

COMPLETE PRESCRIBING INFORMATION

PrMINT-LEUCOVORIN

Leucovorin calcium tablets, USP

5 mg Leucovorin (as Leucovorin Calcium)

Folic Acid Derivative

**Mint Pharmaceuticals Inc.
6575 Davand Drive
Mississauga, Ontario
L5T 2M3**

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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

MINT-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 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.

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, leucovorin (leucovorin calcium) should be administered as promptly as possible. As the time interval between the administration of antifolate and 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 leucovorin or prolonged administration may be indicated.

Treatment-related deaths have been sporadically reported in patients treated with leucovorin 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

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 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:

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 MINT-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 ≥ 7.0 .

ADVERSE REACTIONS

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

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

System Organ Class	Adverse Reaction
<i>Immune system disorders</i>	
Frequency undetermined	Allergic reactions, urticarial
Very Rare	Anaphylactoid/ anaphylactoid reactions (including shock)
<i>Nervous System disorders</i>	
Rare	Seizures and/or syncope ³⁰
<i>General disorders and administration site conditions</i>	
Frequency undetermined	Fever ²⁹

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 in Combination with 5-FU

In combination regimens, the toxicity profile of 5FU is enhanced by Leucovorin (leucovorin calcium). 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 cheilitis

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), 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 leucovorin (leucovorin calcium) 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 overdosage of the combination of 5-fluorouracil and leucovorin calcium occur, the overdosage 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

Impaired Methotrexate Elimination or Accidental Overdosage:

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 solution³⁵. 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 μ m).

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 $\leq 10 \mu\text{M}$ at 24 hours after administration, $\leq 1 \mu\text{M}$ at 48 hours, and $< 0.1 \mu\text{M}$ 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 $> 0.1 \mu\text{M}$ at 72 hours, and $> 0.1 \mu\text{M}$ at 96 hours after administration.	Continue 15 mg PO, IM, or IV every 6 hours, until methotrexate level is less than $0.1 \mu\text{M}$.
Delayed early methotrexate elimination and/or evidence of acute renal failure	Serum methotrexate level of $> 10 \mu\text{M}$ at 24 hours, or $> 1 \mu\text{M}$ 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 $1 \mu\text{M}$; then 15 mg IV every 3 hours until methotrexate level is less than $0.1 \mu\text{M}$.

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.

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

Doses up to 15 mg daily have been suggested.³⁵

PHARMACEUTICAL INFORMATION

DRUG SUBSTANCE

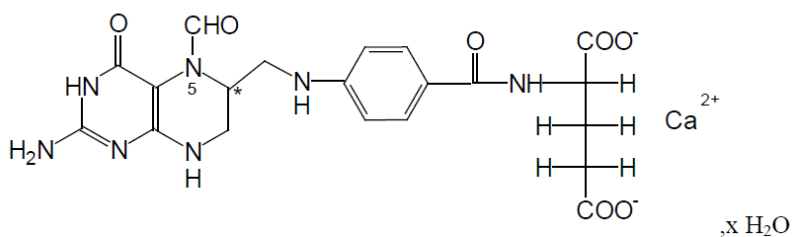
Proper Name:

Leucovorin Calcium (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:

- Calcium (2S)-2-[[4[[[(6RS)-2-amino-5-formyl-4-oxo-1,4,5,6,7,8-hexahydropteridin-6-yl]methyl]amino]benzoyl]amino]pentanedioate.
- Calcium N-[4-[[[(2-amino-5-formyl-1,4,5,6,7,8-hexahydro-4-oxo-6-pteridiny]methyl]amino]benzoyl]-L-glutamate

Structural Formula:



* chiral center

Empirical Formula: C₂₀H₂₁CaN₇O₇ · H₂O

Molecular Weight: 511.5g/mol (anhydrous substance)

Description:

White or light yellow crystalline hygroscopic powder. It is sparingly soluble in water, practically insoluble in acetone. and in ethanol 96 %.

COMPOSITION

Leucovorin (Leucovorin calcium Tablets) 5 mg:

Each tablet contains 5 mg of Leucovorin as Leucovorin Calcium. Non-medicinal ingredients are: Lactose Monohydrate, Magnesium Stearate, Microcrystalline Cellulose, Sodium Starch

Glycolate and Partially Pregelatinized Maize Starch.

