

Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Folinic acid (as calcium folinate) 10mg/ml solution for injection or infusion, ampoules

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

12.71 mg of calcium folinate $5H_2O$ equivalent to 10 mg of folinic acid per ml

Each 3 ml ampoule contains 30 mg of folinic acid provided as calcium folinate.

Each 5 ml ampoule contains 50 mg of folinic acid provided as calcium folinate.

Each 10 ml ampoule contains 100 mg of folinic acid provided as calcium folinate.

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Solution for injection or infusion

Folinic acid (as calcium folinate) 10mg/ml is a clear, colourless to pale yellow solution for injection or infusion.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Calcium folinate is indicated

- o to diminish the toxicity and counteract the action of folic acid antagonists such as methotrexate in cytotoxic therapy and overdose in adults and children. In cytotoxic therapy, this procedure is commonly known as "Calcium Folate Rescue".
- o in combination with 5-fluorouracil in cytotoxic therapy.

4.2 Posology and method of administration

Calcium folinate should only be given by intramuscular or intravenous injection and must not be administered intrathecally.

Death has been reported when folinic acid has been administered intrathecally, following intrathecal overdose of methotrexate.

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

For intravenous infusion, calcium folinate may be diluted with 0.9% sodium chloride solution or 5% glucose solution before use. Refer also to sections 6.3 and 6.6.

Calcium Folate Rescue in methotrexate therapy:

Refer to the applied intermediate- or high-dose methotrexate protocol for posology and method of administration of calcium folinate. The methotrexate protocol will dictate the dosage regimen of Calcium Folate Rescue because it depends heavily on the posology and method of the intermediate- or high-dose methotrexate administration.

The following guidelines may serve as an illustration of regimens used in adults, elderly and children:

Calcium Folate Rescue is necessary when methotrexate is given at doses exceeding 500 mg/m² body surface and has to be considered with doses of 100 mg – 500 mg/m² body surface. Calcium Folate Rescue should be performed by parenteral administration in patients with malabsorption syndromes or other gastrointestinal disorders where enteral absorption is not assured. Dosages above 25-50mg should be given parenterally due to saturable enteral absorption of calcium folinate.

Dosage and duration of use of Calcium folinate primarily depend on the type and dosage of methotrexate therapy, the occurrence of toxicity symptoms, and the individual excretion capacity for methotrexate. As a rule, the first dose of Calcium folinate is 15 mg (6-12 mg/m²) to be given 12-24 hours (24 hours at the latest) after the beginning of the methotrexate infusion. The same dose is given every 6 hours throughout a period of 72 hours. After several parenteral doses treatment can be switched over to the oral form.

In addition to calcium folinate administration, measures to ensure the rapid excretion of methotrexate (maintenance of high urine output and alkalinisation of urine) are integral parts of the Calcium Folate Rescue treatment. Renal function should be monitored by measuring serum creatinine levels daily.

The residual methotrexate-level, in the blood, should be measured, forty-eight hours after the start of the methotrexate-infusion. If the residual methotrexate-level is > 0.5 µmol/l, then the dosage of calcium folinate dosages should be adapted according to the following table:

Residual methotrexate level in the blood 48 hours after the start of the methotrexate administration:	Additional Calcium folinate to be administered every 6 hours for 48 hours or until levels of methotrexate are lower than 0.05µmol/l:
≥ 0.5 µmol/l	15 mg/m ²
≥ 1.0 µmol/l	100 mg/m ²
≥ 2.0 µmol/l	200 mg/m ²

In combination with 5-fluorouracil in cytotoxic therapy:

Different regimens and different dosages are used, however, no optimal dosage or regimen have been determined. The following regimens have been used in adults and the elderly in the treatment of advanced or metastatic colorectal cancer and are given as examples. There are no data on the use of calcium folinate in combination with 5-fluorouracil in children:

Bimonthly regimen: Calcium folinate 200mg/m² by intravenous infusion over two hours, followed by an intravenous bolus of 400 mg/m² of 5-Fluorouracil and a 22-hour intravenous infusion of 5-Fluorouracil (600 mg/m²) for 2 consecutive days, every 2 weeks on days 1 and 2.

