SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT
Calcium folinate; Solution for Injection 50 mg/5 ml

2. QUALITATIVE AND QUANTITATIVE COMPOSITION
Each ml contains:
Calcium folinate equivalent to folinic acid 10 mg
For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM
Calcium folinate solution for injection is a clear and yellowish solution. Practically free of foreign matte

4. CLINICAL PARTICULARS
4.1 Therapeutic indications
Calcium folinate 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 Folinate 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 160 mg 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.

Calcium folinate 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 Folinate 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 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 25-50 mg 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 should be considered with doses of 100-500 mg/m² body surface.

Dosage and duration of calcium folinate rescue primarily depend on the type and dosage of methotrexate therapy, the occurrence of toxicity symptoms, and the individual excretion capacity for methrotrexate.

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 alkalinization 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 is >0.5 µmol/l, 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 after 48 hours or until levels of Methotrexate are lower than 0.05 µmol/l
≥ 0.5 µmol/l	15 mg/m²
≥ 1.0 µmol/l	100 mg/m²
≥2.0 µmol/l	200 mg/m²

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

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

Monthly regimen
Calcium folinate 20 mg/m² by bolus IV injection or 200 to 500 mg/m² as IV infusion over a period of 2 hours immediately followed by 425 or 370 mg/m² 5-fluorouracil as an IV 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 used 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 the intravenous route at a dose of 20 mg/m² for 5 to 10 minutes every 6 hours for a total daily dose of 80 mg/m², or by oral route with four doses of 20 mg/m² administered at equal time intervals. Daily doses of calcium folinate should be adjusted depending on the hematological toxicity of trimetrexate.

- Overdosage (possibly occurring with trimetrexate doses above 90 mg/m² without concomitant administration of calcium folinate): after stopping trimetrexate, calcium folinate 40 mg/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.

For instructions on reconstitution of the medicinal product before administration, see section 6.6.

4.3 Contraindications
- Known hypersensitivity to calcium folinate or to any of the excipients.
- Pernicious anemia or other anaemias due to vitamin B12 deficiency.

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. When folinic 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 anemia and other anaemias resulting from vitamin B12 deficiency.

Many cytotoxic medicinal products (direct or indirect DNA synthesis inhibitors such as hydroxycarbamide, cytarabine, mercaptopurine, tioguanine) lead to macrocytosis. Such macrocytosis should not be treated with folinic 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 antiepileptic drugs. Clinical monitoring, possibly monitoring of the plasma concentrations and, if necessary, dose adaptation of the antiepileptic drug during calcium folinate administration and after discontinuation is recommended (see Drug 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 diarrhea, 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 diarrhea may be a sign of gastrointestinal toxicity, patients presenting with diarrhea must be carefully monitored until the symptoms have disappeared completely, since a rapid clinical deterioration leading to death can occur. If diarrhea 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 folinate must not be mixed with 5-fluorouracil in the same IV 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 product information of methotrexate.
Calcium folinate has no effect on nonhematological 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. 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 antitumor activity of methotrexate, especially in CNS tumors where calcium folinate accumulates after repeated courses.

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

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

The possibility that the patient is taking other medications that interact with methotrexate (e.g., medications 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., cotrimoxazole, pyrimethamine), the efficacy of the folic acid antagonist may either be reduced or completely neutralized.

Calcium folinate may diminish the effect of antiepileptic substances: phenobarbital, primidone, phenytoin, and 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 Warnings and precautions and Adverse reactions)

Concomitant administration of calcium folinate with 5-fluorouracil has been shown to enhance the efficacy and toxicity of 5-fluorouracil. (see Dosage and administrations, Warnings and precautions, and Adverse reactions).

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 are no indications 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 folate 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.

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

No studies on the effects on the ability to drive and use machines have been performed. However, the ability to drive and use machines may be impaired should the patient experience dizziness, somnolence and visual disturbances being possible undesirable effects of treatment, or resulting from the underlying disease.

