Product Monograph

Including Patient Medication Information

[Pr]LEUCOVORIN CALCIUM INJECTION, USP

Leucovorin calcium injection

Solution, for intravenous and intramuscular use

10 mg / mL

USP

Folic Acid Derivative

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Certain sections or subsections that are not applicable at the time of preparation of the most recent authorized product monograph are not listed.

PART I: HEALTHCARE PROFESSIONAL INFORMATION

1 INDICATIONS

Leucovorin Calcium Injection, USP (leucovorin calcium) is indicated:

- To diminish the toxicity and counteract the effect of impaired methotrexate elimination, and of accidental overdosages of folic acid antagonist
- To treat megaloblastic anemias due to folate deficiency, as in sprue and other nutritional deficiencies; and megaloblastic anemias of pregnancy and infancy (see 2 CONTRAINDICATIONS).
- For pre-treatment followed by fluorouracil to prolong survival in the palliative treatment of patients with advanced colorectal cancer.

1.1 Pediatrics

Pediatrics (<18 years of age): No data are available to Health Canada; therefore, Health Canada has not authorized an indication for pediatric use (see 7.1.3 Pediatrics).

1.2 Geriatrics

Geriatrics: Evidence from clinical studies and experience suggests that use in the geriatric population is associated with differences in safety or effectiveness (see 7 WARNINGS AND PRECAUTIONS, General, and 7.1.4 Geriatrics).

2 CONTRAINDICATIONS

Leucovorin Calcium Injection, USP is contraindicated for:

- Pernicious anemia therapy or other megaloblastic anemias secondary to a deficiency of vitamin B_{12}. Its use can lead to an apparent response of the hematopoietic system, but neurological damage may occur or progress if already present.
- Known hypersensitivity to this drug or to any ingredient in the formulation or component of the container (see 6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING).
- Intrathecal administration.

3 SERIOUS WARNINGS AND PRECAUTIONS BOX

Serious Warnings and Precautions

- **Leucovorin Calcium Injection, USP should only be given by intramuscular or intravenous injection and must not be administered intrathecally (see 2 CONTRAINDICATIONS and 4 DOSAGE AND ADMINISTRATION). Death has been reported when folinic acid has been administered intrathecally following intrathecal overdose of methotrexate.**
- **Leucovorin Calcium Injection, USP should only be used with 5-fluorouracil under the direct supervision of a clinician experienced in the use of cancer chemotherapeutic agents.**
- **Patients receiving any combination therapy regimen involving leucovorin and fluorouracil should be carefully monitored for diarrhea and/or stomatitis/mucositis as these are the first indications that severe and potentially life-threatening toxicity could develop (see 7 WARNINGS AND PRECAUTIONS and 9 DRUG INTERACTIONS).**
- **Fatalities have occurred as a result of gastrointestinal toxicity (predominantly mucositis and diarrhea) (see 7 WARNINGS AND PRECAUTIONS and 8 ADVERSE REACTIONS).**
- **Fatalities have occurred as a result of myelosuppression (see 7 WARNINGS AND PRECAUTIONS and 8 ADVERSE REACTIONS).**
- **Cases of Stevens-Johnson Syndrome (SJS) and Toxic Epidermal Necrolysis (TEN), some fatal, have been reported in patients receiving leucovorin in combination therapy (see 8 ADVERSE REACTIONS).**
- **Leucovorin may diminish the effect of anti-epileptic substances such as phenobarbital, primidone and phenytoin. During leucovorin administration in epileptic patients treated with these substances, there is a risk to increase the frequency of seizures due to a decrease of plasma concentrations of anti-epileptic drugs (see 9 DRUG INTERACTIONS).**

4 DOSAGE AND ADMINISTRATION

4.2 Recommended Dose and Dosage Adjustment

Due to calcium content of leucovorin solution, no more than 160 mg of leucovorin should be injected, per minute, intravenously.

Impaired Methotrexate Elimination or Inadvertent Overdosage:

For the treatment of accidental overdosage of folic acid antagonists, it is generally given in amounts equal to the weight of the antagonist used.

Rescue with Leucovorin Calcium Injection, USP should begin as soon as possible after an inadvertent overdosage and within 24-36 hours of methotrexate administration when there is delayed excretion. Leucovorin Calcium Injection, USP 10 mg/m^2 should be administered intravenously, or intramuscularly every 6 hours until the serum methotrexate level is less than 5 x 10^{-8}M. In the presence of gastrointestinal toxicity, nausea or vomiting due to methotrexate, Leucovorin Calcium Injection, USP should be administered. Because absorption is saturable, doses greater than 25 mg should be given intravenously.

Serum creatinine and methotrexate levels should be determined at 24-hour intervals. If the 24-hour serum creatinine has increased 50% over baseline or if the 24-hour methotrexate level is greater than 5 x 10^{-6} M or the 48-hour level is greater than 9 x 10^{-7} M, the dose of Leucovorin Calcium Injection, USP should be increased to 100 mg/m^2 intravenously every 3 hours until the methotrexate level is less than 5 X 10^{-8} M.

