PRODUCT MONOGRAPH

Lederle LEUCOVORIN CALCIUM
calcium folinate
cryodesiccated powder for injection
liquid injection and oral tablets

Folic Acid Derivative

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SINCE LEUCOVORIN MAY ENHANCE THE TOXICITY OF FLUOROURACIL, LEUCOVORIN/FLUOROURACIL COMBINATION THERAPY 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 AND FLUOROURACIL. CONCOMITANT GRANULOCYTOPENIA AND FEVER WERE PRESENT IN SOME BUT NOT ALL OF THE PATIENTS.

CAUTION: DO NOT ADMINISTER LEUCOVORIN INTRATHECALLY.

ACTIONS, CLINICAL PHARMACOLOGY

Lederle LEUCOVORIN Calcium (calcium folinate), the calcium salt of folinic acid (citrovorum factor), is a mixture of the diastereoisomers of the 5-formyl derivative of tetrahydrofolic acid. The biologically active compound of the mixture is the (-)-L-isomer. It is a metabolite of folic acid and an essential coenzyme for nucleic acid synthesis.

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 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 may limit METHOTREXATE action on normal cells by competing with METHOTREXATE for the same transport processes into the cell. LEUCOVORIN rescues bone marrow and gastrointestinal cells from METHOTREXATE but has no apparent effect on pre-existing METHOTREXATE nephrotoxicity.

LEUCOVORIN is extensively converted to 5-methyltetrahydrofolate in the intestine prior to absorption. In this form, it is a major component of the total active human serum folate. Oral absorption is saturable at doses above 25 mg.

LEUCOVORIN enhances the cytotoxicity of fluoropyrimidines such as 5-fluorouracil (5FU) 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.

INDICATIONS

a) to diminish the toxicity and counteract the effect of impaired METHOTREXATE elimination.

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

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

d) for modulation of fluorouracil (5FU) as adjuvant therapy for patients with Dukes' B and C colon cancer.

CONTRAINDICATIONS

Not to be administered for the treatment of pernicious anemia or other megaloblastic anemias where Vitamin B_{12} is deficient. A hematologic remission may occur while neurologic manifestations continue to progress.

WARNINGS

In the treatment of accidental overdosages of folic acid antagonists, LEUCOVORIN should be administered as promptly as possible. As the time interval between the administration of antifolate and LEUCOVORIN increases, the effectiveness of LEUCOVORIN in counteracting toxicity decreases. Monitoring of the serum MTX concentration is essential in determining the optimal dose and duration of therapy. Delayed MTX excretion may be caused by a third space fluid accumulation (i.e., ascites, pleural effusion), renal insufficiency, low pH of urine, or inadequate hydration. Under such circumstances, higher doses of LEUC0VORIN or prolonged administration may be indicated. DO NOT ADMINISTER LEUCOVORIN INTRATHECALLY.

Cryodesiccated powder reconstituted with Bacteriostatic Water for Injection containing benzyl alcohol should only be used at doses below l0 mg/m^2. (See PRECAUTIONS).

Treatment-related deaths have been sporadically reported in patients treated with LEUC0VORIN plus fluorouracil combination therapy regimens. In general, diarrhea 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 incorporating LEUCOVORIN plus fluorouracil should be carefully followed and further therapy should be withheld until these symptoms resolve.

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 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/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 monitored with particular care 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 receiving 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 solutions, no more than 160 mg of LEUCOVORIN should be injected intravenously per minute.

If the cryodesiccated powder is reconstituted with Bacteriostatic Water for Injection containing 0.9% benzyl alcohol, doses greater than 10 mg/m^2 are not recommended due to the benzyl alcohol content. If greater doses are required (see DOSAGE & ADMINISTRATION), LEUCOVORIN Calcium for Injection (cryodesiccated powder) should be reconstituted with Sterile Water for Injection USP and used immediately, or the preservative-free liquid form, LEUCOVORIN Calcium Injection, should be used.

Leucovorin should not be mixed in the same infusion as 5-fluorouracil as a precipitate may form.

Drug Interactions:

Folic acid in large amounts 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 CSF primarily as 5-methyltetrahydrofolate and, in humans, remain 1-3 orders of magnitude lower than the usual METHOTREXATE concentrations following intrathecal administration. However, high doses of LEUCOVORIN may reduce the efficacy of intrathecally administered METHOTREXATE.

LEUCOVORIN may enhance the toxicity of fluorouracil (see WARNINGS).

Pregnancy: Teratogenic Effects:

Reproduction studies have been performed in rats and rabbits at doses at least 50 times the human dose and have revealed no evidence of harm to the fetus due to LEUCOVORIN.

