# Summary of Product Characteristics

## 1 NAME OF THE MEDICINAL PRODUCT

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

## 2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each ml of solution contains calcium folinate hydrate equivalent to 10 mg folinic acid.

Each ml of solution contains calcium folinate hydrate equivalent to 10 mg folinic acid.
Each vial with 5 ml solution contains calcium folinate hydrate equivalent to 50 mg folinic acid.
Each vial with 10 ml solution contains calcium folinate hydrate equivalent to 100 mg folinic acid.
Each vial with 20 ml solution contains calcium folinate hydrate equivalent to 200 mg folinic acid.
Each vial with 30 ml solution contains calcium folinate hydrate equivalent to 300 mg folinic acid.
Each vial with 50 ml solution contains calcium folinate hydrate equivalent to 500 mg folinic acid.
Each vial with 100 ml solution contains calcium folinate hydrate equivalent to 1000 mg folinic acid.

Excipient with known effect
Each ml of solution contains 3.15 mg sodium.

For the full list of excipients, see section 6.1.

## 3 PHARMACEUTICAL FORM

Solution for injection/infusion (injection/infusion).
Clear, colourless or yellowish solution free from visible particles.
pH between 6.5 and 8.5
Osmolality 260-310 mOsmol/kg.

## 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

Posology

**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 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 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 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 (48) hours after the start of the methotrexate infusion, the residual methotrexate level should be measured. If the residual methotrexate level is > 0.5 micromol/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 0.05 micromol/l: |
|---|---|
| ≥ 0.5 micromol/l | 15 mg/m² |
| ≥ 1.0 micromol/l | 100 mg/m² |
| ≥ 2.0 micromol/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 IV infusion over 2 hours, followed by bolus 400 mg/m² of 5-fluorouracil and 22-hour infusion of 5-fluorouracil (600 mg/m² aria-hidden="true">) for 2 consecutive days, every 2 weeks on days 1 and 2.

*Weekly 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 plus 500 mg/m² 5-fluorouracil as 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 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 haematological 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.

Method of administration

For intravenous or intramuscular use.
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, Folinic acid (as calcium folinate) may be diluted before use. For instructions on dilution of the medicinal product before administration, see section 6.6.

**4.3 Contraindications**

Hypersensitivity to the active substance, or to any of the excipients listed in section 6.1.
Pernicious anaemia or other anaemias due to vitamin $B_{12}$ deficiency.

Regarding the use of calcium folinate with methotrexate or 5-fluorouracil during pregnancy and lactation, see section 4.6 and the Summaries of Product Characteristics (SmPCs) 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. When calcium folinate 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 $B_{12}$ deficiency.

Many cytotoxic medicinal products – direct or indirect DNA synthesis inhibitors – lead to macrocytosis (hydroxycarbamide, cytarabine, mercaptopurine, tioguanine). Such macrocytosis should not be treated with calcium folinate.

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 section 4.5).

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-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. 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 SmPC 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 SmPC 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 calcium folinate 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.

Excipients

This medicinal product contains 3.15 mg sodium per ml of solution, equivalent to 0.16 % of the WHO recommended maximum daily intake of 2 g sodium for an adult.

**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, other antibiotics with an antifolate effect, methotrexate) the efficacy of the folic acid antagonist may either be reduced or completely neutralised.

Calcium folinate may reduce the effect of antiepileptic medicines: phenobarbital, phenytoin, primidone 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 co-factors) (see section 4.4).

Concomitant administration of calcium folinate with 5-fluorouracil has been shown to enhance the efficacy and toxicity of 5-fluorouracil (see sections 4.2, 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. Animal studies are insufficient with respect to reproductive toxicity (see section 5.3). However, there are no indications that calcium folinate 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, 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 SmPCs for methotrexate, other folate antagonists and 5-fluorouracil-containing medicinal products.

Breast-feeding
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.

Fertility
Calcium folinate is an intermediate product in the metabolism of folic acid and occurs naturally in the body. No fertility studies have been conducted with calcium folinate in animals.

**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**

The frequencies are defined according to the MedDRA as follows: 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 from the available data).

**All therapeutic indications**

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

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

Nervous system disorders
*Rare:* increase in the frequency of attacks in patients with epilepsy (see section 4.5).

Gastrointestinal disorders
*Rare:* gastrointestinal disorders after high doses.

Skin and subcutaneous tissue disorders
*Not known:* Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN).
In patients receiving folinic acid in combination with other agents known to be associated with these conditions; some cases may be fatal. It cannot be ruled out that folinic acid contributed to the occurrence of SJS/TEN.

General disorders and administration site conditions
*Uncommon:* fever.

**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.

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

Metabolism and nutrition disorders
*Not known:* hyperammonaemia.

Skin and subcutaneous tissue disorders
*Common:* palmar-plantar erythrodysesthesia.

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

**Monthly regimen**

Gastrointestinal disorders
*Very common:* nausea, vomiting and diarrhoea.

