Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Leucovorin-Teva 10mg/ml Concentrate for Solution for Infusion

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Contains 10 mg folinic acid (as calcium folinate) per ml, as active ingredient.
Also contains 3 mg (0.1 mmol) sodium per ml.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Concentrate for solution for infusion.
Clear yellow concentrate for solution for infusion.

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. Refer also to 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 25-50 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/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 (6-12 mg/m^2) 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 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 these combinations in children:

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

Weekly 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 plus 500 mg/m^2 5-fluorouracil as i.v. 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 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 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 for a 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 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 trimetrexate, calcium folinate 40 mg/m^2 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 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.
- 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 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 folinic acid has been administered intrathecally following intrathecal overdoseof 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, mecaptopurine, thioguanine). 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 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 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.

The following provides general advice for monitoring patients receiving calcium folinate/5-fluorouracil treatment, however, specific monitoring recommendations may vary with local medical practice. Full blood count (FBC) with differential and platelets should be carried out prior to each treatment; weekly during the first two courses; at time of anticipated white blood cell (WBC) nadir in all courses thereafter. Electrolytes and liver function tests should be carried out prior to each treatment for the first three courses and prior to every other course thereafter.

Calcium folinate/methotrexate
For specific details on reduction of methotrexate toxicity refer to the Summary of Product Characteristics 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 preexisting- 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 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 30 mg sodium per vial, equivalent to 1.5 % of the WHO recommended maximum daily intake of 2 g sodium for an adult.
20 ml vials:
This medicinal product contains 60 mg sodium per vial, equivalent to 3 % of the WHO recommended maximum daily intake of 2 g sodium for an adult.
30 ml vials:
This medicinal product contains 90 mg sodium per vial, equivalent to 4.5 % of the WHO recommended maximum daily intake of 2 g sodium for an adult.
50 ml vials:
This medicinal product contains 150 mg sodium per vial, equivalent to 7.5 % 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, other antibiotics with an antifolate effect, methotrexate) the efficacy of the folic acid antagonist may either be reduced or completely neutralised.

Caution is required during concurrent administration of folinic acid with fluoropyrimidine as this has been associated with seizures and syncope (see section 4.8).

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 the efficacy and toxicity of 5-fluorouracil (see sections 4.2 and 4.8).

Concurrent administration of chloramphenicol and folic acid in folate deficient patients may result in antagonism of haematopoietic response to folic acid.

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 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 contraindicated during breastfeeding; 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.

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. Hence, nonclinical reproductive toxicity studies were not conducted.

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 of adverse events are ranked according to the following: 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.

Nervous system disorders
Rare: increase in the frequency of attacks in epileptics (see section 4.5)

Gastrointestinal disorders
Rare: gastrointestinal disorders after high doses.
Frequency not known (cannot be estimated from the available data): abdominal pain

General disorders and administration site conditions
Uncommon: fever has been observed after administration of 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:

Blood and lymphatic system disorders
Very common: bone marrow failure, including fatal cases, leukopenia, neutropenia, thrombocytopenia, anaemia

Metabolism and nutrition disorder
Not known: hyperammonaemia

Skin and subcutaneous tissue disorders
Common: Palmar-Plantar Erythrodysaesthesia

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

Monthly regime
Gastrointenstinal disorders
Very common: vomiting and nausea

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

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

Other combination therapy
Neurological disorders
Rare: seizures and/or syncope have been reported in cancer patients receiving folinic acid, usually in association with fluoropyrimidine administration and most commonly in those with CNS metastases or other predisposing factors; however, a causal relationship has not been established.

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 areasked 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-FU 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 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 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--flourouracil) to enhance its cytotoxic activity. 5--flourouracil inhibits thymidylate synthase (TS), a key enzyme involved in pyrimidine biosynthesis, and calcium folinate enhances thymidylate synthase inhibition by increasing the intracellular folate pool, thus stabilising the 5flourouracil-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.

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 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-formyltetrahydrofolate.

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

There are nopreclinical data considered relevant to clinical safety beyond data included inother sections of the SPC.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium chloride
Sodium hydroxide (for pH adjustment)
Hydrochloric acid concentrate (diluted 1:20 for pH adjustment)
Water for injection

6.2 Incompatibilities

This medical product should not be mixed with any medical products except those listed in *section 6.6*

6.3 Shelf life

2 years,

When aseptically diluted, the solution should be used within 24 hours of preparation when stored in the refrigerator (2-8^{o}C), or within 8 hours when stored at room temperature (below 25^{o}C).

6.4 Special precautions for storage

Store in a refrigerator at 2-8^{o}C. Keep this 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

Clear, colourless, glass vial, Ph. Eur. Type 1, with a grey, chlorobutyl, rubber closure (Ph. Eur. 20mm).

The product is supplied in vials of 5ml, 10ml, 20ml, 30ml and 50ml, packed in individual cartons.
Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

- For single use only. Discard any remaining contents after use.
- Vials should be inspected visually before use. If solution is cloudy or particles are visible, solution should be discarded.

<u>Dilution of Leucovorin-Teva 10 mg/ml</u>
Leucovorin-Teva 10 mg/ml is chemically and physically stable for 24 hours when diluted to a concentration of 0.06 mg/ml and to 1 mg/ml, using the following diluents:

Lactated Ringer's Injection
Dextrose 10% in Water for Injection
Dextrose 5% in Water for Injection
Sodium Chloride 0.9% Injection

Leucovorin - Teva 10 mg/ml is chemically and physically stable for 24 hours when diluted in Dextrose 10% in saline at a concentration of 1 mg/ml.

From a microbiological point of view, when aseptically diluted the solution should be used within 24 hours of preparation when stored in the refrigerator (2-8°C), or within 8 hours when stored at room temperature (below 25°C).

- Any portion remaining after this time should be discarded.

7 MARKETING AUTHORISATION HOLDER

Teva Pharma B.V.
Swansweg 5
2031GA Haarlem
Netherlands

8 MARKETING AUTHORISATION NUMBER

PA0749/001/001

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