DRUG NAME: Leucovorin

SYNONYM(S): calcium folinate, citrovorum factor,[1] folinic acid,[2] 5-formyl tetrahydrofolate[2]

COMMON TRADE NAME(S): Lederle LEUCOVORIN®

CLASSIFICATION: folic acid metabolite

Special pediatric considerations are noted when applicable, otherwise adult provisions apply.

MECHANISM OF ACTION:

Leucovorin is an active metabolite of folic acid and an essential coenzyme for nucleic acid synthesis.[1] Leucovorin can be used to selectively "rescue" cells from the adverse effects of methotrexate or to increase the efficacy of fluorouracil. Methotrexate inhibits nucleic acid synthesis by blocking the activation of folic acid. Leucovorin is folic acid in its active (reduced) form, so it allows nucleic acid synthesis to proceed even in the presence of methotrexate. Leucovorin can also compete with methotrexate for the same transport processes into the cell.[2] Leucovorin is usually administered 24 hours after methotrexate so that it does not interfere with the therapeutic effect of methotrexate. Leucovorin can also be used in overdose situations; it should be administered as soon as possible.[2] Fluorouracil inhibits nucleic acid synthesis by several mechanisms, including binding to thymidylate synthetase. A leucovorin metabolite (5-methyl-tetrahydrofolate [5-MTHF]) stabilizes the bond formed between a fluorouracil metabolite (fluorodeoxyuridine monophosphate) and thymidylate synthetase.[3] This causes a decrease in intracellular levels of that enzyme and a resulting decrease in the production of thymidylate. In this way, leucovorin can enhance or modulate the activity of fluorouracil. Leucovorin is usually administered just prior to fluorouracil. In Canada, leucovorin is available as a racemic mixture containing equal parts of d and l isomers (d,l-leucovorin); the biologically active isomer is the l isomer (l-leucovorin).[2,4] In other parts of the world a pure l-leucovorin product is available e.g., in France (ELVORINE®) and in the UK (ISOVORIN®). Dosing for d,l-leucovorin is different than dosing for l-leucovorin.

PHARMACOKINETICS:

Oral Absorption	90% absorbed after oral ingestion[5]; saturable at doses[3] >25 mg	
Distribution	all tissues[6]	
	cross blood brain barrier?	readily[6]
	volume of distribution	3.2 L/kg
	plasma protein binding	35-45%
Metabolism	rapidly and extensively converted to 5-MTHF in the intestine prior to absorption	
	active metabolite	5-methyltetrahydrofolate (5-MTHF)
	inactive metabolite	yes
Excretion	rapidly excreted in the urine	
	urine	80-90%
	feces	5-8%
	terminal half life[7-9]	leucovorin (5-formyltetrahydrofolate): 32-45 min 5-MTHF: 2.3-3.8 h total reduced folates: 3.5-6.2 h
	clearance	3.9 mL/min/kg

Adapted from standard reference[2,10] unless specified otherwise.

USES:

Primary uses:

*Leucovorin rescue after methotrexate

*Enhance cytotoxicity of fluorouracil

*Health Canada approved indication

Other uses:

SPECIAL PRECAUTIONS:

Caution:

- absorption is saturable; doses >25 mg should be given IV[3]
- doses >1000 mg/m^2 q6h are associated with cardiac arrhythmias resulting from hypercalcemia[11]
- intrathecal administration not recommended[2]
- increases the cytotoxicity and toxicity of fluorouracil[2]

Special populations: Elderly patients are at greater risk of developing severe toxicity when treated with the combination of leucovorin plus fluorouracil for the palliative treatment of colorectal cancer.[2] ***Susceptible children*** experience an increase in the frequency of seizures.[2]

Carcinogenicity: no information found.

Mutagenicity: no information found.

Fertility: no problems have been documented.[2]

Pregnancy: FDA Pregnancy Category C[12]. Animal studies have shown fetal risks and there are no controlled studies in women or studies in women and animals are not available. Drug should be given only if the potential benefit justifies the potential risk to the fetus.

Breastfeeding: Leucovorin enters breast milk; caution should be used when administering leucovorin to nursing mothers.[6]

SIDE EFFECTS:

The table includes adverse events that presented during drug treatment but may not necessarily have a causal relationship with the drug. Because clinical trials are conducted under very specific conditions, the adverse event rates observed may not reflect the rates observed in clinical practice. Adverse events are generally included if they were reported in more than 1% of patients in the product monograph or pivotal trials, and/or determined to be clinically important.[13,14] When placebo-controlled trials are available, adverse events are included if the incidence is ≥ 5% higher in the treatment group.

