PRODUCT MONOGRAPH

LEUCOVORIN CALCIUM

Injection and Tablets

Folic Acid Derivative

Lederle
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NAME OF DRUG

LEUCOVORIN CALCIUM

Injection and Tablets

Folic Acid Derivative

ACTION

LEUCOVORIN (folinic acid) is the formyl derivative and one of the active forms of folic acid. LEUCOVORIN CALCIUM is useful clinically in circumventing the action of folate reductase.

It is readily converted to 5-methyltetrahydrofolate in the intestine prior to absorption. In this form, it is a major component of the total active human serum folate.

INDICATIONS

a) To diminish the toxicity and counteract the effects of accidental overdosage of folic acid antagonists.

b) To treat the megaloblastic anemias due to folate deficiency, as in sprue, nutritional deficiency, megaloblastic anemias of pregnancy and infancy. (See WARNINGS).

WARNINGS

LEUCOVORIN is not to be used as exclusive therapy for pernicious anemia and other megaloblastic anemias secondary to Vitamin B_{12} deficiency. Hematologic remissions may occur, while neurologic manifestations remain progressive.

In the treatment of accidental overdosages of folic acid antagonists, LEUCOVORIN should be administered within one hour; it is usually ineffective if administered after a delay of 4 hours.

ADVERSE REACTIONS

Allergic reactions and sensitization have been reported following both oral and parenteral administration of folic acid.

SYMPTOMS AND TREATMENT OF OVERDOSAGE

Folic acid is a water soluble vitamin converted in the body by the action of folate reductase to folinic acid (LEUCOVORIN) which is rapidly eliminated in the urine.

Folic acid has low acute and chronic toxicities in man. No adverse effects have been noted in adults after the ingestion of 400 mg/day for 5 months or 10 mg/day for 5 years.

DOSAGE AND ADMINISTRATION

a) Megaloblastic anemia: 1 mg daily

There is no evidence that doses greater than 1 mg daily have greater efficacy than those of 1 mg. The loss of folate in the urine becomes roughly logarithmic when the amount administered exceeds 1 mg.

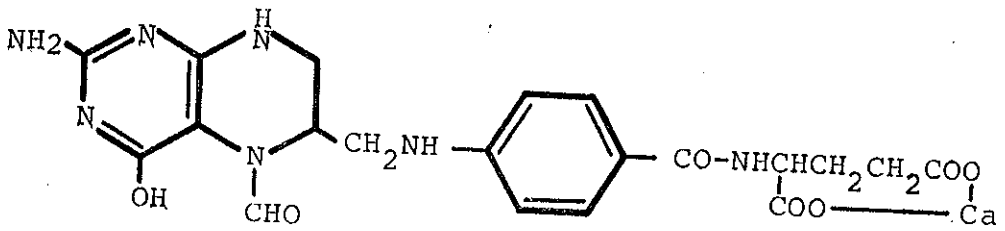
b) For the treatment of accidental overdosage of folic acid antagonists, it is generally given in amounts equal to the weight of the antagonist used.

LEUCOVORIN CALCIUM may be administered orally or by intramuscular injection. LEUCOVORIN injection is intended for administration as received.

PHARMACOLOGICAL INFORMATION

Chemical Name

Calcium N-(p-([2-amino-5-formyl-5,6,7,β-tetrahydro-4-hydroxy-6-pteridinyl)methyl]amino)benzoyl)-L-glutamate.



Empirical Formula: $C_{20}H_{21}CaN_7O_7 5H_2O$ **Molecular Weight:** 601.60

Melting Point: Decomposes above 250°

Description: LEUCOVORIN CALCIUM occurs as a yellowish white or yellow, odourless powder. It is very soluble in water and practically insoluble in alcohol.

Composition:

Each mL of LEUCOVORIN CALCIUM injection contains 3 mg LEUCOVORIN (as the calcium salt) which is the form preferred for intramuscular injection. Preservative: benzyl alcohol 0.9% w/v. The inactive ingredients are sodium chloride 0.56% w/v and water for injection q.s. 100%. Sodium hydroxide or hydrochloric acid is used to adjust the pH to approximately 7.7.

Each tablet contains LEUCOVORIN CALCIUM equivalent to 5 mg, 15 mg or 25 mg of LEUCOVORIN. All tablets are dye free.

Stability and Storage

LEUCOVORIN CALCIUM injection should be protected from light and stored at room temperature.

LEUCOVORIN CALCIUM tablets should be stored at room temperature.

DOSAGE FORMS

Ampoules of 3 mg/mL for intramuscular injection. Boxes of 6 x 1 mL ampoules. Each ampoule contains 3 mg LEUCOVORIN as LEUCOVORIN CALCIUM.

Tablets of 5 mg, 15 mg and 25 mg each of LEUCOVORIN as LEUCOVORIN CALCIUM. Bottles of 24.

CLINICAL PHARMACOLOGY

A folic acid deficiency is produced during therapy with the folic acid antagonists aminopterin and amethopterin (METHOTREXATE) used as antineoplastic agents and with the chemotherapeutic agent pyrimethamine. These agents competitively inhibit the conversion of folic acid to folinic acid. Their affinity for folate reductase is so much greater than that of folic acid that not even large doses of folic acid will correct the drug-induced deficiency. In the event of a severe toxic reaction, the already reduced form, folinic acid, can be given, since it can be used directly to form new coenzyme.

Thirty minutes following oral administration of LEUCOVORIN CALCIUM, 92 to 93% of total reduced folates in serum are assayable as 5-methyltetrahydrofolate. The determination of 5-methyltetrahydrofolate was carried out by the use of a differential microbiological disc assay procedure utilizing METHOTREXATE resistant strains of Lactobacillus casei and Streptococcus faecium var. durans. Peak serum levels of 5-methyltetrahydrofolate were reached earlier following I.M. administration (approximately 45 minutes) than after oral administration (approximately 2 hours). The average serum 5-methyltetrahydrofolate levels following I.M. or oral administration are comparable, as indicated by measuring the areas under the curve from 0-6 hours (2889 nanomoles/mL x hr. after oral administration versus 2992 nanomoles/mL x hr. after I.M. Administration).[7,2]

Similar results were obtained after oral administration of radiolabelled LEUCOVORIN CALCIUM. These studies also indicated substantial metabolism of LEUCOVORIN CALCIUM during transfer from gastrointestinal tract to the systemic circulation, since 90% of the serum folate was identified as 5-methyltetrahydrofolate by chromatographic techniques.[7,8]

The serum half life of citrovorum factor (or 5-formyltetrahydrofolate) was 35-45 minutes following both oral and I.M. administration. The serum half life of 5-methyltetrahydrofolate was about $2\frac{1}{4}$ hours.[7] 5-methyltetrahydrofolate is excreted via the kidneys in a manner proportional to its serum concentration.[8]

METHOTREXATE did not seem to affect the absorption of folate.[8]

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