Clinical Policy Title:	levoleucovorin
Policy Number:	RxA.140
Drug(s) Applied:	Fusilev®
Original Policy Date:	02/07/2020
Last Review Date:	03/09/2021
Line of Business Policy Applies to:	All lines of business

Background

Levoleucovorin (Fusilev®) is a folate analog. It 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.

Dosing Information

Drug Name	Indication	Dosing Regimen	Maximum Dose
levoleucovorin (Fusilev®)	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, or ≥ 5 µM at 48 hours, OR; ≥ 100% increase	See regimen

Dosing Information			
Drug Name	**Indication**	**Dosing Regimen**	**Maximum Dose**
		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 <0.05µM 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.	
levoleucovorin (Fusilev®)	Inadvertent MTX overdose	Administer as soon as possible after overdose and within 24 hours of MTX administration if there is delayed excretion: • Fusilev® 7.5 mg (approximately 5 mg/m^2) IV every 6 hours until serum MTX is < 10^{-8}M.Increase to Fusilev 50 mg/m^2 IV every 3 hours until serum MTX is < 10^{-8} M if one of the following: ○ 24 hour serum creatinine has increased 50% over baseline ○ 24 hour MTX level is > 5 x 10^{-6} M or 48 hour MTX 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

Dosage Forms

- Single-use vial with powder for reconstitution: 50 mg
- Single-use vial with solution: 175 mg/17.5 mL, 250 mg/25 mL

Clinical Policy

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

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 Background;
   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:
Commercial: 6 months
Medicaid: 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 Background;
   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
Commercial: 6 months
Medicaid: 6 months

II. Continued Therapy Approval

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

1. Member meets one of the following (a or b):
   a. Member is currently receiving medication that has been authorized by RxAdvance or the member has met initial approval criteria listed in this policy;

   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 Background;
   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
Commercial: 6 months
Medicaid: 12 months

III. Appendices

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

Below are suggested therapeutic alternatives based on clinical guidance. Please check drug formulary for preferred agents and utilization management requirements.

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 once daily **Colorectal cancer (or other combination chemotherapy with 5-FU*)** Either of the following 2 regimens is recommended:	Varies

Drug Name	Dosing Regimen	Dose Limit/ Maximum Dose
	• 200 mg/m^2 IV followed by 5-FU 370 mg/m^2 IV • 20 mg/m^2 IV followed by 5-FU 425 mg/m^2 IV	

*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):
  - Use in patients who had 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, soft tissue sarcomas)
  - CNS cancer (including primary CNS lymphoma, brain metastases, leptomeningeal metastases)
  - B-cell lymphomas (including mantle cell lymphoma, AIDS-related B-cell lymphoma, Burkitt lymphoma, follicular lymphomas, high grade B-cell lymphomas, diffuse large B-cell lymphoma) Gestational trophoblastic neoplasia
  - Chronic lymphocytic leukemia and acute lymphoblastic 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:
  - 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
  - Hepatobiliary carcinoma

- Pancreatic adenocarcinoma
- Bladder cancer (non-urothelial and urothelial with variant histology)
- Ovarian, fallopian tube, primary peritoneal cancer

References

1. Fusilev Prescribing Information. Irvine, CA: Spectrum Pharmaceuticals, Inc.; April 2011. Available at http://www.fusilev.com. Accessed January 31, 2021
2. Levoleucovorin. In: National Comprehensive Cancer Network Drugs and Biologics Compendium. Available at NCCN.org. Accessed January 31, 2021
3. National Comprehensive Cancer Network. Colon Cancer Version 2.2021. Available at: https://www.nccn.org/professionals/physician_gls/pdf/colon.pdf. Accessed January 31, 2021
4. National Comprehensive Cancer Network. Rectal Cancer Version 1.2021. Available at: https://www.nccn.org/professionals/physician_gls/pdf/rectal.pdf. Accessed January 31, 2021
5. National Comprehensive Cancer Network. Bone Cancer Version 1.2021 Available at: https://www.nccn.org/professionals/physician_gls/pdf/bone.pdf. Accessed January 31, 2021
6. DRUGDEX® System [Internet database]. Greenwood Village, Colo: Thomson Healthcare. Updated periodically.

Review/Revision History	Review/Revised Date	P&T Approval Date
Policy was established	01/2020	02/07/2020
Reviewed criteria and updated appendices	04/2020	
Policy was reviewed: 1. Clinical policy title was updated. 2. Continued therapy approval criteria II.A.1.a was rephrased to “Member is currently receiving this medication…”. 3. References were reviewed and updated.	01/31/2021	03/09/2021