

1. NAME OF THE MEDICINAL PRODUCT

Calciumfolinat "Ebewe"

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

1ml contains 12.71mg calcium folinate x 5H₂O corresponding to 10mg folic acid as active ingredient.

1 capsule contains 19.06mg calcium folinate x 5H₂O corresponding to 15mg folic acid as active ingredient.

For excipients, see 6.1.

3. PHARMACEUTICAL FORM

Solution for injection.

Capsules for oral administration.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Calciumfolinat is indicated

- 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".
- in combination with 5-fluorouracil in cytotoxic therapy.

4.2 Posology and method of administration

For intravenous and intramuscular administration only. 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.

Dosages above 50 mg should be given parenterally, higher doses do not lead to higher blood levels due to saturation of Calcium folinate absorption.

As a rule Calcium folinate rescue has to be performed by parenteral administration in patients with malabsorption syndromes or other gastrointestinal disorders (vomiting, diarrhoea, subileus etc.) where enteral absorption is not assured.

Calcium folinate rescue in methotrexate therapy:

Since the Calcium folinate rescue dosage regimen depends heavily on the posology and method of the intermediate- or high-dose methotrexate administration, the methotrexate protocol will dictate the dosage regimen of Calcium folinate rescue. Therefore it is best refer to the applied intermediate or high dose methotrexate protocol for posology and method of administration of Calcium folinate.

The following guidelines may serve as an illustration of regimens used in adults, elderly and children: Calcium folinate rescue has to 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.

Calcium folinate 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.

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 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 prompt excretion of methotrexate (maintenance of high urine output and alkalinisation of urine) are integral parts of the calcium folinate rescue treatment. Renal function should be monitored through daily measurements of serum creatinine.

Forty-eight hours after the start of the methotrexate-infusion, the residual methotrexate-level should be measured. If the residual methotrexate-level > 0.5 µmol/l, calcium folinate dosages should be adapted according to the following table:

Residual methotrexate blood level 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, without any dosage having been proven to be the optimal one.

Dosages above 50 mg should be given parenterally, higher doses do not lead to higher blood levels due to saturation of folate absorption.

The following regimens have been used in adults and elderly in the treatment of advanced or metastatic colorectal cancer and are given as examples. There are no data on the use of these combinations in children:

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

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

Monthly regimen: Calcium folinate 20mg/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 370mg/m² 5-fluorouracil as i.v. bolus injection during five consecutive days.

For the combination therapy 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 use is at the discretion of the clinician.

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

Trimetrexate toxicity:

- 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 by oral 80mg/m², or by oral route with four doses 20mg/m² administered at equal time intervals. Daily doses of calcium of calcium folinate should be adjusted depending on the haematological toxicity of trimetrexate.

- Over dosage (possibly occurring with trimetrexate doses above 90mg/m² without concomitant administration of calcium folinate): after stopping trimetrexate, calcium folinate 40mg/m² IV every 6 hours for 3 days.

Trimethoprim toxicity:

- After stopping trimethoprim, 3–10 mg/day calcium folinate until recovery of a normal blood count.

Pyrimethamine toxicity:

- In case 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 Contra-indications

- Known hypersensitivity to calcium folinate, or to any of the excipients.
- Pernicious anaemia or other anaemias due to vitamin B₁₂ deficiency

Regarding 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 special precautions for use

Calcium folinate should only be given orally or by intramuscular or intravenous injection and must not be administered intrathecally. When folic acid has been administered intrathecally following intrathecal overdose of methotrexate death has been reported.

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 – lead to macrocytosis (hydroxycarbamide, cytarabine, mecaptopurine, thioguanine). Such macrocytosis should not be treated with folic acid.

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

Calcium folinate / 5-fluorouracil

Calcium folinate may enhance the toxicity risk 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. When Calcium folinate and 5-fluorouracil are used in combination, the 5-fluorouracil dosage has to be reduced more in cases of toxicity than 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. Especially the elderly and patients with a low physical performance due to their illness are 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 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 of the SPC of methotrexate.

