Clinical Policy: Levoleucovorin (Fusilev, Khapzory)

Reference Number: LA.PHAR.151
Effective Date: 09.15.22
Last Review Date: 04.10.24
Line of Business: Medicaid

Coding Implications
Revision Log

See Important Reminder at the end of this policy for important regulatory and legal information.

****Please note: This policy is for medical benefit****

Description

Levoleucovorin (Fusilev®, Khapzory™) is a folate analog.

FDA Approved Indication(s)

Fusilev and Khapzory are indicated for:

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

Khapzory is indicated:

- For rescue after high-dose MTX therapy in patients with osteosarcoma.
- For diminishing the toxicity associated with overdosage of folic acid antagonists or impaired methotrexate elimination.
- For the treatment of adults with metastatic colorectal cancer in combination with fluorouracil.

Limitation(s) of use: Fusilev and Khapzory are 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

Provider must submit documentation (such as office chart notes, lab results or other clinical information) supporting that member has met all approval criteria.

It is the policy of Louisiana Healthcare Connections that Fusilev and Khapzory are **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. For Fusilev or Khapzory: Dose is appropriate and will be adjusted as necessary per section V;
   b. For Fusilev or Khapzory: Dose is supported by practice guidelines or peer-reviewed literature for the relevant use (*prescriber must submit supporting evidence*).

**Prescribed regimen must be FDA-approved or recommended by NCCN*

Approval duration:
Impaired elimination/accidental overdose: 1 month
High-dose MTX therapy rescue: 6 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. For Fusilev or Khapzory: Colorectal cancer: dose does not exceed regimen in section V;
   b. For Fusilev or Khapzory: Dose is supported by practice guidelines or peer-reviewed literature for the relevant use (*prescriber must submit supporting evidence*).

**Prescribed regimen must be FDA-approved or recommended by NCCN*

Approval duration:6 months

C. Other diagnoses/indications (must meet 1 or 2)**:**
1. If this drug has recently (within the last 6 months) undergone a label change (e.g., newly approved indication, age expansion, new dosing regimen) that is not yet reflected in this policy, refer to LA.PMN.255
2. If the requested use (e.g., diagnosis, age, dosing regimen) is NOT specifically listed under section III (Diagnoses/Indications for which coverage is NOT authorized) AND criterion 1 above does not apply, refer to the off-label use policy LA.PMN.53

II. Continued Therapy

A. All Indications in Section I (must meet all)**:**
1. Member meets one of the following (a, or b):
   a. Currently receiving medication via Louisiana Healthcare Connections benefit or member has previously met initial approval criteria;
   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. For Fusilev or Khapzory: New dose does not exceed regimen in section V;
   b. For Fusilev or Khapzory: New dose is supported by practice guidelines or peer-reviewed literature for the relevant use (*prescriber must submit supporting evidence*).

**Prescribed regimen must be FDA-approved or recommended by NCCN*

Approval duration:
Impaired elimination/accidental overdose: 1 month
Medicaid: 12 months

B. Other diagnoses/indications (must meet 1 or 2)**:**
1. If this drug has recently (within the last 6 months) undergone a label change (e.g., newly approved indication, age expansion, new dosing regimen) that is not yet reflected in this policy, refer to LA.PMN.255
2. If the requested use (e.g., diagnosis, age, dosing regimen) is NOT specifically listed under section III (Diagnoses/Indications for which coverage is NOT authorized) AND criterion 1 above does not apply, refer to the off-label use policy LA.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 policy LA.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 require prior authorization.

Drug Name	Dosing Regimen	Dose Limit/ Maximum Dose
leucovorin	**MTX rescue**	Varies

Drug Name	Dosing Regimen	Dose Limit/ Maximum Dose
	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	

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, hepatosplenic T-Cell lymphoma)
  - Bone cancer (including osteosarcoma, dedifferentiated chondrosarcoma, high-grade undifferentiated pleomorphic sarcoma)
  - CNS cancer (including primary CNS lymphoma, brain metastases, leptomeningeal metastases)
  - B-cell lymphomas (including mantle cell lymphoma, HIV-related B-cell lymphoma, Burkitt lymphoma, 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 small lymphocytic lymphoma
  - Blastic plasmacytoid dendritic cell neoplasm
- 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
- Colon cancer
- 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
- Appendiceal adenocarcinoma
- Biliary tract cancers (gallbladder cancer, intrahepatic or extrahepatic cholangiocarcinoma)
- Thymomas and thymic carcinomas

- 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	See regimen

Indication	Dosing Regimen	Maximum Dose
	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, Fusilev or Khapzory therapy should be extended for an additional 24 hours (total of 14 doses over 84 hours) in subsequent course of therapy.	
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 Fusilev or Khapzory, and 5-FU separately. Repeat Fusilev or 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

Drug Name	Availability
Fusilev (levoleucovorin)	• Single-use vial with powder for reconstitution: 50 mg • Single-use vial with solution: 175 mg/17.5 mL, 250 mg/25 mL
Khapzory (levoleucovorin)	Single-use vial with powder for reconstitution: 175 mg and 300 mg

VII. References

1. Fusilev Prescribing Information. East Windsor, NJ: Acrotech Biopharma LLC; November 2020. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/020140s026lbl.pdf. Accessed August 8, 2023.

2. Khapzory Prescribing Information. East Windsor, NJ: Acrotech Biopharma LLC; March 2020. Available at: https://www.khapzory.com/wp-content/uploads/2019/11/Khapzory-PI-03-2020.pdf. Accessed August 9, 2023.
3. National Comprehensive Cancer Network Drugs and Biologics Compendium. Available at: http://www.nccn.org/professionals/drug_compendium. Accessed August 9, 2023.

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 calcium, 0.5 mg

Reviews, Revisions, and Approvals	Date	LDH Approval Date
Converted corporate to local policy.	09.22	9.15.22
No significant changes; updated Appendix D per NCCN Compendium; references reviewed and updated. Template changes applied to other diagnoses/indications and continued therapy section. Added verbiage this policy is for medical benefit only.	06.02.23	10.05.23
Annual review: 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.	04.10.24	

Important Reminder
This clinical policy has been developed by appropriately experienced and licensed health care professionals based on a review and consideration of currently available generally accepted standards of medical practice; peer-reviewed medical literature; government agency/program approval status; evidence-based guidelines and positions of leading national health professional organizations; views of physicians practicing in relevant clinical areas affected by this clinical policy; and other available clinical information. LHCC makes no representations and accepts no liability with respect to the content of any external information used or relied upon in developing this clinical policy. This clinical policy is consistent with standards of medical practice current at the time that this clinical policy was approved.

The purpose of this clinical policy is to provide a guide to medical necessity, which is a component of the guidelines used to assist in making coverage decisions and administering benefits. It does not constitute a contract or guarantee regarding payment or results. Coverage decisions and the administration of benefits are subject to all terms, conditions, exclusions and limitations of the coverage documents (e.g., evidence of coverage, certificate of coverage, policy,

contract of insurance, etc.), as well as to state and federal requirements and applicable LHCC administrative policies and procedures.

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