STABILITY AND STORAGE RECOMMENDATIONS:

Leucovorin Tablets 5 mg:

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

DOSAGE FORMS

Availability:

Tablets:

5 mg tablets: Each tablet contains 5 mg of Leucovorin as Leucovorin Calcium. MINT-LEUCOVORIN is available in HDPE bottles of 24 tablets and 100 tablets.

5 mg Tablet: white to off white, round, biconvex, uncoated tablets debossed with ‘L’ and ‘5’ on either side of break line on one side and ‘MN’ on the other side.

CLINICAL TRIALS

Comparative Bioavailability Studies

A randomized, double blind, balanced, two treatment, two period, two sequence, single dose (1 x 5 mg), two way crossover bioequivalence study was conducted comparing Mint-Leucovorin (Mint Pharmaceuticals Inc.) with ^{Pr}Lederle Leucovorin[®] (Pfizer Canada Inc.) in 36 healthy human adult male subjects under fasting conditions.

Leucovorin (1 × 5 mg) From measured data				
Geometric Mean Arithmetic Mean (CV %)				
Parameter	Test*	Reference†	% Ratio of Geometric Means	90% Confidence Interval
AUC _{0-t} (ng.hr/mL)	3160.93 3298.46 (28.58)	2809.75 2976.51 (31.14)	112.5	103.2 - 122.6
AUC ₁ (ng.hr/mL)	3442.25 3598.08 (29.43)	3075.50 3269.84 (33.24)	111.9	102.9 – 121.6
C _{max} (ng/mL)	288.26 302.11 (29.97)	258.82 270.69 (27.63)	111.2	101.8 - 121.5
T _{max} [§] (hr)	1.50 (0.75-2.50)	1.25 (1.00-2.25)		
T _{1/2} [#] (hr)	9.96 (16.94)	9.96 (16.34)		

* Mint-Leucovorin tablets 5 mg (as leucovorin calcium) (Mint Pharmaceuticals Inc.)

† PrLederle Leucovorin[®] tablets 5 mg (as leucovorin calcium) (Pfizer Canada Inc.)

§ Expressed as the median (range) only

Expressed as the arithmetic mean (CV%) only

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 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 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. 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 is saturable at doses above 25 mg.³⁶ The apparent bioavailability of Leucovorin 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.

BIBLIOGRAPHY

1. Borrie P: Megaloblastic Anaemia during Methotrexate Treatment of Psoriasis. Br Med J. 1966; 1:1339.
2. Izak G: The Effect of Small Doses of Folic Acid in Nutritional Megaloblastic Anaemia. Amer J Clin Nutr. 1973; 13:369-377.
3. Mane J et al: Congenital Folate-Dependent Megaloblastic Anaemia of Unknown Aetiology. Lancet. 1977; Jan:262.
4. Mehta BM et al: Serum Distribution of Citrovorum Factor and 5-methyltetrahydrofolate following Oral and Intramuscular Administration of Calcium Leucovorin in Normal Adults. Cancer Treatment Reports. 1978; 62(3):345-350.
5. Nixon PF and Bertino JR: Effective Absorption and Utilization of Oral Formyltetrahydrofolate in Man. New Eng J of Med. 1972;286:175-179.
6. Pratt RF and Cooper BA: Folates in Plasma and Bile of Man after Feeding Folic Acid - 3H and 5-Formyltetrahydrofolate (Folinic Acid). J Clin Inv. 1971; 50:455-462.
7. Roman J et al: The Occurrence of Megaloblastic Anaemia with Normal Serum Folate during Antipurine Therapy. Clin Res. 1973;21(1):94.
8. Scott JM: Folinic Acid in Megaloblastic Anaemia of Pregnancy. Br Med J. 1957; Aug:270-272.
9. Stokes PL et al: Folate Metabolism in Scurvy. Am J Clin Nutr. 1975; 28:126-139.
10. Su PC: Congenital Folate Deficiency. N Eng J Med. 1976; May:1128.
11. Whitehead VM et al: Response to Folinic Acid In B₁₂ Deficiency. Lancet. 1979; September:552-554.
12. Straw JA, Szapary D and Wynn WT: Pharmacokinetics of the diastereoisomers of Leucovorin after intravenous and oral administration to normal subjects. Cancer Res. 1984; 44:3114-3119.
13. Straw JA, Newman EM, Doroshov JH: Pharmacokinetics of Leucovorin (D, L-formyltetrahydrofolate) after intravenous injection and constant intravenous infusion. NCI Monogr. 1987; 5:41-45.
14. McGuire BW, Sia LL, Stokstad ELR et al: Absorption kinetics of orally administered Leucovorin calcium. NCI Monogr. 1987;5:47-56.