There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Nursing Mothers:

It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when LEUCOVORIN is administered to a nursing mother.

Pediatric Use: See Drug Interactions

ADVERSE REACTIONS

Allergic sensitization, including anaphylactoid reactions and urticaria, has been reported following both oral and parenteral administration of folinic acid.

In combination regimens, the toxicity profile of 5FU 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 reversible with appropriate modification of 5FU administration.

SYMPTOMS & 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 l0 mg/day for 5 years.

Excessive amounts of LEUCOVORIN may nullify the chemotherapeutic effect of folic acid antagonists.

DOSAGE & ADMINISTRATION

Lederle LEUCOVORIN Calcium for Injection cryodesiccated powder 50 mg/vial, 100 mg/vial, 350 mg/vial may be used after reconstitution for intravenous or intramuscular administration. The liquid injection 350 mg/35 mL is used for intravenous or intramuscular administration. DO NOT ADMINISTER LEUCOVORIN INTRATHECALLY. Tablets are administered orally.

When Lederle LEUCOVORIN Calcium is used for LEUCOVORIN pre-treatment followed by 5-fluorouracil (5FU) in the treatment of patients with advanced colorectal cancer, intravenous administration is employed.

Because of the Ca^{++} content of LEUCOVORIN solutions, no more than 160 mg of LEUCOVORIN should be injected intravenously per minute.

Dosage

a) **Impaired METHOTREXATE Elimination or Accidental Overdosage:**

LEUCOVORIN rescue should begin as soon as possible after an inadvertent overdosage and within 24 hours of METHOTREXATE administration when there is delayed excretion (See WARNINGS). LEUCOVORIN 10 mg/m^2 should be administered IV, IM or PO every 6 hours until the serum METHOTREXATE level is less than 10^{-8} M. In the presence of gastrointestinal toxicity, nausea or vomiting, LEUCOVORIN should be administered parenterally. Because absorption is saturable, doses greater than 25 mg should be given intravenously. DO NOT ADMINISTER LEUCOVORIN INTRATHECALLY.

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 5×10^{-6} M or the 48 hour level is greater than 9×10^{-7} M, the dose of LEUCOVORIN should be increased to 100 mg/m^2 IV every 3 hours until the METHOTREXATE level is less than 10^{-8}M.

Hydration (3 L/d) 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.

b) **Megaloblastic Anemia Due to Folic Acid Deficiency:**

Up to 1 mg daily. There is no evidence that doses greater than 1 mg/day have greater efficacy than doses of 1 mg. The loss of folate in the urine becomes roughly logarithmic as the amount administered exceeds 1 mg.

c) **Advanced Colorectal Cancer:**

LEUCOVORIN is administered at 200 mg/m^2 by slow intravenous injection immediately prior to dosing with 370 mg/m^2 5FU (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. For patients who experienced no toxicity in the prior treatment course, fluorouracil dosage may be increased by 10%. LEUCOVORIN dosages are not adjusted for toxicity.

d) **Adjuvant therapy for patients with Dukes B and C colon cancer:**

LEUCOVORIN is administered intravenously as a 2-hour infusion at a dosage of 500 mg/m^2 weekly for 6 consecutive weeks followed by a 2-week rest. This regimen is repeated for a total of six cycles.

Treatment is repeated 21 days after the sixth dose of the previous course. Fluorouracil (5FU) is administered at a dose of 500 mg/m^2, on the same schedule as LEUCOVORIN, intravenously via bolus 1 hour after the IV has been started.

PHARMACEUTICAL INFORMATION

DRUG SUBSTANCE

Proper Name:

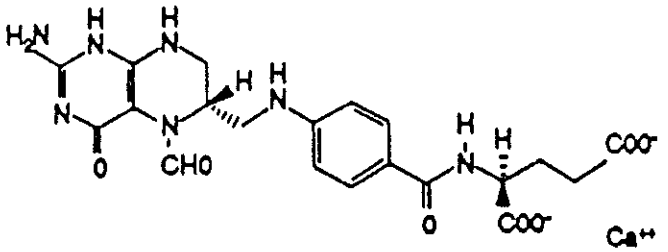
LEUCOVORIN Calcium (folic acid derivative) is also known as calcium folinate, citrovorum factor, or the calcium salt of 5-formyl-5,6,7,8-tetrahydrofolic acid.

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).

