PRODUCT MONOGRAPH

INCLUDING PATIENT MEDICATION INFORMATION

PrLEDERLE LEUCOVORIN®

calcium folinate

Tablets, 5 mg, Oral

USP

Folic Acid Derivative

®Pfizer Canada ULC

17,300 Trans-Canada Highway

Kirkland, Quebec, H9J 2M5

Date of Initial Authorization:
OCT 25, 1996

Date of Revision:
OCT 04, 2022

(Level 3: JUN 20, 2024)

Submission Control Number: 263375

RECENT MAJOR LABEL CHANGES

3 Serious Warnings and Precautions Box	10/2022
4 Dosage and Administration, 4.2 Recommended Dose and Dosage Adjustment	10/2022
7 Warnings and Precautions, 7.1.1 Pregnant Women	10/2022
7 Warnings and Precautions, 7.1.4 Geriatrics	10/2022

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Sections or subsections that are not applicable at the time of authorization are not listed.

PART I: HEALTH PROFESSIONAL INFORMATION

1 INDICATIONS

LEDERLE LEUCOVORIN (calcium folinate) is indicated for:

- diminishing the toxicity and counteracting the effect of impaired methotrexate elimination.
- treatment of megaloblastic anemias due to folate deficiency, as in sprue, nutritional deficiency, megaloblastic anemias of pregnancy and infancy.

1.1 Pediatrics

Pediatrics (< 18 years of age): No data are available to Health Canada; therefore, Health Canada has not authorized an indication for pediatric use (see **7 WARNINGS AND PRECAUTIONS, 7.1.3 Pediatrics**).

1.2 Geriatrics

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

2 CONTRAINDICATIONS

Calcium folinate therapy is contraindicated in patients with:

- Known hypersensitivity to the active substance or to any of the excipients. For a complete listing, see **6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING**.
- Pernicious anemia or other megaloblastic anemias where Vitamin B_{12} is deficient. A hematologic remission may occur while neurologic manifestations continue to progress.

3 SERIOUS WARNINGS AND PRECAUTIONS

Serious Warnings and Precautions

- Calcium folinate should only be used with 5-fluorouracil or methotrexate under the direct supervision of a clinician experienced in the use of cancer chemotherapeutic agents.
- Cases of Stevens - Johnson syndrome (SJS) and Toxic Epidermal Necrolysis (TEN), some fatal, have been reported in patients receiving calcium folinate in combination with other agents known to be associated with these disorders.
- Fatalities have occurred as a result of gastrointestinal toxicity (particularly mucusitis and diarrhea) associated with calcium folinate use.
- Fatalities have occurred as a result of myelosuppression associated with calcium folinate use
- Anaphylactoid/anaphylactic reactions (including shock) have occurred in patients administered calcium folinate.

4 DOSAGE AND ADMINISTRATION

4.2 Recommended Dose and Dosage Adjustment

Impaired methotrexate Elimination or Accidental Overdosage:

LEDERLE 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 **7 WARNINGS AND PRECAUTIONS**). As the time interval between the administration of antifolate and LEDERLE LEUCOVORIN rescue increases, the effectiveness of LEDERLE LEUCOVORIN in counteracting toxicity decreases.

There are no fixed guidelines regarding the dose of methotrexate that triggers an automatic subsequent calcium folinate 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/m^2 and has to be considered with doses of 100 mg - 500 mg/m^2.

Calcium folinate 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, calcium folinate should be administered at a dose of 15 mg (approximately 10 mg/m^2) every 6 hours for 10 doses, either parenterally by intramuscular injection, bolus intravenous injection, intravenous infusion, or orally using calcium folinate tablets.

Monitoring of the serum methotrexate (MTX) concentration is essential in determining the optimal dose and duration of therapy. If serum creatinine increases after methotrexate therapy or if methotrexate plasma concentrations are above certain threshold (see **Table 1**), the dose of calcium folinate 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, calcium folinate should be administered parenterally. In the case of intravenous administration, no more than 160 mg of calcium folinate should be injected per minute due to the calcium content of the solution. Further, oral administration of doses greater than 25 mg is not recommended since the digestive absorption of calcium folinate is saturable; these doses should be administered parenterally.

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

a) Maintenance of urine output above 2,500 mL/24 hr 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 x 10^{-8} molar. (0.05 μm).

