Levoleucovorin (Khapzory®/Fusilev®)

Prior Authorization Drug Coverage Policy

Effective Date: 9/1/2020
Revision Date: n/a
Review Date: 10/4/2021
Lines of Business: Commercial
Policy type: Prior Authorization

This Drug Coverage Policy provides parameters for the coverage of levoleucovorin (Khapzory™). Consideration of medically necessary indications are based upon U.S. Food and Drug Administration (FDA) indications, recommended uses within the Centers of Medicare & Medicaid Services (CMS) five recognized compendia, including the National Comprehensive Cancer Network (NCCN) Drugs & Biologics Compendium (Category 1 or 2A recommendations), and peer-reviewed scientific literature eligible for coverage according to the CMS, Medicare Benefit Policy Manual, Chapter 15, section 50.4.5 titled, "Off-Label Use of Anti-Cancer Drugs and Biologics." This policy evaluates whether the drug therapy is proven to be effective based on published evidence-based medicine.

Drug Description[1]

High-Dose Methotrexate Therapy

Levoleucovorin is the pharmacologically active isomer of 5-formyl tetrahydrofolic acid (THF). Levoleucovorin does not require reduction by dihydrofolate reductase to participate in reactions utilizing folates as a source of "one-carbon" moieties. Administration of levoleucovorin counteracts the therapeutic and toxic effects of folic acid antagonists such as methotrexate, which act by inhibiting dihydrofolate reductase.

Combination with Fluorouracil in Colorectal Cancer

Levoleucovorin enhances the therapeutic and toxic effects of fluorouracil. Fluorouracil is metabolized to 5-fluoro-2'-deoxyuridine-5'-monophosphate (FdUMP), which binds to and inhibits thymidylate synthase (an enzyme important in DNA repair and replication). Levoleucovorin is converted to another reduced folate, 5,10-methylenetetrahydrofolate, which then acts to stabilize the binding of FdUMP to thymidylate synthase, thereby enhancing the inhibition of thymidylate synthase.

FDA Indications[1]

Fusilev®/Khapzory® are FDA indicated for the following:

- Rescue after high-dose methotrexate therapy in patients with osteosarcoma.
- Diminishing the toxicity associated with overdosage of folic acid antagonists or impaired methotrexate elimination.
- Treatment of patients with metastatic colorectal cancer in combination with fluorouracil.

Coverage Determinations[1,2]

Levoleucovorin will require prior authorization. This agent is considered medically necessary for the following oncology and oncology-related indications if all criteria below are met:

High-Dose Methotrexate Rescue

- The member has a cancer diagnosis (including but not limited to osteosarcoma, leukemia, lymphoma, or rhabdomyosarcoma) **AND**
- The member is on a high-dose methotrexate-based regimen **AND**
- Levoleucovorin will be used as a rescue agent after high-dose methotrexate therapy

Recommended dosage:

- Based on a methotrexate dose of 12 grams/m^2 IV over 4 hours
- Initiate rescue at a dose of 7.5 mg (approximately 5 mg/m^2) IV every 6 hours, 24 hours after the beginning of the methotrexate infusion
- Adjust dose if necessary based on methotrexate elimination until methotrexate level is less than 5 x 10^{-8} M (0.05 micromolar)

Folic Acid Antagonist Overdose

- The member has a diagnosis of overdose from folic acid antagonists **AND**
- Levoleucovorin will be used as an antidote to diminish toxicity

Recommended dosage: 7.5 mg (approximately 5 mg/m^2) IV every 6 hours until methotrexate level is less than 5 x 10^{-8} M (0.05 micromolar)

Impaired Methotrexate Elimination

- The member has a diagnosis of impaired methotrexate elimination **AND**
- Levoleucovorin will be used as an antidote to diminish toxicity

Recommended dosage: 7.5 mg (approximately 5 mg/m^2) IV every 6 hours until methotrexate level is less than 5 x 10^{-8} M (0.05 micromolar)

Combination Treatment with Fluorouracil

- The member has a cancer diagnosis (including but not limited to colorectal, pancreatic, anal, hepatobiliary, gastroesophageal, ovarian, cervical, and thymic carcinomas) **AND**
- The member is on a fluorouracil-based regimen **AND**
- Levoleucovorin will be used as treatment in combination with fluorouracil to enhance the effects of fluorouracil

Recommended dosage:

- 100 mg/m^2 IV over a minimum of 3 minutes, followed by fluorouracil 370 mg/m^2 once daily for 5 consecutive days
- 10 mg/m^2 IV followed by fluorouracil 425 mg/m^2 once daily for 5 consecutive days
- 5-day courses may be repeated every 4 weeks for 2 courses, then every 4-5 weeks
- If substituted in place of leucovorin, levoleucovorin is dosed at one-half the usual dose of leucovorin
- Can consider leucovorin 20 mg/m^2 IV push during shortages

All indications:

- Levoleucovorin will be approved through clinical review for up to a 6-month duration.

Coverage Limitations

Treatment with levoleucovorin is not considered medically necessary for members with the following concomitant conditions:

- Levoleucovorin will be used for the treatment of pernicious anemia and megaloblastic anemia secondary to lack of vitamin B12.
- The member is concurrently on leucovorin.
- Indications not supported by NCCN category 2A or higher may not be considered medically necessary

Contraindications/Warnings/Precautions[1]

- Patients who have had severe hypersensitivity reactions to leucovorin products, folic acid, or folinic acid.
- Warnings/Precautions:
    - Increased Gastrointestinal Toxicities with Fluorouracil
    - Drug Interaction with Trimethoprim-Sulfamethoxazole

For specific recommendations on contraindications, warnings and precautions, patient monitoring, and on dose adjustments and discontinuation, please refer to the current prescribing information.

Billing

- Description: inj., levoleucovorin, 1 mg
  - HCPCS: J0641, J0642

Disclaimer

Drug Coverage Policies are developed as needed, regularly reviewed, updated at least annually, and are subject to change. Other policies and coverage determination guidelines may apply. Federal and state regulatory requirements and member specific benefit plan documents, if applicable, must be reviewed prior to this Drug Coverage Policy. This Drug Coverage Policy is for informational purposes only and does not constitute medical advice or dictate how providers should practice medicine. This policy should not be reproduced, stored in a retrieval system, or altered from its original form without written permission from Oncology Analytics, Inc.

References

1. Khapzory™ [package insert]. Acrotech Biopharma LLC, East Windsor, NJ. Available at: http://khapzory.com/KHAPZORY-PI.PDF
2. Levoleucovorin. NCCN Drugs & Biologics Compendium. Available at https://www.nccn.org/professionals/drug_compendium/content/
3. Comella P, De Vita F, Mancarella S, et al. Biweekly irinotecan or raltitrexed plus 6S-leucovorin and bolus 5-fluorouracil in advanced colorectal carcinoma: A Southern Italy Cooperative Oncology Group phase II—III randomized trial. Annals of Oncology. 2000 Jul 21;11:1323-1333.
4. Goldberg RM, Hatfield AK, Kahn M, et al. Prospectively Randomized North Central Cancer Treatment Group Trial of Intensive-Course Fluorouracil Combined With the -Isomer of Intravenous Leucovorin, Oral Leucovorin, or Intravenous Leucovorin for the Treatment of Advanced Colorectal Cancer. J Clin Oncol. 1997;15(11):3320-3329.
5. Koovor PA, Karim SM, and Marshall JL. Is Levoleucovorin an Alternative to Racemic Leucovorin? A Literature Review. Clinical Colorectal Cancer. 2009 Oct;8(4):200-206. DOI: 10.3816/CCC.2009.n.034.
6. Tournigand C, Cervantes A, Figer A, et al. OPTIMOX1: A Randomized Study of FOLFOX4 or FOLFOX7 With Oxaliplatin in a Stop-and-Go Fashion in Advanced Colorectal Cancer—A GERCOR Study. J Clin Oncol. 2006 Jan 20;24(3):394-400. DOI: 10.1200/JCO.2005.03.0106.