

COMPLETE PRESCRIBING INFORMATION

Pr **RIVA LEUCOVORIN**

Leucovorin Calcium Tablets, USP

5 mg Leucovorin (as Leucovorin Calcium)

Folic Acid Derivative

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Leucovorin Calcium Tablets, USP

Folic Acid Derivative

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.

ACTIONS, CLINICAL PHARMACOLOGY

RIVA LEUCOVORIN (leucovorin calcium, also known as 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 component of the mixture is the (-)-L-isomer. It is a metabolite of folic acid and an essential coenzyme for nucleic acid synthesis used in cytotoxic therapy.

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

Leucovorin calcium 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 calcium 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.

CONTRAINDICATIONS

Leucovorin calcium therapy is contraindicated in patients with:

- **Known hypersensitivity to the active substance or to any of the excipients.**
- **Pernicious anemia or other megaloblastic anemias where Vitamin B12 is deficient. A hematologic remission may occur while neurologic manifestations continue to progress.**

For a complete listing, see PHARMACEUTICAL INFORMATION, COMPOSITION.

WARNINGS

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.

In the treatment of accidental overdoses of folic acid antagonists, RIVA LEUCOVORIN (also known as calcium folinate) should be administered as promptly as possible. As the time interval between the administration of antifolate and RIVA LEUCOVORIN rescue increases, the effectiveness of leucovorin in counteracting toxicity decreases. Monitoring of the serum methotrexate (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 RIVA LEUCOVORIN or prolonged administration may be indicated.

Treatment-related deaths have been sporadically reported in patients treated with leucovorin calcium 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 RIVA LEUCOVORIN plus fluorouracil should be carefully followed and further therapy should be withheld until these symptoms resolve.

Leucovorin calcium 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 calcium 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 RIVA 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

Leucovorin calcium treatment may mask pernicious anemia and other megaloblastic anemias resulting from vitamin B12 deficiency.³²

Leucovorin calcium should only be used with 5-fluorouracil or methotrexate under the direct supervision of a clinician experienced in the use of cancer chemotherapeutic agents.

Many cytotoxic medicinal products – direct or indirect DNA synthesis inhibitors – lead to macrocytosis (hydroxycarbamide, cytarabine, mercaptopurine, thioguanine). Such macrocytosis should not be treated with folic acid.

In epileptic patients treated with phenobarbital, phenytoin, primidone, and succinimides there is a risk to increase the frequency of seizures due to a decrease of plasma concentrations of anti-epileptic drugs. Clinical monitoring, possibly monitoring of the plasma concentrations and, if necessary, dose adaptation of the anti-epileptic drug during leucovorin calcium administration and after discontinuation is recommended.^{33, 34}

Drug Interactions:

Leucovorin calcium may diminish the effect of anti-epileptic substances: phenobarbital, primidone, phenytoin and succinimides, and may increase the frequency of seizures (a decrease of plasma levels of enzymatic inductor anticonvulsant drugs may be observed because the hepatic metabolism is increased as folates are one of the cofactors).^{33, 34}

When leucovorin calcium is given in conjunction with a folic acid antagonist (eg, cotrimoxazole, pyrimethamine, methotrexate, antibiotic with antifolic effect) the efficacy of the folic acid antagonist may either be reduced or completely neutralised.²⁹

Preliminary animal and human studies have shown that small quantities of systemically administered leucovorin calcium 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 RIVA LEUCOVORIN may reduce the efficacy of intrathecally administered methotrexate.

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

Pregnancy: Teratogenic Effects:

There are no adequate and well-controlled clinical studies conducted in pregnant or breast-feeding women. There are no indications that folic acid induces harmful effects if administered during pregnancy. During pregnancy, 5-fluorouracil and methotrexate should only be administered on strict indications, where the benefits of the drug to the mother should be weighed against possible hazards to the foetus. Should treatment with methotrexate or other folate antagonists take place despite pregnancy or lactation, there are no limitations as to the use of leucovorin calcium to diminish toxicity or counteract the effects.

