

AUSTRALIAN PRODUCT INFORMATION – [LEUCOVORIN CALCIUM INJECTION (CALCIUM FOLINATE)]

1. NAME OF THE MEDICINE

Calcium folinate

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Calcium folinate as equivalent to folinic acid 50 mg/5 mL, 100 mg/10 mL, containing calcium folinate 54 mg in 5 mL (equivalent to 50 mg folinic acid) and 108 mg in 10 mL (equivalent to 100 mg folinic acid).

Calcium folinate potency is usually expressed in terms of equivalent units of folinic acid.

For the full list of excipients, see Section 6.1 List of excipients.

3. PHARMACEUTICAL FORM

Leucovorin Calcium Injection is a sterile, isotonic, clear, yellowish, preservative-free solution.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Leucovorin Calcium Injection is indicated following high dose methotrexate therapy to reduce toxicity (leucovorin rescue). It is also indicated after inadvertent overdosage with methotrexate and in impaired methotrexate elimination.

4.2 Dose and method of administration

Dosage

Laboratory Tests

Patients treated with Leucovorin Calcium Injection following methotrexate therapy, including inadvertent overdose, or patients with impaired methotrexate elimination, should have serum creatinine and methotrexate concentrations determined 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 Foods, drinks and drugs that may increase urinary acidity should be avoided during the therapy.

Leucovorin Calcium rescue after high-dose methotrexate therapy

The dose of Leucovorin Calcium Injection required depends on the amount of methotrexate administered and whether there is impaired methotrexate elimination. Table 1 provides dosing

guidelines for a methotrexate dose of 12 to 15 g/m² by intravenous infusion over 4 hours. Leucovorin Calcium Injection is commenced 24 hours after the start of the methotrexate infusion.

Table 1. Guidelines for Leucovorin Calcium Injection Dosage

Clinical State	Laboratory Findings	Leucovorin Dose
Normal Methotrexate Elimination	[MTX] approx 10 µM 24 h after admin, 1 µM at 48 h and < 0.2 µM at 72 h	15 mg every 6 h for 60 h (10 doses)
Delayed Late Methotrexate Elimination	[MTX] < 0.2 µM at 72 h and > 0.05 µM at 96 h	15 mg every 6 h until [MTX] < 0.05 µM
Delayed Early Methotrexate Elimination and/or Evidence of Acute Renal Injury	[MTX] ≥ 50 µM at 24 h, or ≥ 5 µM at 48 h, or ≥ 100% increase in [creat] at 24 h	150 mg IV every 3 h until [MTX] < 1 µM, then 15 mg IV every 3 h until [MTX] < 0.05 µM

[MTX] = serum methotrexate concentration, [creat] = serum creatinine concentration.

Delayed methotrexate excretion may be caused by a third space fluid accumulation (i.e. ascites, pleural effusion), renal insufficiency or inadequate hydration.

Patients who experience delayed early methotrexate elimination are likely to develop reversible renal failure. In addition to Leucovorin Calcium Injection, these patients require hydration and urinary alkalinisation (pH 7.0 or greater), and close monitoring of fluid and electrolyte status until the serum methotrexate concentration has fallen below 0.05 µM and the renal failure has resolved.

Inadvertent methotrexate overdose

Leucovorin Calcium Injection should be administered as soon as possible after inadvertent overdosage of methotrexate because the effectiveness of calcium folinate decreases as the time interval between methotrexate and calcium folinate administration increases. The recommended dose is 10 mg/m² IV or IM every 6 hours until the serum methotrexate concentration is less than 0.01 µM.

Serum creatinine and methotrexate concentrations should be determined at 24 hour intervals. If the 24 hour serum creatinine concentration has increased 50% over baseline, or the 24 hour methotrexate concentration is greater than 5 µM or the 48 hour concentration greater than 0.9 µM, the dose of Leucovorin Calcium Injection USP should be increased to 100 mg/m² every 3 hours until the methotrexate concentration is less than 0.01 µM.

Hydration (3 L/day) and urinary alkalinisation with sodium bicarbonate solution should be employed concomitantly.

Method of administration

Leucovorin Calcium Injection may be administered by the intramuscular or intravenous route. Calcium folinate should not be administered intrathecally.

Dilution

For intravenous infusion, Leucovorin Calcium Injection may be diluted in glucose 5% or sodium chloride 0.9%, both in water for injections. Further diluted solutions of calcium folinate

in glucose 5% intravenous infusion and sodium chloride 0.9% intravenous infusion are stable for 24 hours when stored between 2°C to 8°C.

Leucovorin Calcium Injection contains no antimicrobial preservative; use once only and discard any residue. To avoid microbial contamination hazards, infusion should be commenced as soon as practicable after preparation.

