

**COMPLETE PRESCRIBING INFORMATION**

**Pr Lederle LEUCOVORIN<sup>®</sup>  
calcium folinate tablets**

**Folic Acid Derivative**

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## COMPLETE PRESCRIBING INFORMATION

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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**

Lederle LEUCOVORIN (calcium folinate), the calcium salt of folinic acid (citraovorum 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**

**Calcium folinate therapy is contraindicated for the following:**

- **Known hypersensitivity to calcium folinate, or to any components of the product formulation.**
- **Pernicious anemia or other megaloblastic anemias where Vitamin B<sub>12</sub> is deficient. A hematologic remission may occur while neurologic manifestations continue to progress.**

### **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 (calcium folinate) 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**

**Calcium folinate treatment may mask pernicious anemia and other megaloblastic anemias resulting from vitamin B<sub>12</sub> deficiency.<sup>32</sup>**

**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.**

**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 calcium folinate administration and after discontinuation is recommended.<sup>33, 34</sup>**

### **Drug Interactions:**

**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).<sup>33, 34</sup>**

**When calcium folinate is given in conjunction with a folic acid antagonist (eg, cotrimoxazole, pyrimethamine) the efficacy of the folic acid antagonist may either be reduced or completely neutralised.<sup>29</sup>**

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. No formal animal reproductive toxicity studies with calcium folinate have been conducted. There are no indications that folic acid induces harmful effects if administered during pregnancy. During pregnancy, 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 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 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.**

**Nursing Mothers:**

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

**Pediatric Use:**

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/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  $\geq 7.0$ .

**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 (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**

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

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 (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:

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

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.<sup>29</sup>



## **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 calcium folinate than the recommended dosage. However, excessive amounts of LEUCOVORIN (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 calcium folinate occur, the overdose instructions for 5-FU should be followed.**

For the management of suspected drug overdose, contact your regional Poison Control Centre.
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## **DOSAGE & ADMINISTRATION**

Tablets are administered orally.

### **Dosage**

#### **a) 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 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<sup>2</sup> and has to be considered with doses of 100 mg - 500 mg/m<sup>2</sup>.

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<sup>2</sup>) every 6 hours for 10 doses, either parenterally by intramuscular injection, bolus intravenous injection, intravenous infusion, or orally using calcium folinate tablets.

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.<sup>35</sup> 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/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.
- 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 10<sup>-7</sup> molar (0.1µM).

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 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 Folate Rescue

Clinical situation	Laboratory findings	Calcium folinate 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 alkalization with  $\text{NaHCO}_3$  should be employed concomitantly. The bicarbonate dose should be adjusted to maintain the urine pH at 7.0 or greater.

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

Doses up to 15 mg daily have been suggested.<sup>35</sup>

## PHARMACEUTICAL INFORMATION

### DRUG SUBSTANCE

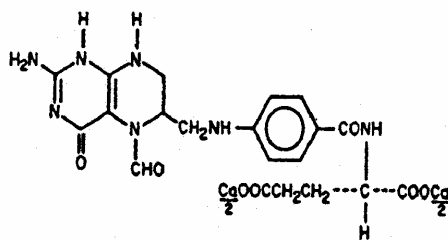
#### Proper Name:

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

#### Structural Formula:



**Empirical Formula:** C<sub>20</sub>H<sub>21</sub>CaN<sub>7</sub>O<sub>7</sub>

**Molecular Weight:** 511.51

#### Description:

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

### COMPOSITION

#### **LEUCOVORIN (Calcium Folate Tablets) 5 mg:**

Each tablet contains 5 mg of LEUCOVORIN as LEUCOVORIN Calcium. Non-medicinal ingredients are: Lactose, Magnesium Stearate, Microcrystalline Cellulose, Sodium Starch Glycolate and Starch Pregelatinized 1500.

## **STABILITY AND STORAGE RECOMMENDATIONS:**

### **LEUCOVORIN Tablets 5 mg:**

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

## **DOSAGE FORMS**

### **Availability:**

#### **Tablets:**

**5 mg tablets:** Each tablet contains 5 mg of LEUCOVORIN as LEUCOVORIN Calcium.

Bottles of 24 tablets

Bottles of 100 tablets

## **PHARMACOLOGY**

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

After intravenous administration, serum total reduced folates (as measured by Lactobacillus casei assay) reached a mean peak of 1259 ng/mL (range 897-1625). The mean time to peak was 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 calcium folinate gives higher peak plasma levels than oral administration, but the total plasma folate pool of folinic acid plus its metabolite (N<sup>5</sup> methyl—H<sub>4</sub>-folate) remains unchanged. Oral absorption of LEUCOVORIN is saturable at doses above 25 mg.<sup>36</sup> The apparent bioavailability of LEUCOVORIN was 97% for 25 mg, 75% for 50 mg and 37% for 100 mg.

