Mono ISS analysis groups (5.3% vs 4.3%, respectively) [EV-302 ISS Table 12.6.1.5.3.4]. All of these serious AESI were considered drug-related by the investigator [EV-302 ISS Table 12.6.1.5.3.5].

A review of postmarketing data up to 17 Jun 2023 showed 1313 postmarketing cases of skin reactions, of which 77 cases were fatal.

**Characterization of the risk:**

Per literature sources, SCAR mainly consists of Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN), drug reaction with eosinophilia and systemic symptoms (DRESS) syndrome and acute generalized exanthematous pustulosis (AGEP). A universal feature of these conditions is the integral role of T-cells, which infiltrate skin lesions and are key effector cells in the pathogenesis of end-organ damage. Unlike Immunoglobulin E-mediated reactions, sensitization is not necessary, and drug reacting T-cells can expand upon their initial encounter with the suspect drug and lead to clinical manifestations [Mustafa et al, 2018]. The most severe forms of SCAR are SJS, TEN, and the combined overall incidence of SJS/TEN ranges from 1.9 cases per million (population) per year in Europe to 6.5 cases per million per year in Asia to approximately 12 cases per million per year in the US [Mustafa et al, 2018; Chung et al, 2016].

Across the enfortumab vedotin program, a broad search strategy comprised of the 5 HLTs of "Bullous conditions", "Dermatitis and eczema", "Rashes, eruptions and exanthemas NEC", “Erythemas” and “Dermatitis ascribed to specific agent" has been used to fully capture rash events. Additionally, the SCAR Standardized MedDRA Query (SMQ) of Severe cutaneous adverse reactions has been used to capture severe cutaneous events. Together, these search strategies have been used to capture events consistent with the medical concept of skin reactions.

In the EV + Pembro Combo ISS analysis group of study EV-302, 91 subjects (16.1%) experienced Grade 3 events (the majority in PT’s of rash maculo-papular [53 subjects (9.4%)], rash macular [9 subjects (1.6%)] and rash papular [7 subjects (1.2%)]. Six (1.1%) subjects experienced Grade 4 events (toxic epidermal necrolysis [2 subjects (0.4%)], rash maculo-papular, dermatitis bullous, erythema multiforme, and dermatitis exfoliative generalized [1 subject each (0.2%)]). No subjects experienced a Grade 5 skin reactions event [EV-302 ISS Table 12.6.1.5.3.2].

In the EV Mono ISS analysis group of study EV-302, 105 (13.2 %) subjects experienced Grade 3 events (the majority in PT’s of rash maculo-papular [43 subjects (5.4%)]. Three (0.4%) subjects experienced Grade 4 events (dermatitis bullous [2 subjects (0.3%)] and rash [1 subject]). No subjects experienced a Grade 5 skin reactions event [EV-302 ISS Table 12.6.1.5.3.2].

For subjects who experienced a skin reactions event, the median time to first onset of any grade skin reactions event was 0.49 months in both EV + Pembro Combo ISS, and the EV Mono ISS analysis groups [EV-302 ISS Table 12.6.1.5.3.10]. For subjects who experienced a ≥ Grade 3 skin reactions event, the median time to first onset was 1.74 and 0.67 months in the EV + Pembro Combo ISS, and the EV Mono ISS analysis groups, respectively [EV-302 ISS Table 12.6.1.5.3.10].

Overall, 15.8% of subjects in the EV + Pembro Combo ISS analysis group and 9.7% of subjects in the EV Mono ISS analysis group experienced a skin reactions event that resulted in dose reductions [EV-302 ISS Table 12.6.1.5.3.8] and 23.2% of subjects in the EV +

Pembro Combo ISS analysis group and 11.2% of subjects in the EV Mono ISS analysis group experienced a skin reactions event that resulted in dose interruption [EV-302 ISS Table 12.6.1.5.3.9]. Most subjects were able to continue treatment despite experiencing a skin reactions event. In total, 6.0% of subjects in the EV + Pembro Combo ISS analysis group, and 3.2% of subjects in the EV Mono ISS analysis group experienced a skin reactions event that resulted in permanent withdrawal of treatment; all were considered drug-related by the investigator [EV-302 ISS Tables 12.6.1.5.3.6 and 12.6.1.5.3.7]. Most skin reactions either resolved or had partial improvement across the analysis groups [EV-302 ISS Table 12.6.1.5.3.11].

Frequencies and event rates for treatment-emergent Adverse events (AEs) within the definition of skin reactions are summarized in Table SVII3.1.1 for the Integrated Safety Population (integrated EV mono ISS analysis group and EV + Pembro combo ISS analysis group).

## Table SVII3.1.1 Treatment-emergent adverse events of Skin Reactions*

| Category | EV Mono ISS (N=793) n (%) | EV + Pembro Combo ISS (N=564) n (%) |
|---|---|---|
| **Any Rashes or Severe Cutaneous Adverse Reactions** | **452 (57.0%)** | **392 (69.5%)** |
| **Any Rash** | **415 (52.3%)** | **363 (64.4%)** |
| Rash maculo-papular | 187 (23.6%) | 203 (36.0%) |
| Rash | 92 (11.6%) | 13 (2.3%) |
| Rash erythematous | 37 (4.7%) | 21 (3.7%) |
| Erythema | 32 (4.0%) | 21 (3.7%) |
| Drug eruption | 31 (3.9%) | 1 (0.2%) |
| Blister | 28 (3.5%) | 18 (3.2%) |
| Dermatitis bullous | 26 (3.3%) | 26 (4.6%) |
| Rash macular | 21 (2.6%) | 64 (11.3%) |
| Rash pruritic | 18 (2.3%) | 10 (1.8%) |
| Rash papular | 17 (2.1%) | 43 (7.6%) |
| Palmar-plantar erythrodysaesthesia syndrome | 15 (1.9%) | 8 (1.4%) |
| Eczema | 12 (1.5%) | 29 (5.1%) |
| Rash vesicular | 10 (1.3%) | 8 (1.4%) |
| Dermatitis | 6 (0.8%) | 27 (4.8%) |
| Erythema multiforme | 6 (0.8%) | 6 (1.1%) |
| Dermatitis contact | 4 (0.5%) | 3 (0.5%) |
| Intertrigo | 4 (0.5%) | 1 (0.2%) |
| Blood blister | 2 (0.3%) | 0 |
| Dermatitis allergic | 2 (0.3%) | 0 |
| Pemphigoid | 2 (0.3%) | 5 (0.9%) |
| Pemphigus | 2 (0.3%) | 0 |
| Skin irritation | 2 (0.3%) | 1 (0.2%) |
| Blister rupture | 1 (0.1%) | 0 |
| Fixed eruption | 1 (0.1%) | 0 |
| Rash maculovesicular | 1 (0.1%) | 0 |
| Stasis dermatitis | 1 (0.1%) | 1 (0.2%) |
| Stevens-Johnson syndrome | 1 (0.1%) | 0 |
| Toxic skin eruption | 1 (0.1%) | 6 (1.1%) |
| **Any Severe Cutaneous Adverse Reactions** | **197 (24.8%)** | **155 (27.5%)** |
| Stomatitis | 63 (7.9%) | 51 (9.0%) |
| Conjunctivitis | 37 (4.7%) | 34 (6.0%) |
| Skin exfoliation | 35 (4.4%) | 15 (2.7%) |
| Drug eruption | 31 (3.9%) | 1 (0.2%) |
| Blister | 28 (3.5%) | 18 (3.2%) |
| Dermatitis bullous | 26 (3.3%) | 26 (4.6%) |
| Mouth ulceration | 7 (0.9%) | 8 (1.4%) |
| Erythema multiforme | 6 (0.8%) | 6 (1.1%) |
| Dermatitis exfoliative generalised | 5 (0.6%) | 4 (0.7%) |
| Exfoliative rash | 2 (0.3%) | 1 (0.2%) |
| Pemphigoid | 2 (0.3%) | 5 (0.9%) |
| Pemphigus | 2 (0.3%) | 0 |
| Blister rupture | 1 (0.1%) | 0 |