ORGAN SITE	SIDE EFFECT
Clinically important side effects are in ***bold, italics***	
allergy/immunology	allergic sensitization (<1%), including anaphylactoid reactions
blood/bone marrow/ febrile neutropenia	in combination with fluorouracil: leucopenia (i.e., fluorouracil toxicity enhanced)
constitutional symptoms	fatigue
dermatology/skin	*extravasation hazard:* none[15]
	erythema, hives, rash, pruritus, urticaria[10]
gastrointestinal	*emetogenic potential:* non-emetogenic
	in combination with fluorouracil: stomatitis, diarrhea (i.e., fluorouracil toxicity enhanced)

ORGAN SITE	SIDE EFFECT
Clinically important side effects are in ***bold, italics***	
neurology	***seizures*** (<1%)
pulmonary	wheezing[10]

Adapted from standard reference[3] unless specified otherwise.

INTERACTIONS:

AGENT	EFFECT	MECHANISM	MANAGEMENT
capecitabine[10]	increased cytotoxic and toxic effects of capecitabine	capecitabine is metabolized to fluorouracil; leucovorin stabilizes the bond to thymidylate synthetase	monitor toxicity
fluorouracil[2]	increased cytotoxic and toxic effects of fluorouracil	leucovorin stabilizes the bond to thymidylate synthetase	some protocols are designed to take advantage of this effect; monitor toxicity closely
methotrexate	decreased toxicity of methotrexate	leucovorin "rescues" normal cells from toxic effects of methotrexate	administer leucovorin after methotrexate if required
phenobarbital[3]	decreased efficacy of phenobarbital	unknown	primarily a concern with high doses of leucovorin; monitor for seizure control
phenytoin[3,16]	decreased efficacy of phenytoin	phenytoin requires folate for microsomal metabolism; leucovorin may interfere with this action	primarily a concern with high doses of leucovorin; monitor for seizure control
primidone[3]	decreased efficacy of primidone	unknown	primarily a concern with high doses of leucovorin; monitor for seizure control
raltitrexed[17]	decreased efficacy of raltitrexed	raltitrexed is a folate analogue that inhibits thymidylate synthetase; leucovorin may interfere with this action	do not coadminister raltitrexed and leucovorin
trimethoprim[2,18]	decreased efficacy of trimethoprim	unknown	if concomitant therapy is necessary, monitor for treatment efficacy

SUPPLY AND STORAGE:

Oral: Wyeth Canada/Pfizer Canada Inc. supplies leucovorin as a 5 mg tablet. Selected non-medicinal ingredients: lactose. Store at room temperature and protect from light.[19]

***Injection*:**
Pfizer Canada Inc. supplies leucovorin as 50 mg and 500 mg ready-to-use vials without preservative in a concentration of 10 mg/mL. Refrigerate. Protect from light.[20]

Teva Canada Limited supplies leucovorin as 500 mg ready-to-use vials without preservative in a concentration of 10 mg/mL. Refrigerate. Protect from light.[7]

For basic information on the current brand used at BC Cancer, see Chemotherapy Preparation and Stability Chart in Appendix.

SOLUTION PREPARATION AND COMPATIBILITY:

For basic information on the current brand used at BC Cancer, see Chemotherapy Preparation and Stability Chart in Appendix.

Additional information[21]: Fluorouracil and leucovorin will precipitate at various concentrations and temperatures; they should not be considered compatible in the same container.

Compatibility: consult detailed reference

PARENTERAL ADMINISTRATION:

BC Cancer administration guideline noted in ***bold***, ***italics***

Subcutaneous	no information found
Intramuscular[2]	can be used[†]
Direct intravenous[22]	***over a minimum of 3 min****
Intermittent infusion	***in a suitable volume of compatible IV solution****
Continuous infusion	no information found
Intraperitoneal[5]	can be used
Intrapleural	no information found
Intrathecal	has been used; not recommended[2,22]
Intra-arterial	no information found
Intravesical	no information found

*rate not exceeding 160 mg/min due to calcium content[21]
[†]for doses >10mg/m^2 do not use diluents containing benzyl alcohol if reconstituting leucovorin from powder[21]

DOSAGE GUIDELINES:

Refer to protocol by which patient is being treated. Numerous dosing schedules exist and depend on disease, response and concomitant therapy. Guidelines for dosing also include consideration of absolute neutrophil count (ANC). Dosage may be reduced, delayed or discontinued in patients with bone marrow depression due to cytotoxic/radiation therapy or with other toxicities.

