54cm

30cm

Folina Tablets 15 mg

(Folinic Acid 15mg)

【COMPOSITION】

Each tablet contains Calcium Folinate 16.21 mg
(equivalent to Folinic Acid 15 mg)

【DESCRIPTION】

Pale yellow round tablets, convex on both sides and scored on one side.

【INDICATIONS】

Calcium folinate is indicated:

- to diminish the toxicity and counteract the action of folic acid antagonist such as methotrexate in cytotoxic therapy and overdose in adults and children. In cytotoxic therapy, this procedure is commonly known as 'Calcium folinate rescue'.
- In combination with 5-fluorouracil for the treatment of colorectal carcinoma.

【DOSAGE AND ADMINISTRATION】

Adults and Children

Calcium Folinate Rescue

Calcium Folinate may be used in conjunction with folic acid antagonists, e.g. methotrexate, to reduce their systemic toxicity. It is given 12 to 24 hours after the antineoplastic drug. Doses of up to 120mg may be given over 12 to 24 hours by intramuscular injection or intravenous injection or infusion, followed by 12 to 15mg intramuscularly, or 15mg orally, every 6 hours for the next 48 hours. With lower doses of methotrexate, folinate 15mg orally every 6 hours for 48 to 72 hours may be sufficient.

Treatment should be accompanied by alkalinisation of urine with maintenance of urinary output at 2000 ml/m^2/24 hours and should be continued until plasma methotrexate is less than 10^{-7} molar. (see WARNINGS)

Treatment of Megaloblastic Anaemia

The dose should not exceed 1mg daily given intramuscularly. When given orally, the recommended dosage is one Calcium Folinate Tablet (15mg) daily. Children up to 12 years: 0.25 mg/kg/day. Normal adult oral dosage: 10 – 20 mg daily.

Treatment of Overdosage of Folic Acid Antagonists

In cases of overdosage of folic acid antagonists, Calcium Folinate may be administered by intravenous infusion in doses of up to 75mg within 12 hours, followed by 12mg intramuscularly every 6 hours for 4 doses.

In general, where overdosage is suspected, the dose of Calcium Folinate should be equal to or greater than the offending dose of the folic acid antagonist administered, and should be given as soon as possible; preferably within the first hour and certainly within 4 hours after which it may not be effective.

Although Calcium Folinate may also be available as a solution for injection, Calcium Folinate should not be administered intrathecally

【CONTRAINDICATIONS】

Calcium Folinate is contraindicated in patients who have previously shown hypersensitivity to folinate or any of the excipients.

Calcium Folinate Injection is contraindicated in the treatment of pernicious anaemia or other megaloblastic anaemias where vitamin B_{12} is deficient. Its use can lead to an apparent response of the haematopoietic system, but neurological damage may occur or progress if already present.

Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take calcium folinate tablets.

【WARNINGS】

Calcium Folinate should only be used with methotrexate or 5-FU 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, folinate should be administered as soon as possible; if a period exceeding 4 hours intervenes, the treatment may not be effective.

In general, Calcium Folinate should not be given simultaneously with folic acid antagonists, e.g. methotrexate, to abort clinical toxicity as the therapeutic effect of the antagonist may be nullified. However, Calcium Folinate given concurrently with folate antagonists, such as pyrimethamine and trimethoprim does not inhibit their antibacterial activity.

Parenteral administration of folinate 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 folinate.

Measures to ensure the prompt excretion of methotrexate are important as part of Calcium Folinate Rescue Therapy. These measures include:

1) Alkalinisation of urine so that the urinary pH is greater than 7.0 before methotrexate infusion (to increase solubility of methotrexate and its metabolites)
2) 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.
3) 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).

【DRUG INTERACTIONS】

Folinates given in large amounts may counteract the antiepileptic effect of phenobarbitone, phenytoin and primidone and increase the frequency of seizures in susceptible patients.

Caution is required during concurrent administration of Calcium Folinate with fluoropyrimidine as this has been associated with seizures and syncope (see ADVERSE REACTIONS)

【PREGNANCY AND LACTATION】

Reproduction studies have been performed in rats and rabbits at doses of at least 50 times the human dose. These studies have revealed no evidence of harm to the foetus due to Calcium Folinate. There are, however, no adequate and well-controlled studies in pregnant women. Because animal studies are not always predictive of human response, Calcium Folinate should only be used in pregnant women if the potential benefit justifies the potential risk to the foetus.

