LEUCOVORIN CALCIUM

DESCRIPTION

Leucovorin Calcium Injection USP is a sterile, preservative-free solution of "one-carbon" moieties. L-Leucovorin (L-5-formyltetrahydrofolate) is a 25 mg dose of leucovorin calcium, which is a mixture of the diastereoisomers of the 5-formyl derivative of folic acid. It is useful as an antidote to drugs which act as folic acid antagonists.

PHARMACOLOGY

Leucovorin is improper therapy for pernicious anemia and other nutritional deficiencies of folate. Treatment with leucovorin must be accompanied by the correction of those deficiencies if they are present. If patient serum folate levels are normal, leucovorin is unnecessary for effective therapy. Folic acid in large amounts may counteract the antiepileptic effect of leucovorin, and increase the frequency of seizures. Monitoring of the serum methotrexate concentration is mandatory in order to optimize the duration and dosage of treatment with methotrexate.

BEFORE ADMINISTRATION

In the treatment of accidental overdosage of folic acid antagonists, intravenous leucovorin should be administered as promptly as possible. As the time interval between antifolate administration and administration of leucovorin increases, the efficacy of leucovorin decreases. In the treatment of accidental overdosages of folic acid antagonists.

In an additional study utilizing higher weekly doses of 5-fluorouracil administration, patients with colorectal cancer who were treated with leucovorin/5-fluorouracil combination therapy for metastatic colorectal cancer, as these patients may be at higher risk for neurotoxicity.

In the treatment of accidental overdosage of folic acid antagonists, intravenous leucovorin should be administered as promptly as possible. As the time interval between antifolate administration and administration of leucovorin increases, the efficacy of leucovorin decreases. In the treatment of accidental overdosages of folic acid antagonists.

In an additional study utilizing higher weekly doses of 5-fluorouracil administration, patients with colorectal cancer who were treated with leucovorin/5-fluorouracil combination therapy for metastatic colorectal cancer, as these patients may be at higher risk for neurotoxicity.

In the treatment of accidental overdosage of folic acid antagonists, intravenous leucovorin should be administered as promptly as possible. As the time interval between antifolate administration and administration of leucovorin increases, the efficacy of leucovorin decreases. In the treatment of accidental overdosages of folic acid antagonists.

In an additional study utilizing higher weekly doses of 5-fluorouracil administration, patients with colorectal cancer who were treated with leucovorin/5-fluorouracil combination therapy for metastatic colorectal cancer, as these patients may be at higher risk for neurotoxicity.

In the treatment of accidental overdosage of folic acid antagonists, intravenous leucovorin should be administered as promptly as possible. As the time interval between antifolate administration and administration of leucovorin increases, the efficacy of leucovorin decreases. In the treatment of accidental overdosages of folic acid antagonists.

In an additional study utilizing higher weekly doses of 5-fluorouracil administration, patients with colorectal cancer who were treated with leucovorin/5-fluorouracil combination therapy for metastatic colorectal cancer, as these patients may be at higher risk for neurotoxicity.

In the treatment of accidental overdosage of folic acid antagonists, intravenous leucovorin should be administered as promptly as possible. As the time interval between antifolate administration and administration of leucovorin increases, the efficacy of leucovorin decreases. In the treatment of accidental overdosages of folic acid antagonists.

In an additional study utilizing higher weekly doses of 5-fluorouracil administration, patients with colorectal cancer who were treated with leucovorin/5-fluorouracil combination therapy for metastatic colorectal cancer, as these patients may be at higher risk for neurotoxicity.

In the treatment of accidental overdosage of folic acid antagonists, intravenous leucovorin should be administered as promptly as possible. As the time interval between antifolate administration and administration of leucovorin increases, the efficacy of leucovorin decreases. In the treatment of accidental overdosages of folic acid antagonists.

In an additional study utilizing higher weekly doses of 5-fluorouracil administration, patients with colorectal cancer who were treated with leucovorin/5-fluorouracil combination therapy for metastatic colorectal cancer, as these patients may be at higher risk for neurotoxicity.

In the treatment of accidental overdosage of folic acid antagonists, intravenous leucovorin should be administered as promptly as possible. As the time interval between antifolate administration and administration of leucovorin increases, the efficacy of leucovorin decreases. In the treatment of accidental overdosages of folic acid antagonists.

