Clinical Policy: Levoleucovorin (Fusilev)

Reference Number: PA.CP.PHAR.151
Effective Date: 01/18
Last Review Date: 10/30/2019

Coding Implications
Revision Log

Description
The intent of the criteria is to ensure that patients follow selection elements established by Pennsylvania Health and Wellness® clinical policy for levoleucovorin (Fusilev®).

FDA Approved Indication(s)
Fusilev is indicated:

- For rescue after high-dose methotrexate (MTX) therapy in osteosarcoma
- For diminishing the toxicity and counteracting the effects of impaired MTX elimination and of inadvertent overdosage of folic acid antagonists
- For the palliative treatment of patients with advanced metastatic colorectal cancer in combination chemotherapy with 5-fluorouracil (5-FU)

Limitation(s) of use: Fusilev is 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
It is the policy of health plans affiliated with Pennsylvania Health and Wellness that Fusilev is **medically necessary** when the following criteria are met:

I. Initial Approval Criteria:

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

1. Meets a or b:
2. 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);
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;
4. Request meets one of the following (a or b):
   a. Dose is appropriate and will be adjusted as necessary per section III;
   b. Dose is supported by practice guidelines or peer-reviewed literature for the relevant use (*prescriber must submit supporting evidence*).

Approval duration: 6 month

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;

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;
6. Request meets one of the following (a or b):
   a. Colorectal cancer: dose does not exceed regimen in section III;
   b. Dose is supported by practice guidelines or peer-reviewed literature for the relevant use (*prescriber must submit supporting evidence*).

Approval duration: 6 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 Pennsylvania Health and Wellness benefit or member has previously met all initial approval criteria, or the Continuity of Care Policy (PA.LTSS.PHAR.01) applies;
   b. Documentation supports that member is currently receiving Fusilev 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 III;
   b. New dose is supported by practice guidelines or peer-reviewed literature for the relevant use (*prescriber must submit supporting evidence*).

Approval duration: 12 months

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

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

III. 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	See regimen

Indication	Dosing Regimen	Maximum Dose
	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 therapy should be extended for an additional 24 hours (total of 14 doses over 84 hours) in subsequent course of therapy.	

Indication	Dosing Regimen	Maximum Dose
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 < 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: • 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 and 5-FU separately. Repeat Fusilev 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

Background
Description/Mechanism of Action:
Fusilev (levoleucovorin) is a folate analog. Levoleucovorin is the levo isomeric form of racemic *d,l*-leucovorin, present as the calcium salt. Levoleucovorin is the pharmacologically active isomer of leucovorin [(6-S)-leucovorin].

- Levoleucovorin effects during high-dose methotrexate therapy

Levoleucovorin is the pharmacologically active isomer of 5-formyl tetrahydrofolic acid. Levoleucovorin does not require reduction by the enzyme dihydrofolate reductase in order to participate in reactions utilizing folates as a source of "one-carbon" moieties. Administration of levoleucovorin can counteract the therapeutic and toxic effects of folic acid antagonists such as methotrexate, which act by inhibiting dihydrofolate reductase.

- Levoleucovorin effects in combination with 5-fluorouracil
  Levoleucovorin can enhance the therapeutic and toxic effects of fluoropyrimidines used in cancer therapy such as 5-fluorouracil. 5-fluorouracil is metabolized to 5-fluoro-2'-deoxyuridine-5'-monophosphate (FdUMP), which binds to and inhibits thymidylate synthase (an enzyme important in DNA repair and replication). Levoleucovorin is readily converted to another reduced folate, 5,10-methylenetetrahydrofolate, which acts to stabilize the binding of FdUMP to thymidylate synthase and thereby enhances the inhibition of this enzyme.

  Formulations:
  Fusilev for Injection
  - 50 mg single use vial of freeze dried powder:
    - Each 50 mg vial of Fusilev for Injection contains a sterile lyophilized powder consisting of 64 mg levoleucovorin calcium pentahydrate (equivalent to 50 mg levoleucovorin) and 50 mg mannitol.

  Fusilev Injection
  - 175 mg/17.5 mL solution; single-use vial:
    - Each mL contains levoleucovorin calcium pentahydrate equivalent to 10 mg levoleucovorin and 8.3 mg sodium chloride.
  - 250 mg/25 mL solution; single-use vial:
    - Each mL contains levoleucovorin calcium pentahydrate equivalent to 10 mg levoleucovorin and 8.3 mg sodium chloride.

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	Varies

Drug Name	Dosing Regimen	Dose Limit/ Maximum Dose
	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 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 (2A 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 [nasal type])
  - 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)
  - Gestational trophoblastic neoplasia
- The NCCN guidelines recommend the combination use of levoleucovorin with fluorouracil-based regimens for the following cancers (2A recommendation) when leucovorin is not available:
  - Thymomas and thymic carcinomas
  - Occult primary adenocarcinoma or squamous cell carcinoma
  - Mucinous carcinoma
  - Colon cancer
  - Gastric cancer
  - Esophageal and esophagogastric junction cancers
  - Anal carcinoma

- Poorly differentiated (high grade)/large or small cell neuroendocrine and adrenal tumors
- Cervical cancer
- Leptomeningeal metastases
- Rectal cancer
- Pancreatic adenocarcinoma
- Bladder cancer (non-urothelial and urothelial with variant histology)
- Ovarian, fallopian tube, primary peritoneal cancer

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	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.	08/18	
4Q 2019 annual review: No changes per Statewide PDL implementation 01-01-2020	10/30/19	

References
1. Fusilev Prescribing Information. Irvine, CA: Spectrum Pharmaceuticals, Inc.; April 2011. Available at http://www.fusilev.com. Accessed August 14, 2018.
2. Levoleucovorin. In: National Comprehensive Cancer Network Drugs and Biologics Compendium. Available at NCCN.org. Accessed August 14, 2018.
3. National Comprehensive Cancer Network. Colon Cancer Version 2.2018. Available at: https://www.nccn.org/professionals/physician_gls/pdf/colon.pdf. Accessed August 14, 2018.
4. National Comprehensive Cancer Network. Rectal Cancer Version 2.2018. Available at: https://www.nccn.org/professionals/physician_gls/pdf/rectal.pdf. Accessed August 14, 2018.
5. National Comprehensive Cancer Network. Bone Cancer Version 2.2018. Available at: https://www.nccn.org/professionals/physician_gls/pdf/bone.pdf. Accessed August 14, 2018.
6. DRUGDEX® System [Internet database]. Greenwood Village, Colo: Thomson Healthcare. Updated periodically. Accessed August 14, 2018.