

Prior Authorization DRUG Guidelines

LEUCOVORIN (calcium folinate)

Effective Date: 7/24/12

Date Developed: 7/3/12 by Albert Reeves MD

Last Approval Date: 1/26/16, 1/24/17, 1/23/18, 1/22/19, 2/18/20,
2/1/22, 1/31/23, 2/13/24, 2/18/25

Calcium folinate is a reduced form of folic acid and supplies the necessary cofactor blocked by methotrexate. It actively competes with methotrexate for transport sites, displaces methotrexate from intracellular binding sites, and restores active folate stores required for DNA/RNA synthesis. When administered with pyrimethamine for the treatment of opportunistic infections, leucovorin reduces the risk for hematologic toxicity

Pre-Authorization Criteria:

Colorectal cancer, advanced: Injection: Palliative treatment of advanced colorectal cancer to prolong survival (in combination with fluorouracil).

Megaloblastic anemia: Injection: Treatment of megaloblastic anemias due to folic acid deficiency (when oral therapy is not feasible).

Methotrexate toxicity:

Injection: Rescue agent after high-dose methotrexate treatment in osteosarcoma and to diminish the toxicity and counteract the effects of impaired methotrexate elimination and of inadvertent overdosage of folic acid antagonists.

Oral: Rescue agent to diminish toxicity and counteract effects of impaired methotrexate elimination and inadvertent overdoses of folic acid antagonists.

Off-Label use (Adult)

Acute lymphocytic leukemia; Bladder cancer (neoadjuvant treatment); Dermatomyositis/polymyositis; Esophageal cancer (advanced or metastatic); Gastric cancer (advanced or metastatic); Gestational trophoblastic neoplasia (high

risk); Graft-vs-host disease, acute (prophylaxis); Granulomatosis with polyangiitis (Wegener granulomatosis) and microscopic polyangiitis (maintenance therapy after remission induction); Hepatobiliary cancers (advanced); Methanol toxicity (adjunctive cofactor therapy); Non-Hodgkin lymphoma; Nonleukemic meningeal cancer; Pancreatic cancer (advanced or metastatic); Pancreatic cancer, potentially curable, adjuvant therapy; Prevention of pyrimethamine hematologic toxicity in patients with HIV; Primary CNS lymphoma (newly diagnosed); Tubal ectopic pregnancy

Note:

VCHCP requires that CALCIUM FOLINATE be prescribed by an Oncologist, Hematologist, Rheumatologist or Infectious Disease Specialists.

Note: Folinic acid is an error prone synonym and should not be used (may be confused with folic acid)

Dosing: Adult

Refer to updated product literature for dosing regimens relevant to the disease process being treated.

Precautions:

- Combination of leucovorin and sulfamethoxazole-trimethoprim for the acute treatment of PCP in patients with HIV infection has been reported to cause increased rates of treatment failure.
- **Never administer leucovorin intrathecally.**

