

UTILIZATION REVIEW MEDICAL POLICY

- POLICY:** Oncology (Injectable) – Levoleucovorin Products Utilization Review (Medical) Policy
- Fusilev[®] (levoleucovorin injection for intravenous use – Spectrum Pharmaceuticals)
 - Khapzory[™] (levoleucovorin injection for intravenous use – Spectrum Pharmaceuticals)
 - Levoleucovorin injection for intravenous use – various manufacturers

REVIEW DATE: 06/17/2020

OVERVIEW

Levoleucovorin (Fusilev, Khapzory, generics) 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.

Levoleucovorin is indicated:

- For rescue after high-dose methotrexate therapy in osteosarcoma, and
- To diminish the toxicity of impaired methotrexate elimination or overdosage of folic acid antagonists, and
- For use in combination chemotherapy with 5-fluorouracil in the treatment of patients with advanced metastatic colorectal cancer.¹

Guidelines

The National Comprehensive Cancer Network (NCCN) Drugs & Biologics Compendium recommends levoleucovorin use in combination with methotrexate for the treatment of gestational trophoblastic neoplasia, rhabdomyosarcoma, T-cell lymphomas, central nervous system cancers, B-cell lymphomas, chronic lymphocytic leukemia/small lymphocytic lymphoma, acute lymphoblastic leukemia, and osteosarcoma.³ The NCCN Compendium recommends levoleucovorin use in combination with fluorouracil-based chemotherapy for the treatment of occult primary cancer, neuroendocrine and adrenal tumors, hepatocellular carcinoma, ovarian/fallopian tube/primary peritoneal cancer, thymomas and thymic carcinomas, esophageal and esophagogastric junction cancer, anal cancer, colon cancer, gastric cancer, small bowel adenocarcinoma, cervical 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 indication(s). 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.

RECOMMENDED AUTHORIZATION CRITERIA

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

FDA-Approved Indications

1. Osteosarcoma. Approve for 1 year if the patient meets the following criteria (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.¹
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2. Colon or Rectal Carcinoma. Approve for 1 year if the patient meets the following criteria (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 100 mg/m² administered intravenously before each dose of 5-fluorouracil.¹

3. 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.¹
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Other Uses with Supportive Evidence

4. Cancer Diagnosis Currently Being Treated With Methotrexate. (Note: Examples include T-cell lymphoma, B-cell lymphoma, gestational trophoblastic neoplasm, central nervous system cancer). Approve for 1 year if 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.¹
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5. Cancer Diagnosis Currently Being Treated With 5-Fluorouracil. (Note: Examples include hepatocellular carcinoma, ovarian cancer, gastric cancer, cervical cancer). Approve for 1 year if levoleucovorin is prescribed by or in consultation with an oncologist.

Dosing. Approve up to 100 mg/m² administered intravenously before each dose of 5-fluorouracil.¹

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Levoleucovorin has not been shown to be effective, or there are limited or preliminary data or potential safety concerns that are not supportive of general approval for the following conditions.

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[®] injection for intravenous use [prescribing information]. Irvine, CA: Spectrum Pharmaceuticals; January 2020.
2. Khapzory[™] injection for intravenous use [prescribing information]. Irvine, CA: Spectrum Pharmaceuticals; March 2020.
3. The NCCN Drugs and Biologics Compendium. © 2020 National Comprehensive Cancer Network, Inc. Available at: <http://www.nccn.org>. Accessed on June 8, 2020. Search term: levoleucovorin.

HISTORY

Type of Revision	Summary of Changes	Review Date
New Policy	--	06/18/2019
Annual Revision	Methotrexate Overdosage, Inadvertent, or Impaired Methotrexate Elimination: Removed "Inadvertent" from indication.	06/17/2020