Calcium Folinate

Lovorin®

10 mg/mL (50 mg/5mL) Solution for Injection (IV/IM)

Detoxifying agent for antineoplastic treatment

FORMULATION
Each vial contains:
Calcium Folinate, BP (Equivalent to Folinic acid)……...…...…50 mg

PRODUCT DESCRIPTION

Folinic acid is a clear, colorless sterile solution sealed in an amber glass vial USP type 1.

CLINICAL PHARMACOLOGY

PHARMACODYNAMICS

Folinic acid is a derivative of tetrahydrofolic acid, the reduced form of folic acid, which is a cofactor in the biosynthesis of purines and pyrimidines of nucleic acids. Because it does not require reduction by dihydrofolate reductase as folic acid does, folinic acid is not affected by blockade of this enzyme by folic acid antagonists. This allows purine and thymidine synthesis and thus DNA, RNA and protein synthesis to occur. Because of this, folinic acid is a potent antidote for both the hematopoietic and reticuloendothelial toxic effects of folic acid antagonists (e.g., methotrexate, trimetrexate, pyrimethamine, and trimethoprim). Folinic acid may limit methotrexate action on normal cells by competing with methotrexate for the same transport processes into the cell.

Folinic acid also enhances the cytotoxicity of fluoropyrimidines such as 5-fluorouracil (5-FU) by their metabolites, methylene tetrahydrofolate and fluorodeoxyuridine monophosphate, forming a stable ternary complex with thymidylate synthase and decreasing intracellular levels of that enzyme and the product thymidylate. The cell then dies of thymine starvation.

PHARMACOKINETICS

Folinic acid is rapidly and extensively converted to other tetrahydrofolic acid derivatives including 5-methyl tetrahydrofolate, which is the major transport and storage form of folate in the body.

Following intramuscular (IM) administration of a 15 mg (7.5 mg/m^2) dose of folinic acid in healthy men, mean peak serum folate concentration of 0.241 mcg/mL occurs within 40 minutes. Areas under the serum folate concentration-time curves (AUCs) are reported to be about 8% less following IM injection in the gluteal region than in the deltoid region and 12% less following IM injection in the gluteal region than following intravenous (IV) or oral administration.

Tetrahydrofolic acid and its derivatives are distributed to all body tissues, being concentrated in the liver (about one-half of total body folate stores) and found in moderate amounts in the cerebrospinal fluid (CSF).

Folinic acid is excreted in urine, mainly as 10-formyl tetrahydrofolate and 5,10-methenyl tetrahydrofolate. Approximately 80 to 90% of the drug is excreted through the renal route while 5 to 8% undergoes fecal elimination. Loss of folate in the urine becomes approximately logarithmic as the amount of folinic acid administered exceeds 1 mg.

INDICATIONS

- In combination with fluorouracil (5-FU) for the treatment of advanced colorectal cancer
- To diminish the toxicity of methotrexate after high-dose methotrexate therapy in the management of several cancer types
- To diminish the toxicity and counteract the effects of overdosage of folic acid antagonists (methotrexate, trimetrexate, pyrimethamine, and trimethoprim)
- For the treatment of megaloblastic anemias due to folate deficiency (e.g., in sprue and other nutritional deficiencies); and megaloblastic anemias of pregnancy and infancy (see **CONTRAINDICATIONS**)

DOSAGE AND MODE OF ADMINISTRATION

Folinic acid should be given by IM or IV injection and must NOT be administered intrathecally.

Folinic acid should be administered parenterally rather than orally in patients with gastrointestinal (GI) toxicity, nausea, or vomiting and when individual doses greater than 25 mg are to be administered. When folinic acid is administered by IV infusion, the infusion should be given over several minutes and the infusion rate should not exceed 16 mL (160 mg of folinic acid) per minute because of the calcium concentration of the solution.