5-fluorouracil use is generally contraindicated during pregnancy and contraindicated during breast-feeding; this applies also to the combined use of leucovorin calcium with 5-fluorouracil.

Please refer also to the health-care professional label for methotrexate, other folate antagonists and 5-fluorouracil-containing medicinal products.

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 RIVA LEUCOVORIN is administered to a nursing mother.

Fertility

No formal animal reproductive toxicity studies with leucovorin calcium have been conducted.

Pediatric Use:

There are no data available in children.

Laboratory Tests

The following provides general advice for monitoring patients; however, specific monitoring recommendations may vary with local medical practice.

5-FU/leucovorin calcium therapy

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.

Methotrexate/leucovorin calcium therapy

Serum creatinine levels and serum methotrexate levels: at least once daily.

Urine pH: in cases of methotrexate overdose or delayed excretion, monitor as appropriate, to ensure maintenance of pH \geq 7.0.

ADVERSE REACTIONS

Allergic sensitization, including anaphylactoid/anaphylactic reactions (including shock) and urticaria, has been reported following administration of leucovorin calcium.

In combination regimens, the toxicity profile of 5FU is enhanced by leucovorin calcium (leucovorin calcium, also known as calcium folinate). 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.

Leucovorin Calcium

System Organ Class

Adverse Reaction

Immune system disorders

Frequency undetermined

Very Rare

Allergic reactions, urticaria

Anaphylactoid/ anaphylactoid reactions (including shock)

Nervous System disorders

Rare

Seizures and/or syncope³⁰

General disorders and administration site conditions

Frequency undetermined

Fever²⁹

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.

Leucovorin Calcium in Combination with 5-FU

In combination regimens, the toxicity profile of 5FU is enhanced by leucovorin calcium (leucovorin calcium, also known as calcium folinate). 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.

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:

System Organ Class	Adverse Reaction
<i>Gastrointestinal disorders</i> Very common	Nausea and Vomiting ³¹ diarrhea
<i>Hepatobiliary disorders</i> Frequency undetermined	Hyperammonemia
<i>Skin and subcutaneous tissue disorders</i> Common	Palmar-Plantar Erythrodysesthesia
<i>General disorders and administration site conditions</i> Very common	Mucositis, including stomatitis and chelitis

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.²⁹

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 calcium), which is rapidly eliminated in the urine.

Folic acid has low acute and chronic toxicity in man. **There have been no reported sequelae in patients who have received significantly more leucovorin calcium than the recommended dosage. However, excessive amounts of RIVA LEUCOVORIN (leucovorin calcium, also known as calcium folinate) may nullify the chemotherapeutic effect of folic acid antagonists.** 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.

Should overdose of the combination of 5-fluorouracil and leucovorin calcium occur, the overdose instructions for 5-FU should be followed.

For the management of suspected drug overdose, contact your regional Poison Control Centre.

DOSAGE & ADMINISTRATION

Tablets are administered orally.

Dosage

a) Impaired Methotrexate Elimination or Accidental Overdosage:

RIVA LEUCOVORIN rescue should begin as soon as possible after an inadvertent overdose and within 24 hours of methotrexate administration when there is delayed excretion (See WARNINGS).

There are no fixed guidelines regarding the dose of methotrexate that triggers an automatic subsequent leucovorin calcium administration, since tolerance to this folate antagonist depends on various factors. The dose of methotrexate varies, nevertheless folinate rescue is necessary when methotrexate is given at doses exceeding 500 mg/m² and has to be considered with doses of 100 mg - 500 mg/m².

Leucovorin calcium rescue treatment should commence approximately 24 hours after the beginning of methotrexate infusion. Dosage regimens vary depending upon the dose of methotrexate administered. In general, leucovorin calcium should be administered at a dose of 15 mg (approximately 10 mg/m²) every 6 hours for 10 doses, either parenterally by intramuscular injection, bolus intravenous injection, intravenous infusion, or orally using leucovorin calcium tablets.