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

**Weekly regimen**

Gastrointestinal disorders

*Very common:* diarrhoea with higher grades of toxicity, and dehydration, resulting in hospital admission for treatment and even death.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via HPRA Pharmacovigilance, Website: www.hpra.ie

**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 agents for antineoplastic treatment, ATC code: V03AF03

Calcium folinate is the calcium salt of 5-formyl tetrahydrofolic acid. It is an active metabolite of folinic acid and an essential co-enzyme 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 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 forms 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, a key enzyme involved in pyrimidine biosynthesis, and calcium folinate enhances thymidylate synthase inhibition by increasing the intracellular folate pool, thus stabilising the 5-fluorouracil-thymidylate synthase 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.

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 IV 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.

Biotransformation
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.

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

**5.3 Preclinical safety data**

Genotoxicity, carcinogenicity, fertility and pre-/postnatal development studies have not been conducted with calcium folinate.

Embryo-foetal reproduction toxicity studies have been performed in rats and rabbits. Rats were dosed up to 1 800 mg/m$^2$ which is 9 times the maximum recommended human dose, and rabbits were dosed up to 3 600 mg/m$^2$ which is 18 times the maximum recommended human dose. There was no embryo-foetal toxicity noted in rats. At the maximum dose in rabbits, there was an increase in embryonic resorptions and no other adverse effects on embryo-foetal development. No resorptions were noted in dose groups at 6 times the maximum recommended human dose.

**6 PHARMACEUTICAL PARTICULARS**

**6.1 List of excipients**

Sodium chloride
Sodium hydroxide (for pH adjustment)
Water for injections

**6.2 Incompatibilities**

Incompatibilities have been reported between injectable forms of calcium folinate and injectable forms of droperidol, 5-fluorouracil, foscarnet and methotrexate.

*Droperidol*

- Droperidol 1.25 mg/0.5 ml with calcium folinate 5 mg/0.5 ml, immediate precipitation in direct admixture in syringe for 5 minutes at 25 °C followed by 8 minutes of centrifugation.
- Droperidol 2.5 mg/0.5 ml with calcium folinate 10 mg/0.5 ml, immediate precipitation when the medicines were injected sequentially into a Y-site 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 glucose50 mg/ml (5 %) solution for injection, 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*
Foscarnet 24 mg/ml with calcium folinate 20 mg/ml; formation of a cloudy yellow solution reported.

This medicinal product must not be mixed with other medicinal products except those mentioned in section 6.6.

**6.3 Shelf life**

2 years

After opening the vial: the product should be used immediately.

Shelf life after dilution
Chemical and physical in-use stability has been demonstrated for 4 days at 25 °C (protected from light) and at 2 to 8 °C after dilution with sodium chloride 9 mg/ml (0.9 %) solution for injection.
From a microbiological point of view, the diluted product should be used immediately. If not used immediately, in-use storage times and conditions prior to the use are the responsibility of the user and would not normally be longer than 24 hours at 2 to 8 °C, unless dilution has taken place in controlled and validated aseptic conditions.

Chemical and physical in-use stability has been demonstrated for 24 hours at 2 to 8 °C after dilution with glucose 50 mg/ml (5 %) solution for injection.
From a microbiological point of view, unless the method of opening/dilution precludes the risk of microbial contamination, the product should be used immediately. If not used immediately, in-use storage times and conditions are the responsibility of user.

**6.4 Special precautions for storage**

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

For storage conditions after dilution of the medicinal product, see section 6.3.

**6.5 Nature and contents of container**

5 ml, 10 ml, 20 ml, 30 ml, 50 ml or 100 ml of solution filled in clear glass vials closed with bromobutyl rubber stoppers sealed with aluminium flip-off seals. Vials are packed into outer cartons.

Pack sizes:
1, 5 or 10 vials of 5 ml
1 or 10 vials of 10 ml
1 or 10 vials of 20 ml
1 or 10 vials of 30 ml
1 or 10 vials of 50 ml
1 or 10 vials of 100 ml

Not all pack sizes may be marketed.

**6.6 Special precautions for disposal and other handling**

For single use only.

The solution should be inspected visually prior to use. Do not use if there are any visible signs of deterioration (e.g. particles). Only clear solutions free from visible particles should be used.

Dilution for intravenous infusion
To administer the dose for a given patient, aseptically withdraw the appropriate amount of Folinic acid (as calcium folinate) 10 mg/ml solution for injection/infusion from the vial, then dilute it with any of compatible solutions mentioned below.
For storage conditions and shelf life after dilution, see section 6.3.

For intravenous infusion may be diluted with:

- sodium chloride 9 mg/ml (0.9 %) solution for injection;
- glucose 50 mg/ml (5 %) solution for injection.

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

**7 MARKETING AUTHORISATION HOLDER**

AS Kalceks
Krustpils Iela 71e
Riga
1057
Latvia

**8 MARKETING AUTHORISATION NUMBER**

PA2165/024/001

**9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION**

Date of first authorisation: 8th December 2023

**10 DATE OF REVISION OF THE TEXT**