

Calcium Folate Ebewe Data Sheet

NAME OF THE MEDICINE

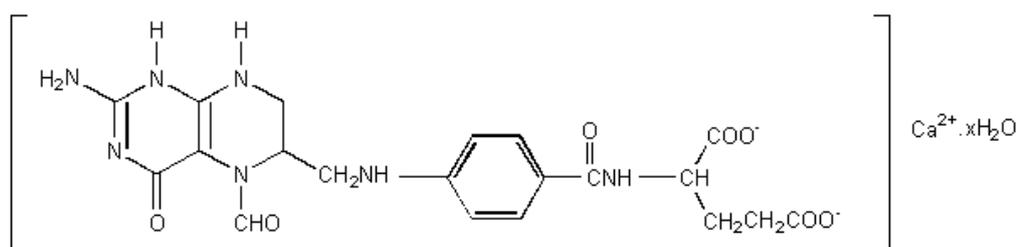
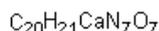
Calcium folinate injection

Composition

Active: Calcium folinate (equivalent to 10 mg folic acid per mL)

Inactive: Sodium chloride (7.7mg/mL), qs Water for Injections. Preservative free.

The structural formula of calcium folinate is:



M.W. = 511.5

(anhydrous calcium salt)

Molecular formula: $C_{20}H_{21}CaN_7O_7$

CAS: 1492-18-8

DESCRIPTION

Calcium folinate is a white or light yellow, amorphous or crystalline powder, sparingly soluble in water and practically insoluble in acetone and ethanol. Calcium folinate potency is usually expressed in terms of equivalent units of folic acid.

PHARMACOLOGY

Folinic acid is the formyl derivative of tetrahydrofolic acid (THF) which is a metabolite and active form of folic acid. It is effective in the treatment of megaloblastic anaemia caused by folic acid deficiency and is a potent antidote for both the haematopoietic and reticuloendothelial toxic effects of folic acid antagonists, e.g. methotrexate, pyrimethamine, trimethoprim. In some cancers, folinic acid enters and 'rescues' normal cells, in preference to tumour cells, from the toxic effects of folic acid antagonists, due to a difference in membrane transport mechanism. This principle is applied in high dose methotrexate therapy with 'folinic acid rescue'.

Pharmacokinetics

Following administration, calcium folinate enters the body's pool of reduced folates. Peak levels of total reduced folates are reached on average 10 minutes and 52 minutes following intravenous and intramuscular administration, respectively. It has been reported that peak plasma levels of folinic acid are achieved 10 minutes and 28 minutes after intravenous and intramuscular administration, respectively. Calcium folinate is rapidly converted in vivo to 5-methyl tetrahydrofolate (5-methyl-THF), the active metabolite. 5-methyl-THF becomes the major circulating form of the drug. Peak levels of 5-methyl-THF are observed at 1.3 and 2.8 hours following intravenous and intramuscular administration.

Calcium Folate Ebewe Data Sheet

Folates are distributed to all tissues and concentrated in the liver with moderate amounts found in the cerebrospinal fluid. Following intravenous or intramuscular administration of 25mg of folinic acid the half life for total reduced folates has been reported to be 6.2 hours. Folinic acid is mainly eliminated as 10-formyl tetrahydrofolate and 5,10-methyl tetrahydrofolate with the metabolites mainly excreted in the urine (approx 80-90%). Elimination is logarithmic in doses exceeding 1 mg.

INDICATIONS

- As rescue therapy to reduce toxicity following high-dose methotrexate therapy.
- Has shown good results in the treatment of certain megaloblastic anaemias resulting from folic acid deficiency. This mainly occurs in infants, during pregnancy, in malabsorption syndromes, liver diseases, sprue and malnutrition. It is not more effective than folic acid for these conditions
- Overdosage of methotrexate and in impaired methotrexate elimination
- Reducing the toxicity and circumventing the effect of folic acid antagonists

CONTRAINDICATIONS

Calcium folinate should not be used as therapy for pernicious anaemia and other megaloblastic anaemias secondary to cyanocobalamin (vitamin B₁₂) deficiency. When treating these conditions with Calcium folinate Ebewe, haematological remission may occur, but neurological manifestations are likely to progress.

Calcium folinate should not be used in patients who are hypersensitive to any of the constituents in the preparation.

PRECAUTIONS

Calcium folinate should only be used with folic acid antagonists, e.g. methotrexate, or fluoropyrimidines, e.g. 5-fluorouracil, under the direct supervision of a clinician experienced in the use of cancer chemotherapeutic agents.

Because of the calcium ion content of Calcium folinate Ebewe no more than 160mg (16mL) should be injected intravenously per minute.

Calcium folinate may enhance the toxicity of fluorouracil. Deaths from severe enterocolitis, diarrhoea and dehydration have been reported in elderly patients receiving calcium folinate and fluorouracil. Concomitant granulocytopenia and fever were present in some, but not all, of the patients.

