Clinical Policy: Levoleucovorin (Fusilev, Khapzory)

Reference Number: CP.PHAR.151
Effective Date: 02.01.16
Last Review Date: 11.24
Line of Business: Commercial, HIM, Medicaid

Coding Implications
Revision Log

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

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

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 health plans affiliated with Centene Corporation® 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:
Medicaid/HIM – 6 months
Commercial – 6 months or to the member's renewal date, whichever is longer

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 prescribed for 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:
Medicaid/HIM – 6 months
Commercial – 6 months or to the member's renewal date, whichever is longer

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 one of the following policies (a or b):
   a. For drugs on the formulary (commercial, health insurance marketplace) or PDL (Medicaid), the no coverage criteria policy for the relevant line of business: CP.CPA.190 for commercial, HIM.PA.33 for health insurance marketplace, and CP.PMN.255 for Medicaid; or
   b. For drugs NOT on the formulary (commercial, health insurance marketplace) or PDL (Medicaid), the non-formulary policy for the relevant line of business: CP.CPA.190 for commercial, HIM.PA.103 for health insurance marketplace, and CP.PMN.16 for Medicaid; or

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 for the relevant line of business: CP.CPA.09 for commercial, HIM.PA.154 for health insurance marketplace, and CP.PMN.53 for Medicaid.

II. Continued Therapy

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

1. Member meets one of the following (a, b, or c):
   a. Currently receiving medication via Centene benefit or member has previously met initial approval criteria;
   b. Member is currently receiving medication and is enrolled in a state and product with continuity of care regulations (*refer to state specific addendums for CC.PHARM.03A and CC.PHARM.03B);*
   c. 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
All other indications:
Medicaid/HIM – 12 months
Commercial – 6 months or to the member's renewal date, whichever is longer

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 one of the following policies (a or b):
   a. For drugs on the formulary (commercial, health insurance marketplace) or PDL (Medicaid), the no coverage criteria policy for the relevant line of business: CP.CPA.190 for commercial, HIM.PA.33 for health insurance marketplace, and CP.PMN.255 for Medicaid; or
   b. For drugs NOT on the formulary (commercial, health insurance marketplace) or PDL (Medicaid), the non-formulary policy for the relevant line of business: CP.CPA.190 for commercial, HIM.PA.103 for health insurance marketplace, and CP.PMN.16 for Medicaid; or
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 for the relevant line of business: CP.CPA.09 for commercial, HIM.PA.154 for health insurance marketplace, and CP.PMN.53 for Medicaid.

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 – CP.CPA.09 for commercial, HIM.PA.154 for health insurance marketplace, and CP.PMN.53 for Medicaid, or evidence of coverage documents;

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 for all relevant lines of business 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, 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
  - Vaginal cancer
  - 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 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.	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	See regimen

Indication	Dosing Regimen	Maximum Dose
	• 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.	

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 July 17, 2024.
2. Khapzory Prescribing Information. East Windsor, NJ: Acrotech Biopharma LLC; March 2020. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/211226s002lbl.pdf. Accessed July 15, 2024.
3. National Comprehensive Cancer Network Drugs and Biologics Compendium. Available at: http://www.nccn.org/professionals/drug_compendium. Accessed August 23, 2024.

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	P&T Approval Date
4Q 2020 annual review: modified HIM-Medical Benefit to HIM line of business; added Khapzory to policy; updated FDA approved indications for addition of pediatric use; references reviewed and updated.	08.13.20	11.20

Reviews, Revisions, and Approvals	Date	P&T Approval Date
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); updated redirections to off-label policies to current policy names; references reviewed and updated.	07.01.21	11.21
4Q 2022 annual review: no significant changes; updated Appendix D per NCCN Compendium; references reviewed and updated. Template changes applied to other diagnoses/indications and continued therapy section.	08.25.22	11.22
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.	08.09.23	11.23
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.	07.17.24	11.24

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. The Health Plan 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. "Health Plan" means a health plan that has adopted this clinical policy and that is operated or administered, in whole or in part, by Centene Management Company, LLC, or any of such health plan's affiliates, as applicable.

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 Health Plan-level administrative policies and procedures.

This clinical policy is effective as of the date determined by the Health Plan. The date of posting may not be the effective date of this clinical policy. This clinical policy may be subject to applicable legal and regulatory requirements relating to provider notification. If there is a

discrepancy between the effective date of this clinical policy and any applicable legal or regulatory requirement, the requirements of law and regulation shall govern. The Health Plan retains the right to change, amend or withdraw this clinical policy, and additional clinical policies may be developed and adopted as needed, at any time.

This clinical policy does not constitute medical advice, medical treatment, or medical care. It is not intended to dictate to providers how to practice medicine. Providers are expected to exercise professional medical judgment in providing the most appropriate care, and are solely responsible for the medical advice and treatment of members. This clinical policy is not intended to recommend treatment for members. Members should consult with their treating physician in connection with diagnosis and treatment decisions.

Providers referred to in this clinical policy are independent contractors who exercise independent judgment and over whom the Health Plan has no control or right of control. Providers are not agents or employees of the Health Plan.

This clinical policy is the property of the Health Plan. Unauthorized copying, use, and distribution of this clinical policy or any information contained herein are strictly prohibited. Providers, members, and their representatives are bound to the terms and conditions expressed herein through the terms of their contracts. Where no such contract exists, providers, members and their representatives agree to be bound by such terms and conditions by providing services to members and/or submitting claims for payment for such services.

Note:
For Medicaid members, when state Medicaid coverage provisions conflict with the coverage provisions in this clinical policy, state Medicaid coverage provisions take precedence. Please refer to the state Medicaid manual for any coverage provisions pertaining to this clinical policy.