| Category | EV Mono ISS (N=793) n (%) | EV + Pembro Combo ISS (N=564) n (%) |
|---|---|---|
| Dermatitis exfoliative | 1 (0.1%) | 1 (0.2%) |
| Fixed eruption | 1 (0.1%) | 0 |
| Stevens-Johnson syndrome | 1 (0.1%) | 0 |
| Toxic skin eruption | 1 (0.1%) | 6 (1.1%) |
| **Any SAE of Rashes** | **31 (3.9%)** | **27 (4.8%)** |
| Rash | 7 (0.9%) | 1 (0.2%) |
| Rash maculo-papular | 7 (0.9%) | 8 (1.4%) |
| Drug eruption | 5 (0.6%) | 0 |
| Dermatitis bullous | 4 (0.5%) | 4 (0.7%) |
| Rash vesicular | 4 (0.5%) | 0 |
| Blister | 1 (0.1%) | 0 |
| Eczema | 1 (0.1%) | 1 (0.2%) |
| Stevens-Johnson syndrome | 1 (0.1%) | 0 |
| Toxic skin eruption | 1 (0.1%) | 0 |
| **Any SAE of Severe Cutaneous Adverse Reactions** | **15 (1.9%)** | **12 (2.1%)** |
| Drug eruption | 5 (0.6%) | 0 |
| Dermatitis bullous | 4 (0.5%) | 4 (0.7%) |
| Blister | 1 (0.1%) | 0 |
| Conjunctivitis | 1 (0.1%) | 0 |
| Dermatitis exfoliative | 1 (0.1%) | 1 (0.2%) |
| Stevens-Johnson syndrome | 1 (0.1%) | 0 |
| Stomatitis | 1 (0.1%) | 0 |
| Toxic skin eruption | 1 (0.1%) | 0 |

Integrated Safety Population (Safety Analysis Set). Integrated data includes patients in Studies who received at least 1 dose of enfortumab vedotin in, EV-101, EV-102, EV-103, EV-201, EV-203, EV-301 and EV-302

Number of subjects (n) and percentage of subjects (%) are shown.

*Skin reactions search strategy: Any rash: 5 HLTs of Bullous conditions, Dermatitis and eczema, Rashes, eruptions and exanthemas NEC, Erythemas, Dermatitis ascribed to specific agent; SCAR: SMQ_B Severe cutaneous adverse reactions (MedDRA v24.0)

EV: Enfortumab vedotin; SAE: Serious Adverse Event

Source: EV-302 ISS Tables 12.6.1.5.3.1, 12.6.1.5.3.4.

A review of postmarketing data up to 17 Jun 2023 showed 1313 postmarketing cases of skin reactions of which 77 cases were fatal. There were a total of 1544 events in these 1313 cases, of which 1103 were non-serious, and the remaining 441 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 (638), Erythema (121), Blister (104), Stevens-Johnson syndrome (94), Drug eruption (90), Toxic epidermal necrolysis (82).

**Risk factors and risk groups**

In general, 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 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 the 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 the development of SCAR detected.

**Preventability**

Starting with the first cycle and throughout the enfortumab vedotin treatment, patients should be monitored for skin reactions. Fever or flu-like symptoms may be the first sign of a severe skin reaction, and patients should be observed, if this occurs. Consider appropriate treatment such as topical corticosteroids and antihistamines for mild to moderate skin reactions. 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 specialized care; histologic confirmation, including consideration of multiple biopsies, is critical to early recognition, as diagnosis and intervention can improve prognosis. Permanently discontinue enfortumab vedotin treatment for confirmed SJS or TEN, Grade 4 or recurrent severe skin reactions. Further guidance is provided in the European Union-Summary of Product Characteristics (EU-SmPC), Package leaflet (PL), and Patient card.

**Impact on the risk-benefit balance of the product**

Given the severity of the indication being treated, the majority of Grade 1 SCAR events in clinical trials, pre-existing risk factors in the post-marketing cases, the impact on the benefit-risk balance is considered acceptable. Along with the communication of the risk in the EU-

SmPC and PL, the overall benefits outweigh the risk in the treatment of metastatic Urothelial Cancer (mUC).

**Public health impact**

In clinical trials, the overall rate of skin reactions (including SCAR) was 55.6%, and the rate of SCARs was 24.1%. However, the majority of skin reaction events were Grades 1 or 2 (76.7%) and there were multiple pre-existing risk factors in this elderly study population. With communication to prescribers of the importance of monitoring patients for skin reactions including SCAR and the dose recommendations in the label, the impact on public health is reduced.

**Important Identified Risk: Hyperglycemia**

**Potential mechanisms:**

The potential mechanism for the events of hyperglycemia observed in enfortumab vedotin clinical trials is unknown.

**Evidence source(s) and strength of evidence:**

The safety population includes all patients who received at least 1 dose of study drug in studies EV-101, EV-103, EV-102, EV-201, EV-203, EV-301, and EV-302.

In study EV-302, the frequency of TEAEs in the AESI of hyperglycemia observed in the EV + Pembro Combo ISS analysis group was similar to that observed in the EV Mono ISS analysis group (19.0% vs 16.8%). By PT, there were no AESI of hyperglycemia reported at a > 10% difference frequency in the EV + Pembro Combo ISS analysis group compared to the EV Mono ISS analysis group [EV-302 ISS Table 12.6.1.5.4.1]. The most common PTs observed in the EV + Pembro Combo ISS analysis group were hyperglycemia (16.7%), diabetes mellitus (1.4%), and glucose tolerance impaired (1.2%). In EV Mono ISS analysis group, the most common PTs observed were hyperglycemia (14.9%) and diabetes mellitus (1.0%) [EV-302 ISS Table 12.6.1.5.4.1].

The frequency of serious hyperglycemia events was also similar between the EV + Pembro Combo ISS and EV Mono ISS analysis groups (2.0% vs 2.5%, respectively) [EV-302 ISS Table 12.6.1.5.4.4]. Of these serious AESI, 10 of 11 in the EV + Pembro Combo ISS analysis group and 18 of 20 in the EV Mono ISS analysis group were considered drug-related by the investigator [EV-302 ISS Table 12.6.1.5.4.4 and EV-302 ISS Table 12.6.1.5.4.5].