In Combination with 5-FU for the Treatment of Advanced Colorectal Cancer

Different regimens and dosages are used, without any dosage having been proven to be the optimal one. The following regimens have been used in adults and elderly in the treatment of advanced or metastatic colorectal cancer:

Bimonthly regimen: Folinic acid 200 mg/m^2 by IV infusion over two hours, followed by IV bolus 5-FU 400 mg/m^2 and 22-hour infusion of 5-FU 600 mg/m^2 for two consecutive days, every two weeks on days 1 and 2.

Weekly regimen: Folinic acid 20 mg/m^2 IV bolus injection or 200 to 500 mg/m^2 as IV infusion over two hours plus IV bolus injection of 5-FU 500 mg/m^2 in the middle or at the end of the folinic acid infusion.

Monthly regimen: Folinic acid 20 mg/m^2 IV bolus injection or 200 to 500 mg/m^2 as IV infusion over two hours immediately followed by IV bolus injection of 5-FU 425 or 370 mg/m^2 during five consecutive days.

Modification of 5-FU dosage and the treatment-free interval should be determined by toxicity and/or tolerance to the previous course. Dosage of 5-FU in subsequent doses should be adjusted based on the tolerance of the patient; the dose of folinic acid is generally not adjusted according to toxicity (see **WARNINGS AND PRECAUTIONS, Folinic acid/5-FU**) (*see 5-FU product information*).

Use After Chemotherapy with Methotrexate

As part of high dose methotrexate regimen in cancer chemotherapy, start folinic acid rescue therapy within 24 hours of methotrexate administration. Folinic acid rescue is necessary when methotrexate is given at doses exceeding 500 mg/m^2 and should be considered with methotrexate doses of 100 to 500 mg/m^2. The use of high-dose methotrexate and folinic acid rescue therapy in treating certain types of cancer is an evolving science and the optimum dosage schedule has not been established.

A typical folinic acid rescue dosage schedule: 10 mg/m^2 administered parenterally followed by 10 mg/m^2 orally (if there is adequate GI function) every six hours until serum methotrexate concentration has declined to $<10^{-8}$ M. Serum creatinine and methotrexate levels should be determined at 24 hour intervals. If at 24 hours after methotrexate administration the patient's serum creatinine has increased to 50% or more above the serum creatinine prior to methotrexate or the serum methotrexate concentration is $>5 \times 10^{-6}$ M, or if at 48 hours after methotrexate administration the serum methotrexate concentration is $<9 \times 10^{-7}$ M, increase folinic acid dosage immediately to 100 mg/m^2 every three hours until the serum methotrexate concentration is less than 10^{-8} M.

To Diminish the Toxicity and Counteract the Effects of Overdosage of Folic Acid Antagonists

Administer IV or IM folinic acid in amounts equal to the suspected dose of the folic acid antagonist given, as soon as the overdosage is detected and preferably within the first hour. The treatment may be ineffective if a period of more than four hours intervenes.

- ***Antidote to Methotrexate Toxicity***

Generally, folinic acid can be administered six to 24 hours after methotrexate infusion without affecting the activity of the antineoplastic drug. When large doses or overdoses of methotrexate are given, administer folinic acid by IV infusion in doses up to 75 mg within 12 hours, followed by 12 mg IM every six hours for four doses. When average methotrexate doses appear to have an adverse effect, 6 to 12 mg of folinic acid may be given IM every six hours for four doses. Prompt administration of folinic acid is essential.

- ***Antidote to Trimetrexate Toxicity***

The usual folinic acid dose for the prevention of potentially serious and life-threatening toxicities in immunocompromised patients receiving trimetrexate is 20 mg/m^2 every six hours (total daily dose of 80 mg/m^2). Folinic acid should be given daily during trimetrexate treatment either orally or IV (over five to 10 minutes) and should be continued for at least 72 hours after the last trimetrexate dose. The recommended course of trimetrexate therapy is 21 days and that of folinic acid is 24 days.

