Leucovorin Calcium for Injection is a sterile product indicated for intramuscular (IM) or intravenous (IV) administration and is supplied in 200 mg and 500 mg vials.

Each 200 mg vial of Leucovorin Calcium for Injection, when reconstituted with 20 mL of sterile diluent, contains leucovorin (as the calcium salt) 10 mg/mL

Each 500 mg vial of Leucovorin Calcium for Injection, when reconstituted with 50 mL of sterile diluent, contains leucovorin (as the calcium salt) 10 mg/mL.

In each dosage form, one milligram of leucovorin calcium contains 0.002 mmol of leucovorin and 0.002 mmol of calcium.

These lyophilized products contain no preservative. The inactive ingredient is sodium chloride added to adjust to tonicity.

Reconstitute with Water for Injection, USP. Which contains benzyl alcohol (see WARNINGS), or with Sterile Water for Injection, USP.

The inactive ingredient is sodium chloride 180 mg/vial for the 200 mg and 450 mg/vial for the 500 mg. Sodium hydroxide and/or hydrochloric acid may be added for pH adjustment.

pH adjusted to approximately 7.8.

There is 0.004 mEq of calcium per mg of leucovorin. Solution contains no bacteriostat or antimicrobial agents.

**CLINICAL PHARMACOLOGY:**

Leucovorin is a mixture of the diastereoisomers of the 5-formyl derivative of tetrahydrofolic acid (THF). Its biologic activity is due to its conversion to folates such as 5-methyltetrahydrofolate (5-MTHF) which are important in DNA repair and replication.

Leucovorin calcium is used for the treatment of megaloblastic anemia and is used to reverse the toxic effects of folic acid antagonists. It is especially useful in combination with 5-fluorouracil (5-FU) in the treatment of colorectal cancer.

**INDICATIONS AND USAGE:**

Leucovorin calcium is indicated for the treatment of megaloblastic anemia due to folic acid antagonists. Leucovorin is also indicated for use in combination with 5-fluorouracil (5-FU) in the treatment of colorectal cancer.

**DOSAGE AND ADMINISTRATION**

Leucovorin calcium is administered by intramuscular or intravenous injection. The recommended dosage of leucovorin calcium is 200 mg/m² of body surface area given over five consecutive days as a single daily intravenous injection of 200 mg, or as an intermittent intravenous injection of 400 mg over five consecutive days. Leucovorin 200 mg should be given at the beginning of each course of 5-FU therapy. Leucovorin calcium should be administered separately to avoid the formation of a folic acid antagonist.

**ADVERSE REACTIONS:**

The common adverse reactions of leucovorin calcium include nausea, vomiting, diarrhea, constipation, dermatitis, alopecia, and headache. Other adverse reactions include fever, myalgia, arthralgia, and rash.

**NURSING MOTHERS**

It is not known whether this drug is excreted in human milk. Caution should be exercised when leucovorin calcium is administered to nursing mothers.

**PEDIATRIC USE**

Leucovorin calcium has not been studied in children; therefore, its use in children is not recommended.

**PREGNANCY**

The use of leucovorin calcium in pregnant women is not recommended. There is no evidence that leucovorin calcium has been shown to be effective in the treatment of megaloblastic anemias in pregnant women.

**CONTRAINDICATIONS**

Leucovorin calcium is contraindicated in patients who have had a hypersensitivity reaction to leucovorin calcium or any component of the formulation.
bination with 5-fluorouracil to prolong survival in the palliative treatment of patients with advanced colorectal cancer. Leucovorin should not be used in the same infusion as 5-fluoro-
uracil because a precipitate may form.

CONTRAINDICATIONS:
Leucovorin is improper therapy for pernicious anemia and other megaloblastic anemias sec-
ondary to the lack of vitamin B12. A hematologic remission may occur while neurologic manifes-
tations continue to progress.

WARNINGS:
In the treatment of accidental overdosages of folate antagonists, intravenous leucovorin should be administered as promptly as pos-
sible. As the time interval between antifolate administration (e.g., methotrexate) and leu-
covorin rescue increases, leucovorin’s effec-
tiveness in reversing folate deficiency decreases. In the treatment of accidental overdosages of intrathecally administered folic acid antagonists, do not administer leucovorin intrathecally. LEU-
COVORIN MAY BE HARMFUL OR FATAL IF GIVEN INTRATHECALLY.