A review of post-marketing data up to 17 Jun 2023 showed 226 postmarketing cases of the Hyperglycemia/new onset diabetes SMQ (Narrow). There were a total of 244 events in these 226 cases, of which 165 were non-serious, and the remaining 79 were serious events.

**Characterization of the risk**

A literature search was done to find urothelial cancer clinical trials with reports of hyperglycemia, including hyperglycemia (adverse event or laboratory abnormality), diabetic ketoacidosis, and diabetes. In these trials, the incidence of any grade hyperglycemia ranged from 1-4% with PD-L1 inhibitor atezolizumab in the neoadjuvant setting [Powles et al, 2019;

Pal et al, 2018; Ning, et al. 2017] to 58% with the Mechanistic Target of Rapamycin (mTOR) inhibitor sunitinib [Gallagher et al, 2010].

Overall, the literature review shows that the chemo-treated population had a lower rate of all-grade hyperglycemia than mTOR inhibitors. Although rates of Grade 3 hyperglycemia were lowest for PD-1/PD-L1 inhibitor monotherapy (pembrolizumab and atezolizumab, ranging from 0% to 5%) [Powles et al, 2019; Pal et al, 2018; Balar et al, 2017, Ning et al, 2017; Sharma et al, 2016], rates of high grade and SAEs of diabetes and diabetic ketoacidosis were only reported from clinical trials with the PD-1 inhibitors, pembrolizumab, and nivolumab.

In non-clinical trials, investigations in vitro studies in human skeletal muscle and pancreatic islet cells did not demonstrate a link between antibody-drug conjugate (ADC) and the development of hyperglycemia. In in vivo repeat dose toxicity studies conducted in rats (n=168) and cynomolgus monkeys (n=74), there were no observed effects on blood glucose levels, nor were there relevant histopathological findings in liver, pancreas, skeletal muscle, or adipose tissue at systemic antibody-drug conjugate exposures up to approximately 9-fold higher than the human exposure at the recommended clinical dose. While hyperglycemia has been observed in clinical trials, there were no indications of altered glucose homeostasis in the nonclinical safety program.

The search strategy Hyperglycemia/new onset diabetes SMQ (Narrow), and PT Blood glucose abnormal, PT Blood glucose fluctuation, PT Metabolic syndrome was used to define the medical concept of hyperglycemia.

The frequency of Grade ≥ 3 events of hyperglycemia was generally similar across EV + Pembro Combo ISS analysis group (9.2%) and the EV Mono ISS analysis group (7.7%) [EV-302 ISS Table 12.6.1.5.4.2].

In the EV + Pembro Combo ISS analysis group, 45 (8.0%) subjects experienced Grade 3 events (hyperglycemia [40 subjects (7.1%)], diabetes mellitus [4 subjects (0.7%)], Type 2 diabetes mellitus [3 subjects (0.5%)], glucose tolerance impaired and Type 1 diabetes mellitus [1 subject (0.2%)]). Seven (1.2%) subjects experienced a Grade 4 hyperglycemia event (hyperglycemia [6 subjects (1.1%)] and diabetic hyperglycemic coma [1 subject (0.2%)]). No subjects experienced a Grade 5 hyperglycemia event [EV-302 ISS Table 12.6.1.5.4.2].

In the EV Mono ISS analysis group, 52 (6.6%) subjects experienced Grade 3 events (hyperglycemia [49 subjects (6.2%)], diabetes mellitus [6 subjects (0.8%)], glucose tolerance impaired, Type 2 diabetes mellitus and diabetes mellitus inadequate control [1 subject (0.1%)]). Six (0.8%) subjects experienced a Grade 4 hyperglycemia event. Two (0.3%) subjects experienced a Grade 5 hyperglycemia event [EV-302 ISS Table 12.6.1.5.4.2].

For subjects that experienced a hyperglycemia event, the median time to first onset of any grade was 0.72, and 0.53 months in the EV + Pembro Combo ISS, and EV Mono ISS analysis groups, respectively [EV-302 ISS Table 12.6.1.5.4.10]. The median time to first onset of any ≥ Grade 3 hyperglycemia event was 0.80, and 0.56 months in the EV + Pembro

Combo ISS, and EV Mono ISS analysis groups, respectively [EV-302 ISS Table 12.6.1.5.4.10].

Overall, 0.7% of subjects in the EV + Pembro Combo ISS analysis group and 0.5% of subjects in the EV Mono ISS analysis group experienced a hyperglycemia event that resulted in dose reductions [EV-302 ISS Tables 12.6.1.5.4.8] and 4.3% of subjects in the EV + Pembro Combo ISS analysis group and 3.4% of subjects in the EV Mono ISS analysis group experienced hyperglycemia event that resulted in dose interruption [EV-302 ISS Table 12.6.1.5.4.9]. The majority of subjects were able to continue treatment despite experiencing a hyperglycemia event [EV-302 ISS Table 12.6.1.5.4.6]. In total, 0.2% of subjects in the EV + Pembro Combo ISS analysis group, and 0.6% of subjects in the EV Mono ISS analysis group experienced a hyperglycemia event that resulted in treatment withdrawal; all were considered drug-related by the investigator [EV-302 ISS Table 12.6.1.5.4.6 and EV-302 ISS Table 12.6.1.5.4.7]. The majority of hyperglycemia events had either resolved or partial improvement across the analysis groups [EV-302 ISS Table 12.6.1.5.4.15].

Frequencies for treatment-emergent AEs within the Standardized Search Query for Hyperglycemia are summarized in [Table SVII.3.1.2] for the Integrated Safety Population (integrated EV mono ISS analysis group and EV + Pembro combo ISS analysis group) by PT.

**Table SVII 3.1.2 Treatment-emergent adverse events of Hyperglycemia***

| Category | EV Mono ISS (N=793) n (%) | EV + Pembro Combo ISS (N=564) n (%) |
|---|---|---|
| **Any Hyperglycemia** | **133 (16.8%)** | **107 (19.0%)** |
| Hyperglycemia | 118 (14.9%) | 94 (16.7%) |
| Diabetes mellitus | 8 (1.0%) | 8 (1.4%) |
| Glucose tolerance impaired | 5 (0.6%) | 7 (1.2%) |
| Type 2 diabetes mellitus | 4 (0.5%) | 5 (0.9%) |
| Blood glucose increased | 7 (0.9%) | 3 (0.5%) |
| Glycosylated haemoglobin increased | 2 (0.3%) | 1 (0.2%) |
| Diabetic hyperglycemic coma | 0 | 1 (0.2%) |
| Impaired fasting glucose | 0 | 1 (0.2%) |
| Type 1 diabetes mellitus | 0 | 1 (0.2%) |
| Diabetes mellitus inadequate control | 1 (0.1%) | 0 |
| Diabetic ketoacidosis | 1 (0.1%) | 0 |
| **Any SAE of Hyperglycemia** | **20 (2.5%)** | **11 (2.0%)** |
| Hyperglycemia | 17 (2.1%) | 8 (1.4%) |
| Diabetic hyperglycaemic coma | 0 | 1 (0.2%) |
| Diabetes mellitus | 2 (0.3%) | 1 (0.2%) |
| Diabetic ketoacidosis | 1 (0.1%) | 0 |
| Type 2 diabetes mellitus | 1 (0.1%) | 1 (0.2%) |
| Diabetes mellitus | 8 (1.0%) | 8 (1.4%) |

Integrated Safety Population (Safety Analysis Set). Integrated data includes patients in Studies who received at least 1 dose of enfortumab vedotin in EV-101, EV-102, EV-103, EV-201, EV-203, EV-301 and EV-302.