Dosage of trimetrexate and folinic acid should be adjusted according to the hematologic response of the patient. For overdosage with trimetrexate (possibly occurring with doses above 90 mg/m^2 without concomitant folinic acid administration), Folinic acid is given at 40 mg/m^2 IV every six hours for three days (*see specific product information for trimetrexate dosage adjustments*).

- ***Antidote to Pyrimethamine Toxicity***

The dosage of folinic acid necessary to prevent hematologic toxicity associated with pyrimethamine varies depending on the dosage of the folic acid antagonist and the clinical status of the patient. The usual dosage is 3 to 9 mg per day IM for three days or until platelet and leukocyte counts have reached safe levels. Folinic acid does not impair the effectiveness of pyrimethamine.

- ***Antidote to Trimethoprim Toxicity***

After stopping trimethoprim, 3 to 10 mg/day folinic acid until recovery of blood cell counts.

For the Treatment of Megaloblastic Anemias Due to Folate Deficiency

Folinic Acid IM, up to 1 mg Folinic Acid daily; larger doses do not increase the effect. The duration of therapy depends on the hematologic response to leucovorin. Oral Folinic Acid is preferred to parenteral therapy, except where cases of severe vomiting impair drug absorption when administered orally.

Direction for Dilution:

Preparation of Infusion Solution

Folinic Acid injection contains no antimicrobial agent. This product is for single use in one patient only.

When required for intravenous infusion Folinic Acid injection may be diluted in one liter of 5% w/v glucose in water for injection or normal saline. Such solutions are stable for 24 hours when stored between 2ºC to 8ºC. However, to avoid microbial contamination hazards, infusion should be commenced as soon as practicable after preparation of the solution. Infusion should be completed within 24 hours and any residue discarded.

Admixed solutions for parenteral administration should be visually inspected for particulate matter and discoluoration prior to administration where solution and container permit. Do not use if solution is cloudy or precipitated.

Incompatibilities

Incompatibilities leading to precipitation of the product have been reported between injectable forms of folinic acid and injectable forms of droperidol, 5-FU, foscarnet, and methotrexate.

CONTRAINDICATIONS

- Hypersensitivity to folinic acid or any ingredients in the product
- Undiagnosed anemia, pernicious anemia, vitamin B_{12} deficiency or other megaloblastic anemia secondary to vitamin B_{12} deficiency

WARNINGS AND PRECAUTIONS

General

Consider the possibility of allergic reactions to folinic acid as these have been reported following parenteral folic acid administration.

There is potential danger in administering folinic acid to patients with undiagnosed anemia. Folinic acid may obscure the diagnosis of pernicious anemia by alleviating hematologic manifestations of the disease while allowing neurologic complications to progress. This may result in severe nervous system damage before the correct diagnosis is made. Adequate doses of vitamin B_{12} may prevent, halt or improve neurologic changes caused by pernicious anemia.

The use of cytotoxic medicines such as direct or indirect DNA synthesis inhibitors (e.g., hydroxycarbamide, cytarabine, mercaptopurine, thioguanine) may lead to macrocytosis. Macrocytosis caused by these medicines should not be treated with folinic acid.

Toxicity Potentiation with Concomitant Treatment

Folinic acid/Methotrexate

Folinic acid should be used with caution when used after methotrexate in the following conditions:

- Aciduria (urine pH less than 7)
- Ascites
- Dehydration
- Gastrointestinal obstruction
- Pleural or peritoneal effusions
- Renal function impairment (See **STATEMENT ON USAGE FOR HIGH RISK GROUPS, Renal Impairment**)

When folinic acid rescue is used in conjunction with high-dose methotrexate therapy, it is highly recommended that the drug be administered only by physicians experienced in cancer chemotherapy and in centers where facilities for measuring blood methotrexate concentrations are available. Folinic acid is usually effective at counteracting severe methotrexate toxicity in these regimens, but toxic reactions to methotrexate may occur despite folinic acid therapy, especially when methotrexate's half-life is increased. Therefore, it is extremely important that folinic acid be administered until methotrexate's blood concentration declines to nontoxic concentrations.