Since it is not known if Folinate is distributed into milk, the drug should be used with caution in nursing women.

【ADVERSE REACTIONS】

Adverse reactions are rare but occasional allergic reactions including anaphylactoid reactions and urticaria have been reported; pyrexia has occurred after parenteral administration.

Seizures and/or syncope have been reported rarely in cancer patients receiving folinate, usually in association with fluoropyrimidine administration and most commonly in those with CNS metastases or other predisposing factors; however, a causal relationship has not been established.

【OVERDOSAGE】

There is no specific antidote to calcium folinate overdose. In cases of overdosage patients should be given appropriate supportive care.

Should overdosage of the combination of 5-FU with Calcium Folinate occur, the overdosage instruction for 5-FU should be followed.

【PHARMACOLOGY】

Pharmacodynamic properties

Folinate is a derivative of tetrahydrofolic acid, the reduced form of folic acid, which is involved as a cofactor for 1-carbon transfer reactions in the biosynthesis of purine and pyrimidines of nucleic acids.

Impairment of thymidylate synthesis in patients with folic acid deficiency is thought to account for the defective DNA synthesis that leads to megaloblast formation and megaloblastic and macrocytic anemias. Because of its ready conversion to other tetrahydrofolic acid derivatives, Folinate is a potent antidote for both hematopoietic and reticuloendothelia toxic effects of folic acid antagonists, (e.g. Methotrexate, Pyrimethamine, Trimethoprim). It is postulated that in some cancers, Folinate enters and "rescues" normal cells from the toxic effects of folic acid antagonists, in preference to tumour cells, because of a difference in membrane transport mechanisms; this principle is the basis of high-dose Methotrexate therapy with "Folinate rescue".

Pharmacokinetic properties

ABSORPTION AND DISTRIBUTION

In vivo, Calcium Folinate 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.

Normal total serum folate concentrations have been reported to range from 0.005-0.015 μg/mL. Folate is actively concentrated in CSF, and normal CSF concentrations are reported to be about 0.016-0.021 μg/mL. Normal erythrocyte folate concentrations range from 0.175-0.316 μg/mL.

In general, serum folate concentrations less than 0.005 μg/mL indicate folate deficiency and concentrations less than 0.002 μg/mL usually result in megaloblastic anemia.

Following I.M. administration of a 15mg (7.5mg/m²) dose in healthy men, mean peak serum folate concentrations of 0.241 μg/mL occur within about 40 minutes. Following oral administration of a 15mg (7.5mg/m²) dose in healthy men, mean peak serum folate concentrations of 0.268 μg/mL occur within about 1.72 hours. Areas under the serum folate concentration-time curves (AUCs) are reported to be about 8% less following I.M. injection in the gluteal region than in the deltoid region and about 12% less following I.M. injection in the gluteal region than following I.V. or oral administration.

Tetrahydrofolic acid and its derivatives are distributed to all body tissues; the liver contains about one-half of total body folate stores. In a small number of patients, biliary concentration of folates was about 4.5 times the plasma folate concentration after oral administration of a 2mg dose of Folinate; this is believed to represent the hepatic folate pool rather than excretion of the administered dose.

ELIMINATION

Folinate is excreted in urine, mainly as 10-formyl tetrahydrofolate and 5, 10-methenyl tetrahydrofolate. There are some evidence that 5-methyl tetrahydrofolate may be conserved by the kidneys in preference to 5-formyl tetrahydrofolate (Folinate). Loss of folate in the urine becomes approximately logarithmic as the amount of Folinate administered exceeds 1mg.

【PACKAGE】

2 ~1000 tablets per plastic bottle or in blister per carton.

【STORAGE】

Store below 30℃.

Keep out of the reach of children.

【SHELF LIFE】

For the expiration date, please refer to the label in the box.

【MANUFACTURER】

TTY Biopharm Company Limited Lioudu Factory. No.5, Gongjian W. Rd., Qidu District, Keelung , Taiwan, R.O.C.

【PRODUCT REGISTRATION HOLDER】

Pharm-D Sdn. Bhd.

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