receiving leucovorin and fluorouracil. Concomitant granulocytopenia and fever were present in some but not all of the patients.

Dilution for I.V. Infusion: When required for i.v. infusion, the injection may be diluted with 5% Dextrose Injection, 0.9% Sodium Chloride Injection, Lactated Ringer's injection or Ringer's injection to give a final concentration of 0.05 mg/mL leucovorin. These dilutions may be stored for 24 hours at room temperature. Due to the possibility of antimicrobial contamination, unused solution should be discarded after that time.Dilutions with the hypertonic infusion solutions, 10% Dextrose injection and 5% Dextrose in 0.9% sodium chloride injection, may also be prepared to a final concentration of 0.05mg/mL of leucovorin. However these dilutions should be stored for no longer than 8 hours at room temperatures. Unused solution should be discarded after that time.

Warning: As with all parenteral drug products, i.v. admixtures should be inspected visually for clarity, particulate matter, precipitate, discoloration and leakage prior to administration, whenever solution and container permit. Solutions showing haziness, particulate matter, precipitate, discoloration or leakage should not be used.

Availability:
Leucocin - 15mg Injection
Each vial contains:
Leucovorin Calcium U.S.P. equivalent to
Leucovorin .....15mg.
Amber glass vial packed in unit carton.

Leucocin - 50mg Injection
Each vial contains:
Leucovorin Calcium U.S.P. equivalent to
Leucovorin .....50mg.
Amber glass vial packed in unit carton.

DOSAGE: As directed by the physician.
INSTRUCTIONS: Store below 25°C.
Protect from heat, light & moisture. Keep all medicines out of the reach of children.
To be sold on prescription only.

انجکشن

لیکوسن 15 ملی گرام، 50 ملی گرام

(لیکوورین کیلشیم) یو۔ایس۔پی

خوراک: ڈاکٹر کی ہدایت کے مطابق استعمال کریں۔

مزید معلومات کے لئے دیا گیا پرچہ ملاحظہ فرمائیں۔

ہدایات: 25 ڈگری سینٹی گریڈ سے کم درجہ حرارت پر رکھیں۔ گرمی، روشنی اور نمی سے بچائیں۔

تمام دوائیں بچوں کی پہنچ سے دور رکھیں۔

صرف مستند ڈاکٹر کے نسخہ پر فروخت کریں۔

Revised Dec. 2021

Manufactured by :
Pharmedic Laboratories (Pvt) Limited.
16 Km. Multan Road, Lahore - Pakistan
Phone : (92-42) 37511861 - 65, Fax : (92-42) 37511396

INJECTION
LEUCOCIN 15mg & 50mg
U.S.P. Spec.
(LEUCOVORIN CALCIUM U.S.P.)

Action and clinical pharmacology: Leucovorin is a reduced form of folic acid, which is readily converted to other reduced folic acid derivatives (e.g., tetrahydrofolate). Because it does not require reduction by dihydrofolate reductase as does folic acid, leucovorin is not affected by blockages of this enzyme by folic acid antagonists (dihydrofolate reductase inhibitors). This allows purine and thymidine synthesis, and thus DNA, RNA and protein synthesis, to occur. Leucovorin may limit methotrexate action on normal cells by competing with methotrexate for the same transport processes into the cell. Leucovorin enhances the cytotoxicity of fluoropyrimidines such as fluorouracil by their metabolites, methylene tetrahydrofolate and fluorodeoxyuridine monophosphate, forming a stable ternary complex with thymidylate synthase, and thereby, decreasing intracellular levels of that enzyme and the product thymidylate. The cell then dies as a result of thymine starvation.

Indications and clinical uses: To diminish the toxicity and counteract the effects of overdosage of folic acid antagonists. To diminish the systemic toxicity of methotrexate after administration of methotrexate as a chemotherapeutic agent, as part of chemotherapeutic treatment programs in the management of several forms of cancer. To treat megaloblastic anemias due to folate deficiency, as in sprue and other nutritional deficiencies; and megaloblastic anemias of pregnancy and infancy (see Contraindications). For pre-treatment followed by fluorouracil to prolong survival in the palliative treatment of patients with advanced colorectal cancer.

