Prior Authorization Review Panel

CHC-MCO Policy Submission

A separate copy of this form must accompany each policy submitted for review.
Policies submitted without this form will not be considered for review.

Plan: PA Health & Wellness	**Submission Date: 11/01/2022**
Policy Number: PA.CP.PHAR.393	**Effective Date: 01/2020** **Revision Date: 10/2022**
Policy Name: Leucovorin Injection	

Type of Submission – Check all that apply:

- ☐ **New Policy**
- ✓ **Revised Policy***
- ☐ **Annual Review - No Revisions**
- ☐ **Statewide PDL** - *Select this box when submitting policies for Statewide PDL implementation and when submitting policies for drug classes included on the Statewide PDL.*

***All revisions to the policy must be highlighted using track changes throughout the document.**

Please provide any changes or clarifying information for the policy below:

4Q 2022 annual review: no significant changes; references reviewed and updated.

Name of Authorized Individual (Please type or print): **Venkateswara R. Davuluri, MD**	**Signature of Authorized Individual:**

Clinical Policy: Leucovorin Injection

Reference Number: PA.CP.PHAR.393
Effective Date: 10/2018
Last Review Date: 10/2022

Coding Implications
Revision Log

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 PA Health & Wellness® 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*).

Approval duration:
Impaired elimination/accidental overdose: 1 month
High-dose MTX therapy rescue: 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: 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 a category 1, 2A, or 2B 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*).

Approval duration: 6 months

D. Other diagnoses/indications
1. Refer to the off-label use policy if diagnosis is NOT specifically listed under section III (Diagnoses/Indications for which coverage is NOT authorized): PA.CP.PMN.53.

II. Continued Therapy

A. Megaloblastic Anemia (must meet all)**:**
1. Currently receiving medication via PA Health & Wellness benefit or member has previously met all initial approval criteria or the Continuity of Care Policy (PA.LTSS.PHAR.01) applies;
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: 12 months

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 PA Health & Wellness benefit or member has previously met all initial approval criteria or the Continuity of Care Policy (PA.LTSS.PHAR.01) applies;
   b. Documentation supports that member is currently receiving leucovorin for high-dose MTX rescue as part of chemotherapy or combination chemotherapy with 5-FU;
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*).

Approval duration:
Impaired elimination/accidental overdose: 1 month
All other indications: 12 months

C. Other diagnoses/indications (must meet 1 or 2)**:**

1. Currently receiving medication via PA Health & Wellness benefit or member has previously met all initial approval criteria or the Continuity of Care Policy (PA.LTSS.PHAR.01) applies.
   Approval duration: Duration of request or 6 months (whichever is less); or
2. Refer to the off-label use policy if diagnosis is NOT specifically listed under section III (Diagnoses/Indications for which coverage is NOT authorized): PA.CP.PMN.53.

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 – PA.CP.PMN.53 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 (Note: not an all-inclusive list):
  - 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, 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 (Note: not an all-inclusive list):

- 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
- 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
- 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	See regimen

Indication	Dosing Regimen	Maximum Dose
	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/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: • 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, 500mg

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	P&T Approval Date
Policy created	10/2018	
4Q 2019 annual review: No changes per Statewide PDL implementation 01-01-2020	10/2019	
4Q 2020 annual review: Updated Appendix D per NCCN Compendium; references reviewed and updated.	07/2020	
4Q 2021 annual review: no significant changes; references reviewed and updated.	10/2021	
4Q 2022 annual review: no significant changes; updated Appendix D per NCCN Compendium; references reviewed and updated.	10/2022	