Evolent Clinical Guideline 3058 for Fusilev™/Khapzory™ (levoleucovorin)

Guideline Number:	Applicable Codes	
Evolent_CG_3058		
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Original Date: April 2016	**Last Revised Date:** April 2025	**Implementation Date:** April 2025

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STATEMENT

Purpose

To define and describe the accepted indications for Fusilev/Khapzory (levoleucovorin) 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.

Colorectal Cancer

- Fusilev/Khapzory (levoleucovorin) is being used in combination with fluorouracil-based regimens in ONE of the following conditions:
  - For potentiation of fluorouracil therapy in the treatment of colorectal cancer
  - For treatment of colorectal cancer in combination regimens consisting of fluorouracil, leucovorin, and either irinotecan and/or oxaliplatin.

Osteosarcoma

- Fusilev/Khapzory (levoleucovorin) is being used following administration of high-dose methotrexate greater than 500 mg/m^2 over less than 4 hours OR greater than 1 g/m^2 over less than 4 hours AND
- Is administered 24 hours after the start of methotrexate infusion so that it does not interfere with the therapeutic effect of methotrexate.

Overdosages of Folic Acid Antagonists

- Fusilev/Khapzory (levoleucovorin) is being used to diminish the toxicity and counteract the effects of impaired methotrexate elimination and of inadvertent overdosages of methotrexate in ONE of the following conditions:
  - Used in combination with cerebral spinal fluid (CSF) exchange and dexamethasone for intrathecal methotrexate overdose

- Used in combination with forced diuresis and alkalization of urine to prevent potentially toxic blood levels of methotrexate
- Used in high-dose methotrexate-induced nephrotoxicity.

CONTRAINDICATIONS/WARNINGS

- Contraindications
  - Patients who have had severe hypersensitivity reactions to leucovorin products, folic acid, or folinic acid.

EXCLUSION CRITERIA

- Dosing exceeds single dose limit of Fusilev/Khapzory (levoleucovorin) 400 mg/m^2.
- Investigational use of Fusilev/Khapzory (levoleucovorin) 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 definition 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

- J0641 - Injection, levoleucovorin, not otherwise specified, 0.5 mg
- J0642 - Injection, levoleucovorin (khapzory), 0.5 mg

Applicable Lines of Business

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

POLICY HISTORY

Date	Summary
April 2025	• Converted to new Evolent guideline template • This guideline replaces UM ONC_1288 Fusilev/Khapzory (levoleucovorin)
April 2024	• Updated NCH verbiage to Evolent

LEGAL AND COMPLIANCE

Guideline Approval

Committee

Reviewed / Approved by Evolent Specialty 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. 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

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4. Clinical Pharmacology Elsevier Gold Standard 2025.
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7. AHFS Drug Information. American Society of Health-Systems Pharmacists or Wolters Kluwer Lexi-Drugs. Bethesda, MD 2025.
8. 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.
9. Medicare Benefit Policy Manual Chapter 15 Covered Medical and Other Health Services: https://www.cms.gov/Regulations-and-Guidance/Guidance/Manuals/Downloads/bp102c15.pdf.
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