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 **7 WARNINGS AND PRECAUTIONS**). Under such circumstances, higher doses of calcium folinate and/or prolonged administration may be indicated. Some dosage and administration guidelines are given in **Table 1**.

Table 1: Dosage and Administration Guidelines for Calcium Folinate Rescue

Clinical situation	Laboratory findings	Calcium folinate dosage and duration
Normal methotrexate Elimination	Serum methotrexate level ≤ 10 µM at 24 hours after administration, ≤ 1 µM at 48 hours, and < 0.1 µM 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 µM at 72 hours, and > 0.1 µM at 96 hours after administration.	Continue 15 mg PO, IM, or IV every 6 hours, until methotrexate level is less than 0.1 µM.
Delayed early methotrexate elimination and/or evidence of acute renal failure	Serum methotrexate level of > 10 µM at 24 hours, or > 1 µM 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 µM; then 15 mg IV every 3 hours until methotrexate level is less than 0.1 µM.

Hydration (3 L/d) and urinary alkalinization with $NaHC0_3$ should be employed concomitantly. The bicarbonate dose should be adjusted to maintain the urine pH at 7.0 or greater.

Megaloblastic Anemia Due to Folic Acid Deficiency:

Doses up to 15 mg daily have been suggested.

Health Canada has not authorized an indication for pediatric use.

4.4 Administration

Tablets are administered orally.

5 OVERDOSAGE

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

Folic acid has low acute and chronic toxicity in humans. **There have been no reported sequelae in patients who have received significantly more calcium folinate than the recommended dosage. However, excessive amounts of 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 overdosage of the combination of 5-fluorouracil and calcium folinate occur, the overdosage instructions for 5-FU should be followed.

For management of a suspected drug overdose, contact your regional poison control centre.

6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING

Table 2 – Dosage Forms, Strengths, Composition and Packaging

Route of Administration	Dosage Form / Strength/Composition	Non-medicinal Ingredients
Oral	Tablet 5 mg Each tablet contains 5 mg of folinic acid as calcium folinate	Lactose, Magnesium Stearate, Microcrystalline Cellulose, Sodium Starch Glycolate and Starch Pregelatinized 1500

Availability:

Bottles of 24 tablets
Bottles of 100 tablets

7 WARNINGS AND PRECAUTIONS

General

Since calcium folinate may enhance the toxicity of fluorouracil, calcium folinate/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 (see **9 DRUG INTERACTIONS** and **7.1.4 Geriatrics**).

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

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

Gastrointestinal

Gastrointestinal toxicities (particularly stomatitis and diarrhea) are observed more commonly and may be more severe in patients receiving LEDERLE LEUCOVORIN plus fluorouracil combination (see **9 DRUG INTERACTIONS,** 9.2 Drug Interactions Overview).

Therapy with LEDERLE 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.

Hematologic

LEDERLE LEUCOVORIN (calcium folinate) treatment may mask pernicious anemia and other megaloblastic anemias resulting from vitamin B_{12} deficiency.

LEDERLE LEUCOVORIN should not be used for the treatment of macrocytosis caused by direct or indirect DNA synthesis inhibitors (e.g. hydroxycarbamide, cytarabine, mercaptopurine, thioguanine).

Monitoring and Laboratory Tests

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

5-fluorouracil/calcium folinate 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/calcium folinate 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.

Neurologic

Seizures and/or syncope have been reported rarely in cancer patients receiving calcium folinate, usually in association with fluoropyrimidine and anti-epileptic drugs such as phenobarbital, phenytoin, primidone, and succinimides administration (see **9 DRUG INTERACTIONS).**

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 calcium folinate administration and after discontinuation is recommended.

Reproductive Health: Female and Male Potential

Fertility

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

Skin

Cases of Stevens - Johnson syndrome (SJS) and Toxic Epidermal Necrolysis (TEN), some fatal, have been reported in patients receiving calcium folinate 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 (see **3 SERIOUS WARNINGS AND PRECAUTIONS**).

7.1 Special Populations

7.1.1 Pregnant Women

There are no adequate and well-controlled clinical studies conducted in pregnant or breast-feeding women. Animal studies do not indicate reproductive toxicity (see **16 Non-clinical toxicology**). 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 LEDERLE LEUCOVORIN (calcium folinate) 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 LEDERLE LEUCOVORIN (calcium folinate) with 5-fluorouracil.