Calcium folinate has no effect on 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 all toxicities associated with methotrexate (please refer to the SPC 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 implies also resistance to folic 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 folinate rescuer increases, calcium folinate effectiveness in counteracting 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 Phenytoin, 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 the efficacy and toxicity of 5-fluorouracil (see section 4.5, 4.4 and 4.8)

4.6 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 are no indication that folic 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 fomite 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 high doses.

Gastrointestinal disorders

Rare (0.01–0.1%): gastrointestinal disorders after 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 has been observed after administration of calcium folinate as solution for injection.

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 on 5-fluorouracil and calcium folinate occur, the over dosage instructions for 5-FU should be followed.

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 folic 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 the transport into cells, stimulating folate antagonist efflux. It also protects cells from the effects of folate antagonist by repletion of the reduce 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-FU) to enhance its cytotoxic activity. 5-FU 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-FU-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 administration of folic acid by the oral route. 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 folic acid is 5-methyl-tetrahydrofolic acid (5-methyl-THF) which is predominantly produced in the liver and intestinal mucosa.

Distribution

The distribution volume of folic acid is not known.

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

AUC for L-5-formyl-THF and 5-methyl-THF were 28.4 ± 3.5 mg.min/l and 129 ± 11 mg.min/l 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 intravenous and intramuscular administration) with the urine (5- and 10-formyl-tetrahydrofolates as inactive metabolites), 5–8% with the faeces.

5.3 Preclinical safety data

There are no preclinical data considered relevant to clinical safety beyond data included in other section of the SPC.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Ampoules/Vials: Water for injection.

Capsules: Microcrystalline cellulose, colloidal anhydrous silica, magnesium stearate, gelatine, water, E 171, E 172, E 132.

6.2 Incompatibilities

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

Droperidol

1. Droperidol 1.25mg/0.5ml with calcium folinate 5mg/0.5ml, immediate precipitation in direct admixture in syringe for 5 minutes at 25°C followed by 8 minutes of centrifugation.

2. Droperidol 2.5mg/0.5ml with calcium folinate 10mg/0.5ml, immediate precipitation when the drugs were injected sequentially into a Y-site without flushing the Y-side arm between injections.

Fluorouracil

A mixture of 1000mg Calcium folinate "Ebewe" (100ml Calciumfolinat 10mg/ml) with 5000mg 5-Fluorouracil "Ebewe" (100mg at 50mg/ml) and 40ml physiologic saline solution in infusion pumps (e.g. type "Easy pump") has been stable at room temperature for 48 hours. There are no results about other mixtures. Therefore the Calciumfolinat "Ebewe" solution for injection/infusion may not be mixed with other drugs, as well as with oxaliplatin or irinotecan.

Foscarnet

Foscarnet 24mg/ml with calcium folinate 20mg/ml formation of a cloudy yellow solution reported.

Capsules: Not applicable.

6.3 Shelf life

Ampoules/Vials: 36 months

Capsules: 36 months

6.4 Special precautions for storage

Ampoules / Vials: Store at 2°C–8°C (in a refrigerator).

Store in original container to protect from light.

Capsules: Do not store above 25°C.

The chemical and physical in-use stability of the solution diluted with Sodium Chloride 0.9% or Glucose 5% 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.

6.5 Nature and contents of the container

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

Vials are closed with a rubber stopper with an aluminium crimp cap with flip-off.

Capsules: Polypropylene container.

20 capsules containing 15mg of folic acid, each.

5 ampoules containing 3ml equivalent to 30mg of folic acid, each.

5 ampoules containing 5ml equivalent to 50mg of folic acid, each.

5 ampoules containing 10ml equivalent to 100mg of folic acid, each.

1 vial containing 10ml equivalent to 100mg of folic acid.

1 vial containing 20ml equivalent to 200mg of folic acid.

1 vial containing 30ml equivalent to 300mg of folic acid.

1 vial containing 35ml equivalent to 350mg of folic acid.

1 vial containing 80ml equivalent to 800mg of folic acid.

6.6 Instructions for use/handling

Ampoules / Vials:

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 only for single use. Any unused portion of the solution should be disposed of in accordance with the local requirements.

Capsules:

None

7. MANUFACTURER

EBEWE Pharma Ges.m.b.H. Nfg.KG

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8. DATE OF (PARTIAL) REVISION OF THE TEXT

July 2004