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Medical benefit drug policies are a source for BCBSM and BCN medical policy information only. These documents are not to be used to determine benefits or reimbursement. Please reference the appropriate certificate or contract for benefit information. This policy may be updated and therefore subject to change.

P&T Date: 02/12/2026

Khapzory™ (levoleucovorin)

HPCPS: J0642

Policy:

Requests must be supported by submission of chart notes and patient specific documentation.

- A. Criteria:
 - a. FDA approved indications
 - b. FDA approved age
 - c. Leucovorin is under shortage, which has been identified by the Food and Drug Administration and no other alternative therapies are appropriate
 - d. Prescribed by or in consultation with an oncologist
 - e. Trial and failure, intolerance, or contraindication of a generic levoleucovorin product as specified in the BCBSM/BCN utilization management medical drug list
- B. Quantity Limitations, Authorization Period and Renewal Criteria
 - a. Quantity Limits: Align with FDA recommended dosing
 - b. Authorization Period: Aligns with FDA recommended or guideline supported treatment duration and provided for at least 60 days and up to 6 months at a time
 - c. Renewal Criteria:
 - i. Member must fit one of these criteria:
 - 1. High dose methotrexate therapy
 - 2. Toxic serum levels of methotrexate
 - 3. Combination chemotherapy with 5-fluorouracil
 - ii. For high dose methotrexate therapy or toxic serum levels of methotrexate, physician must include documentation of:
 - 1. Patients serum creatinine levels
 - 2. Daily methotrexate levels greater than 0.05 µM
 - 3. Urinary pH of 7 or higher
 - iii. Continued leucovorin shortage

***Note: Coverage and approval duration may differ for Medicare Part B members based on any applicable criteria outlined in Local Coverage Determinations (LCD) or National Coverage Determinations (NCD) as determined by Center for Medicare and Medicaid Services (CMS). See the CMS website at <http://www.cms.hhs.gov/>. Determination of coverage of Part B drugs is based on medically accepted indications which have supported citations included or approved for inclusion determined by CMS approved compendia.

This policy and any information contained herein is the property of Blue Cross Blue Shield of Michigan and its subsidiaries, is strictly confidential, and its use is intended for the P&T committee, its members and BCBSM employees for the purpose of coverage determinations.

Background Information:

- Khapzory is indicated as rescue therapy after high-dose methotrexate (MTX) in patients with osteosarcoma; for diminishing the toxicity associated with overdosage of folic acid antagonists or impaired methotrexate elimination; and for the treatment of patients with metastatic colorectal cancer in combination with fluorouracil. Khapzory is not indicated for the treatment of pernicious anemia and megaloblastic anemia secondary to lack of vitamin B12 because of the risk of progression of neurologic manifestations despite hematologic remission.
- Khapzory can be used in adult patients for all indications and pediatric patients for osteosarcoma and toxicity due to overdose of folic acid antagonists or impaired methotrexate elimination. Safety and efficacy in pediatric patients has not been established when used for colorectal cancer.
- Leucovorin and levoleucovorin are the mainstays of rescue therapy and reducing toxicity due to overdose of folic acid antagonists. Leucovorin has been commercially available for decades but from time to time it can be in short supply. If it is currently unavailable due to supply chain issues, the FDA will list the drug as such on its website. Both the 2025 National Comprehensive Cancer Network treatment guidelines for bone cancers and colon cancers have leucovorin listed with treatment regimens. While the bone cancer guidelines do not mention use of levoleucovorin, the colon cancer guidelines state there is no data to manage guidance in situations of leucovorin shortage but one strategy is the use of levoleucovorin in its place. Guidelines state levoleucovorin should only be considered in times of leucovorin shortage due to the cost being much more expensive than leucovorin.
- Methotrexate is considered high-dose at doses greater than or equal to 500 mg/m². To eliminate the toxic effects, multiple leucovorin doses are given over a period of two to three days. Successful rescue by leucovorin depends on rapid elimination of methotrexate by the kidneys, which requires aggressive pretreatment and posttreatment hydration and urinary alkalinization to a pH greater than 7. Once methotrexate drug concentrations are below 0.05 µM and any renal failure issues have been resolved, rescue therapy can be discontinued.
- Generic levoleucovorin is available. Khapzory has not been studied against any generic levoleucovorin and has no known safety or efficacy advantages over the generic products.

References:

1. Khapzory [prescribing information]. Irvine, CA: Spectrum Pharmaceuticals, Inc.; December 2024.
2. National Comprehensive Cancer Network. Bone cancer (Version 1.2026). 2025 Sept 11. Available at: https://www.nccn.org/professionals/physician_gls/pdf/bone.pdf. Accessed on December 12, 2025.
3. National Comprehensive Cancer Network. Colon Cancer (Version 5.2025). 2025 Oct 30. Available at: https://www.nccn.org/professionals/physician_gls/pdf/colon.pdf. Accessed on December 12, 2025.

Policy History												
#	Date	Change Description										
1.9	Effective Date: 02/12/2026	Annual review of criteria was performed, no changes were made										
1.8	Effective Date: 02/13/2025	Annual review of criteria was performed, no changes were made										
1.7	Effective Date: 02/08/2024	Annual review of criteria was performed, no changes were made										
1.6	Effective Date: 02/02/2023	Updated approval length to allow for FDA recommended dosing for at least 60 days										
1.5	Effective Date: 10/06/2022	Updated approval length to allow for FDA recommended dosing or up to 6 months at a time										
1.4	Effective Date: 10/07/2021	Annual review of policy. No changes were made to the criteria										
1.3	Effective Date: 10/08/2020	Annual Review										
1.2	Effective Date: 11/07/2019	Annual Review of Medical Policy										
1.1	Effective Date: 07/01/2019	UM medical management system update for BCBS <table><tr><th>Line of Business</th><th>PA Required in Medical Management System (Yes/No)</th></tr><tr><td>BCBS</td><td>Yes</td></tr><tr><td>BCN</td><td>Yes</td></tr><tr><td>MAPPO</td><td>No</td></tr><tr><td>BCNA</td><td>No</td></tr></table>	Line of Business	PA Required in Medical Management System (Yes/No)	BCBS	Yes	BCN	Yes	MAPPO	No	BCNA	No
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1.0	Effective Date: 12/06/2018	Abbreviated Drug Review <table><tr><th>Line of Business</th><th>PA Required in Medical Management System (Yes/No)</th></tr><tr><td>BCBS</td><td>No</td></tr><tr><td>BCN</td><td>Yes</td></tr><tr><td>MAPPO</td><td>No</td></tr><tr><td>BCNA</td><td>No</td></tr></table>	Line of Business	PA Required in Medical Management System (Yes/No)	BCBS	No	BCN	Yes	MAPPO	No	BCNA	No
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* The prescribing information for a drug is subject to change. To ensure you are reading the most current information it is advised that you reference the most updated prescribing information by visiting the drug or manufacturer website or <http://dailymed.nlm.nih.gov/dailymed/index.cfm>.