Hydration (3 L/day) and urinary alkalinization with $NaHCO_3$ should be employed concomitantly. The bicarbonate dose should be adjusted to maintain the urine pH at 7.0 or greater.

Treatment of Megaloblastic Anemia:

For treatment of megaloblastic anemia due to folate deficiency, the dose should not exceed 1 mg daily. There is no evidence that doses greater than 1 mg daily have greater efficacy than those of 1 mg. The loss of folates in the urine becomes roughly logarithmic when the amount administered exceeds 1 mg.

Treatment of Advanced Colorectal Cancer:

Leucovorin is administered at 200 mg/m^2 by slow intravenous injection prior to dosing with 370 mg/m^2 fluorouracil by slow intravenous injection, for 5 consecutive days.

This 5-day treatment course may be repeated at 4-week (28 days) intervals, provided that the patient has completely recovered from the toxic effects of the prior treatment course.

In subsequent treatment courses, the dosage of fluorouracil should be adjusted based on patient tolerance of the prior treatment course. The daily dosage of fluorouracil should be reduced by 20% for patients who experienced moderate hematologic or gastrointestinal toxicity in the prior treatment course, and by 30% for patients who experienced severe toxicity. For patients who did not experience toxicity in the prior treatment course, fluorouracil dosage may be increased by 10%. Leucovorin dosages are not adjusted for toxicity.

4.3 Reconstitution

Parenteral Products:

Dilution for Intravenous Infusion: Leucovorin Calcium Injection, USP 10 mg/mL, may be further diluted for intravenous infusion to concentrations of 0.060 mg/mL to 1.0 mg/mL with one of the following solutions:

Dextrose 5% in water

Dextrose 10% in water

Dextrose 10% in saline

Ringer's Injection

Lactated Ringer's Injection

Physiological Saline

The vial contents diluted with Ringer's Injection, Lactated Ringer's Injection, and Physiological Saline are stable for up to 24 hours at room temperature. The vial contents diluted with Dextrose 5% in water and Dextrose 10% in water are stable for up to 12 hours at room temperature. The vial contents diluted with Dextrose 10% in saline are stable for up to 6 hours at room temperature. Due to the possibility of antimicrobial contamination, unused solution should be discarded after that time.

4.4 Administration

Leucovorin Calcium Injection, USP may be administered as received by intramuscular injection or intravenous injection, or it may be diluted for intravenous infusion (see 4.3 Reconstitution, Dilution for Intravenous Infusion).

Warning: As with all parenteral drug products, intravenous admixtures should be inspected visually for clarity, particulate matter, precipitate, discolouration and leakage prior to administration, whenever solution and container permit. Solutions showing haziness, particulate matter, precipitate, discolouration or leakage should not be used.

5 OVERDOSE

Folic acid has low acute and chronic toxicity in man. No adverse effects have been noted in adults after the ingestion of 400 mg/day for 5 months or 10 mg/day for 5 years.

For the most recent information in the management of a suspected drug overdose, contact your regional poison control centre or Health Canada's toll-free number, 1-844 POISON-X (1-844-764-7669).

6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING

Table 1 – Dosage Forms, Strengths, and Composition

Route of Administration	Dosage Form / Strength/Composition	Non-medicinal Ingredients
Intramuscular injection Intravenous injection Intravenous infusion	Leucovorin Calcium Injection, USP is a sterile solution of leucovorin (as the calcium salt), supplied as 10 mg/mL, in water for injection with sodium chloride 8.0 mg/mL, added for isotonicity.	Sodium chloride and water for injection. Sodium hydroxide and hydrochloric acid may be used for pH adjustment. **Contains no preservatives.**

Leucovorin Calcium Injection, USP is supplied as a preservative free, clear yellowish aqueous solution essentially free from visible particles at a concentration of 10 mg/mL leucovorin in 10 mL single-use amber glass vials with a grey rubber stopper and aluminum flip-off seal.

Leucovorin Calcium Injection, USP is supplied as a preservative free, clear yellowish aqueous solution essentially free from visible particles at a concentration of 10 mg/mL leucovorin in 50 mL amber glass vials with a grey rubber stopper and aluminum flip-off seal.

The vial stopper is not made with natural rubber latex.

7 WARNINGS AND PRECAUTIONS

Please see 3 SERIOUS WARNINGS AND PRECAUTIONS BOX.

General

Since leucovorin may enhance the toxicity of fluorouracil, combination therapy consisting of leucovorin and fluorouracil for advanced colorectal cancer should be administered under the supervision of a physician experienced in the use of antimetabolite cancer chemotherapy. Particular care should be taken in the treatment of elderly or debilitated colorectal cancer patients, as these patients may be at increased risk of severe toxicity. Death from severe enterocolitis, diarrhea and dehydration has been reported in elderly patients receiving leucovorin and fluorouracil. Concomitant granulocytopenia and fever were present in some but not all of the patients.

In cases of overdosage of folic acid antagonists, prompt administration of leucovorin calcium is essential. As the time interval between antifolate administration [e.g., methotrexate (MTX)] and Leucovorin Calcium Injection, USP increases, the effectiveness of leucovorin in counteracting the toxicity decreases.

Monitoring of the serum methotrexate concentration is essential in determining the optimal dose of leucovorin to give and duration of therapy. Delayed methotrexate excretion may be an indication of a third space fluid accumulation (i.e. ascites, pleural effusion), renal insufficiency, low pH of urine or inadequate hydration. Higher doses of leucovorin or prolonged administration may be indicated in such cases. Leucovorin has no apparent effect on pre-existing methotrexate nephrotoxicity.

Excessive leucovorin doses must be avoided since this might impair the antitumour activity of methotrexate, especially in CNS tumours where leucovorin accumulates after repeated courses.

Resistance to methotrexate as a result of decreased membrane transport also implies resistance to folinic acid rescue as both medicinal products share the same transport system.

In case of co-administration of leucovorin and fluorouracil, diarrhea and/or stomatitis/mucositis are the first indications that severe and potentially life-threatening toxicity could develop. Patients who experience these symptoms while receiving any combination therapy regimen involving leucovorin and fluorouracil should be carefully monitored. Further therapy should be withheld until these symptoms resolve. Treatment-related deaths have been sporadically reported in patients receiving leucovorin/fluorouracil combination therapy.

Leucovorin enhances the toxicity of fluorouracil. When these drugs are administered concurrently in the palliative therapy of advanced colorectal cancer, the dosage of fluorouracil must be reduced. Although the toxicities observed in patients treated with the combination of leucovorin and fluorouracil are qualitatively similar to those observed in patients treated with fluorouracil alone, gastrointestinal toxicities (particularly stomatitis and diarrhea) are observed more commonly and may be more severe in patients receiving the combination therapy.

Leucovorin should be used with caution after methotrexate chemotherapy, when the following medical problems exist:

- Aciduria (urine pH less than 7)
- Ascites
- Dehydration (Note: Inadequate hydration including that secondary to vomiting may also result in increased methotrexate toxicity.)

- Gastrointestinal obstruction
- Pleural or peritoneal effusions
- Renal function impairment (Note: Risk of methotrexate toxicity is increased because elimination of methotrexate may be impaired and accumulation may occur; even small doses of methotrexate may lead to severe myelosuppression and mucositis; larger doses and/or increased duration of leucovorin treatment may be necessary.)

Patient monitoring is recommended when leucovorin is administered as part of methotrexate chemotherapy programs. Monitoring may include creatinine clearance determinations prior to therapy; plasma or serum methotrexate determinations to detect developing renal function impairment (an increase of greater than 50% within 24 hours is associated with severe renal toxicity); urine pH determination (recommended every 6 hours to ensure that the pH remains greater than 7.0 to minimize the risk of methotrexate nephropathy). Leucovorin has no apparent effect on pre-existing methotrexate nephrotoxicity.

Gastrointestinal

Therapy with leucovorin/fluorouracil must not be initiated or continued in patients who have symptoms of gastrointestinal toxicity of any severity, until those symptoms have resolved. Patients with diarrhea must be closely monitored until the diarrhea has resolved, as rapid clinical deterioration leading to death can occur. Elderly or debilitated patients are at greater risk for severe toxicity when receiving this therapy. In elderly patients, it is recommended to begin with a reduced dosage of fluorouracil.

Monitoring and Laboratory Tests

Calcium levels should be monitored in patients receiving combined leucovorin/5-fluorouracil treatment and calcium supplementation should be provided if calcium levels are low. Complete blood count (CBC) with differential and platelets: prior to each treatment; weekly during the first two courses; at time of anticipated white blood cell (WBC) nadir in all courses thereafter. Electrolytes and liver function tests: prior to each treatment for the first three courses and prior to every other course thereafter.

Neurologic

Seizures and/or syncope have been reported rarely in cancer patients receiving leucovorin, usually in association with fluoropyrimidine administration, and most commonly in those with CNS metastases or other predisposing factors, however, a causal relationship has not been established.

Reproductive Health

- **Fertility:**

Calcium folinate is an intermediate product in the metabolism of folic acid and occurs naturally in the body. No fertility studies have been conducted with calcium folinate in animals.

7.1 Special Populations

7.1.1 Pregnancy

Leucovorin is an intermediate product in the metabolism of folic acid and occurs naturally in the body.

There are no adequate and well-controlled clinical studies conducted in pregnant or breast-feeding women.

7.1.2 Breast-feeding

There has been evidence that folinic acid is excreted in human breast milk, therefore, caution should be exercised when administering leucovorin to nursing mothers. Calcium folinate in combination with 5-fluorouracil is not recommended for use in woman who are breast-feeding.

7.1.3 Pediatrics

No data are available to Health Canada; therefore, Health Canada has not authorized an indication for pediatric use. Leucovorin may increase the frequency of seizures in susceptible children.

7.1.4 Geriatrics

No information is available regarding the use of leucovorin in geriatrics. 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.

8 ADVERSE REACTIONS

8.1 Adverse Reaction Overview

Table 2 – Adverse Drug Reactions during Leucovorin Calcium Monotherapy

System Organ Class	ADR Term
General disorders and administrations site conditions	Pyrexia
Immune system disorders	Hypersensitivity
	Anaphylactic reaction
	Anaphylactic shock
Nervous system disorders	Seizure
	Syncope
Skin and subcutaneous tissue disorders	Urticaria Stevens-Johnson Syndrome Toxic Epidermal Necrolysis

Generally, the safety profile depends on the applied regimen of 5-fluorouracil due to enhancement of the 5-fluorouracil induced toxicities. Additional undesirable effects, when used in combination with 5-fluorouracil, are presented in Table 3.

Table 3 – Adverse Drug Reactions during Leucovorin Calcium Combination Therapy with 5-fluorouracil

System Organ Class	Adverse Drug Reaction
Blood and lymphatic system disorders	Anemia
	Neutropenia

System Organ Class	Adverse Drug Reaction
	Leucopenia
	Thrombocytopenia
Gastrointestinal disorders	Diarrhea
	Nausea
	Vomiting
	Stomatitis
General disorders and administration site conditions	Mucosal inflammation
Metabolism and nutrition disorders	Hyperammonemia
Skin and subcutaneous tissue disorders	Palmar-plantar erythrodysesthesia syndrome (hand-foot syndrome)

8.2 Clinical Trial Adverse Reactions

Clinical trials are conducted under very specific conditions. The adverse reaction rates observed in the clinical trials; therefore, may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse reaction information from clinical trials may be useful in identifying and approximating rates of adverse drug reactions in real-world use.

Allergic reactions, wheezing, skin rash, hives or itching occur rarely. In combination regimens, the toxicity of fluorouracil is enhanced by leucovorin. The most common manifestations are mucositis, stomatitis, leukopenia and/or diarrhea which may be dose-limiting. In clinical trials with this drug combination, these toxicities were found to be controllable by appropriately reducing the dose of fluorouracil.

8.5 Post-Market Adverse Reactions

Cases of Stevens-Johnson Syndrome (SJS) and Toxic Epidermal Necrolysis (TEN), some fatal, have been reported in patients receiving leucovorin in combination with other agents known to be associated with these disorders. A contributory role of leucovorin in these occurrences of SJS/TEN cannot be excluded.

Fatalities have occurred as a result of gastrointestinal toxicity (predominantly mucositis and diarrhea) and myelosuppression. In patients with diarrhea, rapid clinical deterioration leading to death can occur.

9 DRUG INTERACTIONS

9.1 Serious Drug Interactions

Serious Drug Interactions
• **Patients receiving any combination therapy regimen involving leucovorin and fluorouracil should be carefully monitored for diarrhea and/or stomatitis/mucositis as these are the**

first indications that severe and potentially life-threatening toxicity could develop (see 7 WARNINGS AND PRECAUTIONS and 9 DRUG INTERACTIONS).

- **Leucovorin may diminish the effect of anti-epileptic substances such as phenobarbital, primidone and phenytoin. During leucovorin administration in epileptic patients treated with these substances, there is a risk to increase the frequency of seizures due to a decrease of plasma concentrations of anti-epileptic drugs (see 9 DRUG INTERACTIONS).**
- **Leucovorin enhances the cytotoxicity and toxicity of fluorouracil. Leucovorin must not be mixed with fluorouracil in the same intravenous injection or infusion (see 9 DRUG INTERACTIONS).**

9.4 Drug-Drug Interactions

The following drugs or combinations containing these drugs may interact with leucovorin with clinical significance:

- Anticonvulsants, barbiturate
- Anticonvulsant, hydantoin
- Primidone

Large doses of leucovorin may counteract the anticonvulsant effects of these medications.

Leucovorin has been administered simultaneously with pyrimethamine without interfering with its anti-malarial therapy.

Table 4 – Established or Potential Drug-Drug Interactions

Leucovorin Calcium	Source of Evidence	Effect	Clinical comment
anti-epileptic substances such as phenobarbital, primidone and phenytoin	Unknown	diminished	Leucovorin may diminish the effect of anti-epileptic substances such as phenobarbital, primidone and phenytoin. During leucovorin administration in epileptic patients treated with these substances, there is a risk to increase the frequency of seizures (a diminution of plasma levels of enzymatic inductor anticonvulsant drugs may be observed because the hepatic metabolism is increased, as folates are one of the cofactors). Clinical monitoring, possibly monitoring of the plasma concentrations and, if necessary, dose adaptation of the anti-epileptic drug during leucovorin administration and after discontinuation is recommended.

Leucovorin Calcium	Source of Evidence	Effect	Clinical comment
folic acid antagonist (e.g., cotrimoxazole, pyrimethamine, methotrexate, antibiotic with antifolic effect)	Unknown	Reduced or neutralized	When leucovorin is given in conjunction with a folic acid antagonist (e.g., cotrimoxazole, pyrimethamine, methotrexate, antibiotic with antifolic effect), the efficacy of the folic acid antagonist may either be reduced or completely neutralized.
Di-aminopyrimidines (e.g., trimethoprim or co-trimoxazole)	Unknown	Inhibit antibiotic effect	Di-aminopyrimidines (there is some evidence that concomitant administration of leucovorin and trimethoprim (or co-trimoxazole) may inhibit the antibiotic effect of trimethoprim)
Methotrexate	Unknown	Nullify antitumour effect	Leucovorin administered concomitantly with methotrexate may nullify the antitumour chemotherapeutic effect of the latter drug (see 4 DOSAGE AND ADMINISTRATION).
Methotrexate (intrathecal)	Unknown	Reduced	High doses of leucovorin may reduce the efficacy of intrathecally administered methotrexate.
Fluorouracil	Unknown	Enhance cytotoxicity	Leucovorin enhances the cytotoxicity and toxicity of fluorouracil. Leucovorin must not be mixed with fluorouracil in the same intravenous injection or infusion.

9.5 Drug-Food Interactions

Interactions with food have not been established.

9.6 Drug-Herb Interactions

Interactions with herbal products have not been established.

9.7 Drug-Laboratory Test Interactions

Interactions with laboratory tests have not been established.

10 CLINICAL PHARMACOLOGY

10.1 Mechanism of Action

Leucovorin is a reduced form of folic acid, which is readily converted to other reduced folic acid derivatives (e.g., tetrahydrofolate). Because it does not require reduction by dihydrofolate reductase as does folic acid, leucovorin is not affected by blockages of this enzyme by folic acid antagonists (dihydrofolate reductase inhibitors). This allows purine and thymidine synthesis, and thus DNA, RNA and protein synthesis to occur. Leucovorin may limit methotrexate action on normal cells by competing with methotrexate for the same transport processes into the cell.

Leucovorin enhances the cytotoxicity of fluoropyrimidines such as fluorouracil by their metabolites, methylene tetrahydrofolate and fluorodeoxyuridine monophosphate, forming a stable ternary complex with thymidylate synthase and thereby decreasing intracellular levels of that enzyme and the product thymidylate. The cell then dies as a result of thymine starvation.

10.2 Pharmacodynamics

A folic acid deficiency is produced during therapy with the folic acid antagonists aminopterin and amethopterin (methotrexate) used as antineoplastic agents and with the chemotherapeutic agent pyrimethamine. These agents competitively inhibit the conversion of folic acid to folinic acid. Their affinity for folate reductase is so much greater than that of folic acid that not even large doses of folic acid will correct the drug-induced deficiency. In the event of a severe toxic reaction, the already reduced form, folinic acid, can be given, since it can be used directly to form new coenzyme.

10.3 Pharmacokinetics

The pharmacokinetics of leucovorin was evaluated after intravenous, intramuscular and oral administration of a 25 mg dose of leucovorin calcium to healthy male subjects in a randomized crossover study.

Serum total reduced folates (as measured by Lactobacillus casei assay) reached a mean peak of 1259 ng/mL (range-1625) at 10 minutes and 436 ng/mL (range 240-725) at 52 minutes after intravenous and intramuscular administration respectively. This initial rise in total reduced folates was primarily due to the parent compound 5-formyl-tetrahydrofolate (measured by Streptococcus faecalis assay) which rose to 1206 ng/mL at 10 minutes and 360 ng/mL at 28 minutes after intravenous and intramuscular administration, respectively. A sharp drop in parent compound followed and coincided with the appearance of the metabolite (also active) 5- methyl-tetrahydrofolate which became the predominant circulating form of the drug (intravenous administration). The mean peak of 5- methyl tetrahydrofolate was 258 ng/mL and occurred at 1.3 hours. The level of the metabolite 5-methyl-tetrahydrofolate increased subsequently over time until at 1.5 hours it represented 50% of the circulating total folates (intramuscular administration). The terminal half-life of total reduced folates was 6.2 hours with parenteral administration. There was no statistically significant difference between i.m. and i.v. administration in the AUC for total reduced folates, 5- formyl-tetrahydrofolate, or 5-methyl-tetrahydrofolate.

Leucovorin distributes to all tissues, readily penetrates the blood brain barrier and actively concentrates in the cerebrospinal fluid. Leucovorin (5-formyl-tetrahydrofolate) is rapidly and extensively metabolized to other tetrahydrofolate derivatives, the major metabolite being 5- methyltetrahydrofolate.

Approximately 80-90% of the dose is excreted in the urine. Elimination half-lives of parent drug and active metabolite are 32 and 227 minutes respectively.

Leucovorin has an onset of action of 20-30 minutes with peak levels occurring at 1.7 hours. Similar serum levels are produced after oral and intravenous administration, approximately 12% greater than after intramuscular use. Onset of action is 10-20 minutes after intramuscular administration with peak levels occurring at 0. 7 hours. Leucovorin has a 3-6 hour duration of action. Absorption from the deltoid is 8% higher than from the gluteal muscle after intramuscular injection.

