Evolent Clinical Guideline 3121 for Padcev™ (enfortumab vedotin-ejfv)

Guideline Number:	Applicable Codes	
Evolent_CG_3121		
"Evolent" refers to Evolent Health LLC and Evolent Specialty Services, Inc. *© 2020 - 2026 Evolent. All rights Reserved.*		
Original Date:	**Last Revised Date:**	**Implementation Date:**
February 2020	August 2026	August 2026

TABLE OF CONTENTS

STATEMENT **2**
PURPOSE 2
INDICATIONS **2**
UROTHELIAL CARCINOMA 2
CONTRAINDICATIONS/WARNINGS **3**
EXCLUSION CRITERIA **3**
CODING AND STANDARDS **4**
CODES 4
APPLICABLE LINES OF BUSINESS 4
POLICY HISTORY **4**
LEGAL AND COMPLIANCE **5**
GUIDELINE APPROVAL 5
Committee *5*
DISCLAIMER 5
REFERENCES **6**

STATEMENT

Purpose

To define and describe the accepted indications for Padcev (enfortumab vedotin-ejfv) usage in the treatment of cancer, including FDA approved indications, and off-label indications.

Evolent is responsible for processing all medication requests from network ordering providers. Medications not authorized by Evolent may be deemed as not approvable and therefore not reimbursable.

The use of this drug must be supported by one of the following: FDA approved product labeling, CMS-approved compendia, National Comprehensive Cancer Network (NCCN), American Society of Clinical Oncology (ASCO) clinical guidelines, or peer-reviewed literature that meets the requirements of the CMS Medicare Benefit Policy Manual Chapter 15.

INDICATIONS

Continuation requests for a not-approvable medication shall be exempt from this Evolent policy provided

- The member has not experienced disease progression on the requested medication AND
- The requested medication was used within the last year without a lapse of more than 30 days of having an active authorization AND
- Additional medication(s) are not being added to the continuation request.

Urothelial Carcinoma

- Padcev (enfortumab vedotin-ejfv) may be used in combination with Keytruda (pembrolizumab) in adult members with muscle invasive bladder cancer (MIBC) as follows: neoadjuvant treatment for 3 cycles, then adjuvant treatment for 6 cycles after cystectomy, and then continue Keytruda (pembrolizumab) as a single agent for 8 cycles.
- Padcev (enfortumab vedotin-ejfv) may be used in combination with Keytruda (pembrolizumab) as first line therapy for locally advanced/metastatic urothelial carcinoma
- The member has locally advanced or metastatic urothelial carcinoma and Padcev (enfortumab vedotin-ejfv) is being used as a single agent in members who:
    - Have previously received Immune Checkpoint Inhibitor therapy (e.g., pembrolizumab, avelumab, atezolizumab, nivolumab) and a platinum (cisplatin/carboplatin) containing chemotherapy regimen in the neoadjuvant/adjuvant, locally advanced, or metastatic setting OR
    - Have previously received Immune Checkpoint Inhibitor therapy (e.g., pembrolizumab, atezolizumab, nivolumab) and are ineligible for platinum-based therapy.

CONTRAINDICATIONS/WARNINGS

- US Boxed Warning
  - Enfortumab vedotin 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 enfortumab vedotin and consider referral for specialized care for suspected SJS or TEN, or severe skin reactions. Permanently discontinue enfortumab vedotin in patients with confirmed SJS or TEN, or grade 4 or recurrent grade 3 skin reactions.

EXCLUSION CRITERIA

- Padcev (enfortumab vedotin-ejfv) is being used after disease progression with enfortumab containing regimen.
- Concurrent use with other chemotherapy and targeted therapies, with the exception of Keytruda (pembrolizumab).
- Dosing exceeds single dose limit of Padcev (enfortumab vedotin-ejfv) 1.25 mg/kg (maximum 125 mg).
- Investigational use of Padcev (enfortumab vedotin-ejfv) with an off-label indication that is not sufficient in evidence or is not generally accepted by the medical community. Sufficient evidence that is not supported by CMS recognized compendia or acceptable peer reviewed literature is defined as any of the following:
  - Whether the clinical characteristics of the patient and the cancer are adequately represented in the published evidence.
  - Whether the administered chemotherapy/biologic therapy/immune therapy/targeted therapy/other oncologic therapy regimen is adequately represented in the published evidence.
  - Whether the reported study outcomes represent clinically meaningful outcomes experienced by patients. Generally, the definitions of Clinically Meaningful outcomes are those recommended by ASCO, e.g., Hazard Ratio of less than 0.80 and the recommended survival benefit for OS and PFS should be at least 3 months.
  - Whether the experimental design, considering the drugs and conditions under investigation, is appropriate to address the investigative question. (For example, in some clinical studies, it may be unnecessary or not feasible to use randomization, double blind trials, placebos, or crossover).
  - That non-randomized clinical trials with a significant number of subjects may be a basis for supportive clinical evidence for determining accepted uses of drugs.
  - That case reports are generally considered uncontrolled and anecdotal information and do not provide adequate supportive clinical evidence for determining accepted uses of drugs.

- That abstracts (including meeting abstracts) without the full article from the approved peer-reviewed journals lack supporting clinical evidence for determining accepted uses of drugs.