In an additional study utilizing higher weekly doses of 5-fluorouracil administration, patients with colorectal cancer who were treated with leucovorin/5-fluorouracil combination therapy for metastatic colorectal cancer, as these patients may be at higher risk for neurotoxicity.

In the treatment of accidental overdosage of folic acid antagonists, intravenous leucovorin should be administered as promptly as possible. As the time interval between antifolate administration and administration of leucovorin increases, the efficacy of leucovorin decreases. In the treatment of accidental overdosages of folic acid antagonists.

In an additional study utilizing higher weekly doses of 5-fluorouracil administration, patients with colorectal cancer who were treated with leucovorin/5-fluorouracil combination therapy for metastatic colorectal cancer, as these patients may be at higher risk for neurotoxicity.

In the treatment of accidental overdosage of folic acid antagonists, intravenous leucovorin should be administered as promptly as possible. As the time interval between antifolate administration and administration of leucovorin increases, the efficacy of leucovorin decreases. In the treatment of accidental overdosages of folic acid antagonists.

In an additional study utilizing higher weekly doses of 5-fluorouracil administration, patients with colorectal cancer who were treated with leucovorin/5-fluorouracil combination therapy for metastatic colorectal cancer, as these patients may be at higher risk for neurotoxicity.

In the treatment of accidental overdosage of folic acid antagonists, intravenous leucovorin should be administered as promptly as possible. As the time interval between antifolate administration and administration of leucovorin increases, the efficacy of leucovorin decreases. In the treatment of accidental overdosages of folic acid antagonists.

In an additional study utilizing higher weekly doses of 5-fluorouracil administration, patients with colorectal cancer who were treated with leucovorin/5-fluorouracil combination therapy for metastatic colorectal cancer, as these patients may be at higher risk for neurotoxicity.

In the treatment of accidental overdosage of folic acid antagonists, intravenous leucovorin should be administered as promptly as possible. As the time interval between antifolate administration and administration of leucovorin increases, the efficacy of leucovorin decreases. In the treatment of accidental overdosages of folic acid antagonists.

In an additional study utilizing higher weekly doses of 5-fluorouracil administration, patients with colorectal cancer who were treated with leucovorin/5-fluorouracil combination therapy for metastatic colorectal cancer, as these patients may be at higher risk for neurotoxicity.

In the treatment of accidental overdosage of folic acid antagonists, intravenous leucovorin should be administered as promptly as possible. As the time interval between antifolate administration and administration of leucovorin increases, the efficacy of leucovorin decreases. In the treatment of accidental overdosages of folic acid antagonists.

In an additional study utilizing higher weekly doses of 5-fluorouracil administration, patients with colorectal cancer who were treated with leucovorin/5-fluorouracil combination therapy for metastatic colorectal cancer, as these patients may be at higher risk for neurotoxicity.

In the treatment of accidental overdosage of folic acid antagonists, intravenous leucovorin should be administered as promptly as possible. As the time interval between antifolate administration and administration of leucovorin increases, the efficacy of leucovorin decreases. In the treatment of accidental overdosages of folic acid antagonists.

In an additional study utilizing higher weekly doses of 5-fluorouracil administration, patients with colorectal cancer who were treated with leucovorin/5-fluorouracil combination therapy for metastatic colorectal cancer, as these patients may be at higher risk for neurotoxicity.

In the treatment of accidental overdosage of folic acid antagonists, intravenous leucovorin should be administered as promptly as possible. As the time interval between antifolate administration and administration of leucovorin increases, the efficacy of leucovorin decreases. In the treatment of accidental overdosages of folic acid antagonists.

In an additional study utilizing higher weekly doses of 5-fluorouracil administration, patients with colorectal cancer who were treated with leucovorin/5-fluorouracil combination therapy for metastatic colorectal cancer, as these patients may be at higher risk for neurotoxicity.
Leucovorin calcium is indicated in the treatment of neoplastic disease for the treatment of cytotoxic drug-induced toxicity (i.e., myelosuppression, mucositis, neutropenia, stomatitis, and alopecia) associated with the administration of 5-fluorouracil. When these drugs are administered concurrently, the toxicity of leucovorin given at doses of 5 mg/day should be increased approximately 10-fold above the usual daily dose of 1 mg/day.

Leucovorin enhances the toxicity of 5-fluorouracil. When these drugs are administered concurrently, the toxicity of leucovorin given at doses of 5 mg/day should be increased approximately 10-fold above the usual daily dose of 1 mg/day.