Number of subjects (n) and percentage of subjects (%) are shown.

*Hyperglycemia search strategy: SSQ of hyperglycemia including SMQ_N Hyperglycemia/new onset diabetes mellitus, PT Blood glucose abnormal, PT Blood glucose fluctuation, PT Metabolic syndrome

EV: Enfortumab vedotin; SAE: Serious Adverse Event

Source: EV-302 ISS Tables 12.6.1.5.4.1, 12.6.1.5.4.4

A review of post-marketing data up to 17 Jun 2023 showed 226 postmarketing cases of the Hyperglycemia/new onset diabetes mellitus SMQ (Narrow), of which 29 cases were fatal. There were a total of 244 events in these 226 cases, of which 165 were non-serious, and the remaining 79 were serious events. The most frequently reported PTs were Hyperglycemia (152), Blood glucose increased (49), and diabetic ketoacidosis (10).

**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.

**Preventability**

Effective management relies on clinical monitoring of 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 hyperglycemia. Appropriate treatment and interruption of enfortumab vedotin in patients whose blood glucose is elevated >13.9 mmol/L (>250 mg/dL); until blood glucose is ≤13.9 mmol/L (≤250 mg/dL) is recommended. Treatment should be continued at the same dosage.

**Impact on the benefit-risk balance of the product**

Given the severity of the indication being treated, the higher incidence of concurrent diabetes mellitus in the patient population of bladder cancer (as described in the subsection 'Characterization of the risk' above), and the readily available management strategies for hyperglycemia including prevention, early diagnosis, and treatment, the impact on the benefit-risk balance is considered acceptable. Along with communication of the risk in the EU-SmPC and PL, the overall benefits outweigh the risk in the treatment of metastatic urothelial carcinoma.

**Public health impact**

Hyperglycemia, if left untreated, can cause serious health problems and untimely deaths. In order to reduce the clinical and public health impact, it is important to monitor blood glucose levels, especially in patients at risk for diabetes mellitus or hyperglycemia. This is communicated to prescribers through the local label. The recommendation is to interrupt the dose of enfortumab vedotin in patients who experience a significant increase in blood sugar levels.

**Important Identified Risk: Pneumonitis/Interstitial lung disease**

**Potential mechanisms:**

Pneumonitis is a general term that refers to inflammation of lung tissue from either a non-infectious or infectious cause. Symptoms include shortness of breath and dry cough and is occasionally accompanied by low grade fever. Drug-related pneumonitis refers to non-infectious lung inflammation temporally associated with drug administration in the absence of other etiologies and can occur with chemotherapy (e.g., docetaxel, gemcitabine), PD-1/PD-L1 monoclonal antibodies (e.g., pembrolizumab, avelumab), targeted therapy like epidermal growth factor receptor inhibitors (e.g., cetuximab, erlotinib), mammalian target of rapamycin inhibitors, and radiation therapy. 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. The potential mechanism for the events of Pneumonitis/Interstitial lung disease observed in enfortumab vedotin clinical trials is unknown.

**Evidence source(s) and strength of evidence:**

The safety population includes all patients who received at least 1 dose of study drug in studies EV-101, EV-103, EV-102, EV-201, EV-203, EV-301, and EV-302.

In study EV-302, the frequency of TEAEs of pneumonitis/ILD were observed at a higher frequency in the EV + Pembro Combo ISS analysis group than in the EV Mono ISS analysis group (10.3% vs 3.3%). However, no PTs within the search strategy of pneumonitis/ILD were reported at a > 10% difference between EV + Pembro ISS and EV Mono ISS groups [EV-302 ISS Table 12.6.1.5.9.1]. The higher frequency of pneumonitis/ILD observed between these analysis groups was likely due to a contribution of both drugs and a longer duration of exposure during combination therapy (9.43 months) than in previous experience with enfortumab vedotin monotherapy (4.70 months) [EV-302 ISS Table 12.2.1.1]. The frequency of serious pneumonitis/ILD events was higher between the EV + Pembro Combo ISS and EV Mono ISS analysis groups (4.3% vs 0.8%, respectively) [EV-302 ISS Table 12.6.1.5.9.4]. With the exception of 1 (5/6) pneumonitis/ILD event in the EV Mono ISS analysis group, all of the serious events in both ISS groups were considered drug-related by the investigator [EV-302 ISS Table 12.6.1.5.9.4 and EV-302 ISS Table 12.6.1.5.9.5].

A review of post-marketing data up to 17 Jun 2023 showed 95 postmarketing cases of the Pneumonitis/Interstitial lung disease. There were a total of 98 events in these 95 cases, of which 1 was non-serious, and the remaining 97 were serious events.

**Characterization of the risk**

The incidence of Interstitial lung disease (ILD) in the general population ranges from 1.0 to 31.5 per 100 000 person-years and the prevalence ranges from 6.3 to 97.9 per 100 000 people [Kaul et al, 2021; Sesé et al, 2020]. These ranges may reflect true differences based on underlying characteristics of the source populations or methodological differences in disease classification and patient recruitment [Kaul et al, 2021]. The incidence and prevalence of ILD in the Urothelial cancer (UC) population, including the UC population prescribed enfortumab vedotin, has not been documented in the epidemiology literature. The incidence of high-grade (≥ Grade 3) pneumonitis adverse events (AEs) has been estimated at 0.99% (95% confidence interval [CI], 0.52% - 1.50%) and the incidence for all grade pneumonitis AEs has been estimated at 2.20% (95% CI, 1.51% – 2.94%) [Gu et al, 2020]. In the above meta-analysis of prospective clinical trials through May 2019, 16 phase I-III UC studies were included, totaling 3084 UC cases (5 studies, 1017 cases, on PD-1 inhibitors and 11 studies, 2067 cases, on PD-L1 inhibitors) [Gu et al, 2020]. A retrospective medical records review of patients with mUC and metastatic renal cell carcinoma (mRCC) who received immune checkpoint inhibitor (ICI)-based therapy at the Dana Farber Cancer Institute between Jul 2013 and

Oct 2018 estimated the prevalence of immune-related adverse events (irAEs) [Nuzzo et al, 2020]. The study included a total of 470 patients, 271 mRCC (57.7%) and 199 mUC (42.3%). In this medical records review, among mRCC and mUC patients, there were 14 (7.5%) pneumonitis irAEs, 13 were Grade 1-2 and 1 was Grade 3-4 [Nuzzo et al, 2020].

In the nonclinical safety program performed in healthy naive animals, there were no enfortumab vedotin-related pulmonary toxicity or changes in safety pharmacology parameters when assessed in exploratory and Good Laboratory Practice (GLP) compliant toxicology studies of up to 4- and 13-weeks in cynomolgus monkeys and rats, respectively.

