Levoleucovorin (Fusilev™, Khapzory®)

NDC CODE(S)

00143-9558-XX LEVOLEUCOVORIN CALCIUM 50MG Solution Reconstituted (WEST-WARD)
00781-3201-XX LEVOLEUCOVORIN CALCIUM 10MG/ML Solution (SANDOZ)
16714-0890-XX LEVOLEUCOVORIN CALCIUM 10MG/ML Solution (NORTHSTAR RX)
16714-0915-XX LEVOLEUCOVORIN CALCIUM 10MG/ML Solution (NORTHSTAR RX)
43598-0771-XX LEVOLEUCOVORIN CALCIUM 175MG/17.5ML Solution (DR.REDDY'S LABORATORIES)
43598-0773-XXLEVOLEUCOVORIN CALCIUM 10MG/ML Solution (DR.REDDY'S LABORATORIES)
50742-0494-XX LEVOLEUCOVORIN CALCIUM 10MG/ML Solution (INGENUS PHARMACEUTICALS)
50742-0495-XX LEVOLEUCOVORIN CALCIUM 10MG/ML Solution (INGENUS PHARMACEUTICALS)
68152-0101-XX FUSILEV 50MG Solution Reconstituted (ACROTECH BIOPHARMA)
70121-1099-XX LEVOLEUCOVORIN CALCIUM 50MG Solution Reconstituted (AMNEAL BIOSCIENCES)
70121-1572-XX LEVOLEUCOVORIN CALCIUM 175MG/17.5ML Solution (AMNEAL BIOSCIEN)
72266-0120-XX LEVOLEUCOVORIN CALCIUM 175MG/17.5ML Solution (FOSUN PHARMA US)
72266-0121-XX LEVOLEUCOVORIN CALCIUM 10MG/ML Solution (FOSUN PHARMA US)
68152-0112-XX KHAPZORY 175MG Solution Reconstituted (ACROTECH BIOPHARMA)
68152-0114-XX KHAPZORY 300MG Solution Reconstituted (ACROTECH BIOPHARMA)
71288-0104-XX LEVOLEUCOVORIN CALCIUM 50MG Solution Reconstituted (MEITHEAL PHARMACEUTICALS)
71288-0105-X LEVOLEUCOVORIN CALCIUM 10MGML Solution (MEITHEAL PHARMACEUTICALS)

DESCRIPTION

Levoleucovorin is a folate analog and the pharmacologically active levo-isomer of *d, l*-leucovorin (racemic leucovorin). It is the pharmacologically active isomer of 5-formyl tetrahydrofolic acid. Administration of levoleucovorin can counteract the therapeutic and toxic effects of folic acid antagonists such as methotrexate which act by inhibiting dihydrofolate reductase. It can enhance the therapeutic and toxic effects of fluoropyrimidines used in cancer therapy such as 5-fluorouracil or 5-FU.

There are two levoleucovorin product formulations available, levoleucovorin (Khapzory™) and levoleucovorin calcium (Fusilev®). Due to the addition of calcium pentahydrate, a warning for hypercalcemia appears on the label for Fusilev™, advising specifically to inject no more than 16 mL (160 mg) of levoleucovorin solution intravenously per minute although uses for the two formulations are the same and both will be referred to in this policy as levoleucovorin.

POLICY

- Levoleucovorin for the treatment of the following is considered ***medically necessary*** if the medical appropriateness criteria are met: **(See Medical Appropriateness below.)**
  - Antidote to folic acid antagonist (Methotrexate rescue)
  - Gestational Trophoblastic Neoplasia
  - Used in combination with fluorouracil-based regimens for diagnoses in criteria
  - Used in combination with high-dose methotrexate for diagnoses in criteria
- Levoleucovorin for the treatment of other conditions/diseases is considered ***investigational.***

MEDICAL APPROPRIATENESS

INITIAL APPROVAL CRITERIA

- Patient is at least 6 years old; **AND**

Universal Criteria

- Patient does not have pernicious anemia or vitamin B12 deficiency megaloblastic anemia; **AND**
- Racemic *d,l*-leucovorin calcium is not obtainable (in any dosage strength) as confirmed by FDA Drug shortage website located at: *http://www.accessdata.fda.gov/scripts/drugshortages/default.cfm ;* **AND**
- Khapzory® ONLY: Patient had an inadequate response, or has a contraindication or intolerance, to Fusilev™ (levoleucovorin); **AND**