The serum half-life of leucovorin (or 5-formyltetrahydrofolate) was 35 to 45 minutes following both oral and intramuscular administration. The serum half-life of 5-methyltetrahydrofolate was about 2 1/4 hours. 5-methyltetrahydrofolate was excreted via the kidneys in a manner proportional to its serum concentration.

Methotrexate did not seem to affect the absorption of folate.

11 STORAGE, STABILITY AND DISPOSAL

Leucovorin Calcium Injection, USP should be stored refrigerated (2 °C to 8 °C) and protected from light. The liquid formulation should be used immediately once removed from refrigeration. Discard any unused portion.

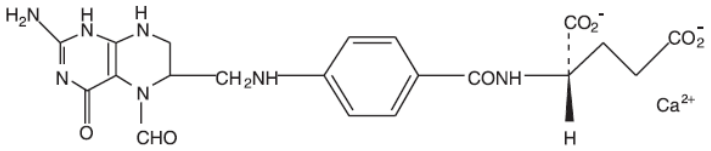
12 SPECIAL HANDLING INSTRUCTIONS

There are no special handling instructions for this drug product.

PART II: SCIENTIFIC INFORMATION

13 PHARMACEUTICAL INFORMATION

Drug Substance

Proper Name:	Leucovorin calcium (folic acid derivative). This drug substance is also known as calcium folinate, citrovorum factor, or the calcium salt of 5-formyl-5,6,7,8-tetrahydrofolic acid.
Chemical Name:	L-Glutamic acid, N-[4[[(2-amino-5-formyl-1-4,5,6,7,8- hexahydro-4-oxo- 6-pteridinyl)methyl]amino]benzoyl]-,calcium salt (1:1).
Molecular formula and molecular mass:	$C_{20}H_{21}CaN_7O_7$, 511.51 g/mol
Structural Formula:	
Physicochemical properties:	Leucovorin Calcium is a yellowish white or yellow, odourless, powder. It is very soluble in water and practically insoluble in alcohol. It decomposes above 250°C.

14 CLINICAL TRIALS

The clinical trial data on which the original indication was authorized are not available.

15 MICROBIOLOGY

No microbiological information is required for this drug product.

16 NON-CLINICAL TOXICOLOGY

General toxicology

In mice, the LD_{50} was 991 mg/kg intravenously. Toxic symptoms included body tremors, marked ataxia, clonic convulsions and deaths within 10 minutes in CD-1 male mice. The single-dose oral LD_{50} could not be determined because, at doses as high as 20,000 mg/kg, no toxicity was observed in CD-1 and Long-Evans male rats. Doses higher than this could not be given because of the limitations of dose volume and viscosity.

In subchronic studies, oral doses of leucovorin at 0, 75, 225 or 675 mg/kg daily for over 30 days to rats and beagle dogs produced no drug-related toxic effects on body weight, food consumption, hematology,

blood chemistry, urinalysis or pathology. No alteration in ECG in dogs occurred. Ophthalmoscopic examinations of rats and dogs revealed no drug-induced toxic effects.

Genotoxicity

No studies have been performed to evaluate the genotoxic potential of leucovorin calcium.

Carcinogenicity

Carcinogenicity studies have not been performed with leucovorin calcium.

Reproductive and developmental toxicology

Embryo-fetal reproduction toxicity studies have been performed in rats and rabbits. Rats were dosed up to 1800 mg/m^2 which is 9 times the maximum recommended human dose, and rabbits were dosed up to 3300 mg/m^2 which is 16 times the maximum recommended human dose. There was no embryo-fetal toxicity noted in rabbits. At the maximum dose in rats, there was a slight increase in early embryonic resorptions and no other adverse effects on embryo-fetal development. No resorptions were noted in dose groups at 5 times the maximum recommended human dose.

No dedicated animal fertility studies have been performed for leucovorin calcium.

17 SUPPORTING PRODUCT MONOGRAPHS

1. PrLEUCOVORIN CALCIUM INJECTION USP (solution, 10 mg/mL), submission control 267164, Product Monograph, Pfizer Canada ULC. DEC 13, 2022.
2. PrLEUCOVORIN CALCIUM INJECTION (solution, 10 mg/mL), submission control 294459, Product Monograph, Teva Canada Limited. MAY 13, 2025.

PATIENT MEDICATION INFORMATION

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

[Pr]LEUCOVORIN CALCIUM INJECTION, USP

Leucovorin calcium injection

This Patient Medication Information is written for the person who will be taking **Leucovorin Calcium Injection, USP**. This may be you or a person you are caring for. Read this information carefully. Keep it as you may need to read it again.

This Patient Medication Information is a summary. It will not tell you everything about this medication. If you have more questions about this medication or want more information about **Leucovorin Calcium Injection, USP,** talk to a healthcare professional.