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
Frequencies are defined using the following convention:

- Very common (≥1/10)
- Common (≥1/100 to <1/10)
- Uncommon (≥1/1,000 to <1/100)
- Rare (≥1/10,000 to <1/1,000)
- Very rare (<1/10,000)
- Not known (cannot be estimated)

Immune system disorders
Very rare: allergic reactions, including anaphylactoid/anaphylactic reactions and urticaria.

Psychiatric disorders
Rare: insomnia, agitation, and depression after high doses.

Gastrointestinal disorders
Rare: gastrointestinal disorders after high doses.
Neurological disorders
Rare: increase in the frequency of attacks in epileptics (see Drug interactions).

General disorders and administration site conditions
Uncommon: fever has been observed after administration of calcium folinate as solution for injection.

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

Metabolism and nutritional disorder
Not known: hyperammonemia.

Blood and lymphatic system disorders
Very common: bone marrow failure, including fatal cases.

General disorders and administration site conditions
Very common: mucositis, including stomatitis and chelitis. Fatalities have occurred as a result of mucositis.

Skin and subcutaneous tissue disorders
Common: Palmar-Plantar Erythrodysesthesia.

Monthly regimen
Gastrointestinal disorders
Very common: vomiting and nausea.
No enhancement of other 5-fluorouracil induced toxicities (e.g., neurotoxicity).

Weekly regimen
Gastrointestinal disorders
Very common: diarrhea 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 overdosage of the combination of 5-fluorouracil and calcium folinate occur, the overdosage instructions for 5-fluorouracil should be followed.

5. PHARMACOLOGICAL PROPERTIES
5.1 Pharmacodynamic properties
Pharmacotherapeutic group:
Detoxifying agent for antineoplastic treatment

ATC code:
V03AF03

Mechanism of action and pharmacodynamic effects

Calcium folinate is the calcium salt of 5-formyl tetrahydrofolic acid. It is an active metabolite of folinic acid and an 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. 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 forms of folic acid.

Calcium folinate is also frequently used in the biochemical modulation of fluorouracil (5-FU) to enhance its cytotoxic activity. 5-FU inhibits thymidylate synthase (TS), a key enzyme involved in pyrimidine biosynthesis, and calcium folinate enhances TS inhibition by increasing the intracellular folate pool, thus stabilizing the 5FU-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 anemia 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 (Cmax) are achieved.

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.minute/l and 129±11 mg.minute/l, respectively, after a dose of 25 mg. The inactive D-isomer is present in higher concentration than L-5- formyl-tetrahydrofolate.

Metabolism

Calcium folinate is a racemate where the L-form (L-5-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.

5.3 Preclinical safety data

Not applicable

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium chloride
Sodium hydroxide
Water for injection

6.2 Incompatibilities

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

Droperidol

Droperidol with calcium folinate:

- Immediate precipitation was observed after direct admixture in syringe.

- Immediate precipitation was observed when the drugs were injected sequentially into a Y-site without flushing the Y-site arm between injections.

Fluorouracil

Calcium folinate must not be mixed in the same infusion as 5-fluorouracil because a precipitate may form.

Foscarnet

The formation of a cloudy yellow solution has been reported when foscarnet is mixed with calcium folinate.

6.3 Shelf life
2 years.

Shelf-life after dilution
After dilution in 0.9% sodium chloride solution or 5% dextrose solution, the solution are stable for 24 hours when stored between 2-8°C

From 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 not be longer than 24 hours at 2-8°C.

6.4 Special precautions for storage
Store at temperatures between 2-8°C. Protect form light. For storage conditions after reconstitution of the medicinal product, see section 6.3.

6.5 Nature and contents of container
5 mL type I amber glass vial closed with 20 mm bromobutyl rubber stopper and sealed with 20 mm flip-off cap

6.6 Special precautions for disposal and other handling
Instructions for use and handling and disposal

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

7. MARKETING AUTHORISATION HOLDER
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