Bone Cancer (Osteosarcoma), Dedifferentiated Chondrosarcoma, High-Grade Undifferentiated Pleomorphic Sarcoma (UPS)

- Patient is undergoing high-dose methotrexate chemotherapy treatment; **OR**
- Used as rescue therapy in combination with a chemotherapy regimen containing high dose methotrexate

Reduction of toxicity due to impaired elimination or inadvertent overdose with folic acid antagonists

- Patient is undergoing treatment with a folic acid antagonist, such as methotrexate; **AND**
- Patient has developed toxicity due to impaired elimination or inadvertent overdosage of the folic acid antagonist (i.e., methotrexate)

Colorectal cancer

- Must be used in combination with fluorouracil-based regimens

Gestational Trophoblastic Neoplasia

- Used in combination with a methotrexate-based regimen

Used in combination with high-dose methotrexate for the following:

- Acute Lymphoblastic Leukemia/Pediatric Acute Lymphoblastic Leukemia
- Adult T-cell Leukemia/Lymphoma
- AIDS-related B-cell Lymphoma
- Blastic Plasmacytoid Dendritic Cell Neoplasm (BPDCN)
- Burkitt Lymphoma
- Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma (CLL/SLL)
- CNS Cancer (Primary CNS Lymphoma, Brain Metastases, & Leptomeningeal Metastases)
- Diffuse Large B-Cell Lymphoma
- Extranodal NK/T-cell Lymphoma (nasal type)
- Follicular Lymphoma
- Hepatosplenic T-Cell Lymphoma
- High Grade B-Cell Lymphomas

- Mantle Cell Lymphoma
- Pediatric Aggressive Mature B-Cell Lymphomas
- Peripheral T-cell Lymphoma
- Post-Transplant Lymphoproliferative Disorders (PTLD)

Used in combination with fluorouracil-based regimens for the following:

- Anal Carcinoma
- Bladder Cancer (non-urothelial and urothelial with variant histology)
- Esophageal, Esophagogastric Junction, & Gastric Cancer
- Gallbladder Cancer, Extrahepatic Cholangiocarcinoma, and Intrahepatic
- Cholangiocarcinoma
- Neuroendocrine and Adrenal Tumors (Poorly Differentiated - High Grade/Large or Small Cell & Tumors of the Pancreas)
- Occult Primary
- Ovarian-Epithelial/Fallopian Tube/Primary Peritoneal/Mucinous Carcinomas
- Pancreatic Adenocarcinoma
- Small Bowel Adenocarcinoma
- Thymoma and Thymic Carcinoma

RENEWAL CRITERIA

- Patient continues to meet universal and other indication-specific relevant criteria such as concomitant therapy requirements (not including prerequisite therapy), performance status, etc. identified in the Initial Approval Criteria.
- Absence of unacceptable toxicity from the drug. Examples of unacceptable toxicity include the following: hypersensitivity reactions, seizures, and severe gastrointestinal disorders such as stomatitis, severe diarrhea, and severe nausea and vomiting.; **AND**
- Patient is responding to therapy

DOSAGE/ADMINISTRATION

Levoleucovorin is dosed at one-half the usual dose of racemic *d,l*-leucovorin

INDICATION	DOSE
In combination with methotrexate (MTX)	• 7.5 mg (approximately 5 mg/m^2) IV every 6 hours for 10 doses starting 24 hours after beginning of methotrexate infusion. Dosing is based on a methotrexate dose of 12 grams/m^2 administered by intravenous infusion over 4 hours. Continue treatment until methotrexate levels are less than 5 x 10-8 M (0.05 micromolar)
Reduction of toxicity due to impaired elimination or inadvertent overdose with folic acid antagonists	• 7.5 mg (approximately 5 mg/m2) IV every 6 hours until methotrexate levels are less than 5 x 10-8 M (0.05 micromolar). • Monitor serum creatinine and methotrexate levels at least every 24 hours. Increase the dose of levoleucovorin to 50 mg/m2 intravenously every 3 hours until the methotrexate level is less than 5 x 10-8 M for the following: ○ if the serum creatinine at 24-hours increases 50% or more compared to baseline ○ if the methotrexate level at 24-hours is greater than 5 x 10-6 M ○ if the methotrexate level at 48-hours is greater than 9 x 10-7 M