Adults:

BC Cancer usual dose noted in ***bold, italics***

Leucovorin modulation of fluorouracil:	Cycle Length: 1-4 weeks[23-31]:	***20 mg/m^2 IV for one dose on days 1-5*** (total dose per cycle [range 20-100 mg/m^2])

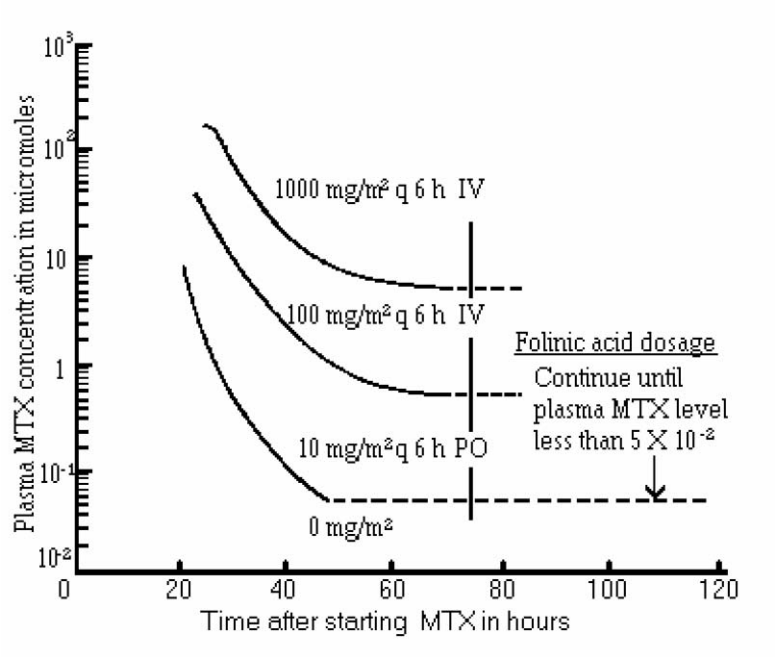
BC Cancer usual dose noted in ***bold, italics***

Cycle Length:
2 weeks[32-35]: ***400 mg/m^2 IV for one dose on day 1.***
(total dose per cycle 400 mg/m^2)

Fluorouracil is usually given after, or at the midpoint of, a leucovorin infusion.[22] Doses of leucovorin are not adjusted for toxicity but would be delayed or omitted if fluorouracil is delayed or omitted.[6]

Leucovorin rescue after methotrexate:

Leucovorin rescue[36]: is required in some methotrexate regimens.
Methotrexate dose:
- >500 mg/m^2 requires leucovorin rescue.
- 100-500 mg/m^2 may require leucovorin rescue.



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

Note: 0.05 µmol/L = 5 x 10^{-2} micromoles/L

Leucovorin dose PO/IV/IM (see Bleyer nomogram):
- ***10-25 mg/m^2 every 6 hours for approximately 8 to 10 doses***, starting 24 hours after the start of methotrexate infusion.[36-41]
- Leucovorin dose modifications ***begin on day 3***, if required, ***based on methotrexate levels taken that morning*** (i.e., level taken 36-48 hours following the start of the methotrexate infusion). Methotrexate levels are repeated every morning and leucovorin adjusted based on the Bleyer nomogram.[37-39]

Continue until the methotrexate level is 0.05 µmol/L.[36,42] Some clinicians use a range for the methotrexate level i.e., continue leucovorin until the methotrexate level is between 0.01-0.1 µmol/L.[22]

BC Cancer usual dose noted in ***bold, italics***

Cycle Length:
Notes:
- Leucovorin doses >25 mg should be given IV[3]
- If impaired elimination of methotrexate is suspected, monitor serum creatinine and methotrexate levels, and adjust the dose of leucovorin upwards according to the Bleyer nomogram.[14] See the **Acute renal failure** paragraph in the methotrexate monograph regarding the possible use of Carboxypeptidase-G2.

Concurrent radiation[25]:	can be used with variable schedules and dosing; specific treatment protocols must be consulted
Dosage in myelosuppression:	no adjustment required
Dosage in renal failure:	no adjustment required
Dosage in hepatic failure:	no adjustment required
Dosage in dialysis:	no information found

Children:

Leucovorin modulation of fluorouracil:	not indicated for colorectal cancer in pediatric patients[36]
Leucovorin rescue after methotrexate:*	15 mg (10 mg/m^2) PO/IV/IM q6h starting 24 h after beginning of methotrexate infusion; continue until methotrexate level < 0.05µmol[36]

*Methotrexate doses above 100 to 300 mg/m^2, which are usually administered by continuous infusion, must be followed by leucovorin rescue.[43]

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