Contra-Indications: Leucovorin is improper therapy for pernicious anemia or other megaloblastic anemias secondary to a deficiency of vitamin B_{12}. Its use can lead to an apparent response of the haematopoietic system, but neurological damage may occur or progress if already present.

Caution: Leucovorin Injection should not be administered intrathecally.

Manufacturers' Warnings in clinical states: In cases of overdosage of folic acid antagonists, prompt administration of leucovorin calcium is essential, if a period of more than 4 hours intervenes, the treatment may be ineffective due to the time delay. Monitoring of the serum MTX concentration is essential in determining the optimal dose of leucovorin to give and duration of therapy. Delayed MTX excretion may be an indication of third space fluid accumulation (i.e. ascites, pleural effusion), renal insufficiency, low pH of urine or inadequate hydration. Higher doses of leucovorin or prolonged administration may be indicated in such cases. Leucovorin has no apparent effect on pre-existing methotrexate nephrotoxicity. In general diarrhea and/or stomatitis/mucositis are the first indications that severe and potentially life-threatening toxicity could develop. Patients who experience these symptoms while receiving any combination therapy regimen involving leucovorin and fluorouracil should be carefully monitored, generally these symptoms are easily controllable by reducing the dose of fluorouracil. Treatment-related deaths have been sporadically reported in patients receiving leucovorin/fluorouracil combination therapy. Leucovorin enhances the toxicity of fluorouracil. when these drugs are administered concurrently in the palliative therapy of advanced colorectal cancer, the dosage of fluorouracil must be reduced. Although the toxicities observed in patients treated with the combination of leucovorin and fluorouracil are qualitatively similar to those observed in patients treated with fluorouracil alone, gastrointestinal toxicities (particularly stomatitis and diarrhea) are observed more commonly and may be more severe in patients receiving the combination therapy. Generally these symptoms are easily controllable by reducing the dose of fluorouracil. Therapy with leucovorin/fluorouracil must not be initiated or continued in patients who have symptoms of gastrointestinal toxicity of any severity, until those symptoms have resolved. Patients with diarrhea must be closely monitored until the diarrhea has resolved, as rapid clinical deterioration leading to death can occur.

Symptoms and treatment of overdose: Symptoms and treatment: Leucovorin has very low acute and subchronic toxicity in animals. There has been no experience with overdosage of parenteral leucovorin in humans.

Dosage and administration: Leucovorin calcium injection may be administered as received by i.m. or i.v. injection, or it may be diluted for i.v. infusion (see Dilution for I.V. Infusion) Due to calcium content of leucovorin solution, no more than 160mg/minute of leucovorin should be injected i.v.

Treatment of overdosage of folic acid antagonists: In cases of overdosage of folic acid antagonists, prompt administration of leucovorin calcium is essential; if a period of more than 4 hours intervenes, the treatment may be ineffective. The dose of leucovorin calcium should be equal to or greater than the suspected dose of folic acid antagonist. Where large doses of methotrexate have been given, leucovorin may be administered by i.v. infusion in doses up to 75mg within 12 hours, followed by 12 mg i.m. every 6 hours for 4 doses. In less severe overdosage, 6 to 12mg of leucovorin may be given i.m. every 6 hours for 4 doses, until the serum methotrexate level is less than 108.

Use after chemotherapy with methotrexate: The dosage and scheduling of doses of leucovorin varies, but it is normally given about 6 to 24 hours following methotrexate administration, in amounts equal to the weight of methotrexate given. Serum creatinine and methotrexate levels should be determined at 24-hours intervals. If the 24-hours serum creatinine has increased 50% over baseline or if the 24-hours methotrexate level is greater than 5'106 or the 48-hours level is greater than 9'107, the dose of leucovorin should be increased to 100mg/mL i.v every 3 hours until the methotrexate level is less than 108. Hydration (3 L/day) and urinary alkalinization with $NaHC0_3$ should be employed concomitantly. The bicarbonate dose should be adjusted to maintain the urine pH at 7 or greater. In most cases, leucovorin should not be administered simultaneously with systemic methotrexate, since the therapeutic effect of the antimetabolite may be nullified. However, when methotrexate is administered by intra-arterial (regional perfusion) or intrathecal injection, leucovorin may be given (i.m. i.v.) concomitantly, to offset systemic methotrexate toxicity without abolishing the local activity of the cytotoxic drug.