Administration

Admixed solutions for parenteral administration should be visually inspected for particulate matter and discolouration prior to administration where solution and container permit. Do not use if solution is cloudy or precipitated.

Because of the calcium content of Leucovorin Calcium Injection, no more than 160 mg (16 mL) should be injected intravenously per minute.

4.3 Contraindications

Folinic acid should not be used for the treatment of pernicious anaemia or other megaloblastic anaemias secondary to vitamin B12 deficiency.

Known hypersensitivity to the active substance(s) or to any of the excipients.

4.4 Special warnings and precautions for use

Calcium folinate should be administered only by intramuscular or intravenous injection and must not be administered intrathecally. **When folinic acid has been administered intrathecally following intrathecal overdose of methotrexate, death has been reported.**

Calcium folinate should be used with folic acid antagonists e.g. methotrexate, or fluoropyrimidines, e.g. fluorouracil, only under the direct supervision of a clinician experienced in the use of cancer chemotherapeutic agents.

Because of the calcium content of Leucovorin Calcium injections, no more than 160 mg (16 mL) should be injected intravenously per minute.

Calcium folinate is not suitable for the treatment of pernicious anaemias and other anaemias resulting from lack of vitamin B12. Haematological remissions may occur, while the neurological manifestations remain progressive.

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

In epileptic patients treated with phenobarbital, phenytoine, 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. (See Section 4.5 Interactions with other medicines and other forms of interactions.)

Simultaneous therapy with a folic acid antagonist is not recommended because the effect of the folic acid antagonist is either reduced or inhibited.

Calcium folinate/methotrexate

Calcium folinate must not be administered intrathecally (see Section 4.2 Dose and method of administration).

An accidental overdose with a folate antagonist, such as methotrexate, should be treated quickly as a medical emergency. As the time interval between methotrexate administration and calcium folinate rescue increases, calcium folinate effectiveness in counteraction toxicity decreases.

Patients who experience delayed early methotrexate elimination are likely to develop reversible renal failure and all toxicities associated with methotrexate (please refer to the health-care professional labeling for methotrexate). The presence of pre-existing or methotrexate-induced renal insufficiency is potentially associated with delayed excretion of methotrexate and may increase the need for higher doses or more prolonged use of calcium folinate. Calcium folinate has no effect on non-haematological toxicities of methotrexate, such as the nephrotoxicity resulting from ~~drug~~ methotrexate and/or metabolite precipitation in the kidney.

Excessive calcium folinate doses must be avoided since this might impair the antitumour activity of methotrexate, especially in CNS tumours where calcium folinate accumulates after repeated courses.

Resistance to methotrexate as a result of decreased membrane transport implies resistance to folinic acid rescue as both medicinal products share the same transport system.

Calcium folinate/fluorouracil

Calcium folinate/fluorouracil Calcium folinate must not be mixed with fluorouracil in the same IV injection or infusion.

Calcium folinate may enhance the toxicity profile of fluorouracil, particularly in elderly or debilitated patients. The most common manifestations are leucopenia, mucositis, stomatitis and/or diarrhoea, which may be dose limiting. In addition, hematological adverse reactions have been observed. Deaths from severe enterocolitis, diarrhoea and dehydration have been reported in elderly patients receiving fluorouracil and calcium folinate. Concomitant granulocytopenia and fever were present in some but not all patients. When calcium folinate and fluorouracil are used in combination, in cases of toxicity the fluorouracil dosage has to be reduced more than when fluorouracil is used alone.

Combined calcium folinate/fluorouracil treatment should not be initiated or maintained in patients with symptoms of gastrointestinal (GI) toxicity, regardless of the severity, until all of these symptoms have completely disappeared. Because diarrhoea may be a sign of GI toxicity, patients presenting with diarrhoea must be carefully monitored until the symptoms have disappeared completely, since rapid clinical deterioration leading to death can occur. If diarrhoea and/or stomatitis occur, it is advisable to reduce the dose of fluorouracil. Seizures and/or syncope have been reported rarely in cancer patients receiving calcium folinate, usually

in association with fluoropyrimidine administration, and most commonly in those with CNS metastases.

In elderly patients and patients who have undergone preliminary radiotherapy, it is recommended to begin with a reduced dosage of fluorouracil.

Calcium levels should be monitored in patients receiving combined calcium folinate/fluorouracil treatment and calcium supplementation should be provided if calcium levels are low.

Under circumstances leading to delayed methotrexate elimination, treatment with calcium folinate may need to be prolonged.

Use in the elderly

Elderly patients are at increased risk of severe toxicity when receiving combination therapy of calcium folinate and fluorouracil. Particular care should be taken when treating these patients.

Paediatric use

There are no data available on use in children.

Effects on laboratory tests

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 ≥ 7.0 .