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

7.1.2 Breast-feeding

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 LEDERLE LEUCOVORIN is administered to a nursing mother.

7.1.3 Pediatrics

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

7.1.4 Geriatrics

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

8 ADVERSE REACTIONS

8.1 Adverse Reaction Overview

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

Table 3 – Adverse Reactions associated with LEDERLE LEUCOVORIN

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

8.2 Clinical Trial Adverse Reactions

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

LEDERLE LEUCOVORIN in Combination with 5-fluorouracil (5-FU)

In combination regimens, the toxicity profile of 5FU is enhanced by LEDERLE 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.

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:

Table 4 – Adverse Reactions associated with LEDERLE LEUCOVORIN in Combination with 5-FU

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

8.5 Post-Market Adverse Reactions

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

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

9 DRUG INTERACTIONS

9.1 Serious Drug Interactions

Serious Drug Interactions

- Treatment-related deaths have been sporadically reported in patients treated with LEDERLE 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 LEDERLE LEUCOVORIN plus fluorouracil should be carefully followed and further therapy should be withheld until these symptoms resolve (see **9.4 Drug-Drug Interactions**).

9.2 Drug Interactions Overview

Calcium folinate 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). 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.

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 calcium folinate administration and after discontinuation is recommended.

When calcium folinate 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.

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

LEDERLE LEUCOVORIN may enhance the toxicity of fluorouracil (see **7 WARNINGS AND PRECAUTIONS**). 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 LEDERLE 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 **7 WARNINGS AND PRECAUTIONS**).

9.3 Drug-Behavioural Interactions

Interactions with behaviour have not been established.

9.4 Drug-Drug Interactions

Table 4 - Established or Potential Drug-Drug Interactions

leucovorin	Source of Evidence	Effect	Clinical comment
Anticonvulsants (phenobarbital, primidone, phenytoin and succinimides)	T	Diminished effect	May increase the frequency of seizures
Folic acid antagonist (eg: cotrimoxazole, pyrimethamine, methotrexate, antibiotic with antifolic effect)	T	Diminished effect	Efficacy may be reduced or completely neutralized

Methotrexate	CT	Diminished effect	small quantities of systemically administered leucovorin enter the CSF primarily as 5-methyltetrahydrofolate and remain 1-3 orders of magnitude lower than the usual methotrexate concentrations following intrathecal administration. High doses of leucovorin may reduce the efficacy of intrathecally administered methotrexate
Fluorouracil	CT	Increased toxicity	toxicities were found to be reversible with appropriate modification of 5FU administration

Legend: C = Case Study; CT = Clinical Trial; T = Theoretical

9.5 Drug-Food Interactions

Interactions with food have not been established.

9.6 Drug-Herb Interactions

Interactions with herbal products have not been established.

9.7 Drug-Laboratory Test Interactions

Interactions with laboratory tests have not been established.

10 CLINICAL PHARMACOLOGY

10.1 Mechanism of Action

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.

10.2 Pharmacodynamics

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

Calcium folinate 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.

Calcium folinate 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.

10.3 Pharmacokinetics

The pharmacokinetics after intravenous, intramuscular and oral administration of a 25 mg dose of calcium folinate 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 calcium folinate 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 calcium folinate 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, calcium folinate 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 calcium folinate gives higher peak plasma levels than oral administration, but the total plasma folate pool of folinic acid plus its metabolite (N^5methyl—H_4-folate) remains unchanged. Oral absorption of calcium folinate is saturable at doses above 25 mg.[36] The apparent bioavailability of calcium folinate was 97% for 25 mg, 75% for 50 mg and 37% for 100 mg.

Calcium folinate 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. Calcium folinate is frequently used to diminish the toxicity and counteract the action of folate antagonists, such as methotrexate. Calcium folinate 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. Calcium folinate 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. Calcium folinate 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 calcium folinate 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.

11 STORAGE, STABILITY AND DISPOSAL

LEDERLE LEUCOVORIN Tablets 5 mg:

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

12 SPECIAL HANDLING INSTRUCTIONS

There are no special handling instructions for this drug product.

PART II: SCIENTIFIC INFORMATION

13 PHARMACEUTICAL INFORMATION

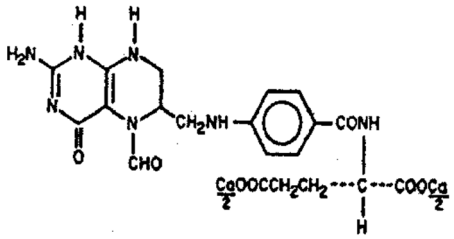
Drug Substance

Proper name: Leucovorin Calcium (folic acid derivative) 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 (l:l).

