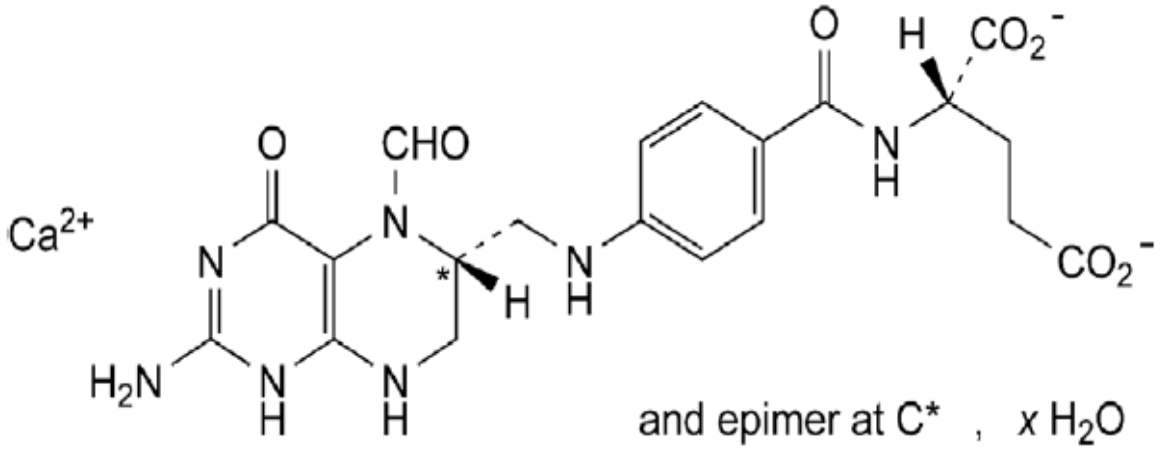
HSP Calcium Folinate 10 mg/mL Injection

Name of the Medicine

Calcium folinate hydrate

The chemical structure of calcium folinate hydrate is shown below, CAS registry number 1492-18-8.



Chemical Name: Calcium (2*S*)-2-[[4-[[[(6*RS*)-2-amino-5-formyl-4-oxo1,4,5,6,7,8-hexahydropteridin-6-yl]methyl]amino]benzoyl]amino]pentanedioate

Chemical Formula: $C_{20}H_{21}CaN_7O_7,xH_2O$

M.W. = 511.5 (Anhydrous)

Description

HSP Calcium folinate10 mg/mL Injection is a clear straw-coloured sterile solution of folinic acid (as calcium salt) in water for injections. HSP Calcium folinate 10 mg/mL Injection is a white to light yellow, amorphous or crystalline hygroscopic powder. Sodium chloride is included for isotonicity. Sodium hydroxide or hydrochloric acid is used to adjust pH. The vial presentation (300 mg/30 mL) does not contain a bactericide.

The following HSP Calcium folinate 10 mg/mL Injection presentation: 300 mg/30 mL contain calcium folinate hydrate equivalent to 300 mg folinic acid.

Pharmacology

Pharmacological actions

Folinic acid is the formyl derivative of tetrahydrofolic acid which is a metabolite and active form of folic acid. Folinic acid as a co-factor participates in many metabolic reactions including purine synthesis, pyrimidine synthesis and amino acid conversion. 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. Folinic acid is used in cytotoxic therapy as an antidote to folic acid antagonists which block conversion of folic acid to tetrahydrofolate by binding enzyme dihydrofolate reductase. In some cancers, folinic acid enters and 'rescues' normal cells, in preference to tumor 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

Distribution: Following administration, folinic acid enters the general body pool of reduced folates. It has been reported that, following intravenous, intramuscular and oral administration, peak serum level of total reduced folates are achieved within a mean time of 10 minutes, 52 minutes and 1.7 hours, respectively. Peak levels of 5-formyl THF appear at 10 minutes and 28 minutes following intravenous and intramuscular administration respectively. Folate is concentrated in the cerebrospinal fluid and liver although distribution occurs to all body tissues. The bioavailability of an oral dose is almost the same as an equivalent intramuscular dose.

Metabolism: Calcium folinate hydrate is rapidly and extensively converted to 5-methyl tetrahydrofolate (an active metabolite) *in vivo,* with less extensive conversion resulting from parenteral, as opposed to oral administration.