4.5 Interactions with other medicines and other forms of interactions

Calcium folinate may enhance the toxicity of fluoropyrimidines e.g. fluorouracil. Calcium folinate may counteract the antiepileptic effect of phenobarbitone, phenytoin, primidone and succinimides, and 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). Clinical monitoring, including plasma concentrations, and dose adjustment of the antiepileptic drugs is recommended during calcium folinate administration and after discontinuation.

High intravenous or intramuscular doses of calcium folinate may reduce the efficacy of intrathecally administered methotrexate.

When calcium folinate is given in conjunction with a folic acid antagonist (eg cotrimoxazole, pyrimethamine, methotrexate, antibiotic with antifolate effect) the efficacy of the folic acid antagonist may either be reduced or neutralised. (see Sections 4.4 Special warnings and precautions for use and 4.8 Adverse effects (Undesirable effects)).

4.6 Fertility, pregnancy and lactation

Effects on fertility

No data available.

Use in pregnancy

Category A

Calcium folinate has been taken by a large number of pregnant women and women of childbearing potential without any proven increase in the frequency of malformations or other direct or indirect harmful effects on the foetus having been observed. However caution is essential in the use of calcium folinate in pregnant women as the safety of calcium folinate in pregnancy has not been established. During pregnancy, flurouracil 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 fetus. 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.

Use in lactation

It is not known whether calcium folinate is excreted in human milk. Calcium folinate should be used with caution in nursing mothers.

Calcium folinate in combination with 5-fluorouracil is not recommended for use in women who are breast-feeding.

4.7 Effects on ability to drive and use machines

The effects of this medicine on a person's ability to drive and use machines were not assessed as part of its registration.

4.8 Adverse effects (undesirable effects)

Leucovorin Calcium

Allergic sensitisations, including anaphylactoid reactions, pyrexia and urticaria have occurred after parenteral administration.

Nausea and vomiting have been reported with very high doses of calcium folinate.

In addition, haematological adverse reactions, such as leucocytopenia and thrombocytopenia, may occur. These adverse reactions are dose dependent and their occurrence can usually be decreased by reducing the dosage of cytotoxic drugs. To control these adverse reactions, haematological values, e.g. blood leucocyte and thrombocyte levels, and serum electrolyte (e.g. Na, K, Ca) and creatinine levels should be closely monitored.

Table 2. Adverse Drug Reactions Leucovorin, Calcium DL - Monotherapy

Frequency undetermined	
Immune system disorders	Allergic reactions, urticaria, Hypersensitivity
General disorders and administration site conditions	Fever
Very rare	
Immune system disorders	Anaphylactoid/anaphylactic reactions (including shock)
Rare	
Nervous system disorders	Seizures and/or syncope

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

Leucovorin Calcium in combination with fluorouracil

Generally the safety profile of calcium folinate depends on the applied regimen of fluorouracil due to enhancement of fluorouracil-induced toxicities.

The most common dose-limiting adverse reaction occurring in patients receiving combination of calcium folinate and fluorouracil are stomatitis and diarrhoea. Fatalities have occurred as a result of gastrointestinal toxicity (predominantly mucositis and diarrhoea) and myelosuppression. In patients with diarrhoea, rapid clinical deterioration leading to death can occur (see Section 4.4 Special warnings and precautions for use).

Seizures and/or syncope have been reported rarely in cancer patients receiving calcium folinate, usually in association with fluoropyrimidine administration (see Section 4.4 Special warnings and precautions for use).

Additional undesirable effects of calcium folinate when used in combination with fluorouracil follow.

Table 3. Adverse Drug Reactions Leucovorin, Calcium DL - Combination Therap

Frequency undetermined	
Hepatobiliary disorders	Hyperammonaemia
Blood and lymphatic system disorders	Leukopenia, Neutropenia, Thrombocytopenia, Anaemia
General disorders and administration site conditions	Mucositis, stomatitis, cheilitis
Skin and subcutaneous tissue disorders	Palmar-Plantar Erythrodysesthesia syndrome (hand-foot syndrome)
Very common	
Gastrointestinal disorders	Nausea and vomiting, diarrhoea, stomatitis

Reporting suspected adverse effects

Reporting suspected adverse reactions after registration of the medicinal product is important. It allows continued monitoring of the benefit-risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions at www.tga.gov.au/reporting-problems.

4.9 Overdose

Folinic acid is an intermediate in the metabolism of folic acid and can therefore be considered as a naturally occurring substance. Large doses have been administered with no apparent adverse effects. Such doses suggest that administration of this drug is relatively safe. Signs of excessive dosing, if they occur, should be treated symptomatically.