REFERENCES

1. Barceloux DG, Bond GR, Krenzelok EP, et al, "American Academy of Clinical Toxicology Practice Guidelines on the Treatment of Methanol Poisoning," *J Toxicol Clin Toxicol*, 2002, 40(4):415-46. [PubMed 12216995]
2. Bleyer WA, "New Vistas for Leucovorin in Cancer Chemotherapy," *Cancer*, 1989, 63(6 Suppl):995-1007.
3. Centers for Disease Control and Prevention, "Guidelines for Prevention and Treatment of Opportunistic Infections in HIV-Infected Adults and Adolescents: Recommendations From CDC, the National Institutes of Health, and the HIV Medicine Association of the Infectious Diseases Society of America," *MMWR Recomm Rep*, 2009, 58(RR-4):1-207. [PubMed 19357635]
4. Centers for Disease Control and Prevention, "Guidelines for the Prevention and Treatment of Opportunistic Infections Among HIV-Exposed and HIV-Infected Children: Recommendations from CDC, the National Institutes of Health, the HIV Medicine Association of the Infectious Diseases Society of America, the Pediatric Infectious Diseases Society, and the American Academy of Pediatrics," *MMWR Recomm Rep*, 2009, 58(RR-11):1-166. Available at http://aidsinfo.nih.gov/contentfiles/Pediatric_OI.pdf [PubMed 19730409]
5. Flombaum CD and Meyers PA. "High-Dose Leucovorin as Sole Therapy for Methotrexate Toxicity," *J Clin Oncol*, 1999, 17(5):1589-94. [PubMed 10334548]
6. Grogan L, Sotos GA, and Allegra CJ, "Leucovorin Modulation of Fluorouracil," *Oncology (Huntingt)*, 1993, 7(8):63-72.
7. Hansen RM, "Systemic Therapy in Metastatic Colorectal Cancer," *Arch Intern Med*, 1990, 150(11):2265-9. [PubMed 2241436]
8. Jacobsen D and McMartin KE, "Methanol and Ethylene Glycol Poisonings. Mechanism of Toxicity, Clinical Course, Diagnosis and Treatment," *Med Toxicol*, 1986, 1(5):309-34. [PubMed 3537623]
9. Jardine LF, Ingram LC, and Bleyer WA, "Intrathecal Leucovorin After Intrathecal Methotrexate Overdose," *J Pediatr Hematol Oncol*, 1996, 18(3):302-4. [PubMed 8689347]
10. Jolivet J, "Role of Leucovorin Dosing and Administration Schedule," *Eur J Cancer*, 1995, 31A(7-8):1311-5.
11. Machover D, "A Comprehensive Review of 5-Fluorouracil and Leucovorin in Patients With Metastatic Colorectal Carcinoma," *Cancer*, 1997, 80(7):1179-87. [PubMed 9317168]
12. McGuire BW, Sia LL, Leese PT, et al, "Pharmacokinetics of Leucovorin Calcium After Intravenous, Intramuscular, and Oral Administration," *Clin Pharm*, 1988, 7(1):52-8. [PubMed 3257913]

13. National Comprehensive Cancer Network® (NCCN), "Clinical Practice Guidelines in Oncology™: Colon Cancer," Version 3.2010. Available at http://www.nccn.org/professionals/physician_gls/PDF/colon.pdf
14. Rustum YM, "Modulation of Fluoropyrimidines by Leucovorin: Rationale and Status," *J Surg Oncol Suppl*, 1991, 2:116-23. [PubMed [1832538](#)]
15. Smith SW and Nelson LS, "Case Files of the New York City Poison Control Center: Antidotal Strategies for the Management of Methotrexate Toxicity," *J Med Toxicol*, 2008, 4(2):132-40. [PubMed [18570175](#)]
16. Stover P and Schirch V, "The Metabolic Role of Leucovorin," *Trends Biochem Sci*, 1993, 18(3):102-6. [PubMed [8480361](#)]
17. Trissel LA, Martinez JF, and Xu QA, "Incompatibility of Fluorouracil With Leucovorin Calcium or Levoleucovorin Calcium," *Am J Health Syst Pharm*, 1995, 52(7):710-5. [PubMed [7627739](#)]
18. Van Delden C and Hirschel B, "Folinic Acid Supplements to Pyrimethamine-Sulfadiazine for *Toxoplasma encephalitis* Are Associated With Better Outcome," *J Infect Dis*, 1996, 173(5):1294-5. [PubMed [8627092](#)]
19. Walker SE, Law S, and Puodziunas A, "Simulation of Y-Site Compatibility of Irinotecan and Leucovorin at Room Temperature in 5% Dextrose in Water in 3 Different Containers," *Can J Hosp Pharm*, 2005, 58(4):212-22.
20. Widemann BC and Adamson PC, "Understanding and Managing Methotrexate Nephrotoxicity," *Oncologist*, 2006, 11(6):694-703. [PubMed [16794248](#)]
21. Leucovorin calcium for injection [prescribing information]. Berkeley Heights, NJ: Hikma Pharmaceuticals USA Inc: October 2021.
22. Zaanen A, Costes L, Gauthier M, et al. Chemotherapy of advanced small-bowel adenocarcinoma: a multicenter AGEO study. *Ann Oncol*. 2010;21(9):1786-1793
23. Eiriksson L, Dean E, Sebastianelli A, et al. Guideline no. 408: management of gestational trophoblastic diseases. *J Obstet Gynaecol Can*. 2021;43(1):91-105.e1.
24. Shah MA, Kennedy EB, Catenacci DV, et al. Treatment of locally advanced esophageal carcinoma: ASCO guideline. *J Clin Oncol*. 2020;38(23):2677-2694.
25. Sohal DPS, Kennedy EB, Cinar P, et al. Metastatic pancreatic cancer: ASCO guideline update. *J Clin Oncol*. Published online August 5, 2020.
26. Al-Batran SE, Homann N, Pauligk C, et al; FLOT4-AIO Investigators. Perioperative chemotherapy with fluorouracil plus leucovorin, oxaliplatin, and docetaxel versus fluorouracil or capecitabine plus cisplatin and epirubicin for locally advanced, resectable gastric or gastro-oesophageal junction adenocarcinoma (FLOT4): a randomised, phase 2/3 trial. *Lancet*. 2019;393(10184):1948-1957.