Methotrexate serum concentrations should be monitored to determine the dose and duration of folinic acid therapy. Folinic acid dose may be increased or the administration may be prolonged in situations that delay methotrexate excretion, such as in ascites, pleural effusion, renal insufficiency or inadequate hydration.

Folinic acid/5-FU

Since folinic acid enhances 5-FU's toxicity, it is recommended that adjunctive therapy with folinic acid and 5-FU be given only by, or under the supervision of, physicians experienced in cancer chemotherapy and in the use of antimetabolites.

There is some evidence suggesting that risk of 5-FU-induced GI toxicity may be increased in patients receiving folinic acid concomitantly with the drug. Death secondary to gastrointestinal toxicity (severe enterocolitis, diarrhea and dehydration) has occurred in geriatric patients receiving the drugs concomitantly. Concomitant granulocytopenia and fever were present but not all cases.

Exercise extreme caution in geriatric or debilitated patients administered with combined folinic acid and 5-FU therapy since these patients are most likely to develop serious 5-FU toxicity. To avoid rapid clinical deterioration leading to death, treatment combination of 5-FU/folinic acid should not be initiated or maintained in patients having symptoms of GI toxicity, regardless of severity, until all of the symptoms have resolved completely. If diarrhea and/or stomatitis occur during treatment, it is recommended to reduce the dose of 5-FU until symptoms are fully resolved.

Folinic acid should not be mixed with 5-FU in the same IV injection or infusion.

Sensitivity Reactions

Since hypersensitivity reactions (including anaphylactoid reactions and urticaria) have been reported with the use of parenteral folinic acid, the possibility of allergic reactions to folinic acid should be considered.

Effects on Ability to Drive and Use Machine

There is no evidence that folinic acid has an effect on the ability to drive or use machines.

INTERACTIONS WITH OTHER MEDICAMENTS

- **Folic acid antagonists (e.g., methotrexate, trimetrexate, pyrimethamine, trimethoprim, raltitrexed):** Folinic acid may reduce or nullify the effect of these antagonists. Moreover, high intravenous or intramuscular doses of folinic acid may reduce the efficacy of methotrexate administered intrathecally.
- **Trimethoprim-sulfamethoxazole:** In a placebo-controlled study, the combination of folinic acid and trimethoprim-sulfamethoxazole for the treatment of acute Pneumocystis carinii pneumonia in patients infected with human immunodeficiency virus (HIV) was associated with increased rates of treatment failure and morbidity.
- **Fluoropyrimidines:** Concurrent use of folinic acid may increase therapeutic and toxic effects (such as the dose-limiting gastrointestinal disorders or hand-foot syndrome) of fluoropyrimidines (e.g., 5-FU, capecitabine, tegafur); however, these medications may be used together for therapeutic advantage. Folinic acid reduces the maximum tolerable dose of capecitabine from 3 g/m^2 (when used alone in the intermittent regimen) to 2 mg/m^2 (if folinic acid 30 mg is given twice daily).
- **Anticonvulsants:** Decreased anticonvulsant effect if used concomitantly with large amounts of folinic acid; possible increase in frequency of seizures in susceptible pediatric patients. Use with caution.

  Clinical monitoring (monitoring of the plasma concentrations) and, if necessary, dose adaptations of the anticonvulsant drug should be done before folinic acid treatment and after discontinuation.
- **Direct or indirect DNA synthesis inhibitors:** These cytotoxic medications (e.g., hydroxycarbamine, cytarabine, mercaptopurine, thioguanine) may lead to macrocytosis, which should not be treated with folinic acid.
- **Glucarpidase:** Since folinic acid is a substrate for glucardipase, it should not be administered within two hours before or after a dose of glucardipase. Glucardipase may also interact with reduced folates and folate inhibitors.

  Administration of glucarpidase within two hours before or after racemic folinic acid reduces peak concentration and exposure of folinic acid and 5-methyltetrahydrofolate.