Weekly regimen: Calcium folinate 20mg/m² by intravenous bolus. injection or 200 to 500 mg/m² intravenous. infusion over a period of 2 hours, plus 500 mg/m² 5-fluorouracil as an intravenous bolus injection in the middle, or at the end, of the calcium folinate infusion.

Monthly regimen: Calcium folinate 20 mg/m² by bolus i.v. injection or 200 to 500 mg/m² as i.v. infusion over a period of 2 hours immediately followed by 425 or 370 mg/m² 5-fluorouracil as an intravenous bolus injection over five consecutive days.

For the use of calcium folinate in combination with 5-fluorouracil, modification of the 5-fluorouracil dosage and the treatment-free interval may be necessary depending on patient condition, clinical response and dose limiting toxicity as stated in the product information of 5-fluorouracil. A reduction of calcium folinate dosage is not required.

The number of repeat cycles used is at the discretion of the clinician.

Antidote to the folic acid antagonists trimetrexate, trimethoprim, and pyrimethamine:

Trimetrexate toxicity:

- o Prevention: Calcium folinate should be administered every day during treatment with trimetrexate and for 72 hours after the last dose of trimetrexate. Calcium folinate can be administered either intravenously at a dose of 20mg/m² for 5 to 10 minutes every 6 hours (total daily dose of 80mg/m²), or orally with four doses of 20mg/m² administered at equal time intervals. Daily doses of calcium or calcium folinate should be adjusted depending on the haematological toxicity of trimetrexate.
- o Over dosage (possibly occurring with trimetrexate doses above 90mg/m² without concomitant administration of calcium folinate): Calcium folinate should be administered intravenously at a dose of 40mg/m² every 6 hours for 3 days, following cessation of treatment with trimetrexate.

Trimethoprim toxicity:

- o Following cessation of treatment with trimethoprim, calcium folinate should be administered intravenously at a dose of 3-10 mg/day calcium folinate until recovery of a normal blood count.

Pyrimethamine toxicity:

- o In cases of high dose pyrimethamine or prolonged treatment with low doses, calcium folinate 5 to 50 mg/day should be simultaneously administered, based on the results of the peripheral blood counts.

4.3 Contraindications

Known hypersensitivity to calcium folinate, or to any of the excipients.

Pernicious anaemia or other anaemias due to vitamin B₁₂ deficiency

For the use of calcium folinate with methotrexate or 5-fluorouracil during pregnancy and lactation, see section 4.6, "Pregnancy and Lactation" and the summaries of product characteristics for methotrexate- and 5-fluorouracil-containing medicinal products.

4.4 Special warnings and precautions for use

Calcium folinate should only be given by intramuscular or intravenous injection and must not be administered intrathecally.

Death has been reported when folinic acid has been administered intrathecally, following intrathecal overdose of methotrexate.

General:

Calcium folinate should be used with methotrexate or 5-fluorouracil only under the direct supervision of a clinician experienced in the use of cancer chemotherapeutic agents.

Calcium folinate treatment may mask pernicious anaemia and other anaemias resulting from vitamin B₁₂ deficiency.

Many cytotoxic medicinal products (direct or indirect DNA synthesis inhibitors such as hydroxycarbamide, cytarabine, mecaptopurine, thioguanine) lead to macrocytosis. Such macrocytosis should not be treated with folinic acid.

In epileptic patients treated with phenobarbital, phenytoine, primidone, and succinimides there is a risk of increased frequency of seizures due to a decrease of plasma concentrations of anti-epileptic drugs. Clinical monitoring, possible monitoring of the plasma concentrations and, if necessary, dose adaptation of the anti-epileptic drug during and after calcium folinate administration is recommended (see also section 4.5. Interactions).