An exploratory anti-Nectin-4 immunohistochemistry study with a different anti-Nectin-4 monoclonal antibody than utilized in the antibody-drug conjugate (ADC; M22-244b3) identified staining on a minor population of bronchiolar epithelial cells in 1 of 9 samples (11%), however, no specific staining was seen in the alveolar epithelium [Study ES10-001]. Further, no specific positive staining was observed with the ADC in the GLP human tissue cross-reactivity study [Study 8236219]. The nonclinical data do not indicate the potential for pulmonary toxicity based on the absence of Nectin-4 in normal lung tissue. This is further supported by the lack of enfortumab vedotin-related pulmonary toxicity findings in the GLP toxicity studies.

An aggregate review of the clinical study data was performed using PTs identified using the Interstitial lung disease (SMQ) [broad].

The majority of pneumonitis/ILD events were Grade 1 or 2 across the EV + Pembro Combo ISS analysis group and EV Mono ISS analysis groups [EV-302 ISS Table 12.6.1.5.9.2].

In the EV + Pembro Combo ISS analysis group, 17 (3.0%) subjects experienced Grade 3 events (PTs: pneumonitis [9 subjects (1.6%)], immune-mediated lung disease, and interstitial lung disease [4 subjects (0.7%)] and organising pneumonia [1 subject (0.2%)]). Three (0.5%) subjects experienced Grade 4 pneumonitis/ILD events (PTs: pneumonitis [2 subjects (0.4%)] and sarcoidosis [1 subject (0.2%)]), and 2 (0.4%) subjects experienced Grade 5 events (PTs: immune-mediated lung disease and pneumonitis) [EV-302 ISS Table 12.6.1.5.9.2].

In the EV Mono ISS analysis group, 4 (0.5%) subjects experienced Grade 3 events (PTs: pneumonitis [2 subjects (0.3%)] and organising pneumonia [1 subject (0.1%)]). Two (0.3%) subjects experienced Grade 4 pneumonitis/ILD events (PTs: pneumonitis [1 subject (0.1%)] and interstitial lung disease [1 subject (0.1%)]). No subjects experienced Grade 5 events [EV-302 ISS Table 12.6.1.5.9.2].

For subjects that experienced a pneumonitis/ILD event, the median time to first onset of any grade was 3.98 and 2.71 months in the EV + Pembro Combo ISS analysis group and the EV Mono ISS analysis group, respectively [EV-302 ISS Table 12.6.1.5.9.10]. The median time to first onset of any ≥ Grade 3 was 4.37, and 3.25 months in the EV + Pembro Combo ISS analysis group, and the EV Mono ISS analysis group, respectively [EV-302 ISS Table 12.6.1.5.9.10].

Overall, 0.2% of subjects in the EV + Pembro Combo ISS analysis group and 0.3% of subjects in the EV Mono ISS analysis group experienced a pneumonitis/ILD event that

resulted in dose reductions [EV-302 ISS Table 12.6.1.5.9.8] and 5.9% of subjects in the EV + Pembro Combo ISS analysis group and 0.6% of subjects in the EV Mono ISS analysis group experienced a pneumonitis/ILD event that resulted in dose interruption [EV-302 ISS Table 12.6.1.5.9.9]. Most subjects were able to continue treatment despite experiencing a pneumonitis/ILD event. In total, 4.8% of subjects in the EV + Pembro Combo ISS analysis group and 0.5% of subjects in the EV Mono ISS analysis group experienced a pneumonitis/ILD event that resulted in treatment withdrawal. Except for 1 subject in the EV Mono ISS analysis group, all pneumonitis/ILD events that resulted in treatment withdrawal were considered drug-related [EV-302 ISS Tables 12.6.1.5.9.6 and 12.6.1.5.9.7].

Frequencies for treatment-emergent AEs within the Standardized Search Query for pneumonitis/interstitial lung disease are summarized in [Table SVII 3.1.3] for the Integrated Safety Population (EV mono ISS analysis group and EV + Pembro combo ISS analysis group) by PT.

**Table SVII 3.1.3 Treatment-emergent adverse events of Pneumonitis/Interstitial lung disease***

| Category | EV Mono ISS (N=793) n (%) | EV + Pembro Combo ISS (N=564) n (%) |
|---|---|---|
| **Any Pneumonitis/Interstitial lung disease** | **26 (3.3%)** | **58 (10.3%)** |
| Pneumonitis | 17 (2.1%) | 41 (7.3%) |
| Immune-mediated lung disease | 0 | 7 (1.2%) |
| Interstitial lung disease | 5 (0.6%) | 5 (0.9%) |
| Lung opacity | 1 (0.1%) | 2 (0.4%) |
| Autoimmune lung disease | 0 | 1 (0.2%) |
| Organising pneumonia | 1 (0.1%) | 1 (0.2%) |
| Pulmonary fibrosis | 1 (0.1%) | 1 (0.2%) |
| Pulmonary toxicity | 0 | 1 (0.2%) |
| Sarcoidosis | 0 | 1 (0.2%) |
| Acute respiratory distress syndrome | 1 (0.1%) | 0 |
| Alveolitis | 0 | 0 |
| **Any SAE of Pneumonitis/Interstitial lung disease** | **6(0.8%)** | **24 (4.3%)** |
| Pneumonitis | 2 (0.3%) | 13 (2.3%) |
| Immune-mediated lung disease | 0 | 5 (0.9%) |
| Interstitial lung disease | 3 (0.4%) | 4 (0.7%) |
| Lung opacity | 0 | 1 (0.2%) |
| Organising pneumonia | 1 (0.1%) | 1 (0.2%) |
| Sarcoidosis | 0 | 1 (0.2%) |

Integrated Safety Population (Safety Analysis Set). Integrated data includes patients in Studies who received at least 1 dose of enfortumab vedotin in EV-101, EV-102, EV-103, EV-201, EV-203, EV-301 and EV-302

Number of subjects (n) and percentage of subjects (%) are shown.

*Pneumonitis/Interstitial lung disease search strategy: Interstitial Lung Disease (SMQ) [broad]

EV: Enfortumab vedotin; SAE: Serious Adverse Event

Source: EV-302 ISS Tables 12.6.1.5.9.1, 12.6.1.5.9.4.

A review of post-marketing data up to 17 Jun 2023 showed 95 postmarketing cases of Pneumonitis/Interstitial lung disease, of which 12 cases were fatal. There were a total of 98 events in these 95 cases, of which 1 was non serious, and the remaining 97 were serious events. The most frequently reported PT was Interstitial lung disease (n = 72), followed by Pneumonitis (n = 17).

## Risk factors and risk groups

Pneumonitis/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.

**Preventability**

Patients should be monitored for signs and symptoms indicative of pneumonitis/interstitial lung disease such as hypoxia, cough, dyspnea or interstitial infiltrates, or radiologic exams. The patients should be evaluated and exclude infections, neoplastic and other causes for such signs and symptoms through appropriate investigations. For Grade 2 pneumonitis, treatment should be withheld until Grade <1, then resume at the same dose level or consider dose reduction by one dose level. Permanently discontinue enfortumab vedotin in all patients with Grade≥3 pneumonitis/ interstitial lung disease.