Revision History:

Date Approved by P&T Committee: 7/24/12; 1/29/13 Date
 Reviewed/No Updates: 1/28/14 by C. Sanders MD Date Approved
 by P&T Committee: 1/28/14
 Date Reviewed/No Updates: 1/13/15 by C. Sanders, MD
 Date Approved by P&T Committee: 1/27/15
 Date Reviewed/Updated: 2/17/15 by C. Sanders, MD; R. Sterling, MD
 Date Approved by P&T Committee: 1/26/16
 Date Reviewed/No Updates: 1/24/17 by C. Sanders, MD; R. Sterling, MD
 Date Approved by P&T Committee: 1/24/17
 Date Reviewed/No Updates: 1/23/18 by C. Sanders, MD; R. Sterling, MD
 Date Approved by P&T Committee: 1/23/18
 Date Reviewed/No Updates: 1/22/19 by C. Sanders, MD; R. Sterling, MD
 Date Approved by P&T Committee: 1/22/19
 Date Reviewed/No Updates: 2/18/20 by H. Taekman, MD; R. Sterling, MD
 Date Approved by P&T Committee: 2/18/20
 Date Reviewed/ Updated: 8/3/21 by H. Taekman, MD; R. Sterling, MD
 Date Approved by P&T Committee: 8/3/21
 Date Reviewed/No Updates: 2/1/22 by H. Taekman, MD; R. Sterling, MD
 Date Approved by P&T Committee: 2/1/22
 Date Reviewed/No Updates: 1/31/23 by H. Taekman, MD; R. Sterling, MD
 Date Approved by P&T Committee: 1/31/23
 Date Reviewed/Updated: 2/18/25 by H. Taekman, MD; R. Sterling, MD
 Date Approved by P&T Committee: 2/18/25

Revision Date	Content Revised (Yes/No)	Contributors	Review/Revision Notes
1/24/17	No	Catherine Sanders, MD; Robert Sterling, MD	Annual review
1/23/18	No	Catherine Sanders, MD; Robert Sterling, MD	Annual review
1/22/19	No	Catherine Sanders, MD; Robert Sterling, MD	Annual review
2/18/20	No	Howard Taekman, MD; Robert Sterling, MD	Annual review
8/3/21	Yes	Howard Taekman, MD; Robert Sterling, MD	Updated Boxed Warning, Precautions and Off Label Sections
2/1/22	No	Howard Taekman, MD; Robert Sterling, MD	Annual review
1/31/23	No	Howard Taekman, MD; Robert Sterling, MD	Annual review
2/13/24	No	Howard Taekman, MD; Robert Sterling, MD	Annual review
2/18/25	Yes	Howard Taekman, MD; Robert Sterling, MD	Added "Note: Folinic acid is an error prone synonym and should not be used (may be confused with folic acid). "Updated dosing and precaution sections