leucovorin

SYNONYM(S):  calcium folinate; citrovorum factor; folinic acid; GA; LV

COMMON TRADE NAME(S): Lederle Leucovorin® (Pfizer)

B - Mechanism of Action and Pharmacokinetics

Leucovorin calcium (folinic acid) is a reduced form of folic acid. It is usually used 24 hours after methotrexate to selectively "rescue" normal cells from the adverse effects of methotrexate caused by inhibition of production of reduced folates. It is not used simultaneously with methotrexate, as it might then nullify the therapeutic effect of the methotrexate. Leucovorin has also been used to enhance the activity of fluorouracil by binding to the enzyme thymidylate synthetase and decreasing intracellular levels of thymidylate. Commercially available leucovorin in Canada is the racemic mixture of D and L isomers; the L stereoisomer is the active moiety.

<table>
<thead>
<tr>
<th>Absorption</th>
<th>Bioavailability</th>
<th>Metabolism</th>
</tr>
</thead>
<tbody>
<tr>
<td>oral: Rapidly absorbed; 97% at 25mg; saturable at doses above 25 mg.</td>
<td></td>
<td>Rapidly and extensively converted to 5-methyltetrahydrofolate derivatives in the intestine prior to absorption.</td>
</tr>
<tr>
<td></td>
<td>Distributed to all tissues, concentrates in liver and CSF.</td>
<td></td>
</tr>
<tr>
<td>Cross blood brain barrier?</td>
<td>yes</td>
<td></td>
</tr>
<tr>
<td>PPB</td>
<td>35 - 45 %</td>
<td></td>
</tr>
<tr>
<td>Volume of distribution</td>
<td>3.2 L/kg</td>
<td></td>
</tr>
</tbody>
</table>
### C - Indications and Status

**Health Canada Approvals:**

- Leucovorin rescue after methotrexate (higher dose regimens/overdose)
- Adjuvant or advanced colorectal cancer in combination with fluorouracil.
- Megaloblastic anemias due to folate deficiency

**Other Uses:**

- In combination with fluorouracil for gastrointestinal cancers (gastroesophageal, hepatobiliary, pancreatic and small bowel and appendix)

### D - Adverse Effects

**Emetogenic Potential:** Minimal

**Extravasation Potential:** None

<table>
<thead>
<tr>
<th>ORGAN SITE</th>
<th>SIDE EFFECT* (%)</th>
<th>ONSET**</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dermatological</td>
<td>Hand-foot syndrome (in combination with fluorouracil i.e., toxicity is enhanced)</td>
<td>E</td>
</tr>
<tr>
<td>System</td>
<td>Side Effect</td>
<td>Incidence</td>
</tr>
<tr>
<td>-----------------</td>
<td>------------------------------------------------------------------------------</td>
<td>-----------</td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td>Diarrhea (common, in combination with fluorouracil, i.e., toxicity is enhanced)</td>
<td>I E</td>
</tr>
<tr>
<td></td>
<td>Mucositis (common; in combination with fluorouracil, i.e., toxicity is enhanced)</td>
<td>I E</td>
</tr>
<tr>
<td>Hematological</td>
<td>Myelosuppression (in combination with fluorouracil, i.e., toxicity is enhanced)</td>
<td>E</td>
</tr>
<tr>
<td>Hypersensitivity</td>
<td>Allergic reaction (skin rash, hives, pruritus, wheezing- rare)</td>
<td>I</td>
</tr>
<tr>
<td></td>
<td>Anaphylaxis (including shock- rare)</td>
<td>I</td>
</tr>
<tr>
<td>Nervous System</td>
<td>Seizure (rare)</td>
<td>E</td>
</tr>
<tr>
<td></td>
<td>Syncope (rare)</td>
<td>E</td>
</tr>
</tbody>
</table>

* "Incidence" may refer to an absolute value or the higher value from a reported range.
* "Rare" may refer to events with < 1% incidence, reported in post-marketing, phase 1 studies, isolated data or anecdotal reports.

Dose-limiting side effects are underlined.

** I = immediate (onset in hours to days)   E = early (days to weeks)   D = delayed (weeks to months)   L = late (months to years)

Deaths from severe enterocolitis, diarrhea and dehydration have been reported in elderly or debilitated patients receiving leucovorin and fluorouracil. Seizures or syncope have been reported rarely, usually in combination with fluorouracil and in patients with cerebral metastases, although a causal relationship has not been confirmed.

**back to top**

**E - Dosing**

Refer to protocol by which patient is being treated. Leucovorin is rarely given to rescue doses of methotrexate <100 mg/m².

**Adults:**

With fluorouracil:

- q4w: 20 mg/m² IV x 5 days
- q2w: 400mg/m² on day 1 (as in FOLFIRI)

Refer to specific regimen for details. Order of administration is important; leucovorin should be given prior to fluorouracil.

Rescue after methotrexate:
Administer as IV, IV infusion, IM, or PO within 24-36 hours. Doses > 25 mg should be given IV. Other than for low dose, methotrexate levels should be monitored daily until <0.1μM and doses of leucovorin adjusted. Delayed methotrexate excretion may be due to third space fluid accumulation, renal insufficiency, low urine pH or inadequate hydration. Ensure patient is hydrated (at least 3L/d) and maintain urine alkalinization at pH ≥ 8 before and during methotrexate and pH > 7 after the dose.