**Impact on the benefit-risk balance of the product**

Given the severity of the indication being treated, the higher incidence of concurrent pneumonitis/interstitial lung disease in the patient population of bladder cancer (as described in the subsection 'Characterization of the risk' above), and the readily available management strategies for pneumonitis/interstitial lung disease including prevention, early diagnosis, and treatment, the impact on the benefit-risk balance is considered acceptable. Along with communication of the risk in the EU-SmPC and PL, the overall benefits outweigh the risk in the treatment of metastatic urothelial carcinoma.

**Public health impact**

Pneumonitis/Interstitial lung disease, if left untreated, can cause serious health problems and untimely deaths. With communication to prescribers of the importance of monitoring patients for pneumonitis/interstitial lung disease and the dose modifications in the label, the impact on public health is reduced. This is communicated to prescribers through the local label.

**Important Potential Risks:** None

### SVII.3.2 Presentation of the missing information

No missing information.

# PART II: MODULE SVIII. SUMMARY OF THE SAFETY CONCERNS

| | |
|---|---|
| Data-lock point for this Module | 31 Aug 2022 |
| Version when Module last updated | 2.0 |

**Table SVIII.1: Summary of safety concerns**

| Summary of safety concerns | |
|---|---|
| Important identified risks | • Skin reactions<br>• Hyperglycemia<br>• Pneumonitis/Interstitial lung disease |
| Important potential risks | None |
| Missing information | None |

# PART III: PHARMACOVIGILANCE PLAN (INCLUDING POSTAUTHORIZATION SAFETY STUDIES)

| | |
|---|---|
| Data-lock point for this Module | 08 Aug 2023 |
| Version when Module last updated | 4.0 |

## III.1 Routine pharmacovigilance activities beyond adverse reaction reporting and signal detection

Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:

**Specific adverse reaction follow-up questionnaires for safety concerns:**

| Description | Purpose | Safety concern(s) addressed |
|---|---|---|
| Not applicable | Not applicable | Not applicable |

**Other forms of routine pharmacovigilance activities:**

| Activity | Objective(s)/Description | Milestone(s) |
|---|---|---|
| Not applicable | Not applicable | Not applicable |

## III.2 Additional pharmacovigilance activities

**Additional Pharmacovigilance Activities**

| | |
|---|---|
| **Study short name and title** | Protocol 7465-PV-0002<br>A non-interventional post authorization safety study (NI-PASS) to evaluate effectiveness of the patient card (ongoing) |
| Rationale and study objectives | 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 |
| Study design | Cross-sectional survey |
| Study population | Patients in European countries with locally advanced or metastatic urothelial carcinoma who previously received platinum and PD-1/L1 inhibitor therapy and have received or are currently receiving Padcev™ therapy. If a patient is unable to participate in the survey, their caregiver will be asked to participate. |
| Milestones | • Submission of final report to EMA: Q3 2025 |

EMA: European Medicines Agency; NI-PASS: Non interventional - Post authorization safety study

# III.3 Summary table of additional pharmacovigilance activities

## Table Part III.1: Ongoing and planned additional pharmacovigilance activities

| Study Status | Summary of objectives | Safety concerns addressed | Milestones | Due dates |
|---|---|---|---|---|
| **Category 1 - Imposed mandatory additional pharmacovigilance activities which are conditions of the marketing authorization** | | | | |
| Not applicable | | | | |
| **Category 2 - Imposed mandatory additional pharmacovigilance activities which are Specific Obligations in the context of a conditional marketing authorization or a marketing authorization under exceptional circumstances** | | | | |
| Not applicable | | | | |
| **Category 3 - Required additional pharmacovigilance activities** | | | | |
| Protocol 7465-PV-0002 A non-interventional post authorization safety study (NI-PASS) to evaluate effectiveness of the patient card (Ongoing) | 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. | Skin reactions | Submission of final study report to EMA | Q3 2025 |

EMA: European Medicines Agency; NI-PASS: Non Interventional - Post Authorization Safety Study.

# PART IV: PLANS FOR POSTAUTHORIZATION EFFICACY STUDIES

| | |
|---|---|
| Data-lock point for this Module | 15 Sep 2020 |
| Version when Module last updated | 0.1 |

**Table Part IV.1: Planned and ongoing postauthorization efficacy studies that are conditions of the marketing authorization or that are specific obligations.**

| Study Status | Summary of objectives | Efficacy uncertainties addressed | Milestones | Due dates |
|---|---|---|---|---|
| **Efficacy studies which are conditions of the marketing authorization** | | | | |
| Not applicable | | | | |
| **Efficacy studies which are Specific Obligations in the context of a conditional marketing authorization or a marketing authorization under exceptional circumstances** | | | | |
| Not applicable | | | | |

# PART V: RISK MINIMIZATION MEASURES (INCLUDING EVALUATION OF THE EFFECTIVENESS OF RISK MINIMIZATION ACTIVITIES)

**Risk Minimization Plan**

| | |
|---|---|
| Data-lock point for this Module | 08 Aug 2023 |
| Version when Module last updated | 3.0 |

## V.1. Routine Risk Minimization Measures

**Table Part V.1: Description of routine risk minimization measures by safety concern**

| Safety concern | Routine risk minimization activities |
|---|---|
| Skin reactions | Routine risk communication:<br>• EU-SmPC Sections 4.2, 4.4 and 4.8;<br>• PL Sections 2 and 4<br><br>Routine risk minimization activities recommending specific clinical measures to address the risk:<br>• 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.<br>- 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.<br>- 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.<br>- Permanently discontinue enfortumab vedotin for confirmed SJS or TEN, Grade 4 or recurrent severe skin reactions.<br>• Recommendations are provided in the EU-SmPC Section 4.2 for treatment interruption, dose reduction and treatment discontinuation of enfortumab vedotin.<br><br>Other routine risk minimization measures beyond the Product Information:<br>• None |

| Safety concern | Routine risk minimization activities |
|---|---|
| Hyperglycemia | Routine risk communication:<br>• EU-SmPC Sections 4.2, 4.4 and 4.8;<br>• PL Sections 2 and 4<br><br>Routine risk minimization activities recommending specific clinical measures to address the risk:<br>• Recommendations are provided in the 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 hyperglycemia.<br>• 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.<br>• Recommendations are provided in the EU-SmPC Section 4.2 for treatment interruption and when to resume treatment of enfortumab vedotin.<br><br>Other routine risk minimization measures beyond the Product Information:<br>• None |
| Pneumonitis/Interstitial lung disease | Routine risk communication:<br>• EU-SmPC Sections 4.2, 4.4 and 4.8;<br>• PL Sections 2 and 4<br><br>Routine risk minimization activities recommending specific clinical measures to address the risk:<br>• 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<br><br>Other routine risk minimization measures beyond the Product Information:<br>• None |

PL: Package Leaflet; EU-SmPC: European Union-Summary of Product Characteristics; SJS: Stevens-Johnson Syndrome; TEN: Toxic Epidermal Necrolysis.

