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.

Dosing: Adult

NOTE: Due to calcium content, do not administer I.V. solutions at a rate >160 mg/minute; not intended for intrathecal use.

Treatment of weak folic acid antagonist overdosage (eg, trimethoprim, pyrimethamine): Oral: 5-15 mg/day

Folate-deficient megaloblastic anemia: I.M.: ≤1 mg/day

High-dose methotrexate-rescue dose: Initial: Oral, I.M., I.V.: 15 mg (~10 mg/m²); start 24 hours after beginning methotrexate infusion; continue every 6 hours for 10 doses, until methotrexate level is <0.05 micromole/L. Adjust dose as follows:

Normal methotrexate elimination: Oral, I.M., I.V.: 15 mg every 6 hours

NOTE: Methotrexate serum concentrations should be monitored to determine dose and duration of leucovorin therapy. Dose may need increased or administration prolonged in situations where methotrexate excretion may be delayed (eg, ascites, pleural effusion, renal insufficiency, inadequate hydration).

Colorectal cancer (also refer to Combination Regimens):

I.V.: 200 mg/m² over at least 3 minutes (used in combination with fluorouracil
370 mg/m²)

or

I.V.: 20 mg/m² (used in combination with fluorouracil 425 mg/m²)

**Methotrexate overdose:** **Note:** The amount of leucovorin administered should equal the amount of methotrexate inadvertently administered.

I.V.: 1 mg per mg of methotrexate inadvertently administered; 100-1000 mg/m² every 3-6 hours has been used; administer until methotrexate levels decrease to goal level or longer if methotrexate levels are unavailable or if patient has renal dysfunction or third-space storage (ascites, pleural effusion)

A nomogram for leucovorin rescue in cancer patients receiving high-dose methotrexate based upon a 48-hour methotrexate level may be helpful (Widemann, 2006). Methotrexate level:

- ≥80 micromole/L: 1000 mg/m² every 6 hours
- ≥8 to <80 micromole/L: 100 mg/m² every 3 hours
- ≥2 to <8 micromole/L: 10 mg/m² every 3 hours
- ≥0.1 to <2 micromole/L: 10 mg/m² every 6 hours

**NOTE:** administer as soon as possible. Do not wait for the results of a methotrexate level before initiating therapy. It is important to adjust the leucovorin dose once a methotrexate level is known. The dose may need to be increased or administration prolonged in situations in which methotrexate excretion may be delayed (eg, ascites, pleural effusion, renal insufficiency, inadequate hydration).

**Pemetrexed toxicity (unlabeled dose):** I.V.: 100 mg/m² once, followed by 50 mg/m² every 6 hours for 8 days (used in clinical trial for CTC grade 4 leukopenia ≥3 days; CTC grade 4 neutropenia ≥3 days; immediately for CTC grade 4 thrombocytopenia, bleeding associated with grade 3 thrombocytopenia, or grade 3 or 4 mucositis)
Off-Label:

**Cofactor therapy in methanol toxicity (unlabeled use):** I.V.: 1 mg/kg (maximum dose: 50 mg) over 30-60 minutes every 4-6 hours. Therapy should continue until methanol and formic acid have been completely eliminated (Barceloux, 2002)

**Prevention of pyrimethamine hematologic toxicity in HIV-positive patients (unlabeled uses; CDC, 2009):** Oral:

Isosporiasis (*Isospora belli*):

Treatment: 10-25 mg once daily (in combination with pyrimethamine)

Chronic maintenance (secondary prophylaxis): 5-10 mg once daily (in combination with pyrimethamine)

*Pneumocystis jirovecii* pneumonia (PCP): Prophylaxis (primary and secondary): 25 mg once weekly (in combination with pyrimethamine [with dapsone]) or 10 mg once daily (in combination with pyrimethamine [with atovaquone])

Toxoplasmosis (*Toxoplasma gondii*):

Primary prophylaxis: 25 mg once weekly (in combination with pyrimethamine [with dapsone]) or 10 mg once daily (in combination with pyrimethamine [with atovaquone])

Treatment: 10-25 mg once daily (in combination with pyrimethamine [with either sulfadiazine, clindamycin, atovaquone, or azithromycin]). **Note:** May increase leucovorin to 50-100 mg/day in divided doses in cases of pyrimethamine toxicity (rash, nausea, bone marrow suppression).

Chronic maintenance (secondary prophylaxis): 10-25 mg once daily (in
combination with pyrimethamine [with either sulfadiazine or clindamycin]) or 10 mg once daily (in combination with pyrimethamine [with atovaquone])

**NOTE**: Consult product literature for other off-label uses

**Precautions:**

**Concurrent drug therapy issues:**

- Fluorouracil: Leucovorin may increase the toxicity of 5-fluorouracil; dose of 5-fluorouracil may need decreased.

- Sulfamethoxazole-trimethoprim: 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


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