

Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Folicid, 10 mg/ml, solution for injection.

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

1 ml Folicid 10 mg/ml Solution for Injection contains 10.8 mg of calcium folinate, equivalent to 10 mg folic acid.

One vial with 10 ml contains 108 mg of calcium folinate equivalent to 100 mg folic acid

One vial with 20 ml contains 216 mg of calcium folinate equivalent to 200 mg folic acid

One vial with 50 ml contains 540 mg of calcium folinate equivalent to 500 mg folic acid

One vial with 100 ml contains 1080 mg of calcium folinate equivalent to 1000 mg folic acid

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Solution for injection

Clear, slightly yellow to yellow solution.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

1. Calcium folinate is used to diminish the toxicity and counteract the action of folic acid antagonists such as methotrexate in cytotoxic therapy. This procedure is commonly known as "Calcium Folate Rescue".
2. Treatment of advanced colorectal cancer in combination with 5-fluorouracil (5-FU).

4.2 Posology and method of administration

Calcium folinate is administered parenterally as intramuscular injection or intravenous injection or infusion. Do not administer calcium folinate intrathecally. 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.

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. Dosages above 50 mg should be given parenterally.

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

Calcium folinate rescue in methotrexate therapy:

Since the calcium folinate rescue dosage regimen heavily depends 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 to 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 for a calcium folinate rescue dosage regimen.

Calcium folinate rescue in intermediate- and high-dose methotrexate therapy:

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.

Since tolerance to folic acid antagonists depends on various factors there are no strict guidelines for the calcium folinate dosage as a function of the methotrexate dose.

Dosage and duration of use of calcium folinate primarily depend on the type and dosage of methotrexate therapy and/or on the occurrence of toxicity symptoms. 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.

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 blood level 48 hours after the start of the methotrexate administration:	Additional calcium folinate to be administered every 6 hours for 48 hours until levels of methotrexate are lower than 0.05 µmol/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

Laboratory tests: Patients receiving calcium folinate after therapy with methotrexate, including overdosage or reduced clearance of methotrexate, should be monitored and the levels of creatinine and methotrexate in serum should be measured in 24 hr intervals. The dosage of calcium folinate should be adjusted according to the results of the laboratory tests.

In combination with 5-fluorouracil as treatment for advanced or metastatic colorectal cancer:

Different regimens and different dosages are used, without any dosage having been proven to be the optimal dosage. The following regimens have been used in adults:

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

Monthly regimen: once a month during 5 consecutive days: 20 or 200 mg/m² calcium folinate bolus immediately followed by 425 or 370 mg/m² 5-fluorouracil as i.v. bolus injection.

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.

4.3 Contraindications

Hypersensitivity to calcium folinate or to any of the excipients.

Calcium folinate should not be used for the treatment of pernicious anaemia or other megaloblastic anaemias caused by vitamin B₁₂ deficiency. Although haematological remissions may occur, the neurological manifestations remain progressive.

4.4 Special warnings and precautions for use

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

Calcium folinate has no effect on non-hematological toxicities of methotrexate such as the nephrotoxicity resulting from methotrexate and/or metabolite precipitation in the kidney.

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 folinic acid rescue as both medicinal products share the same transport system.

For specific details on reduction of methotrexate toxicity refer to the SPC of methotrexate.

Many cytotoxic medicinal products – direct or indirect DNA synthesis inhibitors – lead to macrocytosis (hydroxycarbamide, cytarabine, mecapurine, thioguanine). Such a macrocytosis is not considered to be treated by folinic acid.

In combination regimen with 5-fluorouracil, the toxicity risk of 5-fluorouracil is increased by calcium folinate, particularly in elderly or debilitated patients. The most common manifestations are leucopenia, mucositis, and/or diarrhoea which may be dose limiting. When calcium folinate and 5-fluorouracil are used in the treatment of colorectal cancer, the 5-fluorouracil dosage has to be reduced more in cases of toxicity than when 5-fluorouracil is used alone. The toxicities observed in patients treated with the combination therapy are qualitatively similar to those observed in patients treated with 5-fluorouracil monotherapy. Gastrointestinal toxicities are observed more commonly and may be more severe and even life threatening. In severe cases the combination of calcium folinate and 5-fluorouracil must be withdrawn.

