Drug Monograph

A - Drug Name

leucovorin

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

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

back to top

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.

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

	Active metabolites	5-methyltetrahydrofolate
	Inactive metabolites	yes
Elimination	Mainly eliminated in urine, small amounts in feces.	
	Urine	80-90% of dose.
	Half-life	Parent drug: 32 minutes
		Active metabolite: 227 minutes.
	Clearance	3.9 mL/min/kg.

back to top

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)

back to top

D - Adverse Effects

Emetogenic Potential: Minimal

Extravasation Potential: None

ORGAN SITE	SIDE EFFECT* (%)	ONSET**
Dermatological	Hand-foot syndrome (in combination with fluorouracil i.e., toxicity is enhanced)	E

Gastrointestinal	Diarrhea (common, in combination with fluorouracil, i.e., toxicity is enhanced)	I E
	Mucositis (common; in combination with flourouracil, i.e., toxicity is enhanced)	I E
Hematological	Myelosuppression (in combination with flourouracil, i.e., toxicity is enhanced)	E
Hypersensitivity	Allergic reaction (skin rash, hives, pruritus, wheezing- rare)	I
	Anaphylaxis (including shock- rare)	I
Nervous System	Seizure (rare)	E
	Syncope (rare)	E

* "*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/m^2.

Adults:

With fluorouracil:

- q4w: 20 mg/m^2 IV x 5 days
- q2w: 400mg/m^2 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:

Excretion	Methotrexate levels	Leucovorin dose
Normal	24 hours: ≤ 10μM 48 hours: ≤ 1 μM 72 hours: < 0.1μM	15 mg q6h for 10 doses
Delayed late elimination	72 hours: > 0.1μM	Continue q6h doses until ≤ 0.1 μM
Delayed early elimination and renal failure	24 hours: > 10μM OR 100% ↑ Creatinine 48 hours: > 1 μM	150mg (or 100 mg/m^2) IV q3h until < 1 μM then 15mg q3h until < 0.1 μM

Dosage with Toxicity:

Dosage with myelosuppression:

- No adjustment required

Dosage with Hepatic Impairment:

No adjustment required.

Dosage with Renal Impairment:

No adjustment required.

back to top

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/m^2
- 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.

back to top

G - Special Precautions

Other:

Leucovorin is **not** to be administered for the treatment of pernicious anemia or other megaloblastic anemias where vitamin B_{12} 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.

back to top

H - Interactions

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

back 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.

back to top

J - Supplementary Public Funding

ODB - General Benefit (ODB Formulary)

- oral tablets ()

back to top

K - References

Bleyer WA. The clinical pharmacology of methotrexate: new applications of an old drug. Cancer 1978;41(1):36-51.

Leucovorin: e-Drugdex, Micromedex Healthcare Series.

McEvoy GK, editor. AHFS Drug Information 2009. Bethesda: American Society of Health-System Pharmacists, p. 3680-3.

Leucovorin: Cancer Drug Manual (the Manual), 1994, British Columbia Cancer Agency (BCCA).

Product Monograph: Lederle Leucovorin Calcium. Wyeth Canada, January 25, 2008.

Product Monograph: Leucovorin Calcium Injection. Hospira Healthcare Corp., June 7, 2007.

Product Monograph: Leucovorin Calcium Injection. Novopharm Ltd., December 21, 1998.

August 2016 edited indications

back to top

L - Disclaimer

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

The information set out in the drug monographs, regimen monographs, appendices and symptom management information (for health professionals) contained in the Drug Formulary (the "Formulary") is intended for healthcare providers and is to be used for informational purposes only. The information is not intended to cover all possible uses, directions, precautions, drug interactions or adverse effects of a particular drug, nor should it be construed to indicate that use of a particular drug is safe, appropriate or effective for a given condition. The information in the Formulary is not intended to constitute or be a substitute for medical advice and should not be relied upon in any such regard. All uses of the Formulary are subject to clinical judgment and actual prescribing patterns may not follow the information provided in the Formulary.

The format and content of the drug monographs, regimen monographs, appendices and symptom management information contained in the Formulary will change as they are reviewed and revised on a periodic basis. The date of last revision will be visible on each page of the monograph and regimen. Since standards of usage are constantly evolving, it is advised that the Formulary not be used as the sole source of information. It is strongly recommended that original references or product monograph be consulted prior to using a chemotherapy regimen for the first time.

Some Formulary documents, such as the medication information sheets, regimen information sheets and symptom management information (for patients), are intended for patients. Patients should always consult with their healthcare

provider if they have questions regarding any information set out in the Formulary documents.

While care has been taken in the preparation of the information contained in the Formulary, such information is provided on an "as-is" basis, without any representation, warranty, or condition, whether express, or implied, statutory or otherwise, as to the information's quality, accuracy, currency, completeness, or reliability.

CCO and the Formulary's content providers shall have no liability, whether direct, indirect, consequential, contingent, special, or incidental, related to or arising from the information in the Formulary or its use thereof, whether based on breach of contract or tort (including negligence), and even if advised of the possibility thereof. Anyone using the information in the Formulary does so at his or her own risk, and by using such information, agrees to indemnify CCO and its content providers from any and all liability, loss, damages, costs and expenses (including legal fees and expenses) arising from such person's use of the information in the Formulary.

back to top