**CLINICAL GUIDELINES FOR MEDICAL NECESSITY**

**MEDICAL ONCOLOGY**

# Enfortumab vedotin-ejfv (Padcev®)

Version: 1.0

**EFFECTIVE DATE: 1/1/2024**

NantHealth® | Eviti®

## Please note the following:

## Enfortumab vedotin-ejfv (Padcev®)

**Note: For Medicare members/enrollees, to ensure consistency with the Medicare National Coverage Determinations (NCD) and Local Coverage Determinations (LCD), all applicable NCDs, LCDs, and Medicare Coverage Articles should be reviewed prior to applying the criteria set forth in this clinical policy. Please refer to the CMS website at http://www.cms.gov for additional information.**

**Note: For Medicaid members/enrollees, circumstances when state Medicaid coverage provisions conflict with the coverage provisions within this clinical policy, state Medicaid coverage provisions take precedence. Please refer to the state Medicaid manual for any coverage provisions pertaining to this clinical policy.**

## Enfortumab vedotin-ejfv (Padcev): Discussion

Enfortumab vedotin-ejfv is an antibody-drug conjugate (ADC) comprised of a human IgG1 antibody directed against nectin-4, linked to monomethyl auristatin E (MMAE), a microtubule-disrupting agent. 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-nectin-4 complex, and the release of MMAE via proteolytic cleavage. Monomethyl auristatin E activity induces cell cycle arrest and apoptotic cell death.[1]

Enfortumab vedotin-ejfv is approved by the Food and Drug Administration (FDA) for the treatment of locally advanced or metastatic urothelial cancer as a single agent for adult patients 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;[2] OR in combination with pembrolizumab for the treatment of adult patients with locally advanced or metastatic urothelial cancer who are not eligible for cisplatin-containing chemotherapy.[2]

This indication is approved under accelerated approval based on the tumor response rate and the durability of the response. Continued approval for this indication may be contingent upon verification and description of clinical benefit in the confirmatory trials. [2]

The National Comprehensive Cancer Network (NCCN) endorses enfortumab vendotin-ejfv in the following cancer types: bladder. [3]

**Note:** Enfortumab vendotin-ejfv can cause severe and fatal cutaneous adverse reactions, including Stevens-Johnson syndrome (SJS) and Toxic Epidermal Necrolysis (TEN). [2]

## Enfortumab vedotin-ejfv: Definitions

- **Antibody-drug conjugate (ADC) -** Antibodies (mAbs) engineered to utilize the capability of monoclonal antibodies by combining them with cytotoxic agents.

- **Food and Drug Administration (FDA)** – The FDA is responsible for protecting the public health by assuring the safety, efficacy, and security of human and veterinary drugs, biological products, medical devices, our nation's food supply, cosmetics, and products that emit radiation.
- **Monomethyl auristatin E -** A very potent antimitotic agent that inhibits cell division by blocking the polymerisation of tubulin. Because of its toxicity, it cannot be used as a drug itself.
- **National Comprehensive Cancer Network (NCCN) -** An alliance of thirty-two leading cancer centers devoted to patient care, research, and education. The NCCN guidelines are utilized for Radiation Therapy and Medical Oncology standards. NCCN consensus clinical standards are periodically updated and NantHealth, Inc. reviews these and updates its policies within a timely manner.
- **Stevens-Johnson syndrome (SJS) -** a rare, serious disorder of the skin and mucous membranes. It starts with flu-like symptoms that is followed by a painful rash that spreads and blisters.
- **Toxic Epidermal Necrolysis (TEN) -** a rare, life-threatening skin condition and is the most severe form of Stevens-Johnson syndrome. At least 30% of the body is affected.

