Clinical Policy: Levoleucovorin (Fusilev, Khapzory)

Reference Number: ERX.SPA.181
Effective Date: 01.11.17
Last Review Date: 11.22
Line of Business: Commercial, Medicaid

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 is indicated:
- For rescue after high-dose methotrexate (MTX) therapy in adult and pediatric patients in osteosarcoma
- For diminishing the toxicity with overdosage of folic acid antagonists or impaired methotrexate elimination in adult and pediatric patients
- For the treatment of adults with metastatic colorectal cancer in combination with 5-fluorouracil (5-FU)

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 approved for pernicious anemia and megaloblastic anemias secondary to the lack of vitamin B_{12}. Improper use may cause a hematologic remission while neurologic manifestations continue to progress.

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.

Health plan approved formularies should be reviewed for all coverage determinations. Requirements to use preferred alternative agents apply only when such requirements align with the health plan approved formulary.

It is the policy of health plans affiliated with Envolve Pharmacy Solutions™ 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 a folic acid antagonist (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*).

**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. 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*).

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

Approval duration: 6 months

C. Other diagnoses/indications

1. Refer to ERX.PA.01 if diagnosis is NOT specifically listed under section III (Diagnoses/Indications for which coverage is NOT authorized).

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 a health plan affiliated with Envolve Pharmacy Solutions 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. 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*).

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

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 a health plan affiliated with Envolve Pharmacy Solutions and documentation supports positive response to therapy.
   Approval duration: Duration of request or 6 months (whichever is less); or
2. Refer to ERX.PA.01 if diagnosis is NOT specifically listed under section III (Diagnoses/Indications for which coverage is NOT authorized).

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 – ERX.PA.01 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 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 methotrexate as a rescue for the following cancers (category 2A or higher recommendation) when leucovorin is not available:
  - 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, AIDS-related B-cell lymphoma, Burkitt lymphoma, high grade B-cell lymphomas, diffuse large B-cell lymphoma, post-transplant lymphoproliferative disorders)
  - 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)

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:	See regimen

Indication	Dosing Regimen	Maximum Dose
	• 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	
Colorectal cancer	Regimens used historically include: • Fusilev 100 mg/m^2 IV followed by 5-FU 370 mg/m^2 IV; or • Fusilev 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, 300 mg

VII. References

1. Fusilev Prescribing Information. East Windsor, NJ: Acrotech Biopharma LLC; November 2020. Available at https://dailymed.nlm.nih.gov/dailymed/lookup.cfm?setid=2255268c-b703-42e5-a81a-0fb223a77fd6. Accessed August 25, 2022.
2. Khapzory Prescribing Information. East Windsor, NJ: Acrotech Biopharma LLC; March 2020. Available at https://www.khapzory.com/wp-content/uploads/2019/11/PI-KHAPZORY-092019.pdf. Accessed August 25, 2022.
3. National Comprehensive Cancer Network Drugs and Biologics Compendium. Available at: http://www.nccn.org/professionals/drug_compendium. Accessed August 25, 2022.
4. National Comprehensive Cancer Network. Colon Cancer Version 1.2022. Available at: https://www.nccn.org/professionals/physician_gls/pdf/colon.pdf. Accessed August 25, 2022.
5. National Comprehensive Cancer Network. Rectal Cancer Version 1.2022. Available at: https://www.nccn.org/professionals/physician_gls/pdf/rectal.pdf. Accessed August 25, 2022.
6. National Comprehensive Cancer Network. Bone Cancer Version 1.2023. Available at: https://www.nccn.org/professionals/physician_gls/pdf/bone.pdf. Accessed August 25, 2022.
7. DRUGDEX® System [Internet database]. Greenwood Village, Colo: Thomson Healthcare. Updated periodically. Accessed August 25, 2022.

Reviews, Revisions, and Approvals	Date	P&T Approval 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.	08.14.18	11.18
4Q 2019 annual review: no significant changes; additional cancers amenable to rescue therapy added to Appendix D per NCCN; references reviewed and updated.	09.10.19	11.19
4Q 2020 annual review: added Khapzory to policy; updated FDA approved indications for addition of pediatric use; references reviewed and updated.	08.13.20	11.20
4Q 2021 annual review: no significant changes; contraindications updated to include leucovorin products; changed the language to be consistent with FDA labeling (modified patients to adults): the treatment of adults with	07.01.21	11.21

Reviews, Revisions, and Approvals	Date	P&T Approval Date
metastatic colorectal cancer in combination with 5-FU; references reviewed and updated.		
4Q 2022 annual review: no significant changes; updated Appendix D per NCCN Compendium; references reviewed and updated.	08.25.22	11.22

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.

This Clinical Policy is not intended to dictate to providers how to practice medicine, nor does it constitute a contract or guarantee regarding payment or results. 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.