15. Hines JD, Zakem MH, Adelstein OJ et al: Bioavailability of high-dose oral LEUOVORIN. NCI Monogr. 1987;5:57-60.
16. DeLap RJ: The effort of Leucovorin on the therapeutic index of fluorouracil in cancer patients. Yale J Biol Med. 1988; 61:23-34.
17. O'Connell MJ, Klaassen DJ, Everson LK et al: Clinical studies of biochemical modulation of 5-fluorouracil by Leucovorin in patients with advanced colorectal cancer by the North Central Cancer Treatment Group and Mayo Clinic. NCI Monogr. 1987; 5:185-188.
18. O'Connell MJ, Wieand HS: A controlled clinical trial including folinic acid at two distinct dose levels in combination with 5-fluorouracil (5FU) for the treatment of advanced colorectal cancer: Experience of the Mayo Clinic and North Central Cancer Treatment Group. In: The Expanding Role of Folates and Fluoropyrimidines In Cancer Chemotherapy. An International Symposium. Roswell Park Memorial Institute, Buffalo, NY, April 28-29, 1988.
19. Erlichman C, Fine S, Wong A et al: A randomized trial of fluorouracil and folinic acid in patients with metastatic colorectal carcinoma. J Clin Oncol. 1988;6:469-475.
20. Petrelli N, Herrera L, Rustum Y et al: A prospective randomized trial of 5-fluorouracil versus 5-fluorouracil and high-dose Leucovorin versus 5-fluorouracil and methotrexate in previously untreated patients with advanced colorectal carcinoma. J Clin Oncol. 1987; 5:1559-1565.
21. Creaven PJ: 5-Fluorouracil (5-FU) and citrovorum factor (CF). A review of clinical experience. In The Expanding Role of Folates and Fluoropyrimidines in Cancer Chemotherapy. An International Symposium. Roswell Park Memorial Institute, Buffalo, N.Y., April 28-29, 1988.
22. Laufman LR, Krzeczowski KA, Roach R et al: Leucovorin plus 5-fluorouracil: An effective treatment for metastatic colon cancer. J Clin Oncol. 1987;5:1394-1400.
23. Budd GT, Fleming TR, Bukowski RM et al: 5-Fluorouracil and folinic acid in the treatment of metastatic colorectal cancer: A randomized comparison. A Southwest Oncology Group Study. J Clin Oncol. 1987; 5:272-277.
24. Marini G, Zaniboni A, Gorni F et al: Clinical experience with 5-fluorouracil (5-FU) and high-dose folinic acid in solid tumors. Drug Exptl Clin Res. 1987;XIII:373-376.
25. Bertrand M, Doroshow JH, Multhaus P et al: High-dose continuous infusion folinic acid and bolus 5-Fluorouracil in patients with advanced colorectal cancer: A phase II study. J Clin Oncol. 1986; 4:1058-1061.

