<May> <2022>

Important Drug Warning

Subject:	**Risk of Severe Cutaneous Adverse Reactions with PADCEV™ (enfortumab vedotin)**

Dear Healthcare Provider,

This letter is to provide you with important safety information about the risk of severe cutaneous adverse reactions included in the prescriber information for PADCEV™, a Nectin-4-directed antibody drug conjugate indicated for the treatment of adult patients with locally advanced or metastatic urothelial cancer (mUC) who have previously received a programmed death receptor-1 (PD-1) or programmed death-ligand 1 (PD-L1) inhibitor and platinum-containing chemotherapy in the neoadjuvant/adjuvant, locally advanced or metastatic setting, or are ineligible for cisplatin-containing chemotherapy and have previously received a PD-1/PD-L1 inhibitor. The letter also provides guidance on the steps to take including dose modifications and management in the case that the described risk of severe cutaneous adverse reactions occurs.

Summary

- PADCEV™ can cause severe and fatal cutaneous adverse reactions including Stevens-Johnson syndrome (SJS) and Toxic Epidermal Necrolysis (TEN), which occurred predominantly during the first cycle of treatment, but may occur later.
- Closely monitor patients for skin reactions.
- Immediately withhold PADCEV and consider referral for specialized care for suspected SJS or TEN or severe skin reactions.
- Permanently discontinue PADCEV in patients with confirmed SJS or TEN; or Grade 4 or recurrent Grade 3 skin reactions.

Recommendations to Healthcare Provider

- Inform patients that rashes and severe skin reactions have occurred after administration of PADCEV™.
- Advise patients to contact their healthcare provider if they have signs or symptoms of skin reactions.

Dose Modifications

Adverse Reaction	**Severity***	**Dose Modification***
Skin Reactions *[see Boxed Warning,*	Suspected SJS or TEN	Immediately withhold, consult a specialist to confirm the diagnosis. If not SJS/TEN, see Grade 3 skin reactions.

Warnings and Precautions (5.1)	Confirmed SJS or TEN; Grade 4 or recurrent Grade 3 skin reactions	Permanently discontinue.
	Grade 3 (severe) skin reactions	Withhold until Grade ≤1, then resume treatment at the same dose level or consider dose reduction by one dose level.

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

Recommended Dose Reduction Schedule

	Dose Level
Starting dose	1.25 mg/kg up to 125 mg
First dose reduction	1.0 mg/kg up to 100 mg
Second dose reduction	0.75 mg/kg up to 75 mg
Third dose reduction	0.5 mg/kg up to 50 mg

Additional Information on Safety Concern

Skin reactions occurred in 55% of the 680 patients treated with PADCEV™ in clinical trials. Twenty-three percent (23%) of patients had maculopapular rash and 33% had pruritus. Grade 3-4 skin reactions occurred in 13% of patients, including maculo-papular rash, rash erythematous, rash or drug eruption, symmetrical drug-related intertriginous and flexural exanthema (SDRIFE), dermatitis bullous, dermatitis exfoliative, and palmar-plantar erythrodysesthesia. In clinical trials, the median time to onset of severe skin reactions was 0.6 months (range: 0.1 to 6.4 months).

Among patients experiencing a skin reaction leading to dose interruption who then restarted PADCEV™ (n=59), 24% of patients restarting at the same dose and 16% of patients restarting at a reduced dose experienced recurrent severe skin reactions. Skin reactions led to discontinuation of PADCEV™ in 2.6% of patients.
Adverse reactions have been identified during post-approval use of PADCEV™. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

- Skin and subcutaneous tissue disorders: Epidermal necrosis, Stevens-Johnson syndrome, toxic epidermal necrolysis

Additional Information: Mechanism of Action:

- Enfortumab vedotin is directed antibody-drug conjugate (ADC). The antibody is a human IgG1 directed against Nectin-4, an adhesion protein located on the surface of cells.
- The small molecule, MMAE, is a microtubule-disrupting agent, attached to the antibody via a protease-cleavable linker. Nonclinical data suggest that the anticancer activity of enfortumab vedotin is due to the binding of the ADC to Nectin-4-expressing cells, followed by internalization of the ADC to Nectin-4 complex, and the release of MMAE via proteolytic cleavage.
- Release of MMAE disrupts the microtubule network within the cell, subsequently inducing cell cycle arrest and apoptotic cell death.

The important safety information in this letter is not intended as a complete description of the benefits and risks related to the use of PADCEV™, please refer to the enclosed full Prescribing Information that is updated with the important safety information;

Padcev 20mg
https://israeldrugs.health.gov.il/#!/medDetails/167%2037%2036604%2000

Padcev 30mg
https://israeldrugs.health.gov.il/#!/medDetails/167%2038%2036605%2000

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorization of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form:
/https://sideeffects.health.gov.il

Adverse events can also be reported to Astellas Pharma International B.V using the following email: Pharmacovigilance.IL@astellas.com

Company Contact Point

Should you have any questions regarding the contents of this letter or the use of PADCEV™, please contact Pharmacovigilance.IL@astellas.com

Sincerely,

Dr. Varda Eshed
Head of Medical Affairs
Astellas Pharma International B.V

Astellas Pharma International B.V is processing your personal information, specifically, information about your professional role and your contact details to take appropriate additional risk minimization measures agreed with relevant regulators and agencies, like, for example, provision of additional safety information about our medicinal products to relevant healthcare professionals. Distribution of these materials is part of Astellas' pharmacovigilance risk management obligations

To learn more about Astellas' privacy practices and the rights you have under applicable laws, you may access our full Privacy Notice by visiting https://www.astellas.com/il/he/privacy-policy

If you have questions or concerns about our use of your personal data, you may contact Astellas' Data Protection Officer at privacy@astellas.com