
DBL[®] LEUCOVORIN CALCIUM INJECTION USP AND TABLETS

Name of medicine

Calcium folinate

Presentation

DBL[®] Leucovorin Calcium Injection USP is a sterile solution of folinic acid (as calcium salt) in water for injections. Sodium chloride is included for isotonicity. Neither the ampoules (3 mg/mL and 15 mg/2 mL) nor the vial presentations (50 mg/5 mL) contain a bactericide.

DBL[®] Leucovorin Calcium Tablets contain calcium folinate equivalent to 15 mg folinic acid.

Uses

Actions

Folinic acid is the formyl derivative of folic acid. When treating megaloblastic anaemias, the results are comparable to those obtained with folic acid. Following an overdose of folic acid antagonists, Calcium Leucovorin performs considerably better than folic acid because the folic acid antagonists inhibit the metabolism of folic acid into folinic acid, but have no effect on the folinic acid.

Pharmacokinetics

Peak plasma levels of folinic acid are reached, on average 40 minutes and 1.7 hours after intramuscular and oral administration, respectively. The bioavailability of an oral dose is almost the same as an equivalent intramuscular dose.

Calcium folinate is rapidly and extensively converted to 5-methyl tetrahydrofolate (an active metabolite) in vivo, with less extensive conversion resulting from parenteral, as opposed to oral, administration.

Tetrahydrofolic acid and its derivatives are distributed to all body tissues, being concentrated in the liver and found in moderate amounts in the CSF. Following a 15 mg dose given either orally or intramuscularly, peak serum folate concentrations of 0.268 micrograms/mL and 0.241 micrograms/mL were detected.

Folinic acid is eliminated mainly as 10-formyl tetrahydrofolate and 5, 10-methyl tetra-hydrofolate. The metabolites are mainly excreted via the urine (80-90%), with elimination being logarithmic in doses exceeding 1 mg.

Indications

Calcium Leucovorin has shown good results in the treatment of certain megaloblastic anaemias resulting from folic acid deficiency. This mainly occurs in infants, during pregnancy, in malabsorption syndromes, liver diseases, sprue and malnutrition. It is not more effective than folic acid for these conditions. Calcium Leucovorin also has shown good results in reducing the toxicity and circumventing the effect of folic acid antagonists, if therapeutically desired.

Use in combination with 5-fluorouracil in the treatment of advanced colorectal carcinoma.

Dosage and administration

Calcium Leucovorin may be given orally or parenterally by intravenous infusion or by intramuscular injection. Calcium Leucovorin should not be administered intrathecally.

Parenteral

Calcium Leucovorin may be diluted for infusion with physiological saline solution. Caution: contains no preservative. If intended for multiple dose use, reconstitute with bacteriostatic water for injection containing benzyl alcohol. The pH of the solution is approximately 7.5. Reconstituted solutions should not be kept for more than 3 days and should be stored below 8°C.

Calcium Leucovorin should not be mixed in the same infusion as 5-fluorouracil as a precipitate may form.

Oral

Oral doses should be taken on an empty stomach or in the fasting state since studies of bioavailability of oral tablets have been done on fasting patients only. Because absorption is saturable, oral administration of doses greater than 25 mg is not recommended.

In the treatment of accidental overdosage of folic acid antagonists, e.g. methotrexate (MTX), Calcium Leucovorin should be administered as promptly as possible. As the time interval between antifolate administration and Calcium Leucovorin rescue increases, Calcium Leucovorin's effectiveness in counteracting toxicity diminishes.

Monitoring of serum MTX concentration is essential in determining the optimal dose and duration of treatment with Calcium Leucovorin.

Delayed MTX excretion may be caused by a third space fluid accumulation (i.e. ascites, pleural effusion), renal insufficiency or inadequate hydration. Under such circumstances, higher doses of Calcium Leucovorin or prolonged administration may be indicated. Doses higher than those recommended for oral use must be given intravenously.

Laboratory Tests

Patients being treated with Calcium Leucovorin following methotrexate therapy, including inadvertent overdose, or impaired methotrexate elimination should have serum creatinine and methotrexate levels determined at 24 hour intervals. Calcium Leucovorin dosage should be adjusted based on laboratory test results.

