

## **Clinical Policy: Leucovorin Injection**

Reference Number: CP.PHAR.393

Effective Date: 12.01.18

Last Review Date: 11.21

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**

Leucovorin is a reduced folate.

### **FDA Approved Indication(s)**

Leucovorin injection is indicated:

- After high-dose methotrexate (MTX) therapy in osteosarcoma.
- To diminish the toxicity and counteract the effects of impaired methotrexate elimination and of inadvertent overdoses of folic acid antagonists.
- For the treatment of megaloblastic anemias due to folic acid deficiency when oral therapy is not feasible.
- For use in combination with 5-fluorouracil to prolong survival in the palliative treatment of patients with advanced colorectal cancer

### **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<sup>®</sup> that leucovorin injection 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, 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. 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:**

**Medicaid – 6 months**

**Commercial – 6 months or to the member's renewal date, whichever is longer**

**B. Megaloblastic Anemia (must meet all):**

1. Diagnosis of megaloblastic anemia due to folic acid deficiency;
2. Member is not a candidate for oral folic acid therapy;
3. Dose does not exceed 1 mg per day.

**Approval duration:**

**Medicaid** – 6 months

**Commercial** – 6 months or to the member’s renewal date, whichever is longer

**C. 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. Prescribed in combination with 5-FU;
4. 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:**

**Medicaid** – 6 months

**Commercial** – 6 months or to the member’s renewal date, whichever is longer

**D. Other diagnoses/indications**

1. Refer to the off-label use policy for the relevant line of business if diagnosis is NOT specifically listed under section III (Diagnoses/Indications for which coverage is NOT authorized): CP.CPA.09 for commercial, HIM.PA.154 for health insurance marketplace, and CP.PMN.53 for Medicaid.

**II. Continued Therapy**

**A. Megaloblastic Anemia (must meet all):**

1. Currently receiving medication via Centene benefit or member has previously met initial approval criteria;
2. Member is not a candidate for oral folic acid therapy;
3. Member is responding positively to therapy;
4. If request is for a dose increase, new dose does not exceed 1 mg per day.

**Approval duration:**

**Medicaid** – 12 months

**Commercial** – 6 months or to the member’s renewal date, whichever is longer

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

1. Member meets one of the following (a or b):
  - a. Currently receiving medication via Centene benefit or member has previously met initial approval criteria;

- b. Documentation supports that member is currently receiving leucovorin 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. If request is for a dose increase, request meets any 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:**

**Medicaid** – 12 months

**Commercial** – 6 months or to the member’s renewal date, whichever is longer

**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 the off-label use policy for the relevant line of business if diagnosis is NOT specifically listed under section III (Diagnoses/Indications for which coverage is NOT authorized): 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.

**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*

Not applicable

*Appendix C: Contraindications/Boxed Warnings*

- Contraindication(s): improper therapy for pernicious anemia and other megaloblastic anemias secondary to the lack of vitamin B<sub>12</sub>
- Boxed warning(s): none reported

*Appendix D: General Information*

- The NCCN guidelines recommend the combination use of leucovorin with methotrexate as a rescue for the following cancers (2A recommendation):
  - Acute lymphoblastic leukemia
  - T-cell lymphomas (including peripheral T-cell lymphomas, adult T-cell leukemia/lymphoma, extranodal NK/T-cell lymphoma [nasal type], hepatosplenic gamma-delta T-Cell lymphoma)
  - 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, small lymphocytic lymphoma, and acute lymphoblastic leukemia
- The NCCN guidelines recommend the combination use of leucovorin with fluorouracil-based regimens for the following cancers (2A recommendation):
  - Thymomas and thymic carcinomas
  - Occult primary adenocarcinoma, squamous cell carcinoma, or carcinoma not otherwise specified
  - 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
  - Small bowel adenocarcinoma

