

PRODUCT MONOGRAPH

LEUCOVORIN CALCIUM INJECTION

10 mg/mL
USP

Folic Acid Derivative

Teva Canada Limited
30 Novopharm Court
Toronto, Ontario
M1B 2K9

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10 mg/mL

USP

Therapeutic Classification

Folic Acid Derivative

CAUTION: DO NOT ADMINISTER LEUCOVORIN CALCIUM INJECTION INTRATHECALLY.

ACTION AND CLINICAL PHARMACOLOGY

Leucovorin Calcium or calcium folinate is the calcium salt of folinic acid (citrovorum factor). It is a mixture of the diastereoisomers of the 5 formyl derivative of tetrahydrofolic acid. The (-)-L stereoisomer is the biologically active component of the mixture. It is a metabolite of folic acid and an essential coenzyme for nucleic acid synthesis. Folinic acid acts as an antidote to folic acid antagonists, such as methotrexate, which block the conversion of folic acid to tetra-hydrofolate by binding to the enzyme dihydrofolate reductase.

Leucovorin (folinic acid) is readily converted to other reduced folic acid derivatives such as tetrahydrofolate. Leucovorin does not require reduction by dihydrofolate reductases, therefore, it is not affected by blockage 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 probably acts by competing with methotrexate for the same transport processes into the cell thus limiting the action of methotrexate on normal cells.

Leucovorin rescues bone marrow and gastrointestinal cells from methotrexate toxicity, but does not appear to have an effect on pre-existing methotrexate nephrotoxicity.

Leucovorin enhances the cytotoxicity of fluoropyrimidines such as 5-fluorouracil (5-FU) by the metabolites, methylene tetrahydrofolate and fluorodeoxyuridine monophosphate. It forms a stable ternary complex with thymidylate synthase, and thereby, decreases intracellular levels of that enzyme and the product thymidylate. Cellular necrosis occurs as a result of thymine starvation.

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.

INDICATIONS AND CLINICAL USE

Leucovorin calcium is indicated:

(1) to diminish the toxicity and counteract the effect of impaired METHOTREXATE elimination, and of accidental overdoses of folic acid antagonists

(2) to treat the megaloblastic anemias due to folate deficiency, as in sprue, nutritional deficiency, megaloblastic anemias of pregnancy and infancy.

(3) for pre-treatment followed by 5-fluorouracil to prolong survival in the palliative treatment of patients with advanced colorectal cancer.

(See CONTRAINDICATIONS)

CONTRAINDICATIONS

Leucovorin Calcium Injection is not indicated for use in the treatment of folic acid deficiency. Leucovorin Calcium Injection should never be used for the treatment of pernicious anemia or other megaloblastic anemias secondary to a deficiency of vitamin B₁₂. As with folic acid, its use can result in an apparent response of the hematopoietic system, but neurological damage may occur or progress if already present.

WARNINGS

General

Leucovorin Calcium Injection should be administered as promptly as possible in the treatment of accidental overdosage of folic acid antagonists. As the time interval between antifolate administration [e.g., Methotrexate (MTX)] and Leucovorin Calcium Injection increases, the effectiveness of leucovorin in counteracting the toxicity decreases. It is essential to monitor serum methotrexate concentrations in order to determine the optimal dose and duration of treatment with Leucovorin Calcium Injection.

Delayed excretion of MTX may be caused by a third space fluid accumulation (i.e., ascites, pleural effusion), renal insufficiency, or inadequate hydration. In the above circumstances, higher doses of Leucovorin Calcium Injection or prolonged administration may be required.

Interaction with Fluorouracil

There have been occasional reports of treatment-related deaths in patients on leucovorin calcium and fluorouracil combination therapy. Diarrhea or stomatitis/mucositis are generally the first indication that severe and potentially life-threatening toxicity could develop. Patients who experience these symptoms while receiving any therapy regimen incorporating Leucovorin Calcium Injection plus fluorouracil should be carefully monitored. Further therapy should be withheld until these symptoms resolve.