Serious warnings and precautions box

- You will receive Leucovorin Calcium Injection, USP:
  - as a shot into your muscle (intramuscularly) or as a shot or infusion (drip) into your vein (intravenously). It must not be given into the fluid-filled space between the thin layers of tissue that cover the brain and spinal cord (intrathecally). Deaths have happened in people getting this medicine into the spine.
  - with 5-fluorouracil only under the care of a healthcare professional experienced in the use of anti-cancer medicines.
- If you are receiving leucovorin with fluorouracil (an anticancer medicine), your healthcare professional will monitor you for side effects like diarrhea or painful sores that may make it hard for you to eat, drink, or swallow (stomatitis/mucositis). These are early signs of severe and potentially life-threatening side effects. Talk to your healthcare professional **right away** if you experience any of these side effects.
- Deaths from the following side effects have happened in people getting leucovorin:
  - **Severe problems with the digestive system** (gastrointestinal toxicity): These include diarrhea and mucositis (ulcers (open sores) and swelling of lining of the bowels and mouth).
  - **Severe drop in blood cell counts** (myelosuppression, a condition in which the bone marrow cannot make enough blood cells).
  - **Severe skin reactions:** These include Stevens-Johnson syndrome (SJS) and Toxic Epidermal Necrolysis (TEN). These are more likely to occur if you are taking other medicines known to cause these skin reactions.

For more information on these and other serious side effects, see the **Serious side effects and what to do about them** table, below.

- Leucovorin may lower the effects of anti-epileptic medications such as phenobarbital, primidone and phenytoin. If you are taking anti-epileptic medications, you may be at an increased risk of having seizures more often

What Leucovorin Calcium Injection, USP is used for:

- to lower the toxic effects of:
  - a group of medicines called folic acid antagonists. It is also used to treat an overdose of these medicines
  - methotrexate (a medicine often used to treat cancer)
- to treat some kinds of anemia (low level of red blood cells in the body)
  - due to low level of folate (an essential B vitamin) in the body such as in poor food intake or absorption (sprue, nutritional deficiency); or
  - occurring during pregnancy and infancy.
- before treatment with fluorouracil to improve survival time in the palliative treatment of patients with advanced colorectal cancer.

How Leucovorin Calcium Injection, USP works:

Leucovorin Calcium Injection, USP belongs to a class of medicines called folic acid analogs. It:

- lowers the harmful effects of methotrexate by competing with methotrexate and limiting how much methotrexate enters your cells
- treats anemia by supplying folic acid that is needed to produce red blood cell
- increases the effects of 5-fluorouracil (a medicine used to treat cancer)

The ingredients in Leucovorin Calcium Injection, USP are:

Medicinal ingredients: Leucovorin Calcium (also known as calcium folinate).

Non-medicinal ingredients: Sodium chloride and Water for injection. Sodium hydroxide and Hydrochloric acid may be added to adjust pH.

Leucovorin Calcium Injection, USP comes in the following dosage forms:

Solution: 10 mg / mL

Do not receive Leucovorin Calcium Injection, USP if:

- you have a type of anemia caused by too little Vitamin B_{12}
- you are allergic (hypersensitive) to calcium folinate or any of the other ingredients of Leucovorin Calcium Injection, USP (See **What are the ingredients in Leucovorin Calcium Injection, USP**)?

Leucovorin Calcium Injection, USP must NOT be injected into the fluid-filled space between the thin layers of tissue that cover the brain and spinal cord (intrathecally).

To help avoid side effects and ensure proper use, talk to your healthcare professional before you receive Leucovorin Calcium Injection, USP. Talk about any health conditions or problems you may have, including if you:

- are currently taking methotrexate and:
  - have aciduria (urine pH less than 7)
  - have or have ever had a build-up of fluid in the chest cavity or the belly area

- are dehydrated (feeling thirsty, dark yellow urine, dizzy, lightheaded, tired, dry mouth and peeing less than 4 times a day)
- have stomach or bowel issues such as a blockage
- you have trouble with your kidneys

- have diarrhea
- are pregnant, plan to become pregnant, or are breast-feeding.

Other warnings you should know about:

- **Older people with colorectal cancer.** You could have more side effects. Deaths from severe bowel problems, diarrhea, and dehydration have happened in older people getting leucovorin with fluorouracil.
- **Lab and blood tests:** Your healthcare professional will do blood tests before you receive Leucovorin Calcium Injection, USP and/or during treatment to monitor your progress or check for side effects. These tests may check:
  - the level of blood cells in your body.
  - that your liver or kidneys are working properly.
  - the level calcium and other essential minerals—like sodium and potassium (electrolyte) in your blood.

Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.