When calcium folinate has been administered intrathecally following intrathecal overdose of methotrexate, a death has been reported.

In epileptic patients treated with phenobarbital, phenytoine, primidone, there is a risk to increase the frequency of seizures due to 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 section 4.5, Interaction with other medicinal products and other forms of interactions*).

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 neutralised.

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

Concomitant administration of calcium folinate with 5-fluorouracil has been shown to enhance the efficacy and toxicity of 5-fluorouracil (*see section 4.2, Posology and method of administration, section 4.4, Special warnings and precautions for use and section 4.8, Undesirable effects*).

4.6 Fertility, pregnancy and lactation

Methotrexate therapy is contraindicated during pregnancy and lactation. Should, after corresponding exact diagnosis, treatment with methotrexate take place despite pregnancy or lactation there are no limitations as to the use of calcium folinate for prophylaxis of methotrexate toxicity (calcium folinate rescue).

There is no experience in treatment of pregnant or nursing women with the combination of calcium folinate / 5-fluorouracil and/or other antineoplastic agents, however, such a treatment is generally contraindicated during pregnancy and lactation, even under inclusion of calcium folinate.

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. Calcium folinate is however not expected to affect the ability.

If calcium folinate is used concomitantly with 5-fluorouracil, the risk of experiencing adverse events caused by 5-fluorouracil (eg, dizziness, drowsiness, vision disorders, and nausea) may be enhanced. Therefore, patients receiving this combination should not drive or use machines.

4.8 Undesirable effects

Both therapeutic indications:

Nervous system disorders

Rare ($\geq 1/10,000$ to $< 1/1,000$): increase in the frequency of attacks in epileptics.

Gastrointestinal disorders

Rare ($\geq 1/10,000$ to $< 1/1,000$): gastrointestinal disorders after high doses.

General disorders and administration site conditions

Uncommon ($\geq 1/1,000$ to $< 1/100$): fever has been observed after administration of calcium folinate as solution for injection.

Immune system disorders

Very rare ($< 1/10,000$): allergic reactions, including anaphylactoid reactions and urticaria.

Psychiatric disorders

Rare ($\geq 1/10,000$ to $< 1/1,000$): insomnia, agitation and depression after high doses.

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 disorders

Very common ($\geq 1/10$): vomiting and nausea

General disorders and administration site conditions

Very common ($\geq 1/10$): (severe) mucosal toxicity.

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

Weekly regimen:

Gastrointestinal disorders

Very common ($\geq 1/10$): diarrhoea with higher grades of toxicity, and dehydration, resulting in hospital admission for treatment and even death. Every occurrence of diarrhoea or mucositis (even grade 1) requires immediate cessation of the chemotherapy 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.

4.9 Overdose

The acute toxicity is low. Overdosing does not generally give any symptoms and symptomatic treatment of overdosing is probably not needed.

Should overdosage of the combination of 5-fluorouracil with calcium folinate occur, follow the overdosage instructions for 5-fluorouracil.

When using methotrexate, an overdosage of calcium folinate may result in a decrease of efficacy of methotrexate („over-rescue“)(*see section 4.4, Special warnings and precautions for use*).

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

ATC code: V03AF03

Pharmacotherapeutic group: Detoxifying agents for antineoplastic treatment.

Folinic acid is a formyl derivate of folic acid, a nutritional factor essential for the human organism. It is involved in various metabolic processes, e.g. purine synthesis, pyrimidine nucleotide synthesis and amino acid metabolism.

Folinic acid is mainly used to cancel the effects of folic acid antagonists such as methotrexate. The substance on the other hand strengthens the effect of fluoropyrimidines such as 5-fluorouracil.

