Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Levofolinic Acid Ebewe 10 mg/ml Solution for Injection or Infusion.

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

1 ml solution for injection or infusion contains 12.71 mg calcium levofolinate 5 H_2O, equivalent to 10 mg L-folinic acid.

A 5 ml ampoule/vial contains 50 mg L-folinic acid.
A 10 ml ampoule contains 100 mg L-folinic acid.
A 17.5 ml ampoule contains 175 mg L-folinic acid.
A 20 ml ampoule contains 200 mg L-folinic acid.

Excipients with known effect: Sodium chloride and sodium hydroxide (less than 1 mmol sodium (23 mg) per dose, i.e. practically “sodium-free").

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Solution for injection or infusion
Clear, yellowish solution
Osmolarity: 291-301 mOsm
pH 6.5-8.5

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

L-folinic acid (as calcium levofolinate) is indicated:

- to diminish the toxicity and to 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 “L-folinic acid (as calcium levofolinate) rescue”.
- in combination with 5-fluorouracil in cytotoxic therapy.

4.2 Posology and method of administration

Method of administration

L-folinic acid (as calcium levofolinate) may only be administered intravenously or intramuscularly. In the case of intravenous administration, no more than 160 mg of L-folinic acid (as calcium levofolinate) should be injected per minute due to the calcium content of the solution.

For intravenