# Clinical Policy: Levoleucovorin (Fusilev)

Reference Number: CP.PHAR.151
Effective Date: 02.01.16
Last Review Date: 11.17
Line of Business: Medicaid

Coding Implications
Revision Log

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

## Description

Levoleucovorin (Fusilev®) is a folate analog.

## 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 of use: Fusilev is not approved for pernicious anemia and megaloblastic anemias. Improper use may cause a hematologic remission while neurologic manifestations continue to progress.

## Policy/Criteria

*Provider must submit documentation (which may include office chart notes and lab results) supporting that member has met all approval criteria*

It is the policy of health plans affiliated with Centene Corporation® 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. Prescribed for one of the following uses (a or b):
   a. FDA approved use (i, ii, or iii):
      i. Following high dose (12 grams/$m^2$ IV over 4 hours) MTX therapy as part of a treatment regimen for osteosarcoma;
      ii. For impaired MTX elimination;
      iii. After accidental folic acid antagonist overdose (including MTX);
   b. Off-label NCCN recommended use:
      i. Following high dose (12 grams/$m^2$ IV over 4 hours) MTX therapy as part of a treatment regimen for one of the following (a or b):
         a) Dedifferentiated chondrosarcoma;
         b) High-grade undifferentiated pleomorphic sarcoma;
2. Age ≥ 6 years;
3. Member meets one of the following (a or b):

a. Member is contraindicated or experienced 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 B*);

4. Request meets any 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*).

**Approval duration:**
**Impaired elimination/accidental overdose: 1 month**
**Sarcomas: 6 months**

**B. Colorectal Cancer** (must meet all)**:**

1. Prescribed for one of the following uses (a or b):
   a. FDA approved use (i, ii, and iii):
      i. Diagnosis of colorectal cancer;
      ii. Disease is advanced and metastatic;
      iii. Prescribed for palliative treatment;
   b. Off-label NCCN recommended use (i or ii):
      i. Diagnosis of colon cancer;
      ii. Diagnosis of rectal cancer;
2. Will be used in combination with 5-FU;
3. Member meets one of the following (a or b):
   a. Member is contraindicated or experienced 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 B*);
4. Request meets any of the following (a, b, or c):
   a. Dose does not exceed 100 mg/m$^2$ IV followed by 5-FU 370 mg/m$^2$ IV;
   b. Dose does not exceed 10 mg/m$^2$ IV followed by 5-FU 425 mg/m$^2$ IV;
   c. 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**

1. Refer to CP.PHAR.57 if diagnosis is NOT specifically listed under section III (Diagnoses/Indications for which coverage is NOT authorized).

## II. Continued Therapy

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

1. Currently receiving medication via Centene benefit or member has previously met initial approval criteria;
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. Request meets any 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*).

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

**B. Colorectal Cancer** (must meet all)**:**
1. Currently receiving medication via Centene benefit or member has previously met initial approval criteria;
2. Member is responding positively to therapy (e.g., no disease progression or unacceptable toxicity);
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 any of the following (a, b, or c):
   a. New dose does not exceed 100 mg/m$^2$ IV followed by 5-FU 370 mg/m$^2$ IV;
   b. New dose does not exceed 10 mg/m$^2$ IV followed by 5-FU 425 mg/m$^2$ IV;
   c. New dose is supported by practice guidelines or peer-reviewed literature for the relevant use (*prescriber must submit supporting evidence*).

**Approval duration: 12 months**

**C. Other diagnoses/indications** (must meet 1 or 2)**:**
1. Currently receiving medication via Centene benefit and documentation supports positive response to therapy.
   **Approval duration: Duration of request or 6 months (whichever is less)**; or
2. Refer to CP.PHAR.57 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 – CP.PHAR.57 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: General Information*

- The FDA's Drug Shortages Index can be found at: www.accessdata.fda.gov/scripts/drugshortages/default.cfm.

- The NCCN recommends Fusilev to be used in combination with 5-FU-based regimens for colon and rectal cancer when leucovorin is not available. 400 mg/m$^2$ of leucovorin is equivalent to 200 mg/m$^2$ of levoleucovorin.