Calcium folinate / 5-fluorouracil

Calcium folinate may enhance the toxicity of 5-fluorouracil, particularly in elderly or debilitated patients. The most common manifestations are leucopenia, mucositis, stomatitis and/or diarrhoea which may be dose limiting. In cases of toxicity when calcium folinate and 5-fluorouracil are used in combination, the 5-fluorouracil dosage should be reduced more than in cases of toxicity when 5-fluorouracil is used alone.

Combined 5-fluorouracil/calcium folinate treatment should neither be initiated nor maintained in patients with symptoms of gastrointestinal toxicity, regardless of the severity, until all of these symptoms have completely disappeared.

Because diarrhoea may be a sign of gastrointestinal toxicity, patients presenting with diarrhoea must be carefully monitored until the symptoms have disappeared completely, since a rapid clinical deterioration leading to death can occur. If diarrhoea and / or stomatitis occur, it is advisable to reduce the dose of 5-FU until symptoms have fully disappeared. The elderly and patients with a low physical performance due to their illness are especially prone to these toxicities. Therefore, particular care should be taken when treating these patients.

In elderly patients and patients who have undergone preliminary radiotherapy, it is recommended to begin with a reduced dosage of 5-fluorouracil.

Calcium folinate must not be mixed with 5-fluorouracil in the same intravenous injection or infusion.

Calcium levels should be monitored in patients receiving combined 5-fluorouracil/calcium folinate treatment and calcium supplementation should be provided if calcium levels are low.

Calcium folinate / methotrexate

For specific details on reduction of methotrexate toxicity refer to the Summary of Product Characteristics for methotrexate.

Calcium folinate has no effect on the non –haematological toxicities of methotrexate, such as the nephrotoxicity resulting from methotrexate and/or metabolite precipitation in the kidney. Patients who experience delayed early methotrexate elimination are likely to develop reversible renal failure and other toxicities associated with methotrexate (please refer to the Summary of Product Characteristics for methotrexate). 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 calcium folinate.

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

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

An accidental overdose with a folinate antagonist, such as methotrexate, should be treated as a medicinal emergency. As the time interval between methotrexate administration and Calcium Folate Rescue increases, the effectiveness of calcium folinate to counteract the toxicity decreases.

The possibility that the patient is taking other medications that interact with methotrexate (eg. medication which may interfere with methotrexate elimination or binding to serum albumin) should always be considered when laboratory abnormalities or clinical toxicities are observed.

4.5 Interaction with other medicinal products and other forms of interaction

When calcium folinate is given in conjunction with a folic acid antagonist (e.g. co-trimoxazole, pyrimethamine) the efficacy of the folic acid antagonist may either be reduced or completely neutralised.

Calcium folinate may diminish the effect of the anti-epileptic substances: phenobarbital, primidone and phenytoine, succinimides, and may increase the frequency of seizures (a decrease of plasma levels of enzymatic inductor anticonvulsant drugs may be observed because the hepatic metabolism is increased as folates are one of the cofactors) (see also section 4.4 and 4.8).

Concomitant administration of calcium folinate with 5-fluorouracil has been shown to enhance both the efficacy and toxicity of 5-fluorouracil (see section 4.5, 4.4 and 4.8).

4.6 Fertility, pregnancy and lactation

Pregnancy

There are no adequate and well-controlled clinical studies conducted in pregnant or breast-feeding women. No formal animal reproductive toxicity studies with calcium folinate have been conducted. There is no indication that folinic acid induces harmful effects if administered during pregnancy. During pregnancy, methotrexate should only be administered on strict indications, where the benefits of the drug to the mother should be weighed against possible hazards to the foetus. Should treatment with methotrexate or other folinate antagonists take place despite pregnancy or lactation, there are no limitations as to the use of calcium folinate to diminish toxicity or counteract the effects.