Reduction in the levels of parent compound coincides with the appearance of the active metabolite 5-methyl THF, which becomes the major circulating form of the drug. Peak levels are observed at 1.5 and 2.8 hours following intravenous and intramuscular administration respectively. The terminal half-life for total reduced folates is reported as 6.2 hours. Tetrahydrofolic acid and its derivatives are distributed to all body tissues, being concentrated in the liver and found in moderate amounts in the CSF. Following a 15 mg dose given either orally or intramuscularly, peak serum folate concentrations of 0.268 micrograms/mL and 0.241 micrograms/mL were detected.

Excretion: Folinic acid is eliminated mainly as 10-formyl tetrahydrofolate and 5, 10-methyl tetrahydrofolate. The metabolites are mainly excreted via the urine (80-90%), with elimination being logarithmic in doses exceeding 1 mg.

Indications

HSP Calcium folinate 10 mg/mL Injection is used

- To diminish the toxicity and counteract the effects of inadvertently administered over dosage of folic acid antagonists.
- As a rescue after high dose methotrexate therapy.
- In the treatment of megaloblastic anaemia due to sprue, nutritional deficiency, pregnancy and infancy when oral therapy is not possible.
- For use in combination with fluorouracil to prolong survival in the palliative treatment of patients with advanced colorectal cancer.

Contraindications

HSP Calcium folinate 10 mg/mL Injection is improper therapy for pernicious anaemia and other megaloblastic anaemias secondary to the lack of Vitamin B_{12}. When treating these conditions with folinic acid, haematological remission may occur, but neurological manifestations are likely to progress.

Precautions

HSP Calcium folinate 10 mg/mL

Injection should be administered only by intramuscular or intravenous injection and must not be administered intrathecally. When folinic acid has been administered intrathecally following intrathecal overdose of methotrexate, death has been reported.

HSP Calcium folinate 10 mg/mL

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

Parenteral administration is preferable to oral dosing if there is a possibility that the patient may vomit or not absorb HSP Calcium folinate 10 mg/mL Injection.

Because of the calcium ion content of the HSP Calcium folinate 10 mg/mL Injection, no more than 160 mg (16 mL of the 300 mg/30 mL formulation) should be injected intravenously per minute.

Folinic acid may enhance the toxicity of fluorouracil. Deaths from severe enterocolitis, diarrhoea and dehydration have been reported in elderly patients receiving folinic acid 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 folinic acid, usually in association with fluoropyrimidine administration, and most commonly in those with CNS metastases.

Since three patients had recurrent neurological symptoms on rechallenge with folinic acid, further treatment with folinic acid is not recommended in these circumstances.

Simultaneous therapy with a folic acid antagonist and folinic acid is not recommended because the effect of the folic acid antagonist is either reduced or completely inhibited.

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

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.

Folinic acid is not suitable for the treatment if pernicious anaemias and other anaemias resulting from lack of vitamin B_{12}. Haematological remissions may occur, while the neurological manifestations remain progressive.

Folinic Acid/Methotrexate

An accidental overdose with a folate antagonist, such as methotrexate, should be treated quickly as a medical emergency. As the time interval between methotrexate administration and folinic acid rescues increases, folinic acid effectiveness in counteracting toxicity decreases.

The presence of pre-existing or methotrexate-induced renal insufficiency is potentially associated with delayed excretion of methotrexate and may increase the need for higher doses or more prolonged use of folinic acid. Folinic acid has no effect on non-haematological toxicities of methotrexate, such as nephrotoxicity resulting from drug methotrexate and/or metabolite precipitation in the kidney.

Excessive folinic acid doses must be avoided since this might impair the antitumour activity of methotrexate, especially in CNS tumours where folinic acid accumulates after repeated courses.

Resistance to methotrexate as a result of decreased membrane transport implies resistance to folinic acid rescue as both medicinal products share the same transport system.

Folinic Acid/Fluorouracil

Folinic acid must not be mixed with fluorouracil in the same IV injection or infusion. Folinic acid may enhance the toxicity profile of fluorouracil, particularly in elderly or debilitated patients. Deaths from severe enterocolitis, diarrhoea and dehydration have been reported in elderly patients receiving fluorouracil and folinic acid. Concomitant granulocytopenia and fever were present in some but not all patients. When folinic acid and fluorouracil are used in combination, in cases of toxicity the fluorouracil dosage has to be reduced more than when fluorouracil is used alone.