STATEMENT ON USAGE FOR HIGH RISK GROUPS

Pregnancy

Pregnancy Category C. Animal reproduction studies have not been performed with folinic acid. It is also not known whether folinic acid can cause fetal harm when administered to pregnant women. Folinic acid should be used in pregnancy only when clearly needed.

Lactation

It is not known if folinic acid is distributed into milk. Use with caution.

Renal Impairment

Since folinic acid is known to be excreted by the kidneys, the risk of toxic reactions to the drug may be greater in patients with renal impairment. Care should be exercised in dose selection, and it may be useful in monitoring renal function.

Geriatric Use

Increased risk of developing severe toxicity when used in combination with 5-FU for advanced colorectal cancer (see **WARNINGS AND PRECAUTIONS, Folinic acid/5-FU**).

Deaths secondary to severe enterocolitis, diarrhea, dehydration reported in geriatric patients receiving weekly folinic acid and 5-FU therapy; concomitant granulocytopenia and fever observed in some patients.

Pediatric Use

Possible decreased anticonvulsant effect in pediatric patients receiving anticonvulsant therapy (e.g., phenobarbital, phenytoin, primidone). Possible increased seizures in susceptible patients. (see **INTERACTIONS WITH OTHER MEDICAMENTS, Anticonvulsants**).

UNDESIRABLE EFFECTS

Folinic acid appears to be nontoxic in therapeutic doses. The most common adverse reactions associated with folinic acid are nausea, vomiting and severe mucosal toxicity. Diarrhea with higher grades of toxicity and dehydration are also common, resulting in hospital admission for treatment and even death.

The most common adverse reactions of folinic acid with 5-FU are leukopenia, nausea, vomiting, diarrhea, stomatitis, lethargy, malaise, fatigue, alopecia, dermatitis, anorexia.

Infections and infestations: Infection
Blood and lymphatic system disorders: Leukopenia, thrombocytopenia, thrombocytosis (in patients receiving folinic acid during intra-arterial infusion of methotrexate)
Immune system disorders: Hypersensitivity reactions (including anaphylactoid reactions and urticaria)
Metabolism and nutrition disorders: Anorexia
Psychiatric disorders: Agitation, depression, insomnia
Nervous system disorders: Lethargy, seizure, syncope
Respiratory, thoracic, and mediastinal disorders: Wheezing
Gastrointestinal disorders: Cheleitis, constipation, gastrointestinal disturbances, stomatitis
Hepatic and hepatobiliary disorder: Hyperammonemia
Skin and subcutaneous tissue disorders: Alopecia, dermatitis, erythema, palmar-plantar erythrodysaesthesia, pruritus, rash, Stevens-Johnson Syndrome (SJS), Toxic Epidermal Necrolysis (TEN)
General disorders and administration site conditions: Fatigue, malaise, pyrexia

OVERDOSE AND TREATMENT

Since folinic acid is an intermediate in the metabolism of folic acid, it can be considered as a naturally occurring substance. There have been no reported sequelae in patients who have received significantly more folinic acid than the recommended dosage. However, excessive amounts of folinic acid may nullify the chemotherapeutic effect of folic acid antagonists. Signs of excessive dosing should be treated symptomatically.

Should overdosage of the combination of 5-FU and folinic acid occur, the overdosage instructions for 5-FU should be followed.

STORAGE CONDITIONS

Store between 2º and 8ºC (under refrigeration, no freezing). Protect from light. Keep the product out of sight and reach of children.

CAUTION

Foods, Drugs, Devices, and Cosmetics Act prohibits dispensing without prescription.

ADVERSE DRUG REACTION REPORTING STATEMENT

For suspected adverse drug reaction, seek medical attention immediately and report to the FDA at www.fda.gov.ph AND Unilab at (+632) 858-1000 or productsafety@unilab.com.ph. By reporting undesirable effects, you can help provide more information on the safety of this medicine.

AVAILABILITY

USP Type I amber glass vial in 5 mL (net content), box of 1's - DR-XY41173

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