As an antidote following methotrexate therapy

The recommendations for Calcium Leucovorin rescue are based on a methotrexate dose of 12-15 grams/m² administered by intravenous infusion over 4 hours (see methotrexate package insert for full prescribing information). Calcium Leucovorin rescue starts 24 hours after the beginning of the methotrexate infusion at a dose of 15 mg (approximately 10 mg/m²) every 6 hours for 10 doses.

In the presence of gastrointestinal toxicity, nausea or vomiting, Calcium Leucovorin should be administered parenterally.

Most investigators have successfully used doses of 6-25 mg per dose, repeated at 6 hourly intervals for up to 6-12 doses. Goldie and Price have applied up to a total of 2 grams Calcium Leucovorin in 6 fractions, which is the maximum dose recommended.

To avoid discomfort to patients from multiple injections, Calcium Leucovorin oral tablets may be given for 24 hours after the initial Calcium Leucovorin-Rescue parenteral injection. A complete oral Calcium Leucovorin-Rescue is also possible and has been used by some authors. Patients with malabsorption syndromes or other gastrointestinal disturbances such as vomiting and diarrhoea should not be treated orally.

Serum creatinine and methotrexate levels should be determined at least once daily. Calcium Leucovorin administration, hydration (3 L/day) and urinary alkalisation (with bicarbonate and/or acetazolamide to pH of 7.0 or greater) should be continued until the methotrexate level is below 5×10^{-8} M (0.05 micromolar). The Calcium Leucovorin dose should be adjusted or Calcium Leucovorin rescue extended based on the following guidelines:

GUIDELINES FOR CALCIUM LEUCOVORIN DOSAGE AND ADMINISTRATION

Clinical Situation	Laboratory Findings	Calcium Leucovorin Dosage and Duration
Normal Methotrexate Elimination	Serum methotrexate level approximately 10 micromolar at 24 hours after administration, 1 micromolar at 48 hours, and less than 0.2 micromolar at 72 hours.	15 mg PO, IM or IV q6 hours for 60 hours (10 doses starting at 24 hours after start of methotrexate infusion).
Delayed Methotrexate Elimination	Serum methotrexate level remaining above 0.2 micromolar at 72 hours, and more than 0.05 micromolar at 96 hours after administration.	Continue 15 mg PO, IM or IV q6 hours, until methotrexate level is less than 0.05 micromolar.

Patients who experience delayed methotrexate elimination are likely to develop reversible renal failure.

These patients require continuing hydration, urinary alkalinisation and close monitoring of fluid and electrolyte status, until the serum methotrexate level has fallen to below 0.05 micromolar and the renal failure has resolved.

Some patients will have abnormalities in methotrexate elimination or renal function following methotrexate administration, which are significant but less severe than the abnormalities described above. If these abnormalities are associated with significant clinical toxicity, Calcium Leucovorin rescue should be extended for an additional 24 hours (total of 14 doses over 84 hours) in subsequent courses of therapy. The possibility that the patient is taking other medications which interact with methotrexate (e.g. medications which may interfere with methotrexate elimination or binding to serum albumin) should always be considered when laboratory abnormalities or clinical toxicities are observed.

Impaired methotrexate elimination or inadvertent overdosage

Calcium Leucovorin rescue should begin as soon as possible after an inadvertent overdosage and within 24 hours of methotrexate administration when there is delayed excretion. Calcium Leucovorin 10 mg/m² should be administered IV, IM or PO every 6 hours until the serum methotrexate level is less than 10⁻⁸M. Serum creatinine and methotrexate levels should be determined at 24 hour intervals. If the 24 hours serum creatinine has increased 50% over baseline or if the 24 hour methotrexate level is greater than 5 x 10⁻⁶M or the 48 hour level is greater than 9 x 10⁻⁷M, the dose of Calcium Leucovorin should be increased to 100 mg/m² IV every 3 hours until the methotrexate level is less than 10⁻⁸M.

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

Note: High dose methotrexate therapy should only be administered by qualified specialists and in hospitals where the necessary facilities are available. Recent published literature should be consulted for details at all times.

