Clinical Policy: Leucovorin Injection

Reference Number: CP.PHAR.393
Effective Date: 12.01.18
Last Review Date: 11.24
Line of Business: Commercial, 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 MTX elimination and of inadvertent overdosages 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® 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 (must meet 1 or 2)**:**
1. If this drug has recently (within the last 6 months) undergone a label change (e.g., newly approved indication, age expansion, new dosing regimen) that is not yet reflected in this policy, refer to one of the following policies (a or b):
   a. or drugs on the formulary (commercial) or PDL (Medicaid), the no coverage criteria policy for the relevant line of business: CP.CPA.190 for commercial and CP.PMN.255 for Medicaid; or
   b. For drugs NOT on the formulary (commercial) or PDL (Medicaid), the non-formulary policy for the relevant line of business: CP.CPA.190 for commercial and CP.PMN.16 for Medicaid; or
2. If the requested use (e.g., diagnosis, age, dosing regimen) is NOT specifically listed under section III (Diagnoses/Indications for which coverage is NOT authorized) AND criterion 1 above does not apply, refer to the off-label use policy for the relevant line of business: CP.CPA.09 for commercial and CP.PMN.53 for Medicaid.

II. Continued Therapy

A. Megaloblastic Anemia (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. Member is currently receiving medication and is enrolled in a state and product with continuity of care regulations (*refer to state specific addendums for CC.PHARM.03A and CC.PHARM.03B*);

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. Member is currently receiving medication and is enrolled in a state and product with continuity of care regulations (*refer to state specific addendums for CC.PHARM.03A and CC.PHARM.03B*);
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. If this drug has recently (within the last 6 months) undergone a label change (e.g., newly approved indication, age expansion, new dosing regimen) that is not yet reflected in this policy, refer to one of the following policies (a or b):
   a. For drugs on the formulary (commercial) or PDL (Medicaid), the no coverage criteria policy for the relevant line of business: CP.CPA.190 for commercial and CP.PMN.255 for Medicaid; or
   b. For drugs NOT on the formulary (commercial) or PDL (Medicaid), the non-formulary policy for the relevant line of business: CP.CPA.190 for commercial and CP.PMN.16 for Medicaid; or
2. If the requested use (e.g., diagnosis, age, dosing regimen) is NOT specifically listed under section III (Diagnoses/Indications for which coverage is NOT authorized) AND criterion 1 above does not apply, refer to the off-label use policy for the relevant line of business: CP.CPA.09 for commercial 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 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_{12}. A hematologic remission may occur while neurologic manifestations continue to progress.
- Boxed warning(s): none reported

Appendix D: General Information

- The NCCN guidelines recommend the combination use of leucovorin with MTX as a rescue for the following cancers (2A recommendation):
  - (Pediatric) 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, HIV-related B-cell lymphoma, Burkitt lymphoma, high grade B-cell lymphomas, diffuse large B-cell lymphoma, primary mediastinal 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 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 of the ovary
  - Vaginal cancer
  - Colon cancer (including appendiceal adenocarcinoma)
  - 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
- Biliary tract cancers (gallbladder cancer, intrahepatic or extrahepatic cholangiocarcinoma)

- The NCCN guidelines recommend the combination use of leucovorin with MTX for the management of symptomatic Bing-Neel syndrome (2A recommendation) in Waldenström macroglobulinemia / lymphoplasmacytic lymphoma.

V. Dosage and Administration

Indication	Dosing Regimen	Maximum Dose
Rescue after high-dose MTX therapy	Administer 15 mg (approximately 10 mg/m^2) 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^{-8} M (or 0.05 µM). Adjust or extend rescue based on 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): 15 mg PO, IV, or IM 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): 15 mg PO, IV, or IM 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): 150 mg IV every 3 hours until MTX < 1 µM; then 15 mg IV every 3 hours until MTX < 0.05 µM	See regimen
Inadvertent MTX overdosage	Administer as soon as possible after overdose and within 24 hours of MTX administration if there is delayed excretion:	See regimen

Indication	Dosing Regimen	Maximum Dose
	10 mg/m^2 PO, IV, or IM every 6 hours until serum MTX is < 10^{-8} M. Increase to 100 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 until the MTX level is less than 10^{-8} M	
Megaloblastic anemia	Up to 1 mg, IV or IM, once a day	1 mg/day
Advanced colorectal cancer	Either of the following two regimens is recommended: • Leucovorin is administered at 200 mg/m^2 by slow IV injection over a minimum of 3 minutes, followed by 5-fluorouracil at 370 mg/m^2 by IV injection. • Leucovorin is administered at 20 mg/m^2 by IV injection followed by 5-fluorouracil at 425^2 mg/m by IV injection. 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.	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..; November 2022. Available at: https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=9d0e5356-ff39-4a8e-944c-e808a21ef4b2. Accessed July 15, 2024.
2. Leucovorin. In: National Comprehensive Cancer Network Drugs and Biologics Compendium. Available at NCCN.org. Accessed August 23, 2024.
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
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
4Q 2022 annual review: no significant changes; updated Appendix D per NCCN Compendium; references reviewed and updated. Template changes applied to other diagnoses/indications and continued therapy section.	08.25.22	11.22
4Q 2023 annual review: no significant changes; updated Appendix D per NCCN Compendium; references reviewed and updated.	08.09.23	11.23
4Q 2024 annual review: HIM line of business removed; updated Appendix D per NCCN Compendium; references reviewed and updated.	07.15.24	11.24

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.