Clinical Policy: Leucovorin Injection

Reference Number: LA.PHAR.393
Effective Date: 03.16.23
Last Review Date: ~~02.23~~06.25.23 Coding Implications
Line of Business: Medicaid Revision Log

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

****Please note: This policy is for medical benefit****

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
~~*Prior authorization is required.*~~ *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 Louisiana Healthcare Connections 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**

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**

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

D. Other diagnoses/indications

~~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):~~

~~For drugs on the PDL (Medicaid), the no coverage criteria policy for Medicaid:~~ LA.PMN.255~~; or~~

a. ~~For drugs NOT on the PDL (Medicaid), the non-formulary policy for Medicaid:~~ ~~LA.PMN.16; or~~

2. If the requested us (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 ~~:~~ LA.PMN.53 ~~for Medicaid.~~

~~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): LA.PMN.53 for Medicaid.~~

II. Continued Therapy

A. Megaloblastic Anemia (must meet all):

~~Member meets one of the following (a or b):~~

1. Currently receiving medication via Louisiana Healthcare Connections benefit or member has previously met initial approval criteria~~:~~

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

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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

B. All Other Indications in Section I (must meet all):
~~1. Member meets one of the following (a or b):~~
~~2.~~1.Currently receiving medication via Louisiana Healthcare Connections benefit or member has previously met initial approval criteria;
~~a. 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;~~
~~3.~~2.Member is responding positively to therapy;
~~4.~~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

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 LA.PMN.255
2. If the requested us (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: LA.PMN.
~~1. Currently receiving medication via Louisiana Healthcare Connections 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): LA.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 – LA.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 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)
  - CNS cancer (including primary CNS lymphoma, brain metastases, leptomeningeal metastases)
  - B-cell lymphomas (including mantle cell lymphoma, AIDS-related B-cell lymphoma, Burkitt lymphoma, , high grade B-cell lymphomas, diffuse 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
  - Colon cancer
  - Gastric cancer
  - Esophageal and esophagogastric junction cancers
  - Anal carcinoma
  - Extrapulmonary poorly differentiated neuroendocrine carcinoma/large or small cell carcinoma, mixed neuroendocrine-non-neuroendocrine neoplasm
  - Cervical cancer
  - Rectal cancer
  - Pancreatic adenocarcinoma
  - Bladder cancer (non-urothelial and urothelial with variant histology)
  - Small bowel adenocarcinoma

- Ampullary adenocarcinoma
- Appendiceal adenocarcinoma
- Biliary tract cancers (gallbladder cancer, intrahepatic, or extrahepatic cholangiocarcinoma)

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: 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 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:	See regimen

Indication	Dosing Regimen	Maximum Dose
	• 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.	

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. Accessed August 25, 2022.
2. Leucovorin. In: National Comprehensive Cancer Network Drugs and Biologics Compendium. Available at NCCN.org. Accessed August, 25, 2022.
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	LDH Approval Date
Converted corporate to local policy	02.23	03.16.23
Updated criteria for other diagnoses/indications	06.25.23	

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. LHCC 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.

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 LHCC administrative policies and procedures.

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