**V. Dosage and Administration**

<table>
<tr><th>Indication</th><th>Dosing Regimen</th><th>Maximum Dose</th></tr>
<tr><td>Rescue after high-dose MTX therapy</td><td>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 clinical situation and laboratory findings:
<table>
<tr><th>Clinical situation</th><th>Laboratory findings</th><th>Fusilev dose and duration</th></tr>
<tr><td>Normal MTX elimination</td><td>Serum MTX 10 µM at 24 hours, 1 µM at 48 hours, and < 0.2 µM at 72 hours after administration</td><td>7.5 mg IV every 6 hours for 60 hours (10 doses starting 24 hours after start of MTX infusion)</td></tr>
<tr><td>Delayed late MTX elimination</td><td>Serum MTX > 0.2 µM at 72 hours and > 0.05 µM at 96 hours after administration</td><td>7.5 mg IV every 6 hours until MTX < 0.05 µM</td></tr>
<tr><td>Delayed early MTX elimination and/or evidence of acute renal injury</td><td>Serum MTX ≥ 50 µM at 24 hours, ≥ 5 µM at 48 hours, or ≥ 100% increase in serum creatinine at 24 hours after MTX administration</td><td>75 mg IV every 3 hours until MTX < 1 µM; then 7.5 mg IV every 3 hours until MTX < 0.05 µM</td></tr>
</table></td><td>See regimen</td></tr>
<tr><td>Inadvertent MTX overdosage</td><td>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 24 hour serum creatinine has increased 50% over baseline or if the 24 hour MTX level is > 5 x $10^{-6}$ M or the 48 hour level is > 9 x $10^{-7}$ M</td><td>See regimen</td></tr>
<tr><td>Colorectal cancer</td><td>Regimens used historically include:<br>• Fusilev 100 mg/m$^2$ IV followed by 5-FU 370 mg/m$^2$ IV; or<br>• Fusilev 10 mg/m$^2$ IV followed by 5-FU 425 mg/m$^2$ IV<br>Administer Fusilev and 5-FU separately. Repeat daily for 5 days; may be repeated at 4 week intervals for 2 courses, then repeated at 4-5 week intervals</td><td>See regimen</td></tr>
</table>

**VI. Product Availability**

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

## VII. References

1. Fusilev Prescribing Information. Irvine, CA: Spectrum Pharmaceuticals, Inc.; April 2011. Available at http://www.fusilev.com. Accessed August 8, 2017.
2. Levoleucovorin. In: National Comprehensive Cancer Network Drugs and Biologics Compendium. Available at NCCN.org. Accessed August 8, 2017.
3. National Comprehensive Cancer Network. Colon Cancer Version 2.2017. Available at: https://www.nccn.org/professionals/physician_gls/pdf/colon.pdf. Accessed August 8, 2017.
4. National Comprehensive Cancer Network. Rectal Cancer Version 3.2017. Available at: https://www.nccn.org/professionals/physician_gls/pdf/rectal.pdf. Accessed August 8, 2017.
5. National Comprehensive Cancer Network. Bone Cancer Version 2.2017. Available at: https://www.nccn.org/professionals/physician_gls/pdf/bone.pdf. Accessed August 8, 2017.
6. Methotrexate Injection Prescribing Information. Lake Forest, IL: Hospira; December 2015. Available at: http://labeling.pfizer.com/ShowLabeling.aspx?id=5379. Accessed August 8, 2017.

## 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 | P&T Approval Date |
|---|---|---|
| Policy developed | 01.16 | 02.16 |
| Removed oncologist requirement.<br>Added contraindication (allergy).<br>Added "responding positively to therapy" under "Methotrexate/Folic Acid Antagonist Toxicity Prophylaxis" continuation criteria.<br>Removed detailed language under CRC continuation criteria regarding whether member has recovered between successive regimens and replaced it with "no disease progression or unacceptable toxicity".<br>NCCN recommended uses added.<br>Added formulations | 02.17 | 02.17 |
| Converted to new template.<br>All indications: Removed allergy contraindication as it constitutes a hypersensitivity reaction. Modified leucovorin | 08.08.17 | 11.17 |

| Reviews, Revisions, and Approvals | Date | P&T Approval Date |
|---|---|---|
| criteria to allow for clinically significant adverse effects.<br>Added max dose criteria.<br>Following MTX: Added age limit as safety and efficacy have not been established in patients < 6 years. For impaired elimination/accidental overdose, decreased continued approval duration from 3 months to 1 month as these events do not occur chronically and are typically managed on an inpatient basis. For sarcomas, increased approval duration from 1/3 months to 6/12 months (MTX regimens used in bone cancers are dosed on a schedule through 45 weeks after surgery per MTX's PI, while the NCCN guidelines do not indicate a limit on treatment duration).<br>CRC: Added NCCN off label recommended uses. Increased approval duration from 3/6 months to 6/12 months per new standard.<br>Added megaloblastic and pernicious anemias as diagnoses not covered per PI. | | |

**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.