5-fluorouracil use is generally contraindicated during pregnancy and contraindicated during breast-feeding; this applies also to the combined use of calcium folinate with 5-fluorouracil.

Please refer also to the Summaries of Product Characteristics for methotrexate-, other folate antagonists and 5-fluorouracil containing medicinal products.

Lactation

It is not known whether calcium folinate is excreted into human breast milk. Calcium folinate can be used during breast feeding when considered necessary according to the therapeutic indications.

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

Both therapeutic indications:

Immune system disorders

Very rare (<0.01%): allergic reactions, including anaphylactoid reactions and urticaria.

Psychiatric disorders

Rare (0.01 – 0.1%): insomnia, agitation and depression after following high doses.

Gastrointestinal disorders:

Rare (0.01 – 0.1%): gastrointestinal disorders after following high doses.

Neurological disorders:

Rare (0.01 – 0.1%): increase in the frequency of attacks in epileptics (see also section 4.5 Interactions).

General disorders and administration site conditions

Uncommon (0.1-1%): fever.

Combination therapy with 5-fluorouracil:

Generally, the safety profile depends on the applied regimen of 5-fluorouracil, due to enhancement of the 5-fluorouracil induced toxicities:

Monthly regimen:

Gastrointestinal disorder

Very common(>10%): vomiting and nausea

General disorders and administration site conditions

Very common (>10%): (severe) mucosal toxicity.

No enhancement of other 5-fluorouracil induced toxicities (e.g. neurotoxicity).

Weekly regimen:

Gastrointestinal disorders

Very common (>10%): diarrhoea with higher grades of toxicity, and dehydration, resulting in hospital admission for treatment and even death.

4.9 Overdose

There have been no reported sequelae in patients who have received significantly more calcium folinate than the recommended dosage. However, excessive amounts of calcium folinate may nullify the chemotherapeutic effect of folic acid antagonists.

Should over-dosage of the combination of 5-fluorouracil and calcium folinate occur, the over-dosage instructions for 5-FU should be followed, refer to the Summary of Product Characteristics for 5-fluorouracil containing products.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Detoxifying agents for antineoplastic treatment, ATC-Code: V03A F03

Calcium folinate is the calcium salt of 5-formyl tetrahydrofolic acid. It is an active metabolite of folinic acid and essential coenzyme for nucleic acid synthesis in cytotoxic therapy.

Calcium folinate is frequently used to diminish the toxicity and counteract the action of folate antagonists, such as methotrexate. Calcium folinate and folate antagonists share the same membrane transport carrier and compete for transport into cells, stimulating folate antagonist efflux. Calcium folinate also protects cells from the effects of folate antagonists by repletion of the reduced folate pool. Calcium folinate serves as a pre-reduced source of H₄ folate; it can therefore bypass folate antagonist blockage and provide a source for the various coenzyme form as of folic acid.

Calcium folinate is also frequently used in the biochemical modulation of fluoropyridine (5-fluorouracil) to enhance its cytotoxic activity. 5-fluorouracil inhibits thymidylate synthase (TS), a key enzyme involved in pyrimidine biosyntheses, and calcium folinate enhances TS inhibition by increasing the intracellular folate pool, thus stabilising the 5-fluorouracil-TS complex and increasing activity.

Finally intravenous calcium folinate can be administered for the prevention and treatment of folate deficiency when it cannot be prevented or corrected by the oral administration of folic acid. This may be the case during total parenteral nutrition and severe malabsorption disorders. It is also indicated for the treatment of megaloblastic anaemia due to folic acid deficiency, when oral administration is not feasible.

5.2 Pharmacokinetic properties

Absorption

Following intramuscular administration of the aqueous solution, systemic availability is comparable to an intravenous administration. However, lower peak serum levels ($C_{\max}$) are achieved.

Metabolism

Calcium folinate is a racemate where the L-form (L-formyl-tetrahydrofolate, L-5-formyl-THF), is the active enantiomer.

