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Section:	Prescription Drugs	**Effective Date:**	April 1, 2024
Subsection:	Antineoplastic Agents	**Original Policy Date:**	January 20, 2020
Subject:	Padcev	**Page:**	1 of 6

Last Review Date: March 8, 2024

Padcev

Description

Padcev (enfortumab vedotin-ejfv)

Background
Padcev (enfortumab vedotin-ejfv) is a Nectin-4-directed antibody-drug conjugate (ADC) and microtubule inhibitor conjugate. The anticancer activity of Padcev is thought to be due to the binding of the ADC to Nectin-4-expressing cells, followed by internalization of the ADC-Nectin-4 complex, and the release of monomethyl auristatin E (MMAE) via proteolytic cleavage. Release of MMAE is thought to disrupt the microtubule network within the cell, subsequently inducing cell cycle arrest and apoptotic cell death (1).

Regulatory Status
FDA-approved indications: Padcev is a Nectin-4-directed antibody and microtubule inhibitor conjugate indicated: (1)

- In combination with pembrolizumab for the treatment of adult patients with locally advanced or metastatic urothelial cancer.
- As a single agent 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 death-ligand 1 (PD-L1) inhibitor and platinum-containing chemotherapy, or
  - are ineligible for cisplatin-containing chemotherapy and have previously received one or more prior lines of therapy.

Padcev has a boxed warning regarding the risk of severe and fatal cutaneous adverse reactions, including Stevens-Johnson syndrome (SJS) and Toxic Epidermal Necrolysis (TEN). Due to these risks, patients should be closely monitored for skin reactions. If severe skin reactions, SJS or TEN is suspected, Padcev should be withheld immediately and a referral for specialized care should be considered. In confirmed cases of SJS or TEN that are Grade 4 or recurrent Grade 3 skin reactions, Padcev should be permanently discontinued (1).

Hyperglycemia has occurred in patients treated with Padcev, including death, and diabetic ketoacidosis (DKA) in those with and without pre-existing diabetes mellitus. Blood glucose levels should be monitored closely in patients with, or at risk for, diabetes mellitus or hyperglycemia. If blood glucose is elevated (>250 mg/dL), Padcev should be withheld (1).

Peripheral neuropathy, predominantly sensory, has occurred in patients treated with Padcev. Patients should be monitored for symptoms of new or worsening peripheral neuropathy and dose interruption or dose reduction should be considered when peripheral neuropathy occurs. Padcev should be permanently discontinued in patients that develop Grade $\geq$3 peripheral neuropathy (1).

Padcev can cause fetal harm when administered to a pregnant woman. Female patients of reproductive potential should be advised to use effective contraception during treatment with Padcev and for 2 months after the last dose. Male patients with female partners of reproductive potential should be advised to use effective contraception during treatment with Padcev and for 4 months after the last dose (1).

The safety and effectiveness of Padcev in pediatric patients less than 18 years of age have not been established (1).

Related policies

Policy

This policy statement applies to clinical review performed for pre-service (Prior Approval, Precertification, Advanced Benefit Determination, etc.) and/or post-service claims.

Padcev may be considered **medically necessary** if the conditions indicated below are met.

Padcev may be considered **investigational** for all other indications.

Prior-Approval Requirements

Age 18 years of age or older

Diagnosis

Patient must have the following:

1. Locally advanced or metastatic urothelial cancer
    a. Used as a single agent
    b. Patient has **ONE** of the following:
        i. Previous treatment with platinum-containing chemotherapy **AND ONE** of the following:
            1. programmed death receptor-1 (PD-1) inhibitor
            2. programmed death-ligand 1 (PD-L1) inhibitor
        ii. Patient is ineligible for cisplatin-containing chemotherapy and has previously received one or more prior lines of therapy

AND ALL of the following:

1. Prescriber agrees to monitor for severe skin reactions, such as Stevens-Johnson syndrome (SJS) and Toxic Epidermal Necrolysis (TEN)
2. Prescriber agrees to monitor for new or worsening peripheral neuropathy
3. Prescriber agrees to monitor for hyperglycemia
4. Females of reproductive potential **only**: patient will be advised to use effective contraception during treatment with Padcev and for 2 months after the last dose
5. Males with female partners of reproductive potential **only**: patient will be advised to use effective contraception during treatment with Padcev and for 4 months after the last dose

Diagnosis

Patient must have the following:

1. Locally advanced or metastatic urothelial cancer
    a. Used in combination with Keytruda (pembrolizumab)

AND ALL of the following:

