VENTURA COUNTY
HEALTH CARE PLAN

UTILIZATION MANAGEMENT MEDICAL POLICY

POLICY: Oncology (Injectable) – Levoleucovorin Products Utilization Management Medical Policy
- Fusilev® (levoleucovorin intravenous infusion – Spectrum)
- Khapzory™ (levoleucovorin intravenous infusion – Spectrum)
- Levoleucovorin intravenous infusion – various manufacturers

REVIEW DATE: 06/18/2025

OVERVIEW

Levoleucovorin (Fusilev, Khapzory, generic) is indicated for the following uses:[1,2]
- **Colorectal cancer**, in advanced metastatic disease for use in combination chemotherapy with 5-fluorouracil.
- **Impaired methotrexate elimination** or overdosage of folic acid antagonists.
- **Osteosarcoma**, for rescue after high-dose methotrexate therapy.

Levoleucovorin is the pharmacologically active, levo-isomer of racemic *d,l*-leucovorin.[1,2] Levoleucovorin is a chemically reduced derivative of folic acid, which can counteract the toxic and therapeutic effects of folic acid antagonists, such as methotrexate. In addition, levoleucovorin can enhance the therapeutic and toxic effects of fluoropyrimidines used in oncology.

Guidelines

The National Comprehensive Cancer Network (NCCN) Drugs & Biologics Compendium recommends levoleucovorin use in combination with methotrexate for the treatment of gestational trophoblastic neoplasia, T-cell lymphomas, central nervous system cancers, B-cell lymphomas, chronic lymphocytic leukemia/small lymphocytic lymphoma, acute lymphoblastic leukemia, pediatric aggressive mature B-cell lymphomas, blastic plasmacytoid dendritic cell neoplasm, osteosarcoma, and Waldenstrom macroglobulinemia.[3] The NCCN Compendium recommends levoleucovorin use in combination with fluorouracil-based chemotherapy for the treatment of occult primary cancer, neuroendocrine and adrenal tumors, biliary tract cancers, ovarian/fallopian tube/primary peritoneal cancer, thymomas and thymic carcinomas, esophageal and esophagogastric junction cancer, anal cancer, colon cancer, appendiceal adenocarcinoma, gastric cancer, small bowel adenocarcinoma, ampullary cancer, cervical cancer, vaginal cancer, rectal cancer, pancreatic adenocarcinoma, and bladder cancer.

POLICY STATEMENT

Prior Authorization is recommended for medical benefit coverage of levoleucovorin. Approval is recommended for those who meet the **Criteria** and **Dosing** for the listed indications. Extended approvals are allowed if the patient continues to meet the Criteria and Dosing. Requests for doses outside of the established dosing documented in this policy will be considered on a case-by-case basis by a clinician (i.e., Medical Director or Pharmacist). All approvals are provided for the duration noted below. In cases where the approval is authorized in months, 1 month is equal to 30 days. Because of the specialized skills required for evaluation and diagnosis of patients treated with levoleucovorin as well as the monitoring required for adverse events and long-term efficacy, approval requires levoleucovorin to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of levoleucovorin is recommended in those who meet one of the following:

FDA-Approved Indications

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1. **Colon or Rectal Carcinoma.** Approve for 1 year if the patient meets BOTH of the following (A and B):
   A) Levoleucovorin is used in combination with fluorouracil-based chemotherapy; AND
   B) Levoleucovorin is prescribed by or in consultation with an oncologist.

   Dosing. Approve up to 200 mg/m^2 administered intravenously before each dose of 5-fluorouracil.

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2. **Methotrexate Overdosage, or Impaired Methotrexate Elimination.** Approve for 1 month.

   Dosing. Approve ONE of the following dosing regimens (A or B):
   A) Administer up to 7.5 mg intravenously no more frequently than once every 6 hours; OR
   B) Administer up to 75 mg intravenously no more frequently than once every 3 hours.

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3. **Osteosarcoma.** Approve for 1 year if the patient meets BOTH of the following (A and B):
   A) Levoleucovorin is used in combination with high-dose methotrexate; AND
   B) Levoleucovorin is prescribed by or in consultation with an oncologist.

   Dosing. Approve ONE of the following dosing regimens (A or B):
   A) Administer up to 7.5 mg intravenously no more frequently than once every 6 hours; OR
   B) Administer up to 75 mg intravenously no more frequently than once every 3 hours.

Other Uses with Supportive Evidence

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4. **Cancer Diagnosis Currently Being Treated With Methotrexate**. Approve for 1 year if levoleucovorin is prescribed by or in consultation with an oncologist.
   Note: Examples include T-cell lymphoma, B-cell lymphoma, gestational trophoblastic neoplasm, central nervous system cancer.

   Dosing. Approve ONE of the following dosing regimens (A or B):
   A) Administer up to 7.5 mg intravenously no more frequently than once every 6 hours; OR
   B) Administer up to 75 mg intravenously no more frequently than once every 3 hours.

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5. **Cancer Diagnosis Currently Being Treated With 5-Fluorouracil**. Approve for 1 year if levoleucovorin is prescribed by or in consultation with an oncologist.
   Note: Examples include ovarian cancer, gastric cancer, cervical cancer.

   Dosing. Approve up to 100 mg/m^2 administered intravenously before each dose of 5-fluorouracil.

CONDITIONS NOT RECOMMENDED FOR APPROVAL
Coverage of levoleucovorin is not recommended in the following situations:

1. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

1. Fusilev® intravenous infusion [prescribing information]. Irvine, CA: Spectrum Pharmaceuticals; November 2020.
2. Khapzory™ intravenous infusion [prescribing information]. Irvine, CA: Spectrum Pharmaceuticals; March 2020.
3. The NCCN Drugs and Biologics Compendium. © 2025 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed on June 6, 2025. Search term: levoleucovorin.
4. The NCCN Colon Cancer Clinical Practice Guidelines in Oncology (version 3.2025 – April 24, 2025). © 2025 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed on June 6, 2025.
5. The NCCN Rectal Cancer Clinical Practice Guidelines in Oncology (version 2.2025 – March 31, 2025). © 2025 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed on June 9, 2025.

HISTORY

Type of Revision	Summary of Changes	Review Date
Annual Revision	No criteria changes.	06/28/2023
Annual Revision	No criteria changes.	06/26/2024
Annual Revision	No criteria changes.	06/18/2025