The major metabolic product of folinic acid is 5-methyl-tetrahydrofolic acid (5-methyl-THF) which is predominantly produced in the liver and intestinal mucosa.

Distribution

The distribution volume of folinic acid is not known.

Peak serum levels of the parent substance (D/L-formyl-tetrahydrofolic acid, folinic acid) are reached 10 minutes after intravenous administration.

The AUC for L-5-formyl-THF and 5-methyl-THF were 28.4 ± 3.5 mg.min/l and 129 ± 11 mg.min/l, respectively, after a dose of 25mg. The inactive D-isomer is present in higher concentration than L-5-formyl-tetrahydrofolate.

Elimination

The elimination half-life is 32 – 35 minutes for the active L-form and 352 – 485 minutes for the inactive D-form, respectively.

The total half-life of the active metabolites is about 6 hours (after both intravenous and intramuscular administration).

Excretion

80-90 % is excreted in the urine as the inactive metabolites, 5- and 10-formyl-tetrahydrofolate, 5-8 % is excreted in the faeces.

5.3 Preclinical safety data

There are no preclinical data considered relevant to clinical safety beyond data included in other sections of this Summary of Product Characteristics.

6 PHARMACEUTICAL PARTICULARS**6.1 List of excipients**

Sodium Chloride
Water for Injections

6.2 Incompatibilities

Incompatibilities have been reported between injectable forms of calcium folinate and injectable forms of droperidol, fluorouracil, foscarnet and methotrexate.

Droperidol

1. Droperidol 1.25 mg/0.5 ml with calcium folinate 5 mg/0.5 ml; immediate precipitation was observed after direct admixture in a syringe for 5 minutes at 25°C followed by 8 minutes of centrifugation.
2. Droperidol 2.5 mg/0.5 ml with calcium folinate 10 mg/0.5 ml; immediate precipitation was observed when the drugs were injected sequentially into a Y-connector without flushing the Y-side arm between injections.

Fluorouracil

Calcium folinate must not be mixed in the same infusion as 5-fluorouracil because a precipitate may form. Fluorouracil 50 mg/ml with calcium folinate 20 mg/ml, with or without dextrose 5% in water, has been shown to be incompatible when mixed in different amounts and stored at 4°C, 23°C, or 32°C in polyvinyl chloride containers.

Foscarnet

The formation of a cloudy yellow solution has been reported when Foscarnet 24 mg/ml is mixed with calcium folinate 20 mg/ml.

6.3 Shelf life

Unopened - 24 months.

The chemical and physical in-use stability of the solution diluted with Sodium Chloride 0.9 % or Glucose 5 % for intravenous infusion has been demonstrated for 24 hours at a temperature not exceeding 25°C.

From a microbiological point of view, the product should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at 2 to 8°C, unless dilution has taken place in controlled and validated aseptic conditions.

6.4 Special precautions for storage

Store at 2-8°C (in a refrigerator).

Store in original container to protect from light

6.5 Nature and contents of container

Amber ampoules of hydrolytic type I glass, packed in a carton.

5 ampoules containing 30 mg/3 ml of Calcium folinate, each.

5 ampoules containing 50 mg/5 ml of Calcium folinate, each.

5 ampoules containing 100 mg/10 ml of Calcium folinate, each.

Not all package sizes are marketed.

6.6 Special precautions for disposal of a used medicinal product or waste materials derived from such medicinal product and other handling of the product

Prior to administration, calcium folinate should be inspected visually. The solution for injection or infusion should be a clear yellowish solution. If cloudy in appearance or particles are observed, the solution should be discarded. Calcium folinate solution for injection or infusion is intended for single use only. Any unused portion of the solution should be disposed of in accordance with the local requirements.

7 MARKETING AUTHORISATION HOLDER

EBEWE Pharma Ges.m.b.H. Nfg. KG
Mondseestrasse 11
A-4866 Unterach
Austria

8 MARKETING AUTHORISATION NUMBER

PA 789/11/1

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