Combined folinic acid/fluorouracil treatment should not be initiated or maintained in patients with symptoms of gastrointestinal (GI) toxicity, regardless of the severity, until all of these symptoms have completely disappeared. Because diarrhoea may be a sign of GI toxicity, patients presenting with

diarrhoea must be carefully monitored until the symptoms have disappeared completely, since rapid clinical deterioration leading to death can occur. If diarrhoea and/or stomatitis occur, it is advisable to reduce the dose of fluorouracil until symptoms have fully disappeared. Especially the elderly and patients with a low physical performance due to their illness are prone to these toxicities.

Seizures and/or syncope have been reported rarely in cancer patients receiving folinic acid, usually in association with fluoropyrimidine administration, and most commonly in those with CNS metastases.

Calcium levels should be monitored in patients receiving combined folinic acid/fluorouracil treatment and calcium supplementation should be provided if calcium levels are low.

Under circumstances leading to delayed methotrexate elimination, treatment with folinic acid may need to be prolonged.

Use in pregnancy (Category A†)

There are no adequate and well-controlled clinical studies conducted in pregnant or breastfeeding woman. No formal animal reproductive toxicity studies with folinic acid have been conducted. There are no indications that folic acid induces harmful effects if administered during pregnancy.

Fluorouracil use is generally contraindicated during pregnancy and contraindicated during breastfeeding; this applies also to the combined use of folinic acid with fluorouracil.

Use in lactation

It is not known whether this medicine is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when folinic acid is administered to a breastfeeding mother.

Paediatric use

There are no data available on use in children.

Use in the elderly

Elderly patients are at increased risk of severe toxicity when receiving combination therapy of folinic acid and fluorouracil. Particular care should be taken when treating these patients.

Interactions with Other Medicines

Folic acid in large amounts may counteract the antiepileptic effect of phenobarbitone, phenytoin, primidone and succinimides, and increase the frequency of seizures in susceptible children. Clinical monitoring, possibly monitoring of the plasma concentrations and, if necessary, dose adaptation of the anti-epileptic drug during folinic acid administration and after discontinuation.

High oral, intravenous or intramuscular doses of folinic acid may reduce the efficacy of intrathecally administered methotrexate.

Folinic acid may enhance the toxicity of fluorouracil. When folinic acid is given in conjunction with a folic acid antagonist (e.g. cotrimoxazole, pyrimethamine) the efficacy of the folic acid antagonist may either be reduced or completely neutralized.

---

†*Category A: Drugs which have been taken by a large number of pregnant women and women of childbearing age without proven increase in frequency of malformations or other direct or indirect harmful effects on the fetus having been observed.*

Incompatibilities

Folinic acid has been reported to be incompatible with injectable forms of methotrexate, fluorouracil droperidol and foscarnet.

Adverse Effects

Allergic sensitisation, including anaphylactoid reactions and urticaria, has been reported following both oral and parenteral administration of folic acid. Nausea and vomiting with very high doses of HSP Calcium folinate 10 mg/mL Injection have been reported.

In addition, haematological adverse reactions, such as leucocytopenia and thrombocytopenia, may occur. These adverse reactions are dose dependent and their occurrence can usually be decreased by reducing the dosage of cytotoxic drugs. To control these adverse reactions, haematological values e.g., blood leucocyte and thrombocyte levels, and serum electrolyte (e.g. Na, K, Ca) and creatinine levels should be closely monitored.

Immune system disorders

Frequency undetermined: allergic reactions, urticaria.

Very rare: Anaphylactoid/anaphylactic reactions

Psychiatric disorders

Insomnia, agitation and depression after high doses.

Nervous system disorders

Increase in the frequency of attacks in epileptics.

Rare: Seizures and/or syncope

Gastrointestinal disorders

Gastrointestinal disorders after high disorders, abdominal pain.

General disorders and administrations site conditions

Frequency undetermined: Fever after administration of folinic acid as solution for injection

Cases of Stevens-Johnson syndrome (SJS) and Toxic Epidermal Necrolysis (TEN), some fatal, have been reported in patients receiving folinic acid in combination with other agents known to be associated with these disorders. A contributory role of folinic acid in these occurrences of SJS/TEN cannot be excluded.

Folinic acid in combination with fluorouracil

Generally the safety profile of folinic acid depends on the applied regimen of fluorouracil due to enhancement of fluorouracil-induced toxicities.

The most common dose-limiting adverse reaction occurring in patients receiving combination of HSP Calcium folinate 10 mg/mL Injection and fluorouracil are stomatitis and diarrhoea. Fatalities have occurred as a result of gastrointestinal toxicity (predominantly mucositis and diarrhoea) and myelosuppression. In patients with diarrhoea, rapid clinical deterioration leading to death can occur (see PRECAUTIONS).