If serum creatinine increases after methotrexate therapy or if methotrexate plasma concentrations are above certain threshold (see table 1), the dose of leucovorin calcium should be increased according to the plasma methotrexate concentrations, as soon as the risk is recognized. In the presence of gastrointestinal toxicity, nausea, or vomiting, leucovorin calcium should be administered parenterally. In the case of intravenous administration, no more than 160 mg of leucovorin calcium should be injected per minute due to the calcium content of the solution.³⁵ Further, oral administration of doses greater than 25 mg is not recommended since the digestive absorption of leucovorin calcium is saturable; these doses should be administered parenterally.

In addition to leucovorin calcium administration, measures to ensure the prompt excretion of methotrexate are an integral part of the leucovorin calcium rescue treatment. These measures include:

- a) Maintenance of urine output above 2,500 mL/24hr in adults by increased oral or intravenous fluids 12 hours before and for 36 hours after the end of methotrexate infusion.
- b) Alkalinisation of urine so that the urinary pH is greater than 7.0 before methotrexate infusion. Foods, drinks and drugs that may increase urinary acidity should be avoided during the therapy.
- c) Plasma methotrexate concentration and serum creatinine should be measured at least 24, 48, and 72 hours after the initiation of the methotrexate infusion. These measurements must be continued until the plasma methotrexate level is less than 5×10^{-8} molar (0.05 mcM).

Delayed methotrexate excretion may be seen in some patients. This may be caused by a third space accumulation (as seen in ascites or pleural effusion for example), renal insufficiency or inadequate hydration. See also section 6. Under such circumstances, higher doses of leucovorin calcium and/or prolonged administration may be indicated. Some dosage and administration guidelines are given in Table 1.

Table 1: Dosage and Administration Guidelines for Leucovorin Calcium Rescue

Clinical situation	Laboratory findings	Leucovorin calcium dosage and duration
Normal methotrexate elimination	Serum methotrexate level ≤ 10 mcM at 24 hours after administration, ≤ 1 mcM at 48 hours, and < 0.1 mcM at 72 hours.	15 mg PO, IM, or IV every 6 hours for 60 hours (10 doses starting at 24 hours after start of methotrexate infusion).
Delayed late methotrexate elimination	Serum methotrexate level remaining > 0.1 mcM at 72 hours, and > 0.1 mcM at 96 hours after administration.	Continue 15 mg PO, IM, or IV every 6 hours, until methotrexate level is less than 0.1 mcM.
Delayed early methotrexate elimination and/or evidence of acute renal failure	Serum methotrexate level of > 10 mcM at 24 hours, or > 1 mcM at 48 hours after administration OR a 100% or greater increase in serum creatinine level at 24 hours after methotrexate administration.	150 mg IV every 3 hours, until methotrexate level is less than 1 mcM; then 15 mg IV every 3 hours until methotrexate level is less than 0.1 mcM.

Hydration (3 L/d) and urinary alkalization with NaHCO₃ 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 up to 15 mg daily have been suggested.³⁵