Monitoring of the serum methotrexate con-
centration is essential in determining the optimal dose and duration of treatment with leucovorin.

Drinking alcohol or the consumption of food may be caused by a third space fluid accumulation (i.e., ascites, pleural effusion), renal insuffi-
cency, or hypovolemic shock. Under such circumstances, higher doses of leucovorin or prolonged administration may be indicated. Dose reductions to those recommended for oral use must be given intravenously.

Because of the benzyl alcohol contained in certain preparations for reconstituting Leuco-
von Calcium for Injection, when doses greater than 10 mg/m² are administered, Leucovorin Calcium for Injection should be reconstituted with Sterile Water for Injection, USP, and used immediately (see DOSAGE AND ADMINIS-
TRATION).

Because of the calcium content of the leucov-
orin solution, no more than 160 mg of leucovorin should be injected intravenously (500 mg/ml) per minute (16 mL of a 10 mg/mL, or 8 mL of a 20 mg/mL solution is recommended).

Leucovorin enhances the toxicity of 5-fluo-
uracil. When these drugs are administered con-
currently, therapy may produce an induced colorectal cancer, the dosage of 5-fluorour-
icil must be lower than usually administered. Although the toxicities observed in patients treated with the combination of leucovorin plus 5-fluorouracil are qualitatively similar to those observed in patients treated with 5-fluorouracil alone, gastrointestinal toxicities (particularly stomatitis and diarrhea) are observed more commonly and may be more severe and of prolonged duration in patients treated with the combination.

In the first Mayo/NCCTG controlled trial, tox-
icity, primarily gastrointestinal, resulted in 7% of patients requiring hospitalization when treated with the leucovorin/5-fluorouracil combination with 200 mg/m² of leucovorin and 20% when treated with 5-fluorouracil in combina-
tion with 5-fluorouracil and leucovorin. In the sec-
ond Mayo/NCCTG trial, hospitalizations related to treatment toxicity also appeared to occur more commonly in patients treated with the low dose leucovorin/5-fluorouracil combination than in patients treated with the high dose combination—11% versus 3%. Therapy with leucovorin and 5-fluorouracil must not be initiated or continued in patients who have symptoms of gastrointestinal tox-
icity of any severity, until those symptoms have completely resolved. Patients with diar-
rhrea must be monitored with particular care until the diarrhea has resolved, as rapid clinical deterioration leading to death can occur. In an additional study using higher weekly doses of 5-fluorouracil and leucovorin, elderly and/or debilitated patients were found to be at greater risk of gastrointestinal toxicity.

Seizures and/or syncope have been reported rarely in cancer patients receiving leucovorin, usually in association with fluorouracil and/or high-dose leucovorin administration, and most commonly in those with CNS metastases or other predisposing factors. However, a causal relationship has not been established.

The concomitant use of leucovorin with trimethoprim-sulfamethoxazole for the acute treatment of Pneumocystis carinii pneumonia in patients with HIV infection was associated with increased rates of treatment failure and tox-
icity in a placebo-controlled study.

PRECAUTIONS:
General:
Parenteral administration is preferable to oral
dosing if there is a possibility that the patient may vomit and not absorb the leucovorin. Leu-
covorin has no effect on non-hematologic toxic-
ities of methotrexate such as the nephrotoxicity resulting from drug and/or metabolite precipita-
tion in the kidney.

Since leucovorin enhances the toxicity of fluorouracil, leucovorin/5-fluorouracil combi-
nation therapy for advanced colorectal cancer should be administered under the supervision of a physician experienced in the use of antimalabiles cancer chemother-
apy. 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.

Laboratory Tests
Patients being treated with the leucovorin/5-
fluorouracil combination should be B+C with differential and platelets prior to each treat-
ment. 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 fluorouracil and leucovorin are based as follows, based on the most severe toxicities:

Drug Interactions
Folic acid in large amounts may counteract the antiepileptic effect of phenobarbital, phenytoin and primidone, and increase the frequency of seizures in patients with epilepsy.

PRECAUTIONS:
Talogenic Effects: Pregnancy Category C.

Leucovorin is not known to cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. Leucovorin should be given to a pregnant woman only if clearly needed.