Treatment of advanced colorectal cancer: Leucovorin is administered at 200mg/m^2 by slow i.v. injection prior to dosing with 370mg/m^2 fluorouracil by slow i.v. injection, for 5 consecutive days. This 5-days treatment course may be repeated at 4--weeks (28-days) intervals, provided that the patient has completely recovered from the toxic effects of the prior treatment course. In subsequent treatment courses, the dosage of fluorouracil should be adjusted based on patient tolerance of the prior treatment course. The daily dosage of fluorouracil should be reduced by 20% for patients who experienced moderate hematologic or gastrointestinal toxicity in the prior treatment course, and by 30% for patients who experienced severe toxicity. For patients who did not experience toxicity in the prior treatment course, fluorouracil dosage may be increased by 10%. Leucovorin dosages are not adjusted for toxicity.

Note: Since leucovorin may enhance the toxicity of fluorouracil, combination therapy consisting of Leucovorin and Fluorouracil for advanced colorectal cancer should be administered under the supervision of a physician experienced in the use of antimetabolite cancer chemotherapy. 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. Death from severe enterocolitis, diarrhea and dehydration have been reported in elderly patients

Geriatrics: Elderly or debilitated patients are at greater risk for severe toxicity receiving this therapy.

Precautions: General: Leucovorin should be used with caution after chemotherapeutically administered methotrexate when the following medical problems exist: aciduria (urine pH less than 7); ascites; dehydration (Note: inadequate hydration including that secondary to vomiting may also result in increased methotrexate toxicity), gastrointestinal obstruction; pleural or peritoneal effusions; renal function impairment (Note: risk of methotrexate toxicity is increased because elimination of methotrexate may be impaired and accumulation may occur, even small doses of methotrexate may lead to severe myelosuppression and mucositis; larger doses and/or increased duration of leucovorin treatment may be necessary). Patient monitoring is recommended when leucovorin is administered as part of methotrexate chemotherapy programs. Monitoring may include creatinine clearance determinations prior to therapy; plasma or serum methotrexate determinations to detect developing renal function impairment (an increase of greater than 50% within 24 hours is associated with severe renal toxicity); urine pH determination (recommended every 6 hours to ensure that the pH remains greater than 7 minimize the risk of methotrexate nephropathy). Leucovorin has no apparent effect on pre-existing methotrexate nephrotoxicity.

Pregnancy, Reproduction and Lactation: Problems have not been documented. It is not known whether leucovorin is excreted in breast milk.

Geriatrics: No information is available regarding the use of leucovorin in geriatrics.Elderly patients are at greater risk of developing severe toxicity when treated with the combination of leucovorin plus fluorouracil for the palliative treatment of colorectal cancer.

Children: Leucovorin may increase the frequency of seizures in susceptible children.

Drug Interactions: The following drugs or combinations containing these drugs may interact with leucovorin with clinical significance anticonvulsants, barbiturate or anticonvulsants, hydantoin; primidone (large doses of leucovorin may counteract the anticonvulsant effects of these medications); diaminopyrimidines (there is some evidence that concomitant administration of leucovorin and trimethoprim (or co-trimoxazole) may inhibit the antibiotic effect of trimethoprim) Leucovorin, administered concomitantly with methotrexate, may nullify the antitumor chemotherapeutic effect of the latter drug. Leucovorin has been administered simultaneously with pyrimethamine without interfering with its antimalarial therapy. Leucovorin enhances the cytotoxicity and toxicity of fluorouracil.

Adverse Reactions: Allergic reactions, wheezing, skin rash, hives or itching, occur rarely. In combination regimens, the toxicity of fluorouracil is enhanced by leuocovorin. The most common manifestations are mucositis, stomatitis, leukopenia, and/or diarrhea which may be dose limiting. In clinical trials with this drug combination, these toxicities were found to be easily controllable by appropriately reducing the dose of fluorouracil.