Leucovorin Calcium Injection enhances the toxicity of fluorouracil. When these drugs are administered concurrently to reduce the severity of advanced colorectal cancer, the dosage of fluorouracil must be reduced. Although the toxicities observed in patients treated with combination of Leucovorin Calcium Injection plus 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. (See PRECAUTIONS).

Therapy with Leucovorin Calcium Injection/fluorouracil must be withheld or discontinued in patients who have symptoms of gastrointestinal toxicity of any severity, until those symptoms have resolved. Patients with diarrhea must be carefully 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 with this therapy.

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.

PRECAUTIONS

Because of the Ca^{++} content of Leucovorin Calcium solutions, no more than 160 mg of Leucovorin Calcium Injection should be administered intravenously per minute.

Since Leucovorin Calcium Injection may enhance the toxicity of fluorouracil, combination therapy with these drugs 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. Deaths from severe enterocolitis, diarrhea and dehydration have been reported in elderly patients receiving Leucovorin Calcium Injection and fluorouracil. Concomitant granulocytopenia and fever were present in some, but not all of the patients.

Drug Interactions:

Large amounts of folic acid may counteract the antiepileptic effect of phenobarbital, phenytoin and primidone, and increase the frequency of seizures in susceptible children.

Preliminary animal and human studies have shown that small quantities of systemically administered leucovorin enter the cerebrospinal fluid (CSF) primarily as 5-methyl-tetrahydrofolate and, in humans, remain 1-3 orders of magnitude lower than the usual methotrexate concentration following intrathecal administration. However, high doses of Leucovorin Calcium Injection may reduce the efficacy of intrathecally administered methotrexate. Leucovorin Calcium Injection has no effect on other toxicities of methotrexate, such as the

nephrotoxicity resulting from drug precipitation in the kidney.

Leucovorin Calcium Injection may enhance the toxicity of fluorouracil (see Warnings).

Pregnancy-Teratogenic Effects:

Animal reproduction studies with Leucovorin Calcium Injection have not been conducted. It is not known whether Leucovorin Calcium Injection can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. Leucovorin Calcium Injection should be given to a pregnant woman only if the need is clearly demonstrated and the benefits have been weighed against the possible risks.

Nursing Mothers:

There has been evidence that folinic acid is excreted in human breast milk, therefore, caution should be exercised when administering Leucovorin Calcium Injection to nursing mothers.

Pediatric Use: See Drug Interactions.

ADVERSE EFFECTS

Occasional allergic reactions have been reported following oral and parenteral administration of folic acid; pyrexia has occurred after injections. In combination therapy the toxicity of 5-FU is enhanced by Leucovorin Calcium Injection. The most common manifestations are leukopenia, mucositis, stomatitis, and/or diarrhea which may be dose limiting. Clinical trials with this drug combination demonstrated that these toxicities were reversible with

appropriate modification of 5-FU administration.

SYMPTOMS AND TREATMENT OF OVERDOSAGE

Folic acid is a water soluble vitamin converted in the body by the action of folate reductase to folinic acid (leucovorin) which is rapidly eliminated in the urine.

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.

Excessive amounts of Leucovorin Calcium Injection may nullify the chemotherapeutic effect of folic acid antagonists.

DOSAGE AND ADMINISTRATION

Intravenous administration is employed when Leucovorin Calcium Injection is used for leucovorin pre-treatment followed by 5-fluorouracil (5-FU) in the treatment of patients with advanced colorectal cancer. Because of the Ca^{++} contents of Leucovorin Calcium solutions, no more than 160 mg of Leucovorin Calcium Injection should be administered per minute.

