# SUMMARY OF PRODUCT CHARACTERISTICS

## 1 NAME OF THE MEDICINAL PRODUCT

Calcium Folinate 10 mg/ml solution for injection

## 2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Calcium Folinate 10mg/ml Solution for Injection contains calcium folinate, the formyl derivate of tetrahydrofolic acid in the form of the calcium salt.

Each ml solution for injection contains 10.8 mg of calcium folinate, equivalent to 10.0 mg of folinic acid

Each vial of 5 ml contains 54 mg of calcium folinate, equivalent to 50 mg of folinic acid.

Each vial of 10 ml contains 108 mg of calcium folinate, equivalent to 100 mg of folinic acid.

Each vial of 20 ml contains 216 mg of calcium folinate, equivalent to 200 mg of folinic acid.

Each vial of 30 ml contains 324 mg of calcium folinate, equivalent to 300 mg of folinic acid.

Each vial of 50 ml contains 540 mg of calcium folinate, equivalent to 500 mg of folinic acid.

Excipient with known effect

Each ml of solution for injection contains 0.14 mmol (3.22 mg) sodium.

For the full list of excipients see section 6.1

## 3 PHARMACEUTICAL FORM

Solution for injection.

Calcium Folinate 10 mg/ml, solution for injection is a clear, yellow solution free from particles.

## 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

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 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. See also sections 6.3 and 6.6.

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 - 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/m$^2$ body surface and should be considered with doses of 100 mg – 500 mg/m$^2$ 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 - 12mg/m$^2$) to be given 12 to 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 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 in the blood 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 or 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$^2$ |

***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 calcium folinate in combination with 5-fluorouracil in children:

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

Weekly regimen: Calcium folinate 20 mg/m$^2$ by intravenous bolus injection or 200 to 500 mg/m$^2$ intravenous infusion over a period of 2 hours plus 500 mg/m$^2$ 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/m$^2$ by bolus i.v. injection or 200 to 500 mg/m$^2$ as i.v. infusion over a period of 2 hours immediately followed by 425 or 370 mg/m$^2$ 5-fluorouracil as an intravenous bolus injection over 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/m$^2$ for 5 to 10 minutes every 6 hours (total daily dose of 80 mg/m$^{2)}$, or by oral route with four doses of 20 mg/m$^2$ administered at equal time intervals. Daily doses of calcium or calcium

folinate should be adjusted depending on the haematological toxicity of trimetrexate.

- Overdosage (possibly occurring with trimetrexate doses above 90 mg/m$^2$ without concomitant administration of calcium folinate): after stopping treatment with trimetrexate, calcium folinate should be administered intravenously at a dose of 40 mg/m2 every 6 hours for 3 days.

Trimethoprim toxicity:

- After stopping treatment with trimethoprim, calcium folinate should be administered intravenously at a dose of 3-10 mg/day 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 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 Fertility, 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 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 anaemia and other anaemias resulting from vitamin $B_{12}$ deficiency.

Many cytotoxic medicinal products (direct or indirect DNA synthesis inhibitors such as hydroxycarbamide, cytarabine, mercaptopurine, thioguanine) 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 of increased 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).

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 has to 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-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 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 (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 other 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 also implies 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.

Excipient(s)

*Sodium*
*5 ml vials:*
This medicinal product contains less than 1 mmol sodium (23 mg) per vial, that is to say essentially 'sodium- free'.
*10 ml vials:*
This medicinal product contains 32.2 mg sodium per vial, equivalent to 1.6 % of the WHO recommended maximum daily intake of 2 g sodium for an adult.
*20 ml vials:*
This medicinal product contains 64.4 mg sodium per vial, equivalent to 3.2 % of the WHO recommended maximum daily intake of 2 g sodium for an adult.
*30 ml vials:*
This medicinal product contains 96.6 mg sodium per vial, equivalent to 4.8 % of the WHO recommended maximum daily intake of 2 g sodium for an adult.
*50 ml vials:*
This medicinal product contains 161 mg sodium per vial, equivalent to 8.1 % 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. 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, 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 also sections 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 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. No formal animal reproductive toxicity studies with calcium folinate have been conducted. There is 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 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 is contraindicated during breastfeeding; 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.

