03.01.2022

רופא/ה רוקח/ת נכבד/ה,
ברצוננו להודיעך על עדכון בעלון לרופא ועלון לצרכן של

PADCEV 20mg
PADCEV 20mg
Powder For Concentrate For Solution For Infusion

חומר פעיל:

Enfortumab Vedotin 20 mg
Enfortumab Vedotin 30 mg

התוויה מאושרת:

PADCEV is 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.

להלן עדכונים בעלון לרופא (טקסט מסומן ירוק משמעותו עדכון, טקסט מסומן בצהוב משמעותו החמרה):

WARNING: SERIOUS SKIN REACTIONS

- **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 *[see Dosage and Administration (3.2), Warnings and Precautions (5.1) and Adverse Reactions (6.1)].***

2. Therapeutic Indication

PADCEV™ is 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, or
- are ineligible for cisplatin-containing chemotherapy and have previously received a PD-1/PD-L1 inhibitor.

3. Dosage And Administration

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3.2 Dose Modifications

Table 1. Dose Modifications

Adverse Reaction	Severity*	Dose Modification*
Skin Reactions *[see Boxed Warning, Warnings and Precautions (5.1)]*	Suspected SJS or TEN	Immediately withhold, consult a specialist to confirm the diagnosis. If not SJS/TEN, see Grade 3 skin reactions.
	Confirmed SJS or TEN; Grade 4 or recurrent Grade 3 skin reactions	Permanently discontinue.
	Grade 3 (severe) skin reactions	Withhold until Grade ≤1, then resume treatment at the same dose level or consider dose reduction by one dose level.
Hyperglycemia *[see Warnings and Precautions (5.2)]*	Blood glucose >250 mg/dL	Withhold until elevated blood glucose has improved to ≤ 250 mg/dL, then resume treatment at the same dose level.
Pneumonitis *[see Warnings and Precautions (5.3)]*	Grade 2	Withhold until Grade ≤ 1 for persistent or recurrent Grade 2 pneumonitis, consider dose reduction by one dose level.
	Grade >3	Permanently discontinue.
Peripheral Neuropathy *[see Warnings and Precautions (5.4)]*	Grade 2	Withhold until Grade ≤ 1, then resume treatment at the same dose level (if first occurrence). For a recurrence, withhold until Grade ≤ 1 then, resume treatment reduced by one dose level.
	Grade ≥3	Permanently discontinue.
Other nonhematologic toxicity *[see Adverse Reactions (6)]*	Grade 3	Withhold until Grade ≤ 1, then resume treatment at the same dose level or consider dose reduction by one dose level
	Grade 4	Permanently discontinue.
Hematologic toxicity *[see Adverse Reactions (6)]*	Grade 3, or Grade 2 thrombocytopenia	Withhold until Grade ≤ 1, then resume treatment at the same dose level or consider dose reduction by one dose level.
	Grade 4	Withhold until Grade ≤ 1, then reduce dose by one dose level or discontinue treatment.

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

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5. Warnings And Precautions

5.1 Skin Reactions

Severe cutaneous adverse reactions, including fatal cases of SJS or TEN occurred in patients treated with PADCEV. SJS and TEN occurred predominantly during the first cycle of treatment but may occur later.

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 *[see Adverse Reactions (6.1)]*.

Monitor patients closely throughout treatment for skin reactions. Consider topical corticosteroids and antihistamines, as clinically indicated.

Withhold PADCEV and refer for specialized care for suspected SJS, TEN or for severe (Grade 3) skin reactions.

Permanently discontinue PADCEV in patients with confirmed SJS or TEN; or Grade 4 or recurrent Grade 3 skin reactions *[see Dosage and Administration (3.2)]*.

5.2 Hyperglycemia

Hyperglycemia and diabetic ketoacidosis (DKA), including fatal events, occurred in patients with and without pre-existing diabetes mellitus, treated with PADCEV.

Patients with baseline hemoglobin A1C ≥8% were excluded from clinical trials. In clinical trials, 14% of the 680 patients treated with PADCEV developed hyperglycemia; 7% of patients developed Grade 3-4 hyperglycemia. The incidence of Grade 3-4 hyperglycemia increased consistently in patients with higher body mass index and in patients with higher baseline A1C. Five percent (5%) of patients required initiation of insulin therapy for treatment of hyperglycemia. The median time to onset of hyperglycemia was 0.6 months (range: 0.1 to 20.3 months). Hyperglycemia led to discontinuation of PADCEV in 0.6% of patients. *[see Adverse Reactions (6.1)]*.