Seizures and/or syncope have been reported rarely in cancer patients receiving calcium folinate usually in association with fluoropyrimidine administration, and most commonly in those with CNS metastases. Since three patients had recurrent neurological symptoms on rechallenge with calcium folinate, further treatment with Calcium folinate Ebewe is not recommended in these circumstances.

Simultaneous therapy with antineoplastic folic acid antagonist (eg methotrexate) and Calcium folinate Ebewe is not recommended because the effect of the folic acid antagonist is either reduced or completely inhibited.

Calcium folinate Ebewe should be given as soon as possible after accidental methotrexate overdosage because the effectiveness of calcium folinate decreases as the time interval between methotrexate and calcium folinate administration increases.

Calcium Folate Ebewe Data Sheet

Calcium folinate Ebewe has no effect on nonhaematological toxicities of methotrexate, such as the nephrotoxicity resulting from drug and/or metabolite precipitation in the kidney.

Calcium folinate Ebewe is not suitable for the treatment of pernicious anaemias and other anaemias resulting from lack of vitamin B12. Haematological remissions may occur, while the neurological manifestations remain progressive.

Use in Pregnancy (Category A)

Calcium folinate has been taken by a large number of pregnant women and women of childbearing potential without any proven increase in the frequency of malformations or other direct or indirect harmful effects on the fetus having been observed. However caution is essential in the use of calcium folinate in pregnant women as the safety of calcium folinate in pregnancy has not been established.

Use in Lactation

As it is not known whether calcium folinate is excreted in milk, caution should be exercised when Calcium folinate Ebewe is administered to breastfeeding mothers.

INTERACTION WITH OTHER MEDICINES

Folic acid in large amounts may counteract the antiepileptic effect of phenobarbitone, phenytoin and primidone, and increase the frequency of seizures in susceptible children.

Calcium folinate may enhance the toxicity of fluoropyrimidines e.g. 5-fluorouracil (See Precautions).

High doses of calcium folinate may reduce the efficacy of intrathecally administered methotrexate.

Incompatibilities

Calcium folinate has been reported to be incompatible with droperidol injection and foscarnet injection and sodium bicarbonate.

ADVERSE REACTIONS

Adverse reactions to calcium folinate are rare. Occasional hypersensitivity reactions have been reported; pyrexia, urticaria and anaphylactoid reactions have occurred after parenteral administration. Nausea and vomiting with very high doses of calcium folinate have been reported. Seizures and/or syncope have been reported rarely in cancer patients receiving calcium folinate, usually in association with fluoropyrimidine administration (see Precautions).

DOSAGE AND ADMINISTRATION

Calcium folinate Ebewe may be administered by the intramuscular or intravenous route.

Calcium folinate Ebewe should not be administered intrathecally.

When required for intravenous infusion, Calcium folinate Ebewe may be diluted with either glucose 5% intravenous infusion or sodium chloride 0.9% intravenous infusion to give a final concentration of 0.05 to 0.4 mg/mL. Further diluted solutions of Calcium folinate Ebewe in glucose 5% intravenous infusion and sodium chloride 0.9% intravenous infusion are stable for 24 hours when stored between 2°C to 8°C. To avoid microbial contamination hazards, infusion should be commenced as soon as practicable after preparation.

Calcium Folate Ebewe Data Sheet

In the treatment of accidental overdose of folic acid antagonists e.g methotrexate, Calcium folinate Ebewe should be given as soon as possible. As the time interval between antifolate administration and calcium folinate rescue increases, calcium folinate's effectiveness in counteracting toxicity decreases.

Monitoring of serum methotrexate concentration is essential in determining the optimal dose and duration of treatment with Calcium folinate Ebewe. Delayed methotrexate excretion may be caused by a third space fluid accumulation (i.e. ascites, pleural effusion), renal insufficiency or inadequate hydration. Under such circumstances, higher doses of Calcium folinate Ebewe or prolonged administration may be indicated.

Calcium folinate Ebewe contains no antimicrobial agent. The product is for single use in one patient only. Discard any residue.

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

Calcium folinate Ebewe should not be mixed in the same infusion as fluorouracil as a precipitate may form.

Laboratory Tests

Patients being treated with Calcium folinate Ebewe following methotrexate therapy including inadvertent overdose, or patients with impaired methotrexate elimination should have serum creatinine and methotrexate levels determined at intervals of 24 hours. Calcium folinate Ebewe dosage should be adjusted on the basis of laboratory test results.

Calcium Folate Ebewe Rescue after High Dose Methotrexate Therapy.

The dose of Calcium folinate Ebewe required depends on the amount of methotrexate administered and whether there is impaired methotrexate elimination. The following dosing guidelines are for a methotrexate dose of 12 to 15 g/m² by intravenous infusion over four hours. Calcium folinate Ebewe injection is commenced 24 hours after the start of the methotrexate infusion.

Normal Methotrexate Elimination. *Laboratory findings.*

Serum methotrexate concentration approximately 10 micromolar at 24 hours after administration, 1 micromolar at 48 hours, and < 0.2 micromolar at 72 hours.