## 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

| |
|---|
| 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 and urticaria.

***Psychiatric disorders***

*Rare*

Insomnia, agitation and depression after high doses.

***Gastrointestinal disorders***

*Rare*

Gastrointestinal disorders after high doses.

***Nervous system disorders***

*Rare*

Increase in the frequency of attacks in epileptics (see also section 4.5).

***General disorders and administration site conditions***

*Uncommon*

Fever has been reported 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:

***Metabolism and nutrition disorders***

*Not known*
Hyperammonaemia

***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 cheilitis. Fatalities have occurred as a result of mucositis.

***Skin and subcutaneous tissue disorders***

*Common*
Palmar-Plantar Erythrodysaesthesia

*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*
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 the Yellow Card Scheme Website: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

### 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, refer to the SmPC for 5-fluorouracil containing products.

## 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 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 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 (TS), a key enzyme involved in pyrimidine biosynthesis, 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 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

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

<u>Metabolism</u>

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 intravenous administration.

The AUC for L-5-formyl-THF and 5-methyl-THF were 28.4 ± 3.5 mg/l x min and 129 ± 11 mg/l x min, respectively, 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 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 SmPC.

## 6 PHARMACEUTICAL PARTICULARS

### 6.1 List of excipients

Sodium chloride, sodium hydroxide, hydrochloric acid, water for injection.

### 6.2 Incompatibilities

Calcium Folinate 10mg/ml Solution for Injection should not be mixed with any other drug, unless compatibility has been satisfactorily demonstrated.

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 in direct admixture in 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 when the drugs 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 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***
Foscarnet 24 mg/ml with calcium folinate 20 mg/ml: formation of a cloudy yellow solution reported.

## 6.3 Shelf life

***Shelf-life in unopened packages***
2 years

***Shelf-life after first opening of the vial***

Only for single administration. Any unused portion of the solution must be discarded immediately after the first use.

***Shelf-life after dilution according to directions***
After dilution according to the directions with the recommended infusion fluids, 0.9% NaCl solution or 5% Glucose solution, the physical-chemical in-use stability of the diluted solution has been shown for 72 hours at room temperature (below 25 °C).

From a microbiological point of view, the product should be used immediately after diluting. If the diluted product is not used immediately, the user / person administering the product is responsible for the handled use term and condition for administration. Normally the term in the last case is no longer than 24 hours at 2-8 °C, unless dilution took place under controlled and validated aseptic conditions.

## 6.4 Special precautions for storage

Store in a refrigerator (2°C – 8°C). Store the glass vial in the outer package.

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

## 6.5 Nature and contents of container

Clear Type I glass vial with chlorobutyl rubber stoppers, Type I with aluminium flexible stop. Vials contain 5 ml, 10 ml, 20 ml, 30 ml and 50 ml solution for injection.

Package sizes: 1 vial per primary carton

Not all pack sizes may be marketed.

## 6.6 Special precautions for disposal and other handling

Calcium Folinate 10 mg/ml solution for injection is only intended for single use. Any unused portion of the solution must be discarded immediately after the first use.

For intravenous infusion calcium folinate can be diluted according to the directions with the recommended infusion fluids, 0.9% NaCl solution or 5% Glucose solution.

The administration of Calcium Folinate 10 mg/ml solution for injection is dependent on the individual dosage schedule. See also section 4.2. In case of intravenous administration no more than 160 mg of calcium folinate may be injected per minute due to the amount of calcium in the solution.

Before the administration the sterile solution for injection must be inspected visually for clarity, the presence of particles, discolouration and the appearance of the package. The solution should only be used if it is clear and the package is not damaged.

Any unused portion of the solution, any unused medicinal product or waste material should be disposed in accordance with local requirements.

## 7 MARKETING AUTHORISATION HOLDER

Teva UK Limited, Ridings Point, Whistler Drive, Castleford, WF10 5HX, United Kingdom

## 8 MARKETING AUTHORISATION NUMBER(S)

PL 00289/0851

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

Date of first authorization: 28 April 2006

Date of latest renewal: 11 February 2008

## 10 DATE OF REVISION OF THE TEXT

02/11/2022