Structural Formula:



Empirical Formula: $C_{20}H_{21}CaN_7O_7$

Molecular Weight: 511.51

Description:

LEUCOVORIN Calcium occurs as a yellowish white or yellow, odourless powder. It is very soluble in water and practically insoluble in alcohol. It decomposes above 250° C. There is 0.004 mEq of calcium per mg of LEUCOVORIN in each dosage form.

COMPOSITION

LEUCOVORIN Calcium Injection (350 mg/35 mL):

Each vial of sterile LEUCOVORIN Calcium Injection contains 350 mg/35 mL LEUCOVORIN (as the calcium salt). The non-medicinal ingredients are sodium chloride (7.7 mg/mL) and Sterile Water for Injection. Sodium hydroxide and/or hydrochloric acid are used to adjust the pH to approximately 8.1. CONTAINS NO PRESERVATIVE. SINGLE DOSE VIAL. NOT FOR MULTIDOSE USE.

LEUCOVORIN Calcium for Injection (sterile cryodesiccated powder 50 mg/vial, 100 mg/vial, 350 mg/vial):

i. Each vial contains 50 mg of LEUCOVORIN as a sterile cryodesiccated LEUCOVORIN Calcium powder for Injection. The non-medicinal ingredient is sodium chloride (40 mg). Sodium hydroxide and/or hydrochloric acid are used to adjust the pH to approximately 8.1. CONTAINS NO PRESERVATIVE.

ii. Each vial contains 100 mg of LEUCOVORIN as a sterile cryodessiccated LEUCOVORIN Calcium powder for Injection. The non-medicinal ingredient is sodium chloride (80 mg). Sodium hydroxide and/or hydrochloric acid are used to adjust the pH to approximately 8.1. CONTAINS NO PRESERVATIVE.

iii. Each vial contains 350 mg of LEUCOVORIN as a sterile cryodesiccated LEUCOVORIN Calcium powder for Injection. The non-medicinal ingredient is sodium chloride (140 mg). Sodium hydroxide and/or hydrochloric acid are used to adjust the pH to approximately 8.1. CONTAINS NO PRESERVATIVE.

LEUCOVORIN Calcium Tablets 5 mg and 15 mg:

Each tablet contains 5 mg and 15 mg of LEUCOVORIN as LEUCOVORIN Calcium. These tablets are free of dyes.

RECONSTITUTION OF CRYODESICCATED POWDERS:

Reconstitution Table:

Vial Size	Volume of Diluent* To be Added to Vial	Approximate Available Volume	Nominal Concentration Per mL
50 mg/vial in 10 mL vial	2 mL to 10 mL	2 mL to 10 mL	25 mg/mL to 5 mg/mL
100 mg/vial in 20 mL vial	5 mL to 20 mL	5 mL to 20 mL	20 mg/mL to 5 mg/mL
350 mg/vial in 3O mL vial	17.5 mL to 25 mL	17.5 mL to 25 mL	20 mg/mL to 14 mg/mL

(*) For intravenous administration Sterile Water for Injection USP should be used. For intramuscular administration Sterile Water for Injection USP or Bacteriostatic Water for Injection USP may be used.

NOTE:

Doses greater than 10 mg/m^2 are not recommended when Bacteriostatic Water for Injection USP is used to reconstitute LEUCOVORIN cryodesiccated powders due to the benzyl alcohol content.

Due to the Ca^{++} content of LEUCOVORIN Calcium solutions for injection, no more than 160 mg of LEUCOVORIN Calcium should be administered intravenously per minute.

DILUTION OF RECONSTITUTED SOLUTIONS OR LIQUID FORMULATION FOR IV INFUSION: Reconstituted solutions of LEUCOVORIN Calcium that have been prepared with Sterile Water for Injection USP or the liquid formulation may be further diluted for intravenous infusion to concentrations of 0.060 mg/mL to 1.0 mg/mL with one of the following recommended solutions:

Dextrose 5% and 10% in water

Dextrose 10% in saline

Ringer's Injection USP

Lactated Ringer's Injection USP

Physiological Saline

All parenteral drug products should be visually inspected for particulate matter and discolouration prior to administration. Any solution found to have particulate matter or discolouration should be discarded.

STABILITY AND STORAGE RECOMMENDATIONS:

LEUCOVORIN Calcium Injection (350 mg/35 mL):

Vials of 350 mg/35 mL liquid should be stored at refrigerated temperatures (2-8°C). The liquid formulation should be used within 28 days once removed from refrigeration. Discard any unused

portion. Not for multidose use. The liquid formulation, when diluted with one of the recommended diluents for intravenous infusion, should be used within 24 hours following dilution when stored at room temperature (15-30°C).