The mean peak of 5-formyl-THF was 360 ng/mL with a mean time to peak of 1.3 hours. The terminal half-life for total reduced folates was 6.2 hours. The mean peak of 5-methyl-THF was 258 ng/mL and occurred at 28 minutes. The level of the metabolite 5-methyl-THF in parent compound followed and coincided with the appearance of circulating form of the drug.

The mean of a group of healthy volunteers (N = 12), who received leucovorin calcium 50 mg intravenously and 100 mg orally (single dose), is shown in Figure 1. The mean peak of 5-formyl-THF was 360 ng/mL at 1.3 hours. The terminal half-life for total reduced folates was 6.2 hours. The mean peak of 5-methyl-THF was 258 ng/mL and occurred at 28 minutes. The level of the metabolite 5-methyl-THF coincided with the appearance of circulating form of the drug.

The mean peak of 5-formyl-THF was 360 ng/mL at 1.3 hours. The terminal half-life for total reduced folates was 6.2 hours. The mean peak of 5-methyl-THF was 258 ng/mL and occurred at 28 minutes. The level of the metabolite 5-methyl-THF coincided with the appearance of circulating form of the drug.

The mean peak of 5-formyl-THF was 360 ng/mL at 1.3 hours. The terminal half-life for total reduced folates was 6.2 hours. The mean peak of 5-methyl-THF was 258 ng/mL and occurred at 28 minutes. The level of the metabolite 5-methyl-THF coincided with the appearance of circulating form of the drug.

The mean peak of 5-formyl-THF was 360 ng/mL at 1.3 hours. The terminal half-life for total reduced folates was 6.2 hours. The mean peak of 5-methyl-THF was 258 ng/mL and occurred at 28 minutes. The level of the metabolite 5-methyl-THF coincided with the appearance of circulating form of the drug.
Geriatric Use

See discussion when leucovorin is administered to a nursing mother. Many drugs are excreted in human milk, caution should be exercised. It is not known whether this drug is excreted in human milk. Because some drugs are excreted in human milk, especially in nursing mothers with impaired renal function and in those who have received a large dose of this drug, the decision to use peripheral leucovorin medicinally should weigh the benefits of the drug for the mother against the possible hazards to the nursing infant. Pregnancy

Pregnancy Category C.

In subsequent treatment courses, the dosage of 5-fluorouracil should be repeated daily for five days. This five-day treatment course is repeated every two weeks. Leucovorin is administered at 20 mg/m² by intravenous injection of a 200 mg solution into a single use vial, packaged individually. The bicarbonate dose of 150 mg IV q 3 hours, then 15 mg IV q 3 hours until methotrexate level is less than 0.05 micromolar (see methotrexate package insert for full dosing and use instructions).

Thrombocytopenia 8 2 8 1 18 3
Infection 8 1 3 1 7 2
Nausea 74 10 80 9 60 6
Vomiting 46 8 44 9 40 7
Stomatitis 75 27 84 29 59 16
Hospitalization for Toxicity 5% 15% 7%

Adverse Reactions

The possibility that the patient is taking other medications which may interfere with methotrexate (e.g., medications which may interfere with methotrexate excretion or may interact with methotrexate). The patient should be questioned about medications he is taking, or is likely to begin taking, at least one week before treatment with leucovorin. There has been no significant difference in the incidence or severity of adverse effects between the elderly and younger patients, but greater sensitivity of some older patients cannot be ruled out. This drug is known to be excreted by the kidney and the risk of toxic reactions to the drug may therefore be greater in patients with impaired renal function. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection in this patient population.

Adverse Reactions

Adverse reactions are observed in most patients receiving leucovorin as rescue therapy. Although some of the reactions are very mild and transient, others may be serious and require prompt action. Response to methotrexate is unpredictable, and there is no way of knowing when a patient will become toxic. Thus, all patients should receive leucovorin as rescue therapy. Any manifestations of toxicity should be reported to the local methotrexate treatment center. They may be increased by concurrent use of other folic acid antagonists.

Adverse Reactions

Adverse reactions are usually associated with the use of leucovorin to rescue patients with high or low levels of leucovorin. Leucovorin should not be mixed in the same infusion as 5-fluorouracil, and container permit.