CODING AND STANDARDS

Codes

- J9177 - Injection, enfortumab vedotin-ejfv, 0.25 mg

Applicable Lines of Business

☐	CHIP (Children's Health Insurance Program)
☒	Commercial
☒	Exchange/Marketplace
☒	Medicaid
☐	Medicare Advantage

POLICY HISTORY

Date	Summary
August 2026	• Updated references
April 2026	• Removed cisplatin ineligibility verbiage and criteria from urothelial carcinoma indication • Updated references
January 2026	• Updated urothelial carcinoma indication • Updated references
June 2025	• Converted to new Evolent guideline template • This guideline replaces UM ONC_1381 Padcev (enfortumab vedotin-ejfv) • Updated indication section • Updated exclusion criteria

Date	Summary
	• Updated references
June 2024	• Removed platinum ineligibility with pembrolizumab under first line setting in locally advanced/metastatic urothelial carcinoma • Added new reference • Updated NCH verbiage to Evolent

LEGAL AND COMPLIANCE

Guideline Approval

Committee

Reviewed / Approved by Evolent Specialty Services Clinical Guideline Review Committee

Disclaimer

Evolent Clinical Guidelines do not constitute medical advice. Treating health care professionals are solely responsible for diagnosis, treatment, and medical advice. Evolent uses Clinical Guidelines in accordance with its contractual obligations to provide utilization management. Coverage for services varies for individual members according to the terms of their health care coverage or government program. Individual members' health care coverage may not utilize some Evolent Clinical Guidelines. Evolent clinical guidelines contain guidance that requires prior authorization and service limitations. A list of procedure codes, services or drugs may not be all inclusive and does not imply that a service or drug is a covered or non-covered service or drug. Evolent reserves the right to review and update this Clinical Guideline in its sole discretion. Notice of any changes shall be provided as required by applicable provider agreements and laws or regulations. Members should contact their Plan customer service representative for specific coverage information.

REFERENCES

1. Galsky MD, et al; KEYNOTE-B15/EV-304 Investigators. Enfortumab Vedotin and Pembrolizumab in Cisplatin-Eligible Bladder Cancer. *N Engl J Med*. 2026 Jul 23;395(4):338-348. doi: 10.1056/NEJMoa2601486.
2. Vulsteke C, et al; KEYNOTE-905/EV-303 Investigators. Perioperative Enfortumab Vedotin and Pembrolizumab in Bladder Cancer. *N Engl J Med*. 2026 Feb 18. doi: 10.1056/NEJMoa2511674.
3. Vulsteke C, et al. Perioperative (periop) enfortumab vedotin (EV) plus pembrolizumab (pembro) in participants (pts) with muscle-invasive bladder cancer (MIBC) who are cisplatin-ineligible: The phase III KEYNOTE-905 study. *Annals of Oncology*, Volume 36, S1763. doi: 10.1016/j.annonc.2025.09.124.
4. Hoimes CJ, et al. Enfortumab Vedotin Plus Pembrolizumab in Previously Untreated Advanced Urothelial Cancer. *J Clin Oncol*. 2023 Jan 1;41(1):22-31. doi: 10.1200/JCO.22.01643.
5. Powles T, et al; EV-302 Trial Investigators. Enfortumab Vedotin and Pembrolizumab in Untreated Advanced Urothelial Cancer. *N Engl J Med*. 2024 Mar 7;390(10):875-888. doi: 10.1056/NEJMoa2312117.
6. Powles T, et al. Enfortumab Vedotin in Previously Treated Advanced Urothelial Carcinoma. *N Engl J Med*. 2021 Mar 25;384(12):1125-1135. doi: 10.1056/NEJMoa2035807.
7. Powles T, et al. Avelumab First-Line Maintenance for Advanced Urothelial Carcinoma: Results From the JAVELIN Bladder 100 Trial After ≥2 Years of Follow-Up. *J Clin Oncol*. 2023 Jul 1;41(19):3486-3492. doi: 10.1200/JCO.22.01792.
8. Padcev prescribing information. Astellas Pharma US, Inc. Northbrook, IL 2026.
9. Clinical Pharmacology Elsevier Gold Standard 2026.
10. Micromedex® Healthcare Series: Micromedex Drugdex Ann Arbor, Michigan 2026.
11. National Comprehensive Cancer Network. Cancer Guidelines and Drugs and Biologics Compendium 2026.
12. AHFS Drug Information. American Society of Health-Systems Pharmacists or Wolters Kluwer Lexi-Drugs. Bethesda, MD 2026.
13. Ellis LM, et al. American Society of Clinical Oncology perspective: Raising the bar for clinical trials by defining clinically meaningful outcomes. *J Clin Oncol*. 2014 Apr 20;32(12):1277-80.
14. Medicare Benefit Policy Manual Chapter 15 Covered Medical and Other Health Services: **https://www.cms.gov/Regulations-and-Guidance/Guidance/Manuals/Downloads/bp102c15.pdf**.
15. Current and Resolved Drug Shortages and Discontinuations Reported to the FDA: **http://www.accessdata.fda.gov/scripts/drugshortages/default.cfm**.