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
See PRECAUTIONS, Drug Interactions.

ADVERSE REACTIONS:
Allergic sensitization, including anaphylactoid reactions and urticaria, has been reported fol-
lowing the administration of both oral and par-
enteral leucovorin. No other adverse reactions have been attributed to the use of leucovorin per se.

The following table summarizes significant adverse events occurring in 316 patients treated with the leucovorin/5-fluorouracil combinations compared against 70 patients treated with leucovorin/5-fluorouracil combinations against 70 patients treated with a placebo and/or 5-fluorouracil in colorectal carcinoma. These data are taken from the Mayo/NCCTG large multicenter prospective trial evaluating the efficacy and safety of the combination regimen.

OVERDOSAGE:
Excessive amounts of leucovorin may nullify the chemotherapeutic effect of folic acid antago-
nists.

DOSAGE AND ADMINISTRATION:
Advanced Colorectal Cancer

Either of the following two regimens is recom-
dended:
1. Leucovorin is administered at 200 mg/m² by slow intravenous injection over a mini-
mum of 3 minutes, followed by 5-fluoroura-
icil at 370 mg/m² by intravenous injection.

2. Leucovorin is administered at 20 mg/m² by intravenous injection followed by 5-
fluorouracil at 425 mg/m² by intravenous injection.

5-Fluorouracil and leucovorin should be adminis-
tered separately to avoid the formation of a precipitate.

Treatment is repeated daily for five days. This five-day treatment course may be repeated at 4 week (28-day) intervals, for 2 courses and then repeated at 4 to 5 week (28 to 35 day) intervals provided that the patient has completely recov-
ered from the toxic effects of the prior treatment course.

In subsequent treatment course, 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 hematologic or gastrointestinal tox-
icity in the prior treatment course, and by 50% for patients who experienced severe toxicity (see PRECAUTIONS, Laboratory Tests). For patients who experienced no toxicity in the prior treatment course, 5-fluorouracil dosage may be increased by 10%. Leucovorin dosages are not adjusted for toxicity.

Several other doses and schedules of leucovorin/5-fluorouracil therapy have also been evaluated in patients with colorectal cancer; some of these alternative regimens may also have efficacy in the treatment of this dis-
ease. However, further clinical research will be required to confirm the safety and effectiveness of these alternative leucovorin/5-fluorouracil treatment regimens.

Leucovorin Rescue After High-Dose Methotrexate Therapy

The recommendations for leucovorin rescue are based on a methotrexate dose of 12 to
15 grams/m² administered by intravenous infusion over 4 hours (see methotrexate package insert for full prescribing information). Leucovorin rescue at a dose of 15 mg (approximately 10 mg/m²) every 6 hours for 10 doses starts 24 hours after the beginning of the methotrexate infusion. In the presence of gastrointestinal toxicity, nausea, or vomiting, leucovorin should be administered parenterally. Do not administer leucovorin intrathecally.

Serum creatinine and methotrexate levels should be determined at least once daily. Leucovorin administration, hydration, and urinary alkalization (pH of 7.0 or greater) should be continued until the methotrexate level is below 5 x 10⁻⁸ M (0.05 micromolar). The leucovorin dose should be adjusted or leucovorin rescue extended based on the following guidelines:

**GUIDELINES FOR LEUCOVORIN DOSAGE AND ADMINISTRATION**

**DO NOT ADMINISTER LEUCOVORIN INTRATHECALLY**

<table>
<thead>
<tr>
<th>Clinical Situation</th>
<th>Laboratory Findings</th>
<th>Leucovorin Dosage and Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal Methotrexate Elimination</td>
<td>Serum methotrexate level approximately 10 micromolar at 24 hours after administration, 1 micromolar at 48 hours after administration, and less than 0.2 micromolar at 72 hours.</td>
<td>15 mg PO, IM, or IV q 6 hours for 60 hours (10 doses starting at 24 hours after start of methotrexate infusion).</td>
</tr>
<tr>
<td>Delayed Late Methotrexate Elimination</td>
<td>Serum methotrexate level remaining above 0.2 micromolar at 72 hours, and more than 0.05 micromolar at 96 hours after administration.</td>
<td>Continue 15 mg PO, IM, or IV q 6 hours, until methotrexate level is less than 0.05 micromolar.</td>
</tr>
<tr>
<td>Delayed Early Methotrexate Elimination and/or Evidence of Acute Renal Injury</td>
<td>Serum methotrexate level of 0.5 micromolar or more at 24 hours, or greater increase in serum creatinine level at 24 hours after methotrexate administration (e.g., an increase from 0.5 mg/dL to a level of 1 mg/dL or more).</td>
<td>150 mg IV q 3 hours, until methotrexate level is less than 1 micromolar, then 15 mg IV q 3 hours until methotrexate level is less than 0.05 micromolar.</td>
</tr>
</tbody>
</table>

