CALCIUM FOLINATE (Leucovorin Calcium)

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

CALCIUM FOLINATE is an antidote; chemotherapy modulating agent; rescue agent (chemotherapy); vitamin, water soluble

Pre-Authorization Criteria:

Injection: antidote for folic acid antagonists (methotrexate, trimethoprim, pyrimethamine) and rescue therapy following high-dose methotrexate; in combination with fluorouracil in the treatment of colon cancer; treatment of megaloblastic anemias when folate is deficient as in infancy, sprue, pregnancy, and nutritional deficiency when oral folate therapy is not possible.

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

Off-Label: bladder cancer (in combination with fluorouracil); esophageal cancer (in combination with fluorouracil); gastric cancer (in combination with fluorouracil); pancreatic cancer (in combination with fluorouracil); adjunctive cofactor therapy in methanol toxicity

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

Dosing: Adult

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

**Delayed early methotrexate elimination:** I.V.: 150 mg every 3 hours until methotrexate level is <1 micromole/L, then 15 mg every 3 hours until methotrexate level is <0.05 micromole/L

**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

Use of I.T. leucovorin is not advised (Jardine, 1996; Smith, 2008).

**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)

**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 sulfdiazine or clindamycin]) or 10 mg once daily (in combination with pyrimethamine [with atovaquone])

**Administration**

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

**Warnings/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.

**Dosage form specific issues:**

- Powder for injection: When doses >10 mg/m² are required, reconstitute using sterile water for injection, not a solution containing benzyl alcohol.

- Injection: Due to calcium content, do not administer I.V. solutions at a rate >160 mg/minute. Not intended for intrathecal use.
**Other warnings and precautions:**

Folic acid antagonist overdose: When used for the treatment of accidental folic acid antagonist overdose, administer as soon as possible.

- Methotrexate overdose: When used for the treatment of a methotrexate overdose, 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 (e.g., ascites, pleural effusion, renal insufficiency, inadequate hydration). **Never administer leucovorin intrathecally.**

- Methotrexate rescue therapy: 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 (e.g., ascites, pleural effusion, renal insufficiency, inadequate hydration). **Never administer leucovorin intrathecally.**

**REFERENCES**


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