1. Prescriber agrees to monitor for severe skin reactions, such as Stevens-Johnson syndrome (SJS) and Toxic Epidermal Necrolysis (TEN)
2. Prescriber agrees to monitor for new or worsening peripheral neuropathy
3. Prescriber agrees to monitor for hyperglycemia
4. Females of reproductive potential **only**: patient will be advised to use effective contraception during treatment with Padcev and for 2 months after the last dose
5. Males with female partners of reproductive potential **only**: patient will be advised to use effective contraception during treatment with Padcev and for 4 months after the last dose

Prior – Approval *Renewal* Requirements

Age 18 years of age or older

Diagnosis

Patient must have the following:

1. Locally advanced or metastatic urothelial cancer
    a. Used as a single agent
    b. **NO** disease progression or unacceptable toxicity

AND ALL of the following:

1. Prescriber agrees to monitor for severe skin reactions, such as Stevens-Johnson syndrome (SJS) and Toxic Epidermal Necrolysis (TEN)
2. Prescriber agrees to monitor for new or worsening peripheral neuropathy
3. Prescriber agrees to monitor for hyperglycemia
4. Females of reproductive potential **only**: patient will be advised to use effective contraception during treatment with Padcev and for 2 months after the last dose
5. Males with female partners of reproductive potential **only**: patient will be advised to use effective contraception during treatment with Padcev and for 4 months after the last dose

Diagnosis

Patient must have the following:

1. Locally advanced or metastatic urothelial cancer
    a. Used in combination with Keytruda (pembrolizumab)
    b. **NO** disease progression or unacceptable toxicity

AND ALL of the following:

1. Prescriber agrees to monitor for severe skin reactions, such as Stevens-Johnson syndrome (SJS) and Toxic Epidermal Necrolysis (TEN)
2. Prescriber agrees to monitor for new or worsening peripheral neuropathy
3. Prescriber agrees to monitor for hyperglycemia
4. Females of reproductive potential **only**: patient will be advised to use effective contraception during treatment with Padcev and for 2 months after the last dose
5. Males with female partners of reproductive potential **only**: patient will be advised to use effective contraception during treatment with Padcev and for 4 months after the last dose

Policy Guidelines

Pre – PA Allowance

None

Prior – Approval Limits

Duration 12 months

Prior – Approval *Renewal* Limits

Same as above

Rationale

Summary

Padcev (enfortumab vedotin-ejfv) is a Nectin-4-directed antibody-drug conjugate (ADC) and microtubule inhibitor conjugate indicated for the treatment of patients with locally advanced or metastatic urothelial cancer. The anticancer activity of Padcev is thought to be due to the binding of the ADC to Nectin-4-expressing cells, followed by internalization of the ADC-Nectin-4 complex, and the release of monomethyl auristatin E (MMAE) via proteolytic cleavage. Release of MMAE is

thought to disrupt the microtubule network within the cell, subsequently inducing cell cycle arrest and apoptotic cell death. Padcev carries a boxed warning for the risk of severe cutaneous skin reactions including SJS and TEN. The safety and effectiveness of Padcev in pediatric patients less than 18 years of age have not been established (1).

Prior approval is required to ensure the safe, clinically appropriate, and cost-effective use of Padcev while maintaining optimal therapeutic outcomes.

References

1. Padcev [package insert]. Northbrook, IL: Astellas Pharma US, Inc.; December 2023.
2. NCCN Drugs & Biologics Compendium® Enfortumab vedotin-ejfv 2024. National Comprehensive Cancer Network, Inc. Accessed on February 8, 2024.

Policy History

Date	Action
January 2020	Addition to PA
March 2020	Annual review
June 2020	Annual review
July 2021	Revised indication to include patients that are cisplatin-treatment ineligible and tried at least one other line of therapy. Addition of boxed warning requirement to monitor for serious skin reactions
September 2021	Annual review and reference update
September 2022	Annual review and reference update
April 2023	Per PI update, added option to use in combination with Keytruda (pembrolizumab) in patients who are not eligible for cisplatin-containing chemotherapy in patients of all ages for consistency with Keytruda. Also clarified that other patients must use Padcev as a single agent
June 2023	Annual review and reference update
December 2023	Annual review and reference update
January 2024	Per PI update, removed “ineligible for cisplatin-containing chemotherapy” from urothelial cancer indication in combination with Keytruda
March 2024	Annual review and reference update

Keywords

This policy was approved by the FEP® Pharmacy and Medical Policy Committee on March 8, 2024 and is effective on April 1, 2024.