26. Willke H, Schmoll HJ, Schober C et al: High-dose folinic acid (FA) plus 5-fluorouracil (5-FU) in advanced and progressive colorectal cancer. In *The Expanding Role of Folates and Fluoropyrimidines in Cancer Chemotherapy. An International Symposium*, Roswell Park Memorial Institute, Buffalo, NY, April 28-29, 1988.
27. Machover D, Goldschmidt E, Chollet P et al: Treatment of advanced colorectal and gastric adenocarcinomas with 5-fluorouracil and high-dose folinic acid. *J Clin Oncol.* 1986; 4:685-696.
28. Wolmark N, Rockette H, Fisher B, Wickerham L, Redmond C, Fisher ER, Jones J, Mamounas EP, Ore L, Petrelli NJ, Spurr CL, Dimitrov N, Romond EH, Sutherland CM, Kardinal CG, DeFusco PA, Jochimsen P: The benefit of Leucovorin-modulated Fluorouracil as postoperative adjuvant therapy for primary colon cancer: Results from National Surgical Adjuvant Breast and Bowel Project Protocol C-03. *J Clin Onc.* October 1993; 11(10):1879-1887.
29. Dollery C, editor: *Therapeutic Drugs*. 2nd ed. Edinburg, Scotland: Harcourt Brace and Company Limited; 1999. L18-21
30. Meropol NJ, Creaven PJ, Petrelli NJ, White RM, Arbuck SJ Seizures associated with Leucovorin administration in cancer patients. *J natl Cancer Inst* 1995;87 (1):56-8.
31. Wang WS, Chen PM, Chiou TJ, et al. weekly 24-hour infusion of high-dose 5 – fluorouracil and Leucovorin in patients with advanced colorectal cancer: Taiwan experience. *JJC.* 1998;28(1):16-9.
32. *Harrison's Principles of Internal Medicine*, 15th ed. New York, NY: McGraw-Hill Companies; 2001.p.674-80
33. Reynolds EH, Wales MB. Effects of folic acid on the mental state and fit-frequency of drug-treated epileptic patients. *Lancet* 1967;1(7499):1086-8.
34. Reynolds EH. Mental effects of anticonvulsants and folic acid metabolism *Brain* 91 1968;197-214.
35. *Martindale: the complete drug reference book*. Englewood, CO: Micromedex; 1999. Based on Parfitt K, editor. *Martindale: the complete drug reference*. London: Pharmaceutical Press; 1999. International Healthcare Series.
36. Straw JA, Szapary D, Wynn WT. Pharmacokinetics of the diastereoisomers of Leucovorin after intravenous and oral administration to normal subjects. *Cancer Research* 1984;44:3114-19.
37. Prescribing Information of ^{Pr}Lederle Leucovorin[®] of Pfizer Canada Inc. Submission Control No. 217726, Date of Revision: October 10, 2018.

THE INFORMATION FOR THE CONSUMER

**PrMINT-LEUCOVORIN
Leucovorin calcium tablets**

Read this carefully before you start taking MINT-LEUCOVORIN and each time you get a refill. This leaflet is a summary and will not tell you everything about this drug. Talk to your healthcare professional about your medical condition and treatment and ask if there is any new information about MINT-LEUCOVORIN.

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:

Leucovorin is a reduced form of folic acid. Leucovorin limits 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.

When it should not be used:

- Do not take MINT-LEUCOVORIN
 - if you are allergic (hypersensitive) to leucovorin calcium (also known as calcium folinate) or any of the other ingredients of 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: Lactose Monohydrate, Magnesium Stearate, Microcrystalline Cellulose, Sodium Starch Glycolate and Partially Pregelatinized Maize Starch.

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.

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

BEFORE you use MINT-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.
- If you are Pregnant or Nursing.

INTERACTIONS WITH THIS MEDICATION

MINT-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 Leucovorin may reduce the efficacy of Methotrexate. Leucovorin may enhance the toxicity of fluorouracil.)
- Folic acid antagonists – cotrimoxazole, 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 MINT-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

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 folic acid.

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

HOW TO STORE IT

Tablets should be stored at 15°C-30°C. Keep out of reach and sight of children.

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)		✓	

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/healthcanada/services/drugs-health-products/medeffectcanada/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.

MORE INFORMATION

If you want more information about MINT-LEUCOVORIN:

- Talk to your healthcare professional
- Find the product monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website (<http://hc-sc.gc.ca/index-eng.php>); the manufacturer's website (www.mintpharmaceuticals.com), or by calling 1-877-398-9696.

This leaflet was prepared by:

Mint Pharmaceuticals Inc.
6575 Davand Drive
Mississauga, Ontario
L5T 2M3

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