Dose:

a) 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 should begin as soon as possible after an inadvertent overdosage and within 24-36 hours of methotrexate administration when there is delayed excretion. (See Warnings). Leucovorin Calcium Injection 10 mg/m^2 should be administered intravenously, or intramuscularly every 6 hours until the serum methotrexate level is less than $5 \times 10^{-8} \text{ M}$. In the presence of gastrointestinal toxicity, nausea or vomiting due to methotrexate, Leucovorin Calcium Injection 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 $5 \times 10^{-6} \text{ M}$ or the 48 hour level is greater than $9 \times 10^{-7} \text{ M}$, the dose of Leucovorin Calcium Injection should be increased to 100 mg/m^2 i.v. every 3 hours until the methotrexate level is less than $5 \times 10^{-8} \text{ M}$.

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

b) Megaloblastic Anemia Due to Folic Acid Deficiency

Doses of 15 mg daily by mouth or not greater than 1 mg intravenously have been suggested for the treatment of megaloblastic anemia. 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.

c) Advanced Colorectal Cancer

Leucovorin Calcium Injection is administered at 200 mg/m^2 by slow

intravenous injection immediately prior to dosing with 370 mg/m^2 5-FU (fluorouracil) by slow intravenous injection, for five consecutive days. This 5 day treatment course may be repeated at 4 week (28 day) 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 in the prior treatment course. Fluorouracil dosage may be increased by 10% for patients who experienced no toxicity in the prior treatment course. Dosages of Leucovorin Calcium Injection are not adjusted for toxicity.

Laboratory Tests During Treatment with Leucovorin-5-Fluorouracil Combination:

Myelosuppression is most often the dose-limiting toxicity factor, and stomatitis, mucositis, diarrhea, nausea and abdominal pain are often seen. Myelosuppression, predominantly leukopenia may occur.

Patients should be monitored routinely with complete blood counts, liver function tests, neutrophil and platelet nadir. Tumour measurements and CEA counts may be performed monthly.

The 5-FU dose may be increased by $30 \text{ mg/m}^2/\text{day}$ (from an initial dose of $370 \text{ mg/m}^2/\text{d}$) if the leukocyte nadir is $> 1.5 \times 10^9/\text{L}$ and the platelet nadir is $> 50 \times 10^9/\text{L}$.

Generally, the dose of 5-FU (when given with leucovorin) may be increased by 10% per treatment cycle in the absence of toxicity from the preceding cycle of therapy.

Administration:

Leucovorin Calcium Injection is used for intravenous or intramuscular injection.

Rotate site when giving the drug by intramuscular administration. Absorption from the deltoid muscle is better than from the gluteal muscle.

For direct intravenous injection and intermittent infusion the rate should be < 160 mg/minute because of the calcium content.

Parenteral drug products should be inspected for particulate matter and discolouration prior to administration, whenever solution and container permit.

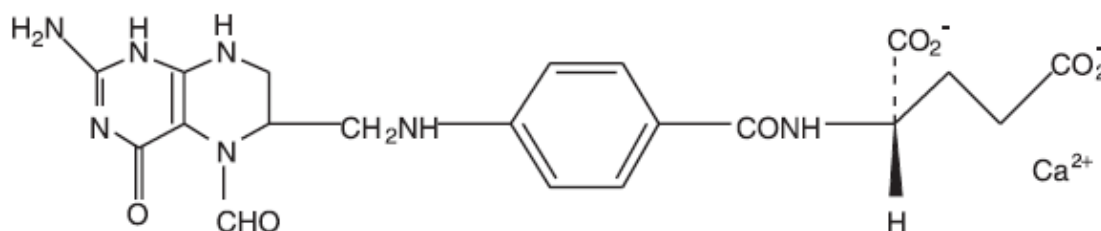
PHARMACEUTICAL INFORMATION

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-pteridiny)methyl]amino]benzoyl]-, calcium salt (1:1).

Structural Formula:



Molecular Formula: C₂₀H₂₁CaN₇O₇

Molecular Weight: 511.51

Description: 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.