PHARMACEUTICAL INFORMATION

DRUG SUBSTANCE

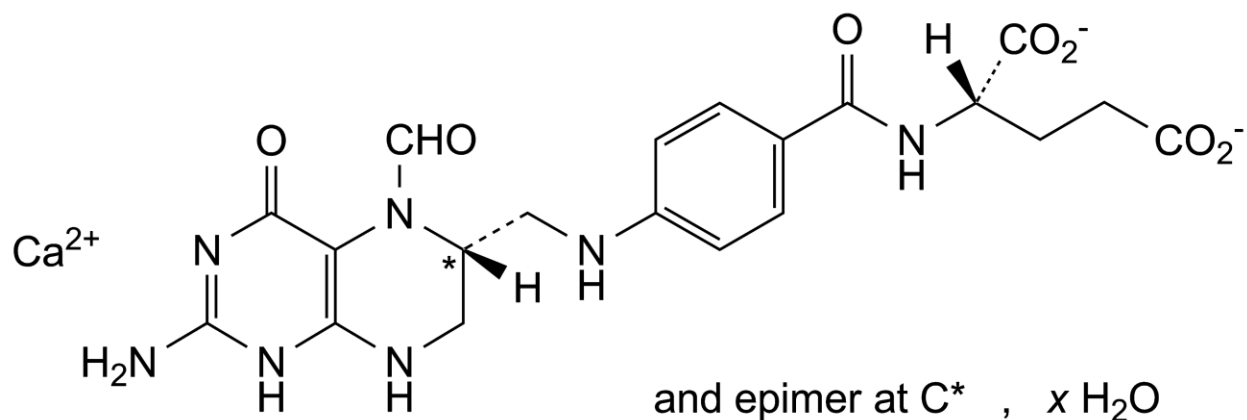
Proper Name:

Leucovorin Calcium (USP) also known as Calcium folinate hydrate in Ph. Eur..

Chemical Name:

Calcium (2S)-2-[4-[[[(6RS)-2-amino-5-formyl-4-oxo-1,4,5,6,7,8-hexahydropteridin-6-yl]methyl]amino]benzamido]pentanedioate hydrate.

Structural Formula:



Empirical Formula: C₂₀H₂₁CaN₇O₇ x H₂O

Molecular Weight: 511.5 g/mol (calculated on the anhydrous basis)

Description: Leucovorin Calcium occurs as a white to light yellow, crystalline powder. There is 0.004 mEq of calcium per mg of leucovorin in each tablet.

Solubility: Leucovorin Calcium is very soluble in water and practically insoluble in ethanol and acetone.

pH: 6.8-8.0

pKa: 3.1 – 4.8 – 10.4

Melting Point: The substance does not have a melting point. It decomposes above 250°C.

Hygroscopicity: The substance is hygroscopic.

COMPOSITION

RIVA LEUCOVORIN (Leucovorin Tablets 5 mg):

Each tablet contains 5 mg of Leucovorin as Leucovorin Calcium (also known as Calcium Folate Tablets). Non-medicinal ingredients are: Colloidal Silicon Dioxide, Croscarmellose Sodium, Magnesium Stearate, Microcrystalline Cellulose and Monohydrate Lactose.

STABILITY AND STORAGE RECOMMENDATIONS:

RIVA LEUCOVORIN Tablets 5 mg:

Tablets should be stored at 15-30°C. Protect from light.

DOSAGE FORMS

Availability:

5 mg tablets: Each tablet contains 5 mg of Leucovorin as Leucovorin Calcium.

RIVA LEUCOVORIN 5 mg tablets are supplied as white to off white, round convex tablets, engraved "IT" above bisect and "54" below bisect on one side, other side is plain.

Bottles of 24 tablets

Bottles of 100 tablets

CLINICAL TRIALS

Comparative Bioavailability Studies

A comparative bioavailability study was performed in 26 normal, healthy, adult, male subjects under fasting conditions. The rate and extent of absorption of leucovorin calcium was measured and compared following a single oral dose of RIVA LEUCOVORIN (Leucovorin Calcium) or Lederle Leucovorin® tablets. The results from measured data are summarized in the table below.

