Clinical Policy: Leucovorin

Reference Number: HIM.PA.138
Effective Date: 12.01.17
Last Review Date:
Line of Business: Health Insurance Marketplace

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 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 fluorouracil to prolong survival in the palliative treatment of patients with advanced colorectal cancer.

Policy/Criteria
Provider must submit documentation (which may include office chart notes and lab results) 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 or b):
   a. FDA-approved use (i, ii, or iii):
      i. Following high dose ($\geq$ 12 grams/m^2 IV over 4 hours) MTX therapy as part of a treatment regimen for osteosarcoma;
      ii. For impaired MTX elimination;
      iii. After accidental folic acid antagonist overdose (including MTX);
   b. Off-label NCCN recommended use:
      i. Following high dose ($\geq$ 12 grams/m^2 IV over 4 hours) MTX therapy as part of a treatment regimen for one of the following:
         1) Dedifferentiated chondrosarcoma;
         2) High-grade undifferentiated pleomorphic sarcoma;
         3) One of the following central nervous system cancers:
            a. Leptomeningeal metastases;
            b. Brain metastases;
            c. Primary CNS lymphoma;
         4) Mantle cell lymphoma;
         5) Burkitt Llmphoma;

6) AIDS-related B-cell lymphoma;
7) Acute lymphoblastic leukemia;

2. Request meets any 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
Sarcomas or off-label NCCN recommended uses: 6 months

B. Megaloblastic Anemia (must meet all):
1. Diagnosis of megaloblastic anemia due to folic acid deficiency;
2. Patient is not a candidate for oral folic acid therapy;
3. Dose does not exceed 1 mg/day.

Approval duration: 1 month

C. Enhancement of Chemotherapy (must meet all)**:**
1. Prescribed for one of the following uses (a or b):
   a. FDA-approved use (i, ii, and iii):
      i. Diagnosis of colorectal cancer;
      ii. Disease is advanced and metastatic;
      iii. Prescribed for palliative treatment;
   b. One of the following off-label NCCN recommended uses:
      i. Diagnosis of colon cancer;
      ii. Diagnosis of rectal cancer;
      iii. Diagnosis of esophageal and esophagogastric junction cancers;
      iv. Diagnosis of gastric cancer;
      v. Non-urothelial and urothelial with variant histology;
      vi. Occult primary;
      vii. Mucinous carcinoma of the ovary;
      viii. Pancreatic adenocarcinoma;
      ix. Adult T-cell leukemia/lymphoma;
      x. Breast implant-associated anaplastic large cell lymphoma;
      xi. Peripheral T-cell lymphoma;
      xii. Thymomas and thymic carcinomas;
2. Will be used in combination with fluorouracil-based chemotherapy regimens;
3. Request meets any of the following (a or b):
   a. Maximum dose does not exceed that indicated 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 HIM.PHAR.21 if diagnosis is NOT specifically listed under section III (Diagnoses/Indications for which coverage is NOT authorized).

II. Continued Therapy

A. Methotrexate/Folic Acid Antagonist Toxicity Prophylaxis (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 cancer diagnoses listed in section IA and has received this medication for at least 30 days;
2. Member is responding positively to therapy;
3. Request meets any 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
Sarcomas or off-label NCCN recommended uses: 12 months

B. Megaloblastic Anemia (must meet all):

1. Currently receiving medication via Centene benefit or member has previously met initial approval criteria;
2. Patient is still 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/day.

Approval duration: **3 months**

C. Enhancement of Chemotherapy (must meet all)**:**

1. Currently receiving medication via Centene benefit, or documentation supports that member is currently receiving leucovorin for enhancement of fluorouracil-based chemotherapy and has received this medication for at least 30 days;
2. Member is responding positively to therapy (e.g., no disease progression or unacceptable toxicity);
3. If request is for a dose increase, request meets any of the following (a, b, or c):
   a. New dose does not exceed maximum indicated 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: 12 months

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

1. Currently receiving medication via health plan benefit and documentation supports positive response to therapy.
   Approval duration: Duration of request or 6 months (whichever is less); or
2. Refer to HIM.PHAR.21 if diagnosis is NOT specifically listed under section III (Diagnoses/Indications for which coverage is NOT authorized).

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 – HIM.PHAR.21 or evidence of coverage documents;

IV. Appendices/General Information

Appendix A: Abbreviation/Acronym Key

FDA: Food and Drug Administration

MTX: methotrexate

V. Dosage and Administration

<table>
<tr><th>Indication</th><th>Dosing Regimen</th><th>Maximum Dose</th></tr>
<tr><td>Rescue after high-dose MTX therapy</td><td>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:
<table>
<tr><th>Clinical situation</th><th>Laboratory findings</th><th>Fusilev dose and duration</th></tr>
<tr><td>Normal MTX elimination</td><td>Serum MTX 10 µM at 24 hours, 1 µM at 48 hours, and < 0.2 µM at 72 hours after administration</td><td>15 mg PO, IV, or IM every 6 hours fo 60 hours (10 doses starting 24 hours after start of MTX infusion)</td></tr>
<tr><td>Delayed late MTX elimination</td><td>Serum MTX > 0.2 µM at 72 hours and > 0.05 µM at 96 hours after administration</td><td>15 mg PO, IV, or IM every 6 hours until MTX < 0.05 µM</td></tr>
<tr><td>Delayed early MTX elimination and/or evidence of acute renal injury</td><td>Serum MTX ≥ 50 µM at 24 hours, ≥ 5 µM at 48 hours, or ≥ 100% increase in serum creatinine at 24 hours after MTX administration</td><td>150 mg IV every 3 hours until MTX < µM; then 7.5 mg IV every 3 hours until MTX < 0.05 µM</td></tr>
</table></td><td>See regimen</td></tr>
<tr><td>Inadvertent MTX overdosage</td><td>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.</td><td>See regimen</td></tr>
</table>

	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	
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 intravenous injection over a minimum of 3 minutes, followed by 5-fluorouracil at 370 mg/m^2 by intravenous injection. • Leucovorin is administered at 20 mg/m^2 by intravenous injection followed by 5-fluorouracil at 425^2 mg/m by intravenous 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. 5-Fluorouracil and leucovorin should be administered separately to avoid the formation of a precipitate.	See regimen

VI. References

1. Leucovorin Prescribing Information. Ahmebadad, India: Cadila Healthcare Ltd..; April 2016. Available at https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=45811482-e358-46b0-bb03-9628f7d340db. Accessed September 1, 2017.
2. Leucovorin. In: National Comprehensive Cancer Network Drugs and Biologics Compendium. Available at NCCN.org. Accessed September 1, 2017.
3. Methotrexate Injection Prescribing Information. Lake Forest, IL: Hospira; December 2015. Available at: http://labeling.pfizer.com/ShowLabeling.aspx?id=5379. Accessed September 1, 2017.
4. 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.

Reviews, Revisions, and Approvals	Date	P&T Approval Date
Policy created.	09.01.17	11.17

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.

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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.

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