**V. Dosage and Administration**

| Indication                         | Dosing Regimen  | Maximum Dose |
|------------------------------------|---|--------------|
| Rescue after high-dose MTX therapy | Administer 15 mg (approximately 10 mg/m <sup>2</sup> ) PO, IV, or IM every 6 hours for 10 doses starting 24 hours after beginning of MTX infusion. Continue leucovorin administration until the MTX level is below 5 x 10 <sup>-8</sup> M (or 0.05 μM). | See regimen  |

| Indication                 | Dosing Regimen   | Maximum Dose |
|----------------------------|--|--------------|
|                            | <p>Adjust or extend rescue based on clinical situation and laboratory findings:</p> <p><u>Normal MTX elimination (serum MTX 10 µM at 24 hours, 1 µM at 48 hours, and &lt; 0.2 µM at 72 hours after administration):</u> 15 mg PO, IV, or IM every 6 hours for 60 hours (10 doses starting 24 hours after start of MTX infusion)</p> <p><u>Delayed late MTX elimination (serum MTX &gt; 0.2 µM at 72 hours and &gt; 0.05 µM at 96 hours after administration):</u> 15 mg PO, IV, or IM every 6 hours until MTX &lt; 0.05 µM</p> <p><u>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):</u> 150 mg IV every 3 hours until MTX &lt; 1 µM; then 15 mg IV every 3 hours until MTX &lt; 0.05 µM</p> |              |
| Inadvertent MTX overdosage | <p>Administer as soon as possible after overdose and within 24 hours of MTX administration if there is delayed excretion: 10 mg/m<sup>2</sup> PO, IV, or IM every 6 hours until serum MTX is &lt; 10<sup>-8</sup> M.</p> <p>Increase to 100 mg/m<sup>2</sup> IV every 3 hours if 24 hour serum creatinine has increased 50% over baseline or if the 24 hour MTX level is &gt; 5 x 10<sup>-6</sup> M or the 48 hour level is &gt; 9 x 10<sup>-7</sup> M until the methotrexate level is less than 10<sup>-8</sup> M</p>   | See regimen  |
| Megaloblastic anemia       | Up to 1 mg, IV or IM, once a day   | 1 mg/day     |
| Advanced colorectal cancer | <p>Either of the following two regimens is recommended:</p> <ul style="list-style-type: none"> <li>Leucovorin is administered at 200 mg/m<sup>2</sup> by slow IV injection over a minimum of 3 minutes, followed by 5-fluorouracil at 370 mg/m<sup>2</sup> by IV injection.</li> <li>Leucovorin is administered at 20 mg/m<sup>2</sup> by IV injection followed by 5-fluorouracil at 425<sup>2</sup> mg/m by IV injection.</li> </ul> <p>Treatment is repeated daily for five days. This five-day treatment course may be repeated at 4 week (28-day) intervals, for 2 courses and then repeated at 4 to 5 week (28 to 35 day) intervals provided that the patient has completely recovered from the toxic effects of the prior treatment course.</p>  | See regimen  |

**VI. Product Availability**

Single-dose vial for injection: 50 mg, 100 mg, 200 mg, 350 mg, 500 mg

**VII. References**

1. Leucovorin Prescribing Information. Schaumburg, IL: Sagent Pharmaceuticals, Inc.; September 2019. Available at: [http://www.sagentpharma.com/wp-content/uploads/2017/06/Leucovorin\\_PI.pdf](http://www.sagentpharma.com/wp-content/uploads/2017/06/Leucovorin_PI.pdf). Accessed July 1, 2021.
2. Leucovorin. In: National Comprehensive Cancer Network Drugs and Biologics Compendium. Available at NCCN.org. Accessed July 1, 2021.
3. Devalia V, Hamilton MS, Molloy AM. Guidelines for the diagnosis and treatment of cobalamin and folate disorders. British Journal of Hematology, 2014. 166:496-513. doi: 10.1111/bjh.12959.

**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                              |
|-------------|--|
| J0640       | Injection, leucovorin calcium, per 50 mg |

| Reviews, Revisions, and Approvals   | Date     | P&T Approval Date |
|---|----------|-------------------|
| Policy created: adapted from previously approved policy HIM.PA.138 which was retired; extended approval duration to standard for megaloblastic anemia; modified and adapted approval durations per standard for commercial and Medicaid lines of business; updated to include NCCN off-label recommended uses; 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; updated off-label dosing per new template; references reviewed and updated.  | 08.25.19 | 11.19             |
| 4Q 2020 annual review: no significant changes; revised HIM-Medical Benefit to HIM line of business; updated Appendix D per NCCN Compendium; references reviewed and updated.  | 07.22.20 | 11.20             |
| 4Q 2021 annual review: no significant changes; revised HIM.PHAR.21 to HIM.PA.154; references reviewed and updated.  | 07.01.21 | 11.21             |

**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.

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**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.

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