Methotrexate competitively inhibits the dihydrofolate reductase and thereby prevents the formation of reduced folates in the cell. As a consequence, it inhibits DNA, RNA and protein synthesis.

The folinic acid released from calcium folinate is rapidly converted into the active 5-methyl-tetrahydrofolic acid (calcium folinate rescue). Unlike folic acid, folinic acid does not require a reduction by dihydrofolate reductase. Therefore, dihydrofolate reductase blockers have no effect on folinic acid.

The effect of methotrexate primarily depends on the rate of cell division and therefore it exerts its cytostatic effect on all rapidly growing tissues, i.e. in addition to tumour tissue also on other rapidly proliferating tissues (skin and mucosa, hematopoietic bone marrow, gonads). These vital tissues and organs can be protected from the cellular toxicity of methotrexate by calcium folinate (5-formyl-THF = folinic acid = citrovorum factor).

The cytotoxic effect of 5-fluorouracil consists of the binding of FdUMP to thymidylate synthase, thereby inhibiting the activity of thymidylate synthase. Administration of calcium folinate results in higher amounts of folate cofactors, which enhance the binding between FdUMP and thymidylate synthase.

5.2 Pharmacokinetic properties

Absorption

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

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.

Distribution

The distribution volume of folinic acid is not known.

Peak serum levels of the parent substance (D/L-5-formyl-tetrahydrofolic acid, folinic 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 ± 112 mg.min/L after a dose of 25 mg. 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 terminal half-life of the active metabolites is about 6 hours (after intravenous and intramuscular administration).

Excretion

80-90 % with the urine (5- and 10-formyl-tetrahydrofolates inactive metabolites), 5-8 % with the faeces.

5.3 Preclinical safety data

Preclinical test results showed no risks not previously known from clinical experience (see other sections of the SPC). No mutagenic effects are expected at physiological dosages. Long-term studies on the tumorigenic potential of folinic acid as well as animal studies for clarification of reproductive toxicological properties are not available.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Trometamol
Hydrochloric acid, conc.
Water for injections

6.2 Incompatibilities

This medicinal product must not be mixed with other medicinal products except those mentioned in *section 6.6., Special precautions for disposal of a used medicinal product or waste materials derived from such a medicinal product and other handling of the product.*

6.3 Shelf life

2 years.

Shelf-life after dilution

Chemical and physical in-use stability after dilution in 5% glucose solution or 0.9% sodium chloride solution has been demonstrated for 72 hours at $+2^{\circ}\text{C}$ to $+8^{\circ}\text{C}$ and at $+25^{\circ}\text{C}$, when protected from light.

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 $+2^{\circ}\text{C}$ to $+8^{\circ}\text{C}$, unless dilution has taken place in controlled and validated aseptic conditions.

6.4 Special precautions for storage

Store (in a refrigerator ($2^{\circ}\text{C} - 8^{\circ}\text{C}$)).

Keep the vial in the outer carton in order to protect from light.

6.5 Nature and contents of container

Brown vials (type I glass) with chlorobutyl/butyl rubber stopper and aluminium overseal.
Clear vials (type I glass) with chlorobutyl/butyl rubber stopper and aluminium overseal.

Package sizes:

1 x 10ml and 5 x 10ml Solution for Injection.
1 x 20ml and 5 x 20ml Solution for Injection.
1 x 50ml and 5 x 50ml Solution for Injection.
1 x 100ml and 5 x 100ml Solution for Injection.

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

If necessary Folicid may be diluted with the following solutions for infusion: 5% glucose solution or 0.9% sodium chloride solution.

The medicinal product is for single use only. Any unused solution should be discarded.
The solution for injection should be inspected visually prior to use. Only clear solutions without particles should be used.

7 MARKETING AUTHORISATION HOLDER

Cell Pharm GmbH
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Feodor-Lynen-Straße 23
30625 Hannover
Germany

8 MARKETING AUTHORISATION NUMBER

PA 1070/001/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

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10 DATE OF REVISION OF THE TEXT

November 2007