Leucovorin Calcium (1 x 5 mg) From measured data Geometric Mean Arithmetic Mean (CV %)

Parameter	RIVA LEUCOVORIN	Lederle Leucovorin®†	%Ratio of Geometric Means*	(90%) Confidence Interval
AUC _T (ng.h/mL)	2823.9436 2893.105 (20.882)	2751.1990 2850.564 (26.229)	102.6441	98.0484 – 107.4552
AUC _I (ng.h/mL)	3105.8066 3178.882 (21.193)	3023.5326 3134.299 (27.057)	102.7211	98.0397 – 107.6260
C _{MAX} (ng/mL)	257.1969 262.408 (18.642)	247.6311 255.324 (24.117)	103.8629	98.7767 – 109.2111
T _{MAX} § (hr)	1.500 (1.000 – 2.670)	1.500 (1.250 – 2.670)	--	--
T _{1/2} € (hr)	10.415 (14.027)	10.337 (14.028)	--	--

* Expressed as Geometric Least Squares Means

† Lederle® (Leucovorin Calcium) Tablets 5 mg - Manufactured by: Pfizer Canada Inc. Kirkland, Quebec H9J 2M5

§ Expressed as the median (min - max)

€ Expressed as the arithmetic mean (CV %) only

PHARMACOLOGY

The pharmacokinetics after intravenous, intramuscular and oral administration of a 25 mg dose of leucovorin calcium 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 10 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 10 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-life 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 calcium 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 calcium 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 calcium is rapidly absorbed and enters the general body pool of reduced folates. Folate is concentrated in the liver and cerebrospinal fluid although distribution occurs to all body tissues. Folates are mainly excreted in the urine, with small amounts in the faeces. Parenteral administration of leucovorin calcium gives higher peak plasma levels than oral administration, but the total plasma folate pool of folinic acid plus its metabolite (N⁵methyl—H₄-folate) remains unchanged. Oral absorption of leucovorin calcium is saturable at doses above 25 mg.³⁶ The apparent bioavailability of leucovorin calcium was 97% for 25 mg, 75% for 50 mg and 37% for 100 mg.

Leucovorin calcium is the calcium salt of 5-formyl tetrahydrofolic acid. It is an active metabolite of folinic acid and an essential coenzyme of nucleic acid synthesis in cytotoxic chemotherapy. Leucovorin calcium is frequently used to diminish the toxicity and counteract the action of folate antagonists, such as methotrexate. Leucovorin calcium and folate antagonists share the same membrane transport carrier and compete for transport into cells, stimulating folate antagonist efflux. It also protects cells from the effect of folate antagonists by repletion of the reduced folate pool. Leucovorin calcium serves as a pre-reduced source of H₄ folate: it can therefore bypass

folate antagonist blockage and provide a source for the various coenzyme forms of folic acid. Leucovorin calcium is also frequently used in the biochemical modulation of fluoropyridine (5-FU) to enhance its cytotoxic activity. 5-FU inhibits thymidylate synthase (TS), a key enzyme involved in pyrimidine biosynthesis, and leucovorin calcium enhances TS inhibition by increasing the intracellular folate pool, thus stabilizing the 5-FU-TS complex and increasing 5-FU activity.

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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THE INFORMATION FOR THE CONSUMER

**Pr RIVA LEUCOVORIN
Leucovorin Calcium Tablets, USP**

This leaflet is designed specifically for Consumers. This leaflet is a summary and will not tell you everything about RIVA LEUCOVORIN. Contact your doctor or pharmacist if you have any questions about the drug.

ABOUT THIS MEDICATION

What the medication is used for:

The medication is used -

- 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.

What it does:

RIVA LEUCOVORIN is a reduced form of folic acid. RIVA LEUCOVORIN limits methotrexate action on normal cells by competing with methotrexate for the same transport processes into the cell. RIVA LEUCOVORIN rescues bone marrow and gastrointestinal cells from methotrexate but has no apparent effect on pre-existing methotrexate nephrotoxicity.

When it should not be used:

Do not take RIVA LEUCOVORIN

- if you are allergic (hypersensitive) to leucovorin calcium or any of the other ingredients of RIVA LEUCOVORIN OR
- If you have megaloblastic anaemia due to Vitamin B₁₂ deficiency

What the medicinal ingredient is:

Leucovorin Calcium (also known as calcium folinate).