Calcium folinate dose. 15 mg every 6 hours for 60 hours (ten doses).

Delayed Late Methotrexate Elimination. *Laboratory findings.* Serum methotrexate concentration > 0.2 microM at 72 hours and > 0.05 microM at 96 hours.

Calcium folinate dose. 15 mg every six hours until serum methotrexate concentration < 0.05 microM.

Delayed Early Methotrexate Elimination and/or Evidence of Acute Renal Injury. *Laboratory findings.* Serum methotrexate concentration greater than or equal to 50 microM at 24 hours, or greater than or equal to 5 microM at 48 hours, or greater than or equal to 100% increase in serum creatinine concentration at 24 hours.

Calcium folinate dose. 150 mg intravenously every three hours until serum methotrexate concentration < 1 microM, then 15 mg intravenously every three hours until serum methotrexate concentration < 0.05 microM.

Calcium Folate Ebewe Data Sheet

Serum creatinine and methotrexate concentrations should be determined at least once daily.

Patients who experience delayed methotrexate elimination are likely to develop reversible renal failure. In addition to Calcium folinate Ebewe, these patients require hydration and urinary alkalinisation (pH 7.0 or greater), and close monitoring of fluid and electrolyte status until the serum methotrexate concentration has fallen below 0.05 microM and the renal failure has resolved.

Some patients will have abnormalities in methotrexate elimination or renal function following methotrexate administration which are significant but less severe than the abnormalities described above. These abnormalities may or may not be associated with significant clinical toxicity. If significant clinical toxicity is observed, folinic acid rescue should be extended for an additional 24 hours (total of 14 doses over 84 hours) in subsequent courses of therapy. The possibility that the patient is taking other medications which interact with methotrexate (e.g. medications which may interfere with methotrexate elimination or binding to serum albumin) should always be reconsidered when laboratory abnormalities or clinical toxicities are observed.

Note. The above dosage recommendations do not necessarily apply to experimental high dose methotrexate therapy. High dose methotrexate therapy should only be administered by qualified specialists and in hospitals where the necessary facilities are available. Recent published literature should be consulted for details at all times.

Inadvertent Methotrexate Overdose.

Calcium folinate Ebewe should begin as soon as possible after inadvertent overdosage of methotrexate. As the time interval between antifolate administration and folinic acid rescue increases, Calcium folinate Ebewe's effectiveness in counteracting toxicity diminishes.

The recommended dose is 10 mg/m² intravenously or intramuscularly every six hours until the serum methotrexate concentration is less than 0.01 microM.

Serum creatinine and methotrexate concentrations should be determined at 24 hour intervals. If the 24 hour serum creatinine concentration has increased 50% over baseline, or the 24 hour methotrexate concentration is greater than 5 microM or the 48 hour concentration greater than 0.9 microM, the dose of Calcium folinate Ebewe should be increased to 100 mg/m² every three hours until the methotrexate concentration is less than 0.01 microM. Hydration (3 L/day) and urinary alkalinisation with sodium bicarbonate solution should be employed concomitantly. The bicarbonate should be adjusted to maintain the urine pH at 7.0 or greater.

Treatment of Megaloblastic Anaemias. Parenteral administration. Up to 1 mg daily. There is no evidence that doses greater than 1 mg/day have greater efficacy than those of 1 mg; additionally, loss of folate in urine becomes roughly logarithmic as the amount administered exceeds 1 mg.

Treatment of Pyrimethamine Overdosage. The dosage of pyrimethamine in treating toxoplasmosis is 10 to 20 times its dosage for malaria and approaches the toxic level. Since Calcium folinate Ebewe is not utilised by protozoa, it can be given simultaneously without impairing the effectiveness of therapy. The usual dosage is 3 to 9 mg/day by intramuscular injection for three days or until the platelet and leucocyte counts have reached safe levels.

Calcium Folate Ebewe Data Sheet

OVERDOSAGE

Contact the Poisons Information Centre on (telephone 0800 POISON or 0800 764766) for advice on management of overdose.

Folinic acid is an intermediate in the metabolism of folic acid and can therefore be considered as a naturally occurring substance. Large doses have been administered with no apparent adverse effects. Such doses suggest that administration of this drug is relatively safe. Signs of excessive dosing, if they occur, should be treated symptomatically.

Excessive amounts of calcium folinate may nullify the chemotherapeutic effect of folic acid antagonists.

PRESENTATION AND STORAGE CONDITIONS

50mg in 5mL glass ampoules: 5's

100mg in 10mL glass vial: 1's

300mg in 30mL glass vial: 1's

1000mg in 100mL glass vial: 1's

Store at 2°C to 8°C. (Refrigerate. Do not freeze). Protect from light.

MEDICINE CLASSIFICATION

Prescription Medicine

NAME AND ADDRESS OF SPONSOR

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DATE OF PREPARATION

09 December 2014