LEUCOVORIN can enhance the therapeutic and toxic effects of fluoropyrimidines used in cancer therapy, such as fluorouracil. Fluorouracil is metabolized to fluorodeoxyuridylic acid, which binds to and inhibits the enzyme thymidylate synthase (an enzyme important in DNA repair and replication). LEUCOVORIN is readily converted to another reduced folate, 5,10-methylene-tetrahydrofolate, which acts to stabilize the binding of fluorodeoxyuridylic acid to thymidylate synthase and thereby enhances the inhibition of this enzyme.

A folic acid deficiency is produced during therapy with the folic acid antagonists, aminopterin and amethopterin (METHOTREXATE), used as antineoplastic agents and with the chemotherapeutic agent, pyrimethamine. These agents competitively inhibit the conversion of folic acid to folinic acid. Their affinity for folate reductase is so much greater than that of folic acid that not even large doses of folic acid will correct the drug-induced deficiency. In the event of a severe toxic reaction, the already reduced form, folinic acid, can be given, since it can be used directly to form new coenzyme.

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## THE INFORMATION FOR THE CONSUMER

### Lederle LEUCOVORIN calcium folinate tablets

**This leaflet is designed specifically for Consumers. This leaflet is a summary and will not tell you everything about Lederle Leucovorin Calcium. 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:

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 LEUCOVORIN

- if you are allergic (hypersensitive) to calcium folinate or any of the other ingredients of LEUCOVORIN OR
- If you have megaloblastic anaemia due to Vitamin B<sub>12</sub> deficiency

##### What the medicinal ingredient is:

LEUCOVORIN Calcium (also known as calcium folinate).

##### What the important nonmedicinal ingredients are:

Non-medicinal ingredients are: Lactose, Magnesium Stearate, Microcrystalline Cellulose, Sodium Starch Glycolate and Starch Pregelatinized 1500.

##### 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.

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

##### **BEFORE you use 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

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 – 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 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 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	
<b>Common</b>	<ul style="list-style-type: none"> <li>▪ Nausea,</li> <li>▪ Vomiting,</li> <li>▪ Diarrhea</li> </ul>		T T T
<b>Uncommon</b>	<ul style="list-style-type: none"> <li>▪ Allergic reactions</li> <li>▪ Any skin disorders</li> </ul>		T T
<b>Rare</b>	<ul style="list-style-type: none"> <li>▪ Seizures /syncope (Fainting / Dizziness)</li> </ul>		T
<b>Very Rare</b>	<ul style="list-style-type: none"> <li>▪ Anaphylactoid / anaphylactic reactions (including shock)</li> </ul>		T
<b>Frequency undetermined</b>	<ul style="list-style-type: none"> <li>▪ Allergic reactions, urticaria</li> <li>▪ Fever</li> <li>▪ Palmar-Plantar Erythrodysesthesia (Hand and Foot Syndrome)</li> <li>▪ Mucositis (mouth ulcers)</li> <li>▪ Stomatitis (mouth ulcers)</li> <li>▪ Chelitis (swelling of the lip)</li> <li>▪ Hyperammonemia (excess ammonia in the blood)</li> </ul>		T T T  T  T  T

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

## HOW TO STORE IT

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

## REPORTING SUSPECTED SIDE EFFECTS

You can report any suspected adverse reactions associated with the use of health products to the Canada Vigilance Program by one of the following 3 ways:

- Report online at [www.healthcanada.gc.ca/medeffect](http://www.healthcanada.gc.ca/medeffect)
- Call toll-free at 1-866-234-2345
- Complete a Canada Vigilance Reporting Form and:
  - Fax toll-free to 1-866-678-6789, or
  - Mail to:
    - Canada Vigilance Program
    - Health Canada
    - Postal Locator 0701D
    - Ottawa, Ontario
    - K1A 0K9

Postage paid labels, Canada Vigilance Reporting Form and the adverse reaction reporting guidelines are available on the MedEffect™ Canada Web site at [www.healthcanada.gc.ca/medeffect](http://www.healthcanada.gc.ca/medeffect).

*NOTE: Should you require information related to the management of side effects, contact your health professional. The Canada Vigilance Program does not provide medical advice.*

## MORE INFORMATION

This document plus the full product monograph, prepared for health professionals can be obtained by contacting the sponsor, Pfizer Canada Inc., at: 1-800-463-6001 or at [www.pfizer.ca](http://www.pfizer.ca)

This leaflet was prepared by Pfizer Canada Inc.

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