Treatment of pyrimethamine overdosage

The dosage of pyrimethamine in treating toxoplasmosis is 10 to 20 times its dosage for malaria and approaches the toxic level. Since Calcium Leucovorin is not utilised by protozoa, it can be given simultaneously without impairing the effectiveness of therapy. The usual dosage is 3 to 9 mg per day intramuscularly for three days or until the platelet and leucocyte counts have reached safe levels.

Treatment of megaloblastic anaemias

Parenteral Administration: Up to 1 mg Calcium Leucovorin daily. Larger dosages do not increase the effect because folate excretion in urine increases roughly logarithmically as the dosage is increased above 1 mg.

Oral Administration: Daily doses of 5 mg to 15 mg of Calcium Leucovorin.

Advanced Colorectal Carcinoma

Various combination regimens have been studied. Based on available clinical evidence, the following regimen has been found to be effective in advanced colorectal carcinoma: Calcium Leucovorin given at a dose of 200 mg/m² by intravenous injection, followed immediately by 5-fluorouracil at an initial dose of 370 mg/m² by intravenous injection. This treatment is repeated daily for 5 consecutive days. Subsequent courses may be given after a treatment-free interval of 21-28 days for 2 courses and then repeated at 28-35 day intervals provided the patient has fully recovered from the toxic effects of the prior treatment course.

In subsequent treatment courses, the dosage of 5-fluorouracil should be adjusted based on patient tolerance of the prior treatment course. The daily dosage of 5-fluorouracil should be reduced by 20% for patients who experienced moderate haematologic and gastrointestinal toxicity in the prior treatment course, and by 30% for patients who experienced severe toxicity (see **Warnings and Precautions: Laboratory Tests - Combination Therapy with 5-Fluorouracil**). For patients who experienced no toxicity in the prior treatment course, 5-fluorouracil dosage may be increased by 10%. Calcium Leucovorin dosages are not adjusted for toxicity.

Contraindications

Calcium Leucovorin is improper therapy for pernicious anaemia and other megaloblastic anaemias secondary to the lack of Vitamin B₁₂. When treating these conditions with Calcium Leucovorin, haematological remission may occur, but neurological manifestations are likely to progress.

Warnings and precautions

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

Because of the Ca²⁺ content of the Calcium Leucovorin injections, no more than 16 mL of the 10 mg/mL formulations (160 mg of Calcium Leucovorin) should be injected intravenously per minute.

Calcium Leucovorin may enhance the toxicity of fluorouracil. Deaths from severe enterocolitis, diarrhoea and dehydration have been reported in elderly patients receiving Calcium Leucovorin and fluorouracil. Concomitant granulocytopenia and fever were present in some, but not all, of the patients.

Seizures and/or syncope have been reported rarely in cancer patients receiving Calcium Leucovorin, usually in association with fluoropyrimidine administration, and most commonly in those with CNS metastases. Since three patients had recurrent neurological symptoms on rechallenge with Calcium Leucovorin, further treatment with Calcium Leucovorin is not recommended in these circumstances.

Parenteral administration is preferable to oral dosing if there is a possibility that the patient may vomit or not absorb the Calcium Leucovorin.

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

Calcium Leucovorin should only be used with folic acid antagonists, e.g. methotrexate, or fluoropyrimidines, e.g. 5-fluorouracil, under the direct supervision of a clinician experienced in the use of cancer chemotherapeutic agents.

Combination therapy with 5-fluorouracil:

Calcium Leucovorin enhances the toxicity of 5-fluorouracil. When these drugs are administered concurrently in the palliative therapy of advanced colorectal cancer, the dosage of 5-fluorouracil should be reduced accordingly.

Although the toxicities observed in patients treated with the combination of leucovorin followed by 5-fluorouracil are qualitatively similar to those observed in patients treated with 5-fluorouracil alone, gastrointestinal toxicities (particularly stomatitis and diarrhoea) are observed more commonly, may be more severe and of prolonged duration in patients treated with the combination.

Combination therapy with Calcium Leucovorin/5-fluorouracil must not be initiated or continued in patients who have symptoms of gastrointestinal toxicity of any severity, until those symptoms have completely resolved. Patients with diarrhoea must be monitored with particular care until the diarrhoea has resolved, as rapid clinical deterioration leading to death can occur.