Molecular formula and molecular mass: $C_{20}H_{21}CaN_7O_7$, 511.51

Structural formula:



Physicochemical properties: Leucovorin Calcium occurs as a yellowish white or yellow, odourless powder. It is sparingly 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 tablet.

14 CLINICAL TRIALS

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

15 MICROBIOLOGY

No microbiological information is required for this drug product.

16 NON-CLINICAL TOXICOLOGY

Genotoxicity, carcinogenicity, and fertility studies have not been conducted with calcium folinate.

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

PATIENT MEDICATION INFORMATION

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

[Pr]LEDERLE LEUCOVORIN®

calcium folinate tablets

Read this carefully before you start taking **LEDERLE 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 **LEDERLE LEUCOVORIN**.

Serious Warnings and Precautions

- LEDERLE LEUCOVORIN should only be used with 5-fluorouracil or methotrexate under the direct supervision of a healthcare professional experienced in the use of anti-cancer medicines.
- LEDERLE LEUCOVORIN can cause serious side effects. In some cases these side effects have been fatal:
    - **Severe skin reactions:** These include Stevens-Johnson syndrome (SJS) and Toxic Epidermal Necrolysis (TEN) and are more likely to occur if you are taking other medicines that are also known to cause these reactions.
    - **Gastrointestinal toxicity:** Inflammation and ulceration of the mucous membranes lining the digestive tract.
    - **Bone marrow suppression:** Large decrease in the production of blood cells and platelets by the bone marrow.
    - **Serious allergic reactions**

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

What is LEDERLE LEUCOVORIN used for?

LEDERLE LEUCOVORIN is used to:

- reduce the toxic effect of the medicine methotrexate if your body does not process methotrexate well.
- treat certain anemias (when your body does not have enough functional red blood cells) due to folate deficiency, such as in sprue, nutritional deficiency, and certain types of anemia that can happen during pregnancy and infancy.

How does LEDERLE LEUCOVORIN work?

LEDERLE LEUCOVORIN is a form of the vitamin folic acid. It reduces the toxic effects of methotrexate by competing with methotrexate to get into normal cells. This means LEDERLE LEUCOVORIN enters normal cells and not methotrexate which keeps them healthy.

What are the ingredients in LEDERLE LEUCOVORIN?

Medicinal ingredients: calcium folinate

Non-medicinal ingredients: lactose, magnesium stearate, microcrystalline cellulose, sodium starch glycolate and starch pregelatinized 1500

LEDERLE LEUCOVORIN comes in the following dosage forms:

Tablet: 5 mg

Do not use LEDERLE LEUCOVORIN if:

- you are allergic (hypersensitive) to calcium folinate or any of the other ingredients of LEDERLE LEUCOVORIN (See **What are the ingredients in LEDERLE LEUCOVORIN?**)
- you have megaloblasic anaemia (a type of anemia where the bone marrow makes large, abnormal red blood cells) due to Vitamin B_{12} deficiency

To help avoid side effects and ensure proper use, talk to your healthcare professional before you take LEDERLE LEUCOVORIN. Talk about any health conditions or problems you may have, including if you:

- have symptoms of stomach or intestinal disorders
- are taking any of the following:
    - anti-cancer medicines, such as hydroxycarbamide cytarabine, mercaptopurine, thioguanine
    - medicines to treat epilepsy, such as phenobarbital, primidone, phenytoin and succinimides
    - any medicine known to cause serious skin reactions like Stevens-Johnson Syndrome (SJS) or Toxic Epidermal Necrolysis (TEN)
- are pregnant or breastfeeding
- are lactose intolerant or have one of the following rare hereditary diseases:
    - Galactose intolerance
    - Lapp lactase deficiency
    - Glucose-galactose malabsorption

  Because lactose is a non-medicinal ingredient in **LEDERLE LEUCOVORIN.**

Other warnings you should know about

Blood tests and monitoring: LEDERLE LEUCOVORIN can cause abnormal blood test results. Your healthcare professional will do blood tests regularly while you are being treated with LEDERLE LEUCOVORIN. They will check the health of your red and white blood cells and platelets as well as the health of your kidneys and liver. They will decide when to perform blood tests and will interpret the results.

