Folipro

Folinic Acid

COMPOSITION
Each tablet contains Calcium Folinate Hydrate BP equivalent to Folinic Acid 5 mg.

PHARMACOLOGY
Folinic Acid is a formyl derivative of tetrahydrofolic acid (H4 folate), vital for DNA synthesis. It acts as an antidote for both hematopoietic and reticuloendothelial toxic effects of Folic Acid antagonists (e.g., Methotrexate, Pyrimethamine, Trimethoprim) by replenishing the reduced folate pool and bypassing the blockage caused by these drugs.

INDICATION
It is indicated as:
• Neutralising the immediate toxic effects of Folic Acid antagonists, e.g. Methotrexate.
• Calcium Folinate Rescue or minimize systemic toxicity of Folic Acid antagonists, e.g. Methotrexate.
• To treat of megaloblastic anaemias due to sprue, nutritional deficiency, pregnancy, infancy, liver disease and malabsorption syndrome.

DOSAGE AND ADMINISTRATION
Folinic Acid Rescue (usually started 24 hours after Methotrexate administration): Up to 120 mg in divided doses over 12-24 hours as IM injection, IV bolus, or infusion in saline, followed by 12-15 mg IM or 15 mg orally, every 6 hours for 48 hours.
Increase the dose if serum creatinine rises or Methotrexate levels exceed the threshold. Doses >25-50 mg should be administrated parenterally due to limited oral absorption. For gastrointestinal toxicity, nausea, or vomiting, administer parenterally.

Dosage and Administration Guidelines for Folinic Acid Rescue

Clinical Situation	Dosage & Duration
Normal Methotrexate elimination	15 mg orally; IM, or IV (switching to the oral form after one or more parenteral doses) every 6 hours for 60 hours (10 doses, starting 24 hours after Methotrexate infusion).
Delayed late Methotrexate elimination	Continue 15 mg orally, IM, or IV every 6 hours until Methotrexate level < 0.05 µM.
Delayed early Methotrexate elimination and/or evidence of acute renal failure	150 mg IV every 3 hours until Methotrexate level < 1 µM, then 15 mg IV every 3 hours until < 0.05 µM.

Neutralising the immediate toxic effects of Folic Acid antagonists:
Trimetrexate toxicity: As preventive (along with everyday treatment or 72 hours after last dose), administer 20 mg/m² IV every 6 hours for 5-10 minutes or orally 4 in equal doses; total dose 80 mg/m² daily. Adjust the doses based on trimetrexate's hematological toxicity.
For overdosage (exceeding 90 mg/m² without Folinic Acid), administer 40 mg/m² IV every 6 hours for 3 days after stopping trimetrexate.
Trimethoprim toxicity (after stopping trimethoprim): Administer 3-10 mg/day until normal blood counts are restored.
Pyrimethamine (high-dose pyrimethamine or prolonged low-dose): Administer 5-50 mg/day based on peripheral blood count results.
Methotrexate overdose: Administer 15 mg (10 mg/m²) every 6 hours until Methotrexate < 0.05 µM. For gastrointestinal toxicity, administer parenterally. If Methotrexate >50 µM (24 hrs) or >5 µM (48 hrs), increase to 150 mg/m² every 3 hrs until <1 µM, then 15 mg every 3 hrs.
Megaloblastic anaemia (folate deficiency): Doses up to 15 mg daily.

CONTRAINDICATION
It is contraindicated in patients with-
• Hypersensitivity to the active substance or any of the excipients.
• Treatment of pernicious anaemia or other megaloblastic anaemias where vitamin B_{12} is deficient.

WARNING & PRECAUTION
General:
• May mask pernicious anaemia and other megaloblastic anaemias.
• Should only be used with Methotrexate under the direct supervision of a clinician experienced in the use of cancer chemotherapeutic agents.
• In the treatment of inadvertent overdosage of a Folic Acid antagonist, it should be administered as soon as possible; if a period exceeding 4 hours intervenes, the treatment may not be effective.
• Should not be given simultaneously with Folic Acid antagonists, such as Methotrexate, to abort clinical toxicity. However, this drug given concurrently with folate antagonists, such as pyrimethamine and trimethoprim does not inhibit their antibacterial activity.
• Parenteral administration of Folinic Acid is preferable to oral dosing following chemotherapy with Folic Acid antagonists if there is a possibility that the patient may vomit and not absorb the drug.
• Many cytotoxic medicinal products, direct or indirect DNA synthesis inhibitors lead to macrocytosis (hydroxycarbamide, cytarabine, mercaptopurine, thioguanine). Such macrocytosis should not be treated with Folinic Acid.
• Epileptic patients taking phenobarbitone, phenytoin, primidone, or succinimides may have more seizures. It's important to monitor their condition and adjust doses if needed during and after using this drug.

Folinic Acid/Methotrexate:
Measures to ensure the prompt excretion of Methotrexate are important as part of Folinic Acid Rescue Therapy. These measures include:
• Alkalinisation of urine so that the urinary pH is greater than 7.0 before Methotrexate infusion (to increase the solubility of Methotrexate and its metabolites).
• Maintenance of urine output of 1800-2000 cc/m^2 /24 hr by increased oral or intravenous fluids on days 2, 3 and 4 following Methotrexate therapy.
• Plasma Methotrexate concentration, BUN and creatinine should be measured on days 2, 3 and 4.
These measures must be continued until the plasma Methotrexate level is less than 10^{-7} molar (0.1µM).
Avoid excessive doses, as they may reduce Methotrexate's antitumor activity, particularly in CNS tumors. Resistance to Methotrexate due to impaired membrane transport also leads to resistance to Folinic Acid rescue.

SIDE EFFECT
Insomnia, agitation, depression, gastrointestinal disorders are rarely reported in general patients after high dosage and seizures are in epileptic patients.

USE IN PREGNANCY & LACTATION
There are no adequate and well-controlled clinical studies conducted in pregnant or breast-feeding women.

USE IN CHILDREN AND ADOLESCENTS
No data is available.

DRUG INTERACTION
• Folic Acid antagonist (e.g., Cotrimoxazole, Pyrimethamine, Methotrexate, antibiotic with antifolic effect): Efficacy of the Folic Acid antagonist may either be reduced or completely neutralized.
• Folinates given in large amounts: May counteract the antiepileptic effect of phenobarbitone, phenytoin and primidone and increase the frequency of seizures in susceptible patients.
• Concurrent administration of Folinic Acid with fluoropyrimidine: Has been associated with seizures and syncope.
• Concurrent administration of Chloramphenicol and Folic Acid in folate-deficient patients: May result in antagonism of haematopoietic response to Folic Acid.

OVERDOSAGE
There have been no reported sequelae in patients who have received significantly more Folinic Acid than the recommended dosage. But excessive amounts of this drug may nullify the chemotherapeutic effect of Folic Acid antagonists. There is no specific antidote to Folinic Acid overdose.

STORAGE
Store below 30°C temperature in a dry place. Protect from light & moisture. Keep out of the reach of children.

HOW SUPPLIED
Each box contains 30 tablets in Alu-Alu blister pack.

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NIPRO JMI Pharma

Manufactured by:
NIPRO JMI Pharma Ltd.
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