What the important nonmedicinal ingredients are:

Non-medicinal ingredients are: Colloidal Silicon Dioxide, Croscarmellose Sodium, Magnesium Stearate, Microcrystalline Cellulose and Monohydrate Lactose.

What dosage forms it comes in:

Tablet: 5 mg Leucovorin as Leucovorin calcium

WARNINGS AND PRECAUTIONS

In very rare cases sloughing of the skin, rarely leading to death, has been reported in patients receiving leucovorin along with other medications known to have similar side-effects.

RIVA LEUCOVORIN should only be used under the direct supervision of a clinician experienced in the use of cancer chemotherapeutic agents.

BEFORE you use RIVA LEUCOVORIN, talk to your doctor or pharmacist if:

- you have symptoms of gastrointestinal disorders.
- you are taking cytotoxic drugs (hydroxycarbamide cytarabine, mercaptopurine, thioguanine).
- you are epileptic and are being treated with phenobarbital, primidone, phenytoin and succinimides.
- you are pregnant or nursing.

INTERACTIONS WITH THIS MEDICATION

RIVA LEUCOVORIN can interfere with the breakdown or metabolism of certain drugs. In particular, you should inform your doctor if you are taking any of the following:

- Cytotoxic drugs - 5-fluorouracil (5FU), Methotrexate (High doses of RIVA LEUCOVORIN may reduce the efficacy of methotrexate. RIVA LEUCOVORIN may enhance the toxicity of fluorouracil.)
- Folic acid antagonists – cotrimxazole, pyrimethamine
- Anti-epileptic substances - phenobarbital, primidone, phenytoin and succinimides.

PROPER USE OF THIS MEDICATION

Usual dose:

Take your dose as prescribed by the physician.

Overdose:

If you take too much RIVA LEUCOVORIN (Overdose):

- Immediately call your doctor or go to the nearest hospital emergency department
- Do this even if you have no signs of discomfort
- Always take the labelled medicine bottle with you, even if it is empty

If you think you have taken too much RIVA LEUCOVORIN, contact your healthcare professional, hospital emergency department or regional poison control centre immediately, even if there are no symptoms.

Missed Dose:

Not Applicable.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

Undesirable effects have been rarely reported.

Allergic sensitization, including anaphylactoid/anaphylactic reactions (including shock) and urticaria, has been reported following administration of folinic acid.

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM

Symptom / effect		Talk with your doctor or pharmacist		Stop taking drug and call your doctor or pharmacist
		Only if severe	In all cases	
Very Common	Mucositis (swelling and/or ulcers of the mouth, lip, throat and upper gastrointestinal tract)		✓	
	Stomatitis (mouth ulcers)		✓	
	Chelitis (swelling of the lip)		✓	
Common	Nausea		✓	
	Vomiting		✓	
	Diarrhea		✓	
	Palmar-Plantar Erythrodysesthesia (Hand and Foot Syndrome)		✓	
Uncommon	Allergic reactions		✓	
	Any skin disorders		✓	
Rare	Seizures /syncope (Fainting / Dizziness)		✓	
Very Rare	Anaphylactoid / anaphylactic reactions (including shock)		✓	
Frequency undetermined	Allergic reactions, urticaria		✓	
	Fever		✓	
	Hyperammonemia (excess ammonia in the blood)		✓	

This is not a complete list of side effects. For any unexpected effects while taking RIVA LEUCOVORIN, contact your doctor or pharmacist.

HOW TO STORE IT

Tablets should be stored at 15-30°C. Protect from light.

Keep out of reach and sight of children.

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 more 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.

MORE INFORMATION

If you want more information about RIVA LEUCOVORIN:

- Talk to your healthcare professional;
- Find the full Product Monograph that is prepared for healthcare professionals and includes this Consumer Information by visiting the Health Canada website (<https://health-products.canada.ca/dpd-bdpp/index-eng.jsp>); the manufacturer's website www.labriva.com, or by calling 1-800-363-7988.

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