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

For information on the management of overdose, contact the Poisons Information Centre on 131126.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Class: Antidote for folic acid antagonists

Mechanism of action

Folinic acid (leucovorin) is the 5-formyl derivative of tetrahydrofolic acid (THF), the active form of folic acid. Folinic acid as a co-factor participates in many metabolic reactions including purine synthesis, pyrimidine synthesis and amino acid conversion. Calcium folinate is used in cytotoxic therapy as an antidote to folic acid antagonists (such as methotrexate), which block conversion of folic acid to tetrahydrofolate by binding the enzyme dihydrofolate reductase.

Clinical trials

No data available.

5.2 Pharmacokinetic properties

Distribution

Following administration, calcium folinate enters the general body pool of reduced folates. It has been reported that, following intravenous and intramuscular administration, peak serum levels of total reduced folates are achieved within a mean time of 10 minutes and 52 minutes respectively. Peak levels of 5-formyl THF appear at 10 minutes and 28 minutes following intravenous and intramuscular administration respectively. Folate is concentrated in the cerebrospinal fluid and liver although distribution occurs to all body tissues.

Metabolism

Reduction in the levels of parent compound coincides with the appearance of the active metabolite 5-methyl THF, which becomes the major circulating form of the drug. Peak levels are observed at 1.5 and 2.8 hours following intravenous and intramuscular administration respectively. The terminal half life for total reduced folates is reported as 6.2 hours.

Excretion

Folates are excreted in the urine.

5.3 Preclinical safety data

Genotoxicity

No data available.

Carcinogenicity

No data available.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium chloride in water for injections

6.2 Incompatibilities

Leucovorin Calcium Injection has been reported to be incompatible with injectable forms of methotrexate, fluorouracil, droperidol and foscarnet.

6.3 Shelf life

The expiry date (month/year) is stated on the package after EXP.

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG).

6.4 Special precautions for storage

Store at 2°C to 8°C. Refrigerate, do not freeze. Protect from light.

6.5 Nature and contents of container

Leucovorin Calcium Injection USP 50 mg (folinic acid) in 5 mL (sterile) Plastic Vial AUST R 12724.

Leucovorin Calcium Injection USP 100 mg (folinic acid) in 10 mL (sterile) Plastic Vial AUST R 49312.

Leucovorin Calcium Injection USP 50 mg (folinic acid) in 5 mL (sterile) Steriluer® ampoule.
AUST R 61885

Leucovorin Calcium Injection USP 100 mg (folinic acid) in 10 mL (sterile) Steriluer® ampoule.
AUST R 61887

Not all pack size maybe marketed.

6.6 Special precautions for disposal

In Australia, any unused medicine or waste material should be disposed of by taking to your local pharmacy.

6.7 Physicochemical properties

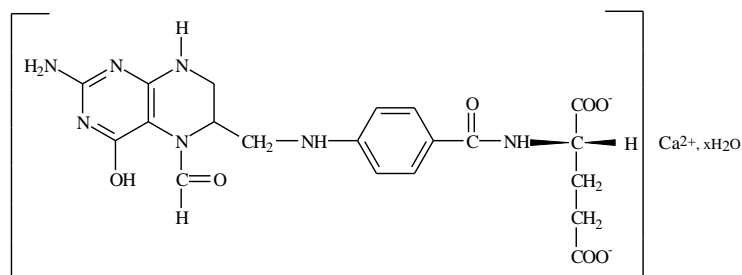
Calcium folinate is a white or light yellow, amorphous or crystalline powder, sparingly soluble in water and practically insoluble in acetone and ethanol.

Chemical structure

Chemical name: calcium 5-formyl-tetrahydropteroylglutamate

The empirical formula is $C_{20}H_{21}CaN_7O_7 \cdot xH_2O$ and the molecular weight 511.5 (anhydrous)

The structural formula is:



CAS number

1492-18-8

7. MEDICINE SCHEDULE (POISONS STANDARD)

S4 (Prescription Medicine)

8. SPONSOR

Pfizer Australia Pty Ltd
Level 17, 151 Clarence Street
Sydney NSW 2000
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9. DATE OF FIRST APPROVAL

13 August 1991

10. DATE OF REVISION

12 December 2019

Summary Table of Changes

Section changed	Summary of new information
All	Reformatted PI to the new format and minor editorial changes throughout the PI
4.2	“Foods, drinks and drugs that may increase urinary acidity should be avoided during the therapy” was added.
4.3	“Known hypersensitivity to the active substance(s) or to any of the excipients” was added
4.4	“Safety regarding epileptic patients”, “Patients experience delayed early methotrexate elimination”, “The most common manifestations are leucopenia, mucositis, stomatitis and/or diarrhoea, which may be dose limiting. In addition, hematological adverse reactions have been observed”, And Laboratory tests were added.
4.5	“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” and “methotrexate, antibiotic with antibiotic effect” were added.
4.6	Use in pregnancy and Use in lactation are updated
4.8	Table 2 and Table 3 updated
8	Sponsor address change