Moderate-dose methotrexate:

- 15-25 mg p.o q6h x 6-12 doses, starting 24 hours after methotrexate

High-dose methotrexate:

Use in specialized cancer units ONLY. Ensure hydrated and urine alkalinized. Follow local recommendations for dosing. The following are general recommendations:

<table>
<thead>
<tr>
<th>Excretion</th>
<th>Methotrexate levels</th>
<th>Leucovorin dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>24 hours: ≤ 10μM 48 hours: ≤ 1 μM 72 hours: &lt; 0.1μM</td>
<td>15 mg q6h for 10 doses</td>
</tr>
<tr>
<td>Delayed late elimination</td>
<td>72 hours: &gt; 0.1μM</td>
<td>Continue q6h doses until ≤ 0.1 μM</td>
</tr>
<tr>
<td>Delayed early elimination and renal failure</td>
<td>24 hours: &gt; 10μM OR 100% ↑ Creatinine 48 hours: &gt; 1 μM</td>
<td>150mg (or 100 mg/m²) IV q3h until &lt; 1 μM then 15mg q3h until &lt; 0.1 μM</td>
</tr>
</tbody>
</table>

**Dosage with Toxicity:**

Dosage with myelosuppression:

- No adjustment required

**Dosage with Hepatic Impairment:**

No adjustment required.
Dosage with Renal Impairment:

No adjustment required.

F - Administration Guidelines

- Doses ≤100mg may be given by IV push through sidearm of free flowing IV (5% Dextrose, Normal Saline or 2/3-1/3). The injection must not exceed 160mg/min of leucovorin (due to calcium content).
- May be mixed in 50mL Normal Saline or 5% Dextrose minibag (doses up to 500mg) or 100mL minibag (doses >500mg) or in 100mL fluid in graduated administration set (5% Dextrose, Normal Saline or 2/3-1/3); Give over 15 minutes.
- Continuous infusion using CADD pump or similar device.
- Cryodesiccated powder reconstituted with Bacteriostatic Water for Injection containing benzyl alcohol should only be used at doses below 10 mg/m².
- Leucovorin should not be mixed in the same infusion as 5-fluorouracil as a precipitate may form.
- Keep refrigerated; protect from light.

LEUCOVORIN ORAL
- Oral self-administration; drug available by outpatient prescription.

G - Special Precautions

Other:

Leucovorin is not to be administered for the treatment of pernicious anemia or other megaloblastic anemias where vitamin B₁₂ is deficient. Hematologic remission may occur while neurologic manifestations continue to progress. It is contraindicated for intrathecal use. The oral formulation contains lactose and should not be used in patients with hereditary glucose-galactose or lactase deficiencies.

Leucovorin should be administered as soon as possible in case of folic acid antagonist overdose. It has no apparent effect on pre-existing methotrexate nephrotoxicity.

Teratogenic, mutagenic and carcinogenic potentials are unknown in humans, although teratogenic effects have been seen in animals. Leucovorin’s safety in pregnancy and its effect on
fertility have not been established. **Breast feeding** is not recommended due to the potential secretion into breast milk.

回 to top

**H - Interactions**

<table>
<thead>
<tr>
<th>AGENT</th>
<th>EFFECT</th>
<th>MECHANISM</th>
<th>MANAGEMENT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fluorouracil</td>
<td>↑ cytotoxic and toxic effects of fluorouracil.</td>
<td>Stabilizes bond to thymidylate synthetase</td>
<td>Monitor toxicity closely</td>
</tr>
<tr>
<td>methotrexate</td>
<td>↓ toxicity of methotrexate.</td>
<td>‘Rescues’ normal cells from toxic effect of methotrexate</td>
<td>Administer within 6-24 hours after methotrexate.</td>
</tr>
<tr>
<td>Methotrexate (intrathecal)</td>
<td>↓ effect</td>
<td>Crosses blood brain barrier and ameliorates effect, especially with high leucovorin doses.</td>
<td>Caution</td>
</tr>
<tr>
<td>Phenobarbital, phenytoin, primidone, succimides.</td>
<td>↑ seizures</td>
<td>↓ plasma concentrations of antiepileptics.</td>
<td>Caution; check levels</td>
</tr>
<tr>
<td>Other folic acid antagonists (i.e. cotrimoxazole, pyrimethamine)</td>
<td>↓ efficacy</td>
<td></td>
<td>If must use, monitor for treatment efficacy</td>
</tr>
</tbody>
</table>

回 to top

**I - Recommended Clinical Monitoring**

Refer to monitoring parameters in related regimen monographs.

Treating physicians may decide to monitor more or less frequently for individual patients but should always consider recommendations from the product monograph.

回 to top

**J - Supplementary Public Funding**

**ODB - General Benefit (ODB Formulary)**

- oral tablets ()

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K - References


Leucovorin: e-Drugdex, Micromedex Healthcare Series.


August 2016 edited indications

L - Disclaimer

Refer to the New Drug Funding Program or Ontario Public Drug Programs websites for the most up-to-date public funding information.

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back to top