Patients who experience delayed early methotrexate elimination are likely to develop reversible renal failure. In addition to appropriate leucovorin therapy, these patients require continuing hydration and urinary alkalization, 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 abnormalities described in the table above. These abnormalities may or may not be associated with significant clinical toxicity. If significant clinical toxicity is observed, 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 reconsidered when laboratory abnormalities or clinical toxicities are observed.

**Impaired Methotrexate Elimination or Indolent Overdosage**

Leucovorin rescue should begin as soon as possible after the indolent overdose and at within 24 hours of methotrexate administration when there is a delayed excretion (see WARNINGS). Leucovorin 10 mg/m² should be administered IM, IV, or PO every 6 hours until the serum methotrexate level is less than 10⁻⁸ M. In the presence of gastrointestinal toxicity, nausea, or vomiting, leucovorin should be administered parenterally. Do not administer leucovorin intrathecally.

Serum creatinine and methotrexate levels should be determined at 24 hour intervals. If the 24 hour serum creatinine has increased 50% over baseline or if the 24 hour methotrexate level is greater than 5 x 10⁻⁶ M or the 48 hour level is greater than 9 x 10⁻⁷ M, the dose of leucovorin should be increased to 100 mg/m² IV every 3 hours until the methotrexate level is less than 10⁻⁸ M. Hydration (3 L/d) and urinary alkalization with sodium bicarbonate solution 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**

Up to 1 mg daily. There is no evidence that doses greater than 1 mg/day have greater efficacy than those of 1 mg; additionally, loss of folic acid in urine becomes roughly logarithmic as the amount administered exceeds 1 mg.

Each 200 mg vial of Leucovorin Calcium for Injection when reconstituted with 20 mL of sterile diluent yields a leucovorin concentration of 10 mg per mL. Each 500 mg vial of Leucovorin Calcium for Injection when reconstituted with 50 mL of sterile diluent yields a leucovorin concentration of 10 mg per mL. Leucovorin Calcium for Injection contains no preservative. Reconstitute the lyophilized vial products with Bacteriostatic Water for Injection, USP (benzyl alcohol preserved), or Sterile Water for Injection, USP. When reconstituted with Bacteriostatic Water for Injection, USP, the resulting solution must be used within 7 days. If the product is reconstituted with Sterile Water for Injection, USP, use immediately and discard any unused portion.

Because of the benzyl alcohol contained in Bacteriostatic Water for Injection, USP, when doses greater than 10 mg/m² are administered, Leucovorin Calcium for Injection should be reconstituted with Sterile Water for Injection, USP, and used immediately (see WARNINGS).

Because of the calcium content of the leucovorin solution, no more than 160 mg of leucovorin should be injected intravenously per minute (16 mL of a 10 mg/mL, or 8 mL of a 20 mg/mL solution per minute).

Parenteral products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit.

Leucovorin should not be mixed in the same infusion container with methotrexate, since this may lead to the formation of a precipitate.

**HOW SUPPLIED:**

Leucovorin Calcium for Injection is supplied as follows:

- **Product**
  - **No.** 701050
  - **NDC No.** 6333-710-50
  - **Strength** 200 mg/vial
  - **Packaged individually.**

- **701100**
  - **NDC No.** 6333-711-00
  - **Strength** 500 mg/vial
  - **Packaged individually.**

Store at 20°C to 25°C (68° to 77°F) [see USP Controlled Room Temperature].

Protect from light. Retain in carton until time of use.

This container closure is not made with natural rubber latex.

**REFERENCES:**


**FRESENIUS KABI**

Fresenius Kabi USA, LLC
Lake Zurich, IL 60047

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