## V.2 Additional Risk Minimization Measures

The product information (Summary of Product Characteristics [SmPC] and PL) is the primary tool for mitigating the important identified risk of skin reactions. The necessary information to ensure the appropriate use of enfortumab vedotin and provide guidance for the management of patients to minimize the risk of skin reactions is included in the relevant sections of the SmPC and PL.

The following additional risk minimization measures are proposed to further inform patients who are prescribed enfortumab vedotin regarding the important identified risk of skin reactions:

- Patient Card

**Additional risk minimization: Patient card**

Objectives:

To provide patients with information on the risk of skin reactions, including SCAR, that can be carried with them. Information will include a description of the signs and symptoms of skin reactions and instructions on seeking medical care.

Rationale for the additional risk minimization activity:

Additional risk minimization is considered needed to minimize the risk of skin reactions as SCAR is a potentially fatal complication that can progress rapidly if treatment is delayed and early intervention is essential for protection of a patient´s health.

Target audience and planned distribution path:

The target audience for the Patient Card are adult patients with locally advanced or metastatic urothelial cancer prescribed enfortumab vedotin and it will be designed to be pocket size and integrated into the package to be supplied along with the patient leaflet and the enfortumab vedotin single dose vial. Any other national aspects of the patient card will be agreed with the National Competent Authority (NCA) of each member state and depending on local regulations or competent authority guideline, the patient card will be available at the NCA's website and/or distributed in printed version if requested.

Additionally, an educational programme will be developed and agreed with the NCA of each member state to ensure that healthcare professionals who are expected to prescribe Padcev are provided with the product information (SmPC and PL) and the patient card prior to use of Padcev in each Member State.

Plans to evaluate the effectiveness of the interventions and criteria for success:

Process indicators:

- Distribution of the Patient Card will be integrated into each new packaging of the drug product and quality control measures are in place as part of Good Manufacturing Practices (GMPs) to ensure that each carton contains required labeling, including the Patient Card.
- Distribution metrics for the patient card will be derived using sales data.
- Distribution metrics for materials included in the educational programme to prescribers targeted will be tracked.

Outcome indicators:

- The content of the Patient Card has been extracted from the Package Leaflet which has undergone readability testing to ensure potential users could locate, understand, and act upon the information contained in the Package Leaflet.
- A non-interventional post authorization safety study (NI-PASS) (Protocol 7465-PV-0002) to evaluate the effectiveness of the patient card is ongoing. The objective of this study is to assess patients' understanding and awareness of the content of the patient card related to risks of skin reactions and patient behaviours to minimize the risk. The study design includes a cross-sectional survey of patients prescribed enfortumab vedotin in selected EU countries. The study protocol with milestone timelines will be submitted to EMA for review 9 months after approval.
- Effectiveness of the intervention will be further assessed by routine pharmacovigilance and the evaluation of post-marketing reports of skin reactions. A summary of the assessment will be included with the enfortumab vedotin Periodic Benefit Risk Evaluation Report (PBRER).

### V.2.1 Removal of additional risk minimization activities

Not applicable

## V.3 Summary of Risk Minimization Measures

**Table Part V.3: Summary table of pharmacovigilance activities and risk minimization activities by safety concern**

| Safety concern | Risk minimization measures | Pharmacovigilance activities |
|---|---|---|
| Skin reactions | Routine risk communication:<br>• EU-SmPC Sections 4.2, 4.4 and 4.8;<br>• PL Sections 2 and 4<br><br>Routine risk minimization activities recommending specific clinical measures to address the risk:<br>• 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.<br>- For Grade 2 worsening, Grade 2 with Fever or Grade | Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:<br>• None<br><br>Additional pharmacovigilance activities:<br>NI-PASS category 3 study to assess evaluation of patients' understanding and awareness of the content of the patient card related to risks of skin reactions and patient behaviours to minimize the risk. |

| Safety concern | Risk minimization measures | Pharmacovigilance activities |
|---|---|---|
| | 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.<br>- 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.<br>- Permanently discontinue enfortumab vedotin for confirmed SJS or TEN, Grade 4 or recurrent severe skin reactions.<br>• Recommendations are provided in the EU-SmPC Section 4.2 for treatment interruption, dose reduction and treatment discontinuation of enfortumab vedotin.<br>Additional risk minimization measures:<br>Patient card | |
| Hyperglycemia | Routine risk communication:<br>EU-SmPC Sections 4.2, 4.4 and 4.8<br>PL Sections 2 and 4<br><br>Routine risk minimization activities recommending specific clinical measures to address the risk:<br>• Recommendations are provided in the 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 | Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:<br>• None<br><br>Additional pharmacovigilance activities:<br>None |

| Safety concern | Risk minimization measures | Pharmacovigilance activities |
|---|---|---|
| | with or at risk for diabetes mellitus or hyperglycemia. 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.<br>• Recommendations are provided in EU-SmPC Section 4.2 for treatment interruption and when to resume treatment of enfortumab vedotin.<br><br>Additional risk minimization measures:<br>None | |
| Pneumonitis/Interstitial lung disease | Routine risk communication:<br>• EU-SmPC Sections 4.2, 4.4 and 4.8;<br>• PL Sections 2 and 4<br><br>Routine risk minimization activities recommending specific clinical measures to address the risk:<br>- 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.<br>-Permanently discontinue enfortumab vedotin for Grade ≥3 pneumonitis/interstitial lung disease<br>Additional risk minimization measures:<br>None | Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:<br>• None<br><br>Additional pharmacovigilance activities:<br>None |

EU-SmPC: European Union-Summary of Product Characteristics; NI-PASS: Non-interventional Post-Authorization Safety Studies; PL: Package Leaflet; SJS: Stevens Johnson Syndrome; TEN: Toxic Epidermal Necrolysis.

# PART VI: SUMMARY OF THE RISK MANAGEMENT PLAN

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| Data-lock point for this Module | 08 Aug 2023 |
| Version when Module last updated | 3.1 |

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

Padcev, in combination with pembrolizumab, is indicated for the first-line treatment of adult patients with unresectable or metastatic urothelial cancer who are eligible for platinum-containing chemotherapy (see EU-SmPC for the full indication).