In combination with 5-FU	• 100 mg/m2 administered by slow intravenous injection over a minimum of 3 minutes, followed by 5-FU at 370 mg/m2 by intravenous injection. **OR** • 10 mg/m2 administered by intravenous injection followed by 5-FU at 425 mg/m2 by intravenous injection. ○ Treatment is repeated daily for five days. This five-day treatment course may be repeated at 4-week (28-day) intervals, for 2 courses and then repeated at 4 to 5 week (28 to 35 day) intervals provided that the patient has completely recovered from the toxic effects of the prior treatment course. <u>Alternate Dosing Regimen</u> • 200 mg/m2 administered by intravenous injection DAY 1 followed by 5-FU 400 mg/m^2 bolus on DAY 1, then 5-FU 1200 mg/m2 /day x 2 days IV continuous infusion; repeat every 14 days.

LENGTH OF AUTHORIZATION

Coverage will be provided for ninety days and may be renewed.

DOSING LIMITS

Max Units (per dose and over time) [HCPCS Unit]:

In combination with methotrexate or for inadvertent overdosage

- 1,200 billable units every 28 days

In combination with fluorouracil

- 2,500 billable units every 28 days

APPLICABLE TENNESSEE STATE MANDATE REQUIREMENTS

BlueCross BlueShield of Tennessee's Medical Policy complies with Tennessee Code Annotated Section 56-7-2352 regarding coverage of off-label indications of Food and Drug Administration (FDA) approved drugs when the off-label use is recognized in one of the statutorily recognized standard reference compendia or in the published peer-reviewed medical literature.

IMPORTANT REMINDER

We develop Medical Policies to provide guidance to Members and Providers. This Medical Policy relates only to the services or supplies described in it. The existence of a Medical Policy is not an authorization, certification, explanation of benefits or a contract for the service (or supply) that is referenced in the Medical Policy. For a determination of the benefits that a Member is entitled to receive under his or her health plan, the Member's health plan must be reviewed. If there is a conflict between the Medical Policy and a health plan, the express terms of the health plan will govern.

ADDITIONAL INFORMATION

For appropriate chemotherapy regimens, dosage information, contraindications, precautions, warnings, and monitoring information, please refer to one of the standard reference compendia (e.g., the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) published by the National Comprehensive Cancer Network®, Drugdex Evaluations of Micromedex Solutions at Truven Health, or The American Hospital Formulary Service Drug Information).

SOURCES

1. Fusilev [package insert]. Irvine, CA; Spectrum Pharmaceuticals, Inc; November 2020. Accessed April January 2021.
2. Khapzory [package insert]. Irvine, CA; Spectrum Pharmaceuticals, Inc; March 2020. Accessed January 2021.
3. Referenced with permission from the NCCN Drugs & Biologics Compendium (NCCN Compendium®) levoleucovorin. National Comprehensive Cancer Network, 2021. The NCCN Compendium® is a derivative work of the NCCN Guidelines®. NATIONAL COMPREHENSIVE CANCER NETWORK®, NCCN®, and NCCN GUIDELINES® are trademarks owned by the National Comprehensive Cancer Network, Inc. To view the most recent and complete version of the Compendium, go online to NCCN.org. Accessed January 2021.
4. Goorin A, Strother D, Poplack D, et al. Safety and efficacy of l-leucovorin rescue following high-dose methotrexate for osteosarcoma. Med Pediatr Oncol. 1995 Jun; 24(6):362-7.
5. Lexicomp Online. (2021). AHFS DI. *Levoleucovorin*. Retrieved March 4, 2021 from Lexicomp Online with AHFS.
6. MICROMEDEX Healthcare Series. Drugdex Evaluations. (2021, January). *Levoleucovorin*. Retrieved March 4, 2021 from MICROMEDEX Healthcare Series.

EFFECTIVE DATE 6/30/2021

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