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

Serious Drug Interactions
If you are taking LEDERLE LEUCOVORIN together with the anti-cancer medicine 5-fluorouracil (5FU) and you experience mouth inflammation, sores or ulcers, stomach or intestinal pain or diarrhea talk to your healthcare professional immediately. These could be signs of a serious, potentially life-threatening, interaction call **gastrointestinal toxicity**. See the **Serious side effects and what to do about them** table, below.

The following may interact with LEDERLE LEUCOVORIN:

- anti-cancer medicines, such as 5-fluorouracil (5FU), methotrexate
- folic acid antagonists, such as cotrimoxazole (used to treat bacterial infections), pyrimethamine (used to treat parasitic infections), and other antibiotics that have an effect on folic acid
- medicines used to treat epilepsy, such as phenobarbital, primidone, phenytoin, succinimides

How to take LEDERLE LEUCOVORIN:

- Take LEDERLE LEUCOVORIN exactly as your healthcare professional tells you to.

Usual dose:

Your healthcare professional will decide on the dose that is right for you based on your weight, other medicines you are taking and the condition that is being treated.

Overdose:

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

What are possible side effects from using LEDERLE LEUCOVORIN?

These are not all the possible side effects you may have when taking LEDERLE LEUCOVORIN. If you experience any side effects not listed here, tell your healthcare professional.

Side effects may include:

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

Serious side effects and what to do about them			
Symptom / effect	**Talk to your healthcare professional**		**Stop taking drug and get immediate medical help**
	Only if severe	**In all cases**	
VERY COMMON			
Gastrointestinal toxicity (inflammation and ulceration of the mucous membranes lining the digestive tract): painful, red, shiny or swollen gums, tongue, mouth or throat sores or ulcers, blood in the mouth, difficult or painful swallowing or talking, dry mouth, mild burning, or pain when eating food, diarrhea			✓
COMMON			

Serious side effects and what to do about them			
Symptom / effect	**Talk to your healthcare professional**		**Stop taking drug and get immediate medical help**
	Only if severe	**In all cases**	
Palmar-plantar erythrodys-aesthesia (hand and foot syndrome): red or swollen palms, thick calluses and blisters of the hands and soles of the feet, tingling or burning, tightness of the skin		✓	
RARE			
Seizures (fit): uncontrollable shaking with or without loss of consciousness			✓
Syncope (fainting): a temporary loss of consciousness due to a sudden drop in blood pressure		✓	
UNKNOWN FREQUENCY			
Allergic reactions: difficulty swallowing or breathing, wheezing, drop in blood pressure, feeling sick to your stomach and throwing up, hives or rash, swelling of the face, lips, tongue or throat, low blood pressure, confusion, reduced alertness, cold, moist skin, fast breathing, fast heartbeat			✓
Bone marrow suppression (large decrease in the production of blood cells and platelets by the bone marrow): bleeding, bruising, chills, fatigue, fever, infections, weakness, shortness of breath or other signs of infection			✓
Hyperammonemia (high ammonia levels in the blood): confusion, irritability, refusal to eat meat or high protein products		✓	
Severe skin reactions [Stevens-Johnson Syndrome (SJS) and Toxic Epidermal Necrolysis (TEN)]: redness, blistering and/or peeling of the skin and/or inside the lips, mouth, eyes, nasal passages or genitals, accompanied by fever, chills, tiredness, headache and			✓

Serious side effects and what to do about them			
Symptom / effect	Talk to your healthcare professional		Stop taking drug and get immediate medical help
	Only if severe	In all cases	
cough, body aches or swollen glands, raised red or purple skin patches, possibly with blister or crust in the center, swollen lips, mild itching or burning			

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

Reporting Side Effects

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

- Visiting the Web page on Adverse Reaction Reporting (https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada.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.

Storage:

Store at 15°C - 30°C. Protect from light.

Keep out of reach and sight of children.

If you want more information about LEDERLE LEUCOVORIN:

- Talk to your healthcare professional
- Find the full product monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website: (https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/drug-product-database.html; the manufacturer's website www. Pfizer.ca, or by calling 1-800-463-6001.

This leaflet was prepared by Pfizer Canada ULC.

Last Revised OCT 04, 2022

(Level 3: JUN 20, 2024)