Clinical Policy: Levoleucovorin (Khapzory)

Reference Number: PA.CP.PHAR.151
Effective Date: 01/2018
Last Review Date: 10/2025

Description
Levoleucovorin (Khapzory™) is a folate analog.

FDA Approved Indication(s)
Khapzory is indicated for:

- Rescue after high-dose methotrexate (MTX) therapy in adult and pediatric patients with osteosarcoma
- Diminishing the toxicity with overdosage of folic acid antagonists or impaired methotrexate elimination in adult and pediatric patients
- The treatment of adults with metastatic colorectal cancer in combination with 5-fluorouracil (5-FU)

Limitation(s) of use: Khapzory is not indicated for pernicious anemia and megaloblastic anemia secondary to the lack of vitamin B_{12} because of the risk of progression of neurologic manifestations despite hematologic remission.

Policy/Criteria
It is the policy of PA Health & Wellness that Khapzory is **medically necessary** when the following criteria are met:

I. Initial Approval Criteria:

A. Methotrexate/Folic Acid Antagonist Toxicity Prophylaxis (must meet all)

1. Prescribed for one of the following uses (a, b, or c):
   a. Rescue after MTX therapy for osteosarcoma or an NCCN-recommended cancer (*see Appendix D)*;
   b. Antidote for impaired MTX elimination;
   c. Antidote for accidental overdose of folic acid antagonists (including MTX);
2. Age ≥ 6 years;
3. Member meets one of the following (a or b):
   a. Documentation supports contraindication or clinically significant adverse effects to leucovorin;
   b. Leucovorin is not available for use due to a national drug shortage documented on the FDA's Drug Shortages Index (*see Appendix D*);
4. Request meets one of the following (a or b):
   a. Dose is appropriate and will be adjusted as necessary per section V;
   b. Dose is supported by practice guidelines or peer-reviewed literature for the relevant use (*prescriber must submit supporting evidence*).

Approval duration:
Impaired elimination/accidental overdose: 1 month
High-dose MTX therapy rescue: 12 months

B. Combination Chemotherapy with 5-FU (must meet all)**:**

1. Prescribed for use in a fluorouracil-based chemotherapy treatment regimen for colorectal cancer or an NCCN-recommended cancer (*see Appendix D)*;
2. Prescribed by or in consultation with an oncologist;
3. Age ≥ 6 years;
4. Prescribed in combination with 5-FU;
5. Member meets one of the following (a or b):
   a. Documentation supports contraindication or clinically significant adverse effects to leucovorin;
   b. Leucovorin is not available for use due to a national drug shortage documented on the FDA's Drug Shortages Index (*see Appendix D*);
6. Request meets one of the following (a or b):
   a. Colorectal cancer: dose does not exceed regimen in section V;
   b. Dose is supported by practice guidelines or peer-reviewed literature for the relevant use (*prescriber must submit supporting evidence*).

Approval duration: 12 months

C. Other diagnoses/indications: Refer to PA.CP.PMN.53

II. Continued Approval

A. All Indications in Section I (must meet all)**:**

1. Member meets one of the following (a or b):
   a. Currently receiving medication via PA Health & Wellness benefit or member has previously met all initial approval criteria, or the Continuity of Care Policy (PA.PHARM.01) applies;
   b. Documentation supports that member is currently receiving the requested drug for high-dose MTX rescue as part of chemotherapy or combination chemotherapy with 5-FU and has received this medication for at least 30 days;
2. Member is responding positively to therapy;
3. Documentation supports contraindication or clinically significant adverse effects to leucovorin, or leucovorin continues to be unavailable due to a national drug shortage;
4. If request is for a dose increase, request meets one of the following (a or b):
   a. New dose does not exceed regimen in section V;
   b. New dose is supported by practice guidelines or peer-reviewed literature for the relevant use (*prescriber must submit supporting evidence*).

Approval duration:
Impaired elimination/accidental overdose: 1 month
All other indications: 12 months

B. Other diagnoses/indications (must meet 1 or 2)**:**

1. Currently receiving medication via PA Health & Wellness benefit and documentation supports positive response to therapy or the Continuity of Care Policy (PA.PHARM.01) applies; or
2. Refer to PA.CP.PMN.53

III. Diagnoses/Indications for which coverage is NOT authorized:

A. Non-FDA approved indications, which are not addressed in this policy, unless there is sufficient documentation of efficacy and safety according to the off label use policies – PA.CP.PMN.53;
B. Pernicious or megaloblastic anemia.