LEUCOVORIN Calcium for Injection (sterile cryodesiccated powder 50 mg/vial, 100 mg/vial, 350 mg/vial):

Vials of cryodesiccated powders should be stored at controlled room temperature (15-30°C).

i) Reconstituted Solutions:

Reconstituted solutions for intravenous or intramuscular administration should be used immediately after reconstitution when Sterile Water for Injection USP is used as the diluent due to the possibility of microbial contamination during preparation. When reconstituted with Bacteriostatic Water for Injection USP for intramuscular injection, solutions should be used within 24 hours when stored at room temperature (15-30°C) or within 72 hours when refrigerated (2-8°C).

ii) Diluted Solutions for IV Infusion:

Reconstituted solutions that have been prepared with Sterile Water for Injection USP and then further diluted with one of the recommended diluents for intravenous infusion should be used within 24 hours following dilution when stored at room temperature (15-30°C).

LEUCOVORIN Calcium Tablets 5 mg and 15 mg:

Tablets should be stored at controlled room temperature (15-30°C).

DOSAGE FORMS

Availability:

Single dose vials of Liquid:

10 mg/mL. Each vial contains 350 mg LEUCOVORIN as LEUCOVORIN Calcium in solution.

Single 35 mL vial

10 x 35 mL vials

Vials of Cryodessicated Powders (50 mg/vial, l00 mg/vial, 350 mg/vial):

i. 50 mg/vial. Each 10 mL vial contains 50 mg LEUCOVORIN as LEUCOVORIN Calcium.

10 x 50 mg vials

ii. 100 mg/vial. Each 20 mL vial contains 100 mg LEUCOVORIN as LEUCOVORIN Calcium.

Single l00 mg vials

iii. 350 mg/vial. Each 30 mL vial contains 350 mg LEUCOVORIN as LEUCOVORIN Calcium.

Single 350 mg vial

10 x 350 mg vials

Tablets:

i. 5 mg tablets. Each tablet contains 5 mg of LEUCOVORIN as LEUCOVORIN Calcium.

Bottles of 24 tablets

Bottles of 100 tablets

ii. 15 mg tablets. Each tablet contains 15 mg of LEUCOVORIN as LEUCOVORIN Calcium.

Bottles of 24 tablets

PHARMACOLOGY

The pharmacokinetics after intravenous, intramuscular and oral administration of a 25 mg dose of LEUCOVORIN were studied in male volunteers.

After intravenous administration, serum total reduced folates (as measured by Lactobacillus casei assay) reached a mean peak of 1259 ng/mL (range 897-1625). The mean time to peak was lO minutes. This initial rise in total reduced folates was primarily due to the parent compound 5-formyl-THF (measured by Streptococcus faecalis assay) which rose to 1206 ng/mL at lO minutes. A sharp drop in parent compound followed and coincided with the appearance of the metabolite (also active), 5-methyl-THF, which became the predominant circulating form of the drug. The mean peak of 5-methyl-THF was 258 ng/mL and occurred at 1.3 hours. The terminal half-life for total reduced folates was 6.2 hours.

After intramuscular injection, the mean peak of serum total reduced folates was 436 ng/mL (range

240-725) and occurred at 52 minutes. Similar to IV administration, the initial sharp rise was due to the parent compound. The mean peak of 5-formyl-THF was 360 ng/mL and occurred at 28 minutes. The level of the metabolite 5-methyl-THF increased subsequently over time until at 1.5 hours it represented 50% of the circulating total folates. The mean peak of 5-methyl-THF was 226 ng/mL at 2.8 hours. The terminal half-1ife of total reduced folates was 6.2 hours. There was no difference of statistical significance between IM and IV administration in the AUC for total reduced folates, 5-formyl-THF or 5-methyl-THF.

After oral administration of LEUCOVORIN reconstituted with the aromatic elixir, the mean peak concentration of serum total reduced folates was 393 ng/mL (range 160-550). The mean time to peak was 2.3 hours and the terminal half-life was 5.7 hours. The major component was the metabolite 5-methyltetrahydrofolate to which LEUCOVORIN is partially converted in the intestinal mucosa. The mean peak of 5-methyl-THF was 367 ng/mL at 2.4 hours. The peak level of the parent compound was 51 ng/mL at 1.2 hours. The AUC of total reduced folates after oral administration of the 25 mg dose 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.

LEUCOVORIN can enhance the therapeutic and toxic effects of fluoropyrimidines used in cancer therapy, such as fluorouracil. 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 enchances the inhibition of this enzyme.

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.

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