Serious drug interactions:

Serious drug interactions with Leucovorin Calcium Injection, USP include:

- If you are receiving leucovorin with fluorouracil (an anticancer medicine):
  - your healthcare professional will monitor you for side effects like diarrhea or painful sores that may make it hard for you to eat, drink, or swallow (stomatitis/mucositis). These are early signs of severe and potentially life-threatening side effects. Talk to your healthcare professional **right away** if you experience any of these side effects. See the **Serious side effects and what to do about them** table, below
  - you may experience increased side effects from fluorouracil
- Leucovorin may lower the effects of anti-epileptic medications such as phenobarbital, primidone and phenytoin. If you are taking anti-epileptic medications you may be at an increased risk of having seizures more often
- Leucovorin must not be mixed in the same infusion as 5-fluorouracil because a precipitate may form

The following may interact with Leucovorin Calcium Injection, USP:

- medicines used to treat epilepsy - phenobarbital, primidone, and phenytoin. Your healthcare professional may check blood levels of these medicines and change your dose to prevent increased convulsions (fits).

- a group of medicines called folic acid antagonists. These include:
    - methotrexate (a medicine often used to treat cancer). High doses of leucovorin may lower how well methotrexate works
    - trimethoprim or co-trimoxazole (an antibiotic)
    - pyrimethamine (a medicine used to treat malaria)
- anti-cancer medicines, such as 5-fluorouracil (5-FU). Leucovorin may increase the harmful effect of fluorouracil

How you will receive Leucovorin Calcium Injection, USP:

- in a healthcare setting under the care of your healthcare professional
- as an injection into the muscle or as an injection or an infusion (drip) into your vein

Usual dose:

Your healthcare professional will work out the right dose of Leucovorin Calcium Injection, USP for you.

Overdose:

If you think you, or a person you are caring for, have taken too much Leucovorin Calcium Injection, USP, contact a healthcare professional, hospital emergency department, regional poison control centre or Health Canada's toll-free number, 1-844 POISON-X (1-844-764-7669) immediately, even if there are no signs or symptoms.

Possible side effects from using Leucovorin Calcium Injection, USP?

These are not all the possible side effects you may have when receiving Leucovorin Calcium Injection, USP. If you experience any side effects not listed here, tell your healthcare professional.

Side effects may include:

- nausea, vomiting
- red, swollen lips
- dizziness
- fever

Serious side effects and what to do about them

Frequency/Side Effect/Symptom	Talk to your healthcare professional		Stop taking drug and get immediate medical help
	Only if severe	In all cases	
Very common			
Gastrointestinal toxicity (Severe problems with the digestive system): • **Diarrhea:** persistent or severe • **Stomatitis** (swelling and redness of the lining of your		✓	

Frequency/Side Effect/Symptom	Talk to your healthcare professional		Stop taking drug and get immediate medical help
	Only if severe	In all cases	
mouth): painful sores that may make it hard for you to eat, drink, or swallow • **Mucositis** (ulcers (open sores) and swelling of lining of the bowels and mouth): red, shiny, or swollen mouth and gums, sores in the mouth or on the gums or tongue, blood in the mouth, pain in the mouth or throat, difficulty swallowing or talking, mild burning, or pain when eating			
Common			
Palmar-plantar erythrodysesthesia (Hand and Foot syndrome): red or swollen palms, thick calluses and blisters of the hands and soles of the feet, tingling or burning, tightness of the skin		✓	
Unknown			
Stevens-Johnson Syndrome (SJS) and Toxic Epidermal Necrolysis (TEN) (severe skin reactions): redness, blistering and/or peeling of the skin and/or inside the lips, mouth, eyes, nasal passages or genitals, accompanied by fever, chills, tiredness, headache and cough, body aches or swollen glands, raised red or purple skin patches, possibly with blister or crust in the center, swollen lips, mild itching or burning			✓
Allergic reactions: difficulty swallowing or breathing, wheezing, drop in blood pressure, feeling sick to your stomach and throwing up, hives or rash, swelling of the face, lips, tongue or throat, low blood			✓

Frequency/Side Effect/Symptom	Talk to your healthcare professional		Stop taking drug and get immediate medical help
	Only if severe	In all cases	
pressure, confusion, reduced alertness, cold, moist skin, fast breathing, fast heartbeat			
Seizures (fit): uncontrollable shaking with or without loss of consciousness			✓
Bone marrow suppression (severe drop in blood cells): bleeding, bruising, chills, fatigue, fever, infections, weakness, shortness of breath or other signs of infection			✓
Syncope (fainting): a temporary loss of consciousness due to a sudden drop in blood pressure		✓	
Hyperammonemia (high ammonia levels in the blood): confusion, irritability, refusal to eat meat or high protein products		✓	

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, tell your healthcare professional.

Reporting side effects

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (canada.ca/drug-device-reporting) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

Storage:

Leucovorin Calcium Injection, USP will be stored by your healthcare professional.

It should be kept:

- refrigerated (2 °C to 8 °C)
- protected from light
- out of reach and sight of children.

If you want more information about Leucovorin Calcium Injection, USP:

- Talk to your healthcare professional.
- Find the full product monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website: (https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/drug-product-database.html); Fresenius Kabi Canada's website (http://www.fresenius-kabi.com/en-ca/), or by calling 1-877-821-7724.

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