Closely monitor blood glucose levels in patients with, or at risk for, diabetes mellitus or hyperglycemia. If blood glucose is elevated (>250 mg/dL), withhold PADCEV *[see Dosage and Administration (3.2)]*.

5.3 Pneumonitis

Severe, life-threatening or fatal pneumonitis occurred in patients treated with PADCEV. In clinical trials, 3.1% of the 680 patients treated with PADCEV had pneumonitis of any grade and 0.7% had Grade 3-4. In clinical trials, the median time to onset of pneumonitis was 2.9 months (range: 0.6 to 6 months).

Monitor patients for signs and symptoms indicative of pneumonitis such as hypoxia, cough, dyspnea or interstitial infiltrates on radiologic exams. Evaluate and exclude infectious, neoplastic and other causes for such signs and symptoms through appropriate investigations.

Withhold PADCEV for patients who develop persistent or recurrent Grade 2 pneumonitis and consider dose reduction. Permanently discontinue PADCEV in all patients with Grade 3 or 4 pneumonitis *[see Dosage and Administration (3.2)]*.

5.4 Peripheral Neuropathy

Peripheral neuropathy occurred in 52% of the 680 patients treated with PADCEV in clinical trials including 39% with sensory neuropathy, 7% with muscular weakness and 6% with motor neuropathy; 4% experienced Grade 3-4 reactions.

Peripheral neuropathy occurred in patients treated with PADCEV with or without preexisting peripheral neuropathy. The median time to onset of Grade ≥2 peripheral neuropathy was 4.6 months (range: 0.1 to 5.8 months). Neuropathy led to treatment discontinuation in 5% of patients [*see Adverse Reactions (6.1)*].

Monitor patients for symptoms of new or worsening peripheral neuropathy and consider dose interruption or dose reduction of PADCEV when peripheral neuropathy occurs. Permanently discontinue PADCEV in patients that develop Grade ≥3 peripheral neuropathy *[see Dosage and Administration (3.2)]*.

5.5 Ocular Disorders

Ocular disorders were reported in 40% of the 384 patients treated with PADCEV in clinical trials in which ophthalmologic exams were scheduled. The majority of these events involved the cornea and included events associated with dry eye such as keratitis, blurred vision, increased lacrimation, conjunctivitis, limbal stem cell deficiency, and keratopathy.

Dry eye symptoms occurred in 34% of patients, and blurred vision occurred in 13% of patients, during treatment with PADCEV. The median time to onset to symptomatic ocular disorder was 1.6 months (range: 0 to 19.1 months).

Monitor patients for ocular disorders. Consider artificial tears for prophylaxis of dry eyes and ophthalmologic evaluation if ocular symptoms occur or do not resolve. Consider treatment with ophthalmic topical steroids, if indicated after an ophthalmic exam. Consider dose interruption or dose reduction of PADCEV for symptomatic ocular disorders.
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6 Adverse Reactions

The following serious adverse reactions are described elsewhere in the labeling:

- Skin Reactions *[see Boxed Warning, Warnings and Precautions (5.1)]*
- Hyperglycemia *[see Warnings and Precautions (5.2)]*
- Pneumonitis *[see Warnings and Precautions (5.3)]*
- Peripheral Neuropathy *[see Warnings and Precautions (5.4)]*
- Ocular Disorders *[see Warnings and Precautions (5.5)]*
- Infusion Site Extravasation *[see Warnings and Precautions (5.6)]*

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מידע עודכן בפרקים הבאים (אנא פנה/י לעלון לרופא המצ"ב למידע המלא):

6.1 Clinical Trials Experience
6.2 Post Marketing Experience
6.3 Immunogenicity
7 Drug Interactions
8.5 Geriatric Use
10 Clinical Pharmacology
12 Clinical Studies

העלון לרופא נשלח למאגר התרופות שבאתר משרד הבריאות www.health.gov.il לצורך העלאתו לאתר וניתן לקבלו מודפס על ידי פניה לבעל הרישום אסטלס פארמה אינטרנשונל בי.וי., ת.ד. 11458, ראש העין, מספר טלפון: 03-7501166.

בברכה

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