Padcev 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<br>• Hyperglycemia<br>• Pneumonitis/Interstitial lung disease |
| Important potential risks | • None |
| Missing information | • None |

## II.B Summary of important risks

### Important identified risk: Skin reactions

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| 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.<br>In study EV-302, the proportion of subjects experiencing skin reactions AESI is 69.5 % in EV + Pembro combo ISS group as compared to 57.0% in the EV Mono ISS group. The most common skin reaction PTs observed in the EV + Pembro Combo ISS analysis group were rash maculo-papular (36.0%), rash macular (11.3%), and rash papular (7.6%). In EV Mono ISS analysis group, the most common PTs observed were rash maculo-papular (23.6%), rash (11.6%), and rash erythematous (4.7%) [EV-302 ISS Table 12.6.1.5.3.1]. The proportion of subjects with severe cutaneous adverse reaction events in the EV + Pembro Combo ISS analysis group (27.5%) was similar to that in the EV Mono ISS analysis group (24.8%) [EV-103 ISS Table 12.6.1.5.3.1]. The higher frequency of skin reactions between these analysis groups was likely due to a contribution of both drugs and a longer duration of exposure during combination therapy (9.43 months) than in previous experience with enfortumab vedotin monotherapy (4.70 months) [EV-302 ISS Table 12.6.1.8.11.3]. In study EV-302, the frequency of serious |

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| | skin reactions was also similar between the EV + Pembro Combo ISS and EV Mono ISS analysis groups (5.3% vs 4.3%, respectively) [EV-302 ISS Table 12.6.1.5.3.4]. All of these serious AESI were considered drug-related by the investigator [EV-302 ISS Table 12.6.1.5.3.5].<br><br>A review of postmarketing data up to 17 Jun 2023 showed 1313 spontaneous cases of skin reactions, of which 77 cases were fatal. There were a total of 1544 events in these 1313 cases, of which 1103 were non-serious, and the remaining 441 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 (638), Erythema (121), Blister (104), Stevens-Johnson syndrome (94), Drug eruption (90), and Toxic epidermal necrolysis (82). |
| 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:<br>• EU-SmPC sections 4.2, 4.4 and 4.8;<br>• PL sections 2 and 4<br><br>Routine risk minimization activities recommending specific clinical measures to address the risk:<br>• 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.<br>- 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. |

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| | - 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.<br>- Permanently discontinue enfortumab vedotin for confirmed SJS or TEN, Grade 4 or recurrent severe skin reactions.<br>• Recommendations are provided in the EU-SmPC Section 4.2 for treatment interruption, dose reduction and treatment discontinuation of enfortumab vedotin.<br><br>Additional risk minimization measures:<br>• 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

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| Evidence for linking the risk to the medicine | In study EV-302, the frequency of TEAEs in the AESI of hyperglycemia observed in the EV + Pembro Combo ISS analysis group was similar to that observed in the EV Mono ISS analysis group (19.0% vs 16.8%). By PT, there were no AESI of hyperglycemia reported at a > 10% difference frequency in the EV + Pembro Combo ISS analysis group compared to the EV Mono ISS analysis group [EV-302 ISS Table 12.6.1.5.4.1]. The frequency of serious hyperglycemia events was also similar between the EV + Pembro Combo ISS and EV Mono ISS analysis groups (2.0% vs 2.5%, respectively) [EV-302 ISS Table 12.6.1.5.4.4]. Of these serious AESI, 10 of 11 in the EV + Pembro Combo ISS analysis group and 18 of 20 in the EV Mono ISS analysis group were considered drug-related by the investigator [EV-302 ISS Table 12.6.1.5.4.5].<br><br>A review of post-marketing data up to 17 Jun 2023 showed 226 postmarketing cases of the Hyperglycemia/new onset diabetes mellitus SMQ (Narrow), of which 29 cases were fatal. There were a total of 244 events in these 226 cases, of which 165 were non serious, and the remaining 79 were serious events. The most frequently reported PTs were Hyperglycemia (152), Blood glucose increased (49), and diabetic ketoacidosis (10). |
| 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 |

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| | population of older adults [Centers for Disease Control and Prevention, 2017].<br>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].<br>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:<br>• EU-SmPC sections 4.2, 4.4 and 4.8;<br>• PL sections 2 and 4.<br>Routine risk minimization activities recommending specific clinical measures to address the risk:<br>• 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 hyperglycemia. 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.<br>• 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; EU-SmPC: European Union-Summary of Product Characteristics; HbA1c: hemoglobin A1C; HIV: Human Immunodeficiency Virus; PL: Package Leaflet; SAE: serious adverse event; SMQ: Standardized MedDRA Query; WHO: World Health Organization.

## Important identified risk: Pneumonitis/Interstitial lung disease

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| Evidence for linking the risk to the medicine | In study EV-302, the frequency of TEAEs of pneumonitis/ILD were observed at a higher frequency in the EV + Pembro Combo ISS analysis group than in the EV Mono ISS analysis group (10.3% vs 3.3%). However, no PTs within the search strategy of pneumonitis/ILD were reported at a > 10% difference between EV + Pembro ISS and EV Mono ISS groups [EV-302 ISS Table 12.6.1.5.9.1]. The higher frequency of pneumonitis/ILD observed between these analysis groups was likely due to a contribution of both drugs and a longer duration of exposure during combination therapy (9.43 months) than in previous experience with EV mono (4.70 months) [EV-302 ISS Table 12.2.1.1]. The frequency of serious pneumonitis/ILD events was higher between the EV + Pembro Combo ISS and EV Mono ISS analysis groups (4.3% vs 0.8%, respectively) [EV-302 ISS Table 12.6.1.5.9.4]. With the |

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| | exception of 1 (5/6) pneumonitis/ILD event in the EV Mono ISS analysis group, all of these serious events were considered drug-related by the investigator [EV-302 ISS Table 12.6.1.5.9.5].<br><br>A review of post-marketing data up to 17 Jun 2023showed 95 postmarketing cases of pneumonitis/interstitial lung disease, of which 12 cases were fatal. There were a total of 98 events in these 95 cases, of which 1 was non serious, and the remaining 97 were serious events. The most frequently reported PT was Interstitial lung disease (n = 72), followed by Pneumonitis (n = 17). |
| 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:<br>• EU-SmPC sections 4.2, 4.4 and 4.8;<br>• PL sections 2 and 4.<br><br>Routine risk minimization activities recommending specific clinical measures to address the risk:<br>• 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 |

EU: European Union; ISS: Integrated Summary of Safety; 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.

# PART VII: ANNEXES

## Table of Contents

# Annex 4 - Specific adverse event follow-up forms

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| Data-lock point for this annex | 15 Sep 2020 |
| Version when annex last updated | 0.1 |

Not applicable

# Annex 6 - Details of proposed additional risk minimization activities (if applicable)

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| Data-lock point for this annex | 15 Sep 2020 |
| Version when annex last updated | 0.5 |

**Key messages of the additional risk minimization measures**

Prior to use of Padcev in each Member State the Marketing Authorization Holder (MAH) shall agree the content and format of the educational programme, including communication media, distribution modalities, and any other aspects of the programme, with the National Competent Authority.

The MAH shall ensure that in each Member State where Padcev is marketed, all healthcare professionals who are expected to prescribe Padcev are provided with the following materials:

The patient information pack:

- Patient information leaflet
- Patient card

Patient card:

- Information for patients that Padcev treatment may cause skin reactions including severe skin reactions such as SJS, TEN or other severe rashes.
- Description of the symptoms of skin reactions and to immediately seek medical care as these may be signs of a severe skin reaction.
- A warning message for healthcare professionals treating the patient at any time, including in conditions of emergency, that the patient is using Padcev.
- Contact details of the treating physician who has prescribed Padcev.
- Needs to be carried all the time and presented to any healthcare professional.

The MAH shall also provide a patient card in each pack of the medicinal product, the text of which is included in Annex 3.

# Annex 7 - Other supporting data (including referenced material)

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|---|---|
| Data-lock point for this annex | 08 Aug 2023 |
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