Composition: Each millilitre of solution contains 10.0 mg of leucovorin as the calcium salt with the following non-medicinal ingredients: 8.0 mg sodium chloride and water for injection.

Sodium hydroxide may be used for pH adjustment.

STABILITY AND STORAGE RECOMMENDATIONS

Vials of 10 mg/mL should be stored at refrigerated temperatures (2-8°C). Leucovorin Calcium Injection is light sensitive and should be protected from light. The liquid formulation should be used immediately once removed from refrigeration. Discard any unused portion.

Parenteral Products:

Leucovorin Calcium Injection, 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.

Parenteral products should be inspected for particulate matter and discolouration whenever solution and container permit.

AVAILABILITY

Leucovorin Calcium Injection is supplied as a solution at a concentration of 10 mg/mL leucovorin in 50 mL vials.

PHARMACOLOGY

(i) Human Pharmacology

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-methyl-tetrahydrofolate. 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.

After oral administration of leucovorin reconstituted with aromatic elixir, the mean peak concentration of serum total folates occurred at 2.3 hours and was 393 ng/mL (range 160-550). The terminal half-life was 5.7 hours. The major metabolite was 5-methyl-tetrahydrofolate to which leucovorin is converted in the intestinal mucosa. The mean peak of the parent compound and 5-methyl-tetrahydrofolate was 51 ng/mL and 367 ng/mL at 1.2 and 2.4 hours, respectively. The AUC (bioavailability) of total reduced folates after oral administration was 92% of the AUC after intravenous administration.

Following oral administration, leucovorin is rapidly absorbed and enters the general body pool of reduced folates. Oral absorption of leucovorin is saturable at doses above 25 mg. The apparent bioavailability of leucovorin was 97% for 25 mg, 75% for 50 mg and 37% for 100 mg.

The serum half-life of citrovorum factor (or 5-formyl-tetrahydrofolate) was 35-45 minutes following both oral and i.m. administration. The serum half-life of 5-methyl-tetrahydrofolate was about 2 1/4 hours. 5-methyl-tetrahydrofolate is excreted via the kidneys in a manner proportional to its serum concentration. Leucovorin can enhance the therapeutic and toxic effects of fluoropyrimidines, such as fluorouracil, used in cancer therapy. Fluorouracil is metabolized to fluorodeoxyuridylic acid, which binds to and inhibits the enzyme thymidylate synthase (an enzyme important in DNA repair and replication). Leucovorin is

readily converted to another reduced folate, 5,10-methylene-tetrahydrofolate, which acts to stabilize the binding of fluorodeoxyuridylic acid to thymidylate synthase and thereby enhance the inhibition of this enzyme.

A folic acid deficiency is produced during therapy with the folic acid antagonists, such as 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.

A clinical study had shown that when pregnant women received folic and folinic acid to determine placental transfer, the new born infants had normal weight and did not show any anomalies. Allergic sensitization has been reported after oral and parenteral administration of folic acid. Such sensitization may also occur with leucovorin calcium since it is a folic acid derivative. However, in general, leucovorin calcium is remarkably free of side effects. Methotrexate does not seem to affect the absorption of folate.

(i) Animal Pharmacology

A study was carried out to determine the differences in pharmacokinetic parameters of the diastereoisomers of citrovorum factor in dogs. The results indicated that d and l isomers have different pharmacokinetic behaviours with respect to the postdistribution plasma decay rates. The l isomer had a half-life of 47 ± 4 (SE) minutes compared to the half life of 143 ± 15 minutes for the d isomer. Plasma clearance of the l isomer was about 2.5 times its urinary clearance, which indicates that nonrenal mechanisms play a major role in the disposition of the l isomer. The apparent volume of distribution was approximately 58% for both isomers.

In animal studies, toxic manifestations from folinic acid were not observed.

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 (<https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada/adverse-reaction-reporting.html>) 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.

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