RXADVANCE
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Clinical Policy Title:	leucovorin Injection
Policy Number:	RxA.403
Drug(s) Applied:	Leucovorin injection
Original Policy Date:	03/06/2020
Last Review Date:	09/14/2020
Line of Business Policy Applies to:	All lines of business

Background

Leucovorin is a reduced folate.
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 anemia 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

Dosing Information

Drug Name	Indication	Dosing Regimen	Maximum Dose
Leucovorin Injection	Rescue after high-dose MTX therapy	Administer 15 mg (approximately 10 mg/m2) 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: <u>Normal MTX elimination (serum MTX 10 µM at 24 hours, 1 µM at 48 hours, and < 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. <u>Delayed late MTX elimination (serum</u>	See regimen

		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/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.	

Dosage Forms

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

Clinical Policy

Provider must submit documentation (such as office chart notes, lab results or other clinical information) supporting that member has met all approval criteria.

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 dosing regimen;
   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: 1 month
Commercial: 6 months
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
Commercial: 6 months
Medicaid: 6 months
HIM: 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 exceeds the dosing regimen in the policy;
   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
Commercial: 6 months
Medicaid: 6 months
HIM: 6 months

II. Continued Therapy Approval

A. Megaloblastic Anemia (must meet all:
1. Currently receiving medication that has been authorized by RxAdvance or member has previously met initial approval criteria listed in this policy.;
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
Commercial: 6 months
Medicaid: 12 months
HIM: 6 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 that has been authorized by RxAdvance or member has previously met initial approval criteria listed in this policy.;
   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 exceeds the dosing regimen in the policy;
   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
Commercial: 6 months
Medicaid: 12 months
HIM: 6 months

III. Appendices

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

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

References

1. Leucovorin Prescribing Information. Lake Zurich, IL, Fresenius Kabi USA, LLC; May 2018. Available at: https://dailymed.nlm.nih.gov/dailymed/fda/fdaDrugXsl.cfm?setid=d5d4f0fd-7520-43a9-9acc-f7e117e1f6ee&type=display . Accessed July 22, 2020.
2. Leucovorin. In: National Comprehensive Cancer Network Drugs and Biologics Compendium. Available at NCCN.org. Accessed July 22, 2020.
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.

Review/Revision History	Review/Revised Date	P&T Approval Date
Policy established.	01/2020	03/06/2020
Policy was reviewed: 1. Clinical Policy Title was updated. 2. Line of Business Policy Applies to was updated to all lines of business. 3. Initial and Continued approval duration was updated to include Commercial, Medicaid & HIM approval duration. 4. Continued therapy criteria II.A.1 & II.B.1.a was rephrased to "Currently receiving medication that has been authorized by RxAdvance…". 5. References were reviewed and updated.	7/22/2020	9/14/2020