Particular care should be taken when treating elderly or debilitated colorectal cancer patients with Calcium Leucovorin/5-fluorouracil, as these patients may be at increased risk of severe toxicity, particularly severe gastrointestinal toxicity.

Laboratory Tests - Combination therapy with 5-Fluorouracil:

Patients being treated with the Calcium Leucovorin /5-fluorouracil combination should have a CBC with differential and platelets prior to each treatment. During the first two courses a CBC with differential and platelets has to be repeated weekly and thereafter, once each cycle at the time of anticipated WBC nadir. Electrolytes and liver function tests should be performed prior to each treatment for the first three cycles then prior to every other cycle. Dosage modifications of 5-fluorouracil should be instituted as follows, based on the most severe toxicities:

Diarrhoea and/or Stomatitis	WBC/mm³ Nadir	Platelets/mm³ Nadir	5-FU Dose
Moderate	1,000-1,900	25-75,000	decrease 20%
Severe	<1,000	<25,000	decrease 30%

If no toxicity occurs, the 5-fluorouracil dose may be increased 10%. Treatment should be deferred until WBC's are 4,000/mm³. If blood counts do not reach these levels within two weeks, treatment should be discontinued. Patients should be followed up with physical examination prior to each treatment course and appropriate radiological examination as needed. Treatment should be discontinued when there is clear evidence of tumour progression.

Pregnancy and Lactation

Pregnancy Category A.

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 Calcium Leucovorin is administered to a nursing mother.

Effects on ability to drive and use machines

Calcium Leucovorin is presumed to be safe since it is unlikely to produce an effect that may impair the patient's ability to concentrate and react and therefore not constitute a risk in the ability to drive and use machines.

Adverse effects

Allergic sensitisation, including anaphylactoid reactions and urticaria, has been reported following both oral and parenteral administration of folic acid. Nausea and vomiting with very high doses of Calcium Leucovorin have been reported. Seizures and/or syncope have been reported rarely in cancer patients receiving Calcium Leucovorin, usually in association with fluoropyrimidine administration - see **Warnings and Precautions**.

Interactions

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

High oral, intravenous or intramuscular doses of Calcium Leucovorin may reduce the efficacy of intrathecally administered methotrexate.

Calcium Leucovorin may enhance the toxicity of fluorouracil (see **Warnings and Precautions**).

Overdosage

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

Pharmaceutical precautions

Incompatibilities

Leucovorin calcium has been reported to be incompatible with droperidol and phosphonosulphate.

Special Precautions for Storage

Injection. Store at 2 to 8°C. (Refrigerate. Do not freeze). Protect from light.

Tablets. Store below 30°C.

Medicine classification

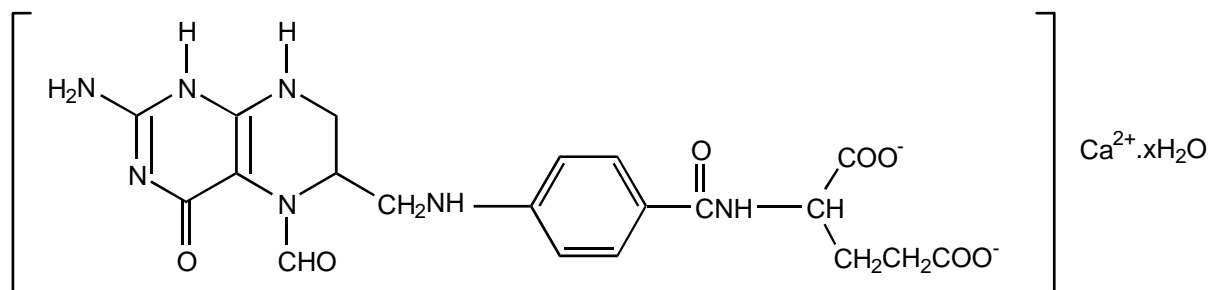
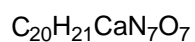
Prescription Medicine.

Package quantities

Strength	Dose Form	Packs
3 mg	1 mL ampoule	5's
15 mg	2 mL ampoule	5's
50 mg	5 mL vial	1's
15 mg	Tablets	10's

Further information

The chemical structure of calcium folinate is shown below, CAS registry number 1492-18-8.



M.W. = 511.5

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