Product Information
LEUCOVORIN CALCIUM INJECTION USP
Calcium folinate as folinic acid 50 mg/5 mL, 100 mg/10 mL

NAME OF DRUG
Leucovorin Calcium Injection USP is calcium folinate (calcium 5-formyl-tetrahydropteroylglutamate).

DESCRIPTION
A sterile, isotonic, clear, yellowish, preservative-free solution containing calcium folinate 54mg in 5mL (equivalent to 50mg folinic acid) and 108mg in 10mL (equivalent to 100mg folinic acid), with Sodium Chloride in Water for Injections. Calcium folinate potency is usually expressed in terms of equivalent units of folinic acid. Calcium folinate is a white or light yellow, amorphous or crystalline powder, sparingly soluble in water and practically insoluble in acetone and ethanol. The structural formula is represented below.

![Structural formula of calcium folinate](image)

Molecular Formula: C$_{20}$H$_{21}$CaN$_7$O$_7$, xH$_2$O
Molecular Weight: 511.5g (anhydrous)
CAS Number: 1492-18-8

PHARMACOLOGY
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.

**Pharmacokinetics**

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. 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. Folate is concentrated in the cerebrospinal fluid although distribution occurs to all body tissues. Folates are excreted in the urine.

**Indications**

Leucovorin Calcium Injection USP 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.

**CONTRAINDICATIONS**

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

**PRECAUTIONS**

Calcium folinate should only be used with folic acid antagonists e.g. methotrexate, or fluoropyrimidines, e.g. fluorouracil, 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 160mg (16mL) should be injected intravenously per minute.

Calcium folinate may enhance the toxicity of fluorouracil. 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.
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.

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 has no effect on non-haematological toxicities of methotrexate, such as the nephrotoxicity resulting from drug and/or metabolite precipitation in the kidney.

Calcium folinate is not suitable for the treatment of pernicious anaemias and other anaemias resulting from lack of vitamin B\textsubscript{12}. Haematological remissions may occur, while the neurological manifestations remain progressive.

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

**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.

**Use in lactation**

Since it is not known whether calcium folinate is excreted in human milk, it should be used with caution in nursing mothers.

**Interactions with other drugs**

Calcium folinate may enhance the toxicity of fluoropyrimidines e.g. fluorouracil.

Folic acid in large amounts may counteract the antiepileptic effect of phenobarbitone, phenytoin and primidone, and increase the frequency of seizures in susceptible children.

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

**Incompatibilities**

Leucovorin Calcium Injection USP has been reported to be incompatible with droperidol injection and foscarnet injection.
ADVERSE REACTIONS

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

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

The most common dose-limiting adverse reaction occurring in patients receiving combination of calcium folinate and fluorouracil are stomatitis and diarrhoea. Seizures and/or syncope have been reported rarely in cancer patients receiving calcium folinate, usually in association with fluoropyrimidine administration (see Precautions).

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.

DOSAGE AND ADMINISTRATION

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

When required for intravenous infusion, Leucovorin Calcium Injection USP 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 2-8ºC. To avoid microbial contamination hazards, infusion should be commenced as soon as practicable after preparation.

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.

Calcium folinate should be given as soon as possible after accidental methotrexate overdosage because the effectiveness of calcium folinate decreases as the time interval between methotrexate and calcium folinate administration increases.

Serum creatinine and methotrexate concentrations should be determined at least once daily.

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

Leucovorin rescue after high-dose methotrexate therapy

The dose of Leucovorin Calcium Injection USP required depends on the amount of methotrexate administered and whether there is impaired methotrexate elimination. The table provides dosing guidelines for a methotrexate dose of 12 to 15g/m² by intravenous infusion
over 4 hours. Leucovorin Calcium Injection USP is commenced 24 hours after the start of the methotrexate infusion.

**GUIDELINES FOR LEUCOVORIN CALCIUM INJECTION USP DOSAGE**

<table>
<thead>
<tr>
<th>Clinical State</th>
<th>Laboratory Findings</th>
<th>Leucovorin Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal Methotrexate Elimination</td>
<td>[MTX] approx 10µM 24h after admin, 1µM at 48h and &lt;0.2µM at 72h</td>
<td>15mg every 6h for 60h (10 doses)</td>
</tr>
<tr>
<td>Delayed Late Methotrexate</td>
<td>[MTX] &gt;0.2µM at 72h and &gt;0.05µM at 96h</td>
<td>15mg every 6h until [MTX] &lt;0.05µM</td>
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<tr>
<td>Elimination</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Delayed Early Methotrexate</td>
<td>[MTX] ≥50µM at 24h, or ≥5µM at 48h, or ≥100% increase in [creat] at 24h</td>
<td>150mg IV every 3h until [MTX] &lt;0.05µM</td>
</tr>
<tr>
<td>Elimination and/or Evidence of</td>
<td></td>
<td></td>
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<tr>
<td>Acute Renal Injury</td>
<td></td>
<td></td>
</tr>
<tr>
<td>[MTX] = serum methotrexate</td>
<td></td>
<td></td>
</tr>
<tr>
<td>concentration, [creat] = serum</td>
<td></td>
<td></td>
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<tr>
<td>creatinine concentration.</td>
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</tbody>
</table>

Patients who experience delayed early methotrexate elimination are likely to develop reversible renal failure. In addition to Leucovorin Calcium Injection USP, 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 0.05µM and the renal failure has resolved.

**Inadvertent methotrexate overdose**

Leucovorin Calcium Injection USP should begin as soon as possible after inadvertent overdosage of methotrexate. The recommended dose is 10mg/m² IV or IM every 6 hours until the serum methotrexate concentration is less than 0.01µM.

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 5µM or the 48 hour concentration greater than 0.9µM, the dose of Leucovorin Calcium Injection USP should be increased to 100mg/m² every 3 hours until the methotrexate concentration is less than 0.01µM.

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

**OVERDOSAGE**

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.

**PRESENTATION**

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

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

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

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

**STORAGE**

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

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

**POISON SCHEDULE**

All States and ACT - S3.

**NAME AND ADDRESS OF THE SPONSOR**

Pfizer Australia Pty Ltd
ABN 50 008 422 348
38-42 Wharf Road
West Ryde NSW 2114

**MANUFACTURER**

Pfizer (Perth) Pty Limited
ABN 32 051 824 956
15 Brodie Hall Drive
Bentley WA 6102

The information in this leaflet was approved by the TGA on the 28th November, 1997.

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