Seizures and/or syncope have been reported rarely in cancer patients receiving HSP Calcium folinate 10 mg/mL Injection, usually in association with fluoropyrimidine administration (see PRECAUTIONS).

Additional undesirable effects of HSP Calcium folinate 10 mg/mL Injection when used in combination with fluorouracil are listed below:

Hepatobiliary disorders

Frequency undetermined: Hyperammonaemia

General disorders and administration site condition

Frequency undetermined: Mucositis, stomatitis, cheilitis

Skin and subcutaneous tissue disorders

Frequency undetermined: Palmar-Palmar Erythrodysaesthesia

Gastrointestinal disorders

Very common: Nausea and vomiting, diarrhoea.

Dosage and Administration

For intravenous and intramuscular administration only. In the case of intravenous administration, no more than 160 mg of calcium folinate hydrate should be injected per minute due to the calcium content of the solution.

For intravenous infusion, calcium folinate hydrate may be diluted with 0.9% sodium chloride solution or 5% glucose solution before use.

Impaired Methotrexate Elimination or Inadvertent Overdosage:

Leucovorin calcium rescue should begin as soon as possible after an inadvertent overdosage and within 24 hours of methotrexate administration when there is delayed excretion. Leucovorin calcium 10 mg/m^2 should be administered IV or IM every 6 hours until the serum methotrexate level is less than 10^{-8} M.

Serum creatinine and methotrexate levels should be determined at 24 hour intervals. If the 24 hours serum creatinine has increased 50% over baseline or if the 24 hour methotrexate level is greater than 5×10^{-6} M or the 48 hour level is greater than 9×10^{-7} M, the dose of Leucovorin calcium should be increased to 100 mg/m^2 IV every 3 hours until the methotrexate level is less than 10^{-8} M.

Hydration (3 L/d) and urinary alkalinisation with sodium bicarbonate solution should be employed concomitantly. The bicarbonate dose should be adjusted to maintain the urine pH at 7.0 or greater.

Leucovorin Rescue After High-dose Methotrexate Therapy:

The recommendations for Leucovorin rescue are based on a methotrexate dose of 12 to 15 gm/m^2 administered by intravenous infusion over 4 hours. Leucovorin rescue at a dose of 15 mg (approximately 10 mg/m^2) every 6 hours for 10 doses starts 24 hours after the beginning of the Methotrexate infusion. Serum creatinine and methotrexate levels should be determined at least once daily. Leucovorin administration, hydration, and urinary alkalinisation (pH of 7.0 or greater) should be continued until the methotrexate level is below 5×10^{-8} M (0.05 micromolar).

Megaloblastic Anaemia due to Folic Acid Deficiency:

Upto 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.

Advanced Colorectal Cancer:

Either of the following two regimens is recommended:

Leucovorin is administered at 200 mg/m^2 by slow intravenous injection over a minimum 3 minutes, followed by 5-fluorouracil at 370 mg/m^2 by intravenous injection.

Leucovorin is administered at 20 mg/m^2 by intravenous injection followed by 5-fluorouracil at 425 mg/m^2 by intravenous injection.

Treatment is repeated daily for 5 days. This 5-treatment course may be repeated at 4-week (28 days) intervals for two courses and then repeated at 4 to 5 week (28-35 days) intervals provided that the patient has completely recovered from toxic effects of the prior treatment course.

In subsequent treatment courses, the dosage of 5-fluorouracil should be adjusted based on patient intolerance of the prior treatment course. The daily dosage of 5-fluorouracil should be reduced by 20% for patients who experienced moderate haematologic or gastrointestinal toxicity in the prior treatment course and by 30% for patients who experienced severe toxicity. For patients who experienced no toxicity in prior treatment course, 5-fluorouracil dosage may be increased by 10%. Leucovorin dosage are not adjusted for toxicity.

Overdosage

Folinic acid is an intermediate in the metabolism of folinic 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 folinic acid nullify the chemotherapeutic effect of folic acid antagonists.

Storage and Presentation

Store in a refrigerator (2°C to 8°C). Keep vial in the outer carton in order to protect from light.

HSP Calcium folinate Injection 300 mg/30 mL vial (single vial per pack)

Name and Address of the Manufacturer

Hospira Australia Pty Ltd.
1 – 5, 7 – 23 and 25 – 39 Lexia Place
Mulgrave,
Victoria, 3170,
Australia.

Date of Revision: 07 JUN 2023

HSP CALCIUM FOLINATE–0623