Clinical Policy: Leucovorin Injection

Reference Number: CP.PHAR.393
Effective Date: 12.01.18
Last Review Date: 11.19
Line of Business: Commercial, Medicaid, HIM-Medical Benefit

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 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
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 and CP.PMN.53 for Medicaid and HIM-Medical Benefit.

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 and CP.PMN.53 for Medicaid and HIM-Medical Benefit.

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 and HIM-Medical Benefit, 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}
- 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])
  - 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 leucovorin with fluorouracil-based regimens for the following cancers (2A recommendation):
  - 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

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	See regimen

Indication	Dosing Regimen	Maximum Dose
	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	
Inadvertent MTX overdosage	Administer as soon as possible after overdose and within 24 hours of MTX administration if there is delayed excretion: 10 mg 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 methotrexate level is less than 10^{-8} M	See regimen
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, 250 mg

VII. References

1. Leucovorin Prescribing Information. Schaumburg, IL: Sagent Pharmaceuticals, Inc..; April 2016. Available at: http://www.sagentpharma.com/wp-content/uploads/2017/06/Leucovorin_PI.pdf. Accessed August 25, 2019.
2. Leucovorin. In: National Comprehensive Cancer Network Drugs and Biologics Compendium. Available at NCCN.org. Accessed August 25, 2019.
3. Devalia V, Hamilaton 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

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.

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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.