Parenteral drug products should be inspected visually for particulate matter and solution clarity prior to administration. In patients with impaired renal function. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection in this patient population.

This drug is known to be excreted by the kidney and the risk of toxic reactions to the drug may therefore be greater in patients with impaired renal function. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection in this patient population.

Adverse Reactions

Adverse reactions are usually associated with the use of leucovorin to rescue patients with high or low levels of leucovorin. Leucovorin should not be mixed in the same infusion as 5-fluorouracil, and container permit.

Parenteral drug products should be inspected visually for particulate matter and solution clarity prior to administration. In patients with impaired renal function. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection in this patient population.

Adverse Reactions

Adverse reactions are usually associated with the use of leucovorin to rescue patients with high or low levels of leucovorin. Leucovorin should not be mixed in the same infusion as 5-fluorouracil, and container permit.

Parenteral drug products should be inspected visually for particulate matter and solution clarity prior to administration. In patients with impaired renal function. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection in this patient population.
In subsequent treatment course, the dosage of 5-fluorouracil should be adjusted based on patient tolerance of the prior treatment course. That is, the patient has completely recovered from the toxic effects of methotrexate and the serum methotrexate level is less than 10⁻⁸ M. In the presence of gastrointestinal toxicity in the prior treatment course, and by 30% loss of folate receptor, the dosage of 5-fluorouracil should be decreased to 150 mg/m² IV every 3 hours until the methotrexate level is less than 1 micromolar; then 15 mg PO, IM, or IV q 6 hours, until methotrexate level is less than 0.2 micromolar at 72 hours.

Leucovorin dose should begin as soon as possible after an inadvertent overdose and within 24 hours of methotrexate administration. Overdosage and within 24 hours of methotrexate administration. Leucovorin rescue should begin as soon as possible after an inadvertent overdose and within 24 hours of methotrexate administration. Overdosage

Leucovorin should not be mixed in the same infusion as 5-fluorouracil, and container permit.

Leucovorin should be increased to 100 mg/m² IV every 3 hours until the methotrexate level is less than 0.2 micromolar at 72 hours.

The table below summarizes significant adverse events occurring in 316 patients treated with the leucovorin/5-fluorouracil combinations compared against 70 patients treated with 5-fluorouracil alone for metastatic colorectal cancer. The NCCTG large multicenter prospective trial evaluating the efficacy and safety of leucovorin/5-fluorouracil therapy in patients with metastatic colorectal cancer randomized 381 patients (patients treated with the leucovorin/5-fluorouracil combinations compared against 70 patients treated with 5-fluorouracil alone for metastatic colorectal cancer. The NCCTG large multicenter prospective trial evaluating the efficacy and safety of leucovorin/5-fluorouracil therapy in patients with metastatic colorectal cancer randomized 381 patients (N=161) to receive leucovorin 200 mg/m² IV every 3 hours starting at 24 hours after start of methotrexate infusion). The table below summarizes significant adverse events occurring in 316 patients treated with the leucovorin/5-fluorouracil combinations compared against 70 patients treated with 5-fluorouracil alone for metastatic colorectal cancer. The NCCTG large multicenter prospective trial evaluating the efficacy and safety of leucovorin/5-fluorouracil therapy in patients with metastatic colorectal cancer randomized 381 patients (N=161) to receive leucovorin 200 mg/m² IV every 3 hours starting at 24 hours after start of methotrexate infusion). The table below summarizes significant adverse events occurring in 316 patients treated with the leucovorin/5-fluorouracil combinations compared against 70 patients treated with 5-fluorouracil alone for metastatic colorectal cancer. The NCCTG large multicenter prospective trial evaluating the efficacy and safety of leucovorin/5-fluorouracil therapy in patients with metastatic colorectal cancer randomized 381 patients (N=161) to receive leucovorin 200 mg/m² IV every 3 hours starting at 24 hours after start of methotrexate infusion). The table below summarizes significant adverse events occurring in 316 patients treated with the leucovorin/5-fluorouracil combinations compared against 70 patients treated with 5-fluorouracil alone for metastatic colorectal cancer. The NCCTG large multicenter prospective trial evaluating the efficacy and safety of leucovorin/5-fluorouracil therapy in patients with metastatic colorectal cancer randomized 381 patients (N=161) to receive leucovorin 200 mg/m² IV every 3 hours starting at 24 hours after start of methotrexate infusion).