## Enfortumab vedotin-ejfv: Policy

Enfortumab vedotin-ejfv will be considered for coverage when the following criteria are met:

**Bladder Cancer (Urothelial Carcinoma)**

1. At least 18 years of age; AND
2. Prescribed by or in consultation with an oncologist; AND
3. Used as first-line systemic therapy in combination with pembrolizumab in cisplatin ineligible patients for one of the following:

    a) Stage II (cT2, N0) disease or stage IIIA (cT3, N0; cT4a, N0; cT1-T4a, N1) disease if the tumor is present following the reassessment of the tumor status 2-3 months after the primary treatment with the bladder preserving concurrent chemoradiotherapy and maximal transurethral resection of bladder tumor (TURBT)
    b) Stage II (cT2, N0) disease or stage IIIA (cT3, N0; cT4a, N0; cT1-T4a, N1) disease if the tumor is present following the reassessment of the tumor status 2-3 months after the primary treatment with radiotherapy alone or TURBT
    c) Stage IIIB (cT1-T4a, N2,3) disease as downstaging systemic therapy
    d) Stage IIIB (cT1-T4a, N2,3) disease following the partial response or progression after the primary treatment with concurrent chemoradiotherapy
    e) Stage IVA (cT4b, any N, M0; any T, any N, M1a) disease
    f) Stage IVA (cT4b, any N, M0) disease as consolidation systemic therapy if no tumor is present following the reassessment of the tumor status 2-3 months after the primary treatment with concurrent chemoradiotherapy

g) Stage IVA (cT4b, any N, M0) disease if the tumor is present following the reassessment of the tumor status 2-3 months after the primary treatment with concurrent chemoradiotherapy
h) Metastatic stage IVB (any T, any N, M1b) disease
i) Muscle invasive local recurrence or persistent disease in a preserved bladder treated with curative intent
j) Metastatic or local recurrence post cystectomy treated with curative intent; OR

4. Used as second-line systemic therapy post-platinum or other chemotherapy for cisplatin-ineligible patients who received one or more prior lines of therapy or post-checkpoint inhibitor as a single agent for one of the following:

a) Stage II (cT2, N0) disease or stage IIIA (cT3, N0; cT4a, N0; cT1-T4a, N1) disease if the tumor is present following the reassessment of the tumor status 2-3 months after the primary treatment with concurrent bladder preserving chemoradiotherapy and maximal transurethral resection of bladder tumor (TURBT)
b) Stage IIIB (cT1-T4a, N2,3) disease following the partial response or progression after the primary treatment with downstaging systemic therapy or concurrent chemoradiotherapy
c) Stage IVA (cT4b, any N, M0) disease if the tumor is present following the reassessment of the tumor status after the primary treatment with first-line systemic therapy or concurrent chemoradiotherapy
d) Stage IVA (any T, any N, M1a) disease if stable disease or progression following the reassessment of the tumor status after primary treatment with first-line systemic therapy
e) Metastatic stage IVB (any T, any N, M1b) disease
f) Muscle invasive local recurrence or persistent disease in a preserved bladder treated with curative intent
g) Metastatic or local recurrence post cystectomy treated with curative intent; OR

5. Used as subsequent-line systemic therapy (patients should have already received platinum and a checkpoint inhibitor, if eligible) as a single agent for patients who received first-line platinum-containing chemotherapy followed by avelumab maintenance therapy for one of the following:

a) Stage II (cT2, N0) disease or stage IIIA (cT3, N0; cT4a, N0; cT1-T4a, N1) disease if the tumor is present following the reassessment of the tumor status 2-3 months after the primary treatment with concurrent bladder preserving chemoradiotherapy and maximal transurethral resection of bladder tumor (TURBT)
b) Stage IIIB (cT1-T4a, N2,3) disease following the partial response or progression after the primary treatment with downstaging systemic therapy or concurrent chemoradiotherapy
c) Stage IVA (cT4b, any N, M0) disease if the tumor is present following the reassessment of the tumor status after the primary treatment with first-line systemic therapy or concurrent chemoradiotherapy

d) Stage IVA (any T, any N, M1a) disease if stable disease or progression following a reassessment of tumor status after primary treatment with first-line systemic therapy
e) Metastatic stage IVB (any T, any N, M1b) disease
f) Muscle invasive local recurrence or persistent disease in a preserved bladder treated with curative intent
g) Metastatic or local recurrence post cystectomy treated with curative intent

**Bladder Cancer – Primary Carcinoma of the Urethra**

1. At least 18 years of age; AND
2. Prescribed by or in consultation with an oncologist; AND
3. Therapy for metastatic disease in combination with pembrolizumab as first-line systemic therapy in cisplatin-ineligible patients; AND
4. Used as a single agent for recurrent or metastatic disease for one of the following:
    a) Second-line systemic therapy for cisplatin-ineligible patients who received one or more prior lines of therapy post-platinum or other chemotherapy
    b) Second-line systemic therapy post-checkpoint inhibitor
    c) Subsequent-line systemic therapy for patients who received a first-line platinum containing chemotherapy followed by avelumab maintenance therapy

**Bladder Cancer – Upper GU Tract**

1. At least 18 years of age; AND
2. Prescribed by or in consultation with an oncologist; AND
3. Therapy for metastatic disease in combination with pembrolizumab as first-line systemic therapy in cisplatin-ineligible patients; AND
4. Therapy for metastatic disease as a single agent for one of the following:
    a) Second-line systemic therapy for cisplatin-ineligible patients who received one or more prior lines of therapy post-platinum or other chemotherapy
    b) Second-line systemic therapy post-checkpoint inhibitor
    c) Subsequent-line systemic therapy for patients who received a first-line platinum-containing chemotherapy followed by avelumab maintenance therapy

**Bladder Cancer – Urothelial Carcinoma of the Prostate**

1. At least 18 years of age; AND
2. Prescribed by or in consultation with an oncologist; AND
3. Therapy for metastatic disease in combination with pembrolizumab as first-line systemic therapy in cisplatin-ineligible patients; AND
4. Therapy for metastatic disease as a single agent for one of the following:
    a) Second-line systemic therapy for cisplatin-ineligible patients who received one or more prior lines of therapy post-platinum or other chemotherapy
    b) Second-line systemic therapy post-checkpoint inhibitor

c) Subsequent-line systemic therapy for patients who received a first-line platinum-containing chemotherapy followed by avelumab maintenance therapy
d) Subsequent-line systemic therapy for patients who received a first-line platinum-containing chemotherapy followed by avelumab maintenance therapy

**Note:**

1. This indication is approved under accelerated approval based on the tumor response rate and the durability of the response. Continued approval for this indication may be contingent upon verification and description of clinical benefit in the confirmatory trials. [2]
2. Coverage of enfortumab vedotin-ejfv will be provided for an FDA-approved indication or National Comprehensive Cancer Network (NCCN) guidelines when it is a Category 1, 2A, or 2B recommendation or when all criteria are met.

## Authorization Period and Renewal Criteria

1. Initial Authorization Period: 12 months
2. Renewal Criteria: No evidence of disease progression or unacceptable toxicity
3. Renewal Authorization Period: 12 months

## Enfortumab vedotin-ejfv: References

1. Advancements in Therapy for Bladder Cancer: Enfortumab Vedotin. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7863123/. Accessed May 15, 2023.
2. Enfortumab vedotin-ejfv (Padcev) Package Insert. https://www.accessdata.fda.gov/drugsatfda_docs/label/2023/761137s019lbl.pdf. Accessed May 15, 2023.
3. National Comprehensive Cancer Network Guidelines. Bladder Cancer (Version 2.2023). https://www.nccn.org/professionals/physician_gls/pdf/bladder.pdf. Accessed May 15, 2023.

## Enfortumab vedotin-ejfv: Coding (CPT®, ICD 10 and HCPCS) *

*Procedure codes appearing in medical policy documents are only included as a general reference. This list may not be all-inclusive and is subject to updates. In addition, the codes listed are not a guarantee of payment.

| CODE | DESCRIPTION |
|---|---|
| C67.0 – 67.9 | Malignant neoplasms of bladder |
| J9177 | Enfortumab vedotin-ejfv (Padcev) |

## Enfortumab vedotin-ejfv: Revision and Review History

| No. | Description | Date(s) |
|---|---|---|
| 1 | Original Effective Date: | 1/1/2024 |
| 2 | Policy Review Dates: | 5/15/2023 |
| 3 | Policy Revision Dates: | |
| 4 | Department Owner: | Medical Affairs |
| 5 | NH Advisory Committee Approval Dates: | 9/20/2023 |
| 6 | Revision Changes: | |