IV. Appendices/General Information

Appendix A: Abbreviation/Acronym Key

5-FU: 5-fluorouracil
FDA: Food and Drug Administration
MTX: methotrexate
NCCN: National Comprehensive Cancer Network

Appendix B: Therapeutic Alternatives

This table provides a listing of preferred alternative therapy recommended in the approval criteria. The drugs listed here may not be a formulary agent and may require prior authorization.

Drug Name	Dosing Regimen	Dose Limit/ Maximum Dose
leucovorin	**MTX rescue** 15 mg (~10 mg/m^2) PO, IM, or IV given 24 hrs after MTX infusion, then every 6 hrs for 10 doses until MTX level is < 0.05 µM (dose may be adjusted based on elimination rates) **Folic acid antagonist overdose** 5 to 15 mg PO QD **Colorectal cancer (or other combination chemotherapy with 5-FU*)** Varies	Varies

Therapeutic alternatives are listed as Brand name® (generic) when the drug is available by brand name only and generic (Brand name®) when the drug is available by both brand and generic.
**Off-label*

Appendix C: Contraindications/Boxed Warnings

- Contraindication(s): previous allergic reactions attributed to leucovorin products, folic acid, or folinic acid
- Boxed warning(s): none reported

Appendix D: General Information

- The FDA's Drug Shortages Index can be found at: www.accessdata.fda.gov/scripts/drugshortages/default.cfm..
- Per NCCN, 400 mg/m^2 of leucovorin is equivalent to 200 mg/m^2 of levoleucovorin.
- The NCCN guidelines recommend the combination use of levoleucovorin with MTX as a rescue for the following cancers (2A recommendation) when leucovorin is not available:
  - (Pediatric) acute lymphoblastic leukemia

- T-cell lymphomas (including peripheral T-cell lymphomas, adult T-cell leukemia/lymphoma, extranodal NK/T-cell lymphoma [nasal type])
- Bone cancer (including osteosarcoma, dedifferentiated chondrosarcoma, high-grade undifferentiated pleomorphic sarcoma, soft tissue sarcomas)
- CNS cancer (including primary CNS lymphoma, brain metastases, leptomeningeal metastases)
- (Pediatric) B-cell lymphomas (including mantle cell lymphoma, HIV-related B-cell lymphoma, Burkitt lymphoma, follicular lymphomas, high grade B-cell lymphomas, diffuse large B-cell lymphoma, post-transplant lymphoproliferative disorders, primary mediastinal large B-cell lymphoma)
- Gestational trophoblastic neoplasia
- Chronic lymphocytic leukemia and acute lymphoblastic leukemia
- Blastic plasmacytoid dendritic cell neoplasm (an acute myeloid leukemia)

- The NCCN guidelines recommend the combination use of levoleucovorin with fluorouracil-based regimens for the following cancers (2A recommendation) when leucovorin is not available:
  - Occult primary adenocarcinoma, squamous cell carcinoma, or carcinoma not otherwise specified
  - Mucinous carcinoma of the ovary
  - Vaginal cancer
  - Colon cancer (including appendiceal adenocarcinoma)
  - Gastric cancer
  - Esophageal and esophagogastric junction cancers
  - Anal carcinoma
  - Extrapulmonary poorly differentiated neuroendocrine carcinoma/large or small cell carcinoma, mixed neuroendocrine-non-neuroendocrine neoplasm
  - Neuroendocrine tumors of the pancreas (well-differentiated Grade 1/2)
  - Well-differentiated Grade 3 neuroendocrine tumors
  - Cervical cancer
  - Rectal cancer
  - Pancreatic adenocarcinoma
  - Bladder cancer (non-urothelial and urothelial with variant histology)
  - Small bowel adenocarcinoma
  - Ampullary adenocarcinoma
  - Biliary tract cancers (gallbladder cancer, intrahepatic or extrahepatic cholangiocarcinoma)The NCCN guidelines recommend the combination use of levoleucovorin with MTX for the management of symptomatic Bing-Neel syndrome in Waldenström macroglobulinemia /lymphoplasmacytic lymphoma when leucovorin is not available (2A recommendation).

V. Dosage and Administration

Indication	Dosing Regimen	Maximum Dose
Rescue after high-dose MTX therapy in osteosarcoma	7.5 mg (approximately 5 mg/m^2) IV every 6 hours for 10 doses starting 24 hours after beginning of MTX infusion; adjust or extend rescue based on the following clinical situation and laboratory findings: Normal MTX elimination (serum MTX 10 µM at 24 hours, 1 µM at 48 hours, and < 0.2 µM at 72 hours after administration): 7.5 mg IV every 6 hours for 60 hours (10 doses starting 24 hours after start of MTX infusion) Delayed late MTX elimination (serum MTX > 0.2 µM at 72 hours and > 0.05 µM at 96 hours after administration): 7.5 mg IV every 6 hours until MTX < 0.05 µM Delayed early MTX elimination and/or evidence of acute renal injury (serum MTX ≥ 50 µM at 24 hours, ≥ 5 µM at 48 hours, or ≥ 100% increase in serum creatinine at 24 hours after MTX administration): 75 mg IV every 3 hours until MTX < 1 µM; then 7.5 mg IV every 3 hours until MTX < 0.05 µM If significant clinical toxicity is observed, Khapzory therapy should be extended for an additional 24 hours (total of 14 doses over 84 hours) in subsequent course of therapy.	See regimen
Inadvertent MTX overdose	Administer as soon as possible after overdose and within 24 hours of MTX administration if there is delayed excretion: 7.5 mg (approximately 5 mg/m^2) IV every 6 hours until serum MTX is < 5 x 10^{-8} M. Increase to 50 mg/m^2 IV every 3 hours if one of the following: • 24 hour serum creatinine has increased 50% over baseline • 24 hour MTX level is > 5 x 10-6 M • 48 hour level is > 9 x 10^{-7} M	See regimen
Colorectal cancer	Regimens used historically include: • 100 mg/m^2 IV followed by 5-FU 370 mg/m^2 IV; or • 10 mg/m^2 IV followed by 5-FU 425 mg/m^2 IV Administer Khapzory, and 5-FU separately. Repeat Khapzory daily for 5 day course. Courses may be repeated at 4 week intervals for 2 courses, then repeated at 4 to 5 week intervals.	See regimen

VI. Product Availability

Single-use vials with powder for reconstitution: 175 mg and 300 mg

VII. References

1. Khapzory Prescribing Information. East Windsor, NJ: Acrotech Biopharma LLC; December 2024. Available at: https://www.khapzory.com/. Accessed July 11, 2025.
2. National Comprehensive Cancer Network Drugs and Biologics Compendium. Available at: http://www.nccn.org/professionals/drug_compendium. Accessed August 25, 2025.

Coding Implications

Codes referenced in this clinical policy are for informational purposes only. Inclusion or exclusion of any codes does not guarantee coverage. Providers should reference the most up-to-date sources of professional coding guidance prior to the submission of claims for reimbursement of covered services.

HCPCS Codes	Description
J0641	Injection, levoleucovorin not otherwise specified, 0.5 mg
J0642	Injection, levoleucovorin (Khapzory), 0.5 mg

Reviews, Revisions, and Approvals	Date
4Q 2018 annual review: specialist requirement added for combo use with 5-FU; added NCCN off-label recommended uses; summarized NCCN- and FDA-approved uses for improved clarity; added COC for 5-FU chemo combo use; references reviewed and updated.	08/2018
4Q 2019 annual review: No changes per Statewide PDL implementation 01-01-2020	10/2019
4Q 2020 annual review: additional cancers amenable to rescue therapy added to Appendix D per NCCN; added Khapzory to policy; updated FDA approved indications for addition of pediatric use; references reviewed and updated.	10/2020
4Q 2021 annual review: contraindications updated to include leucovorin products; change the language to be consistent with FDA labeling (change patients to adults): the treatment of adults with metastatic colorectal cancer in combination with 5-fluorouracil (5-FU); references reviewed and updated.	10/2021
4Q 2022 annual review: no significant changes; updated Appendix D per NCCN	10/2022

Reviews, Revisions, and Approvals	Date
Compendium; references reviewed and updated.	
4Q 2023 annual review: no significant changes; removed request for Fusilev or Khapzory criterion as these are the only two agents covered in the policy and carry the same indications; updated Appendix D per NCCN Compendium; references reviewed and updated.	10/2023
4Q 2024 annual review: no significant changes; updated Appendix D per NCCN Compendium; added HCPCS code J0642 and updated J0641 code description; references reviewed and updated.	10/2024
4Q 2025 annual review: Fusilev removed from policy as it is no longer available; revised initial approval durations for high-dose MTX therapy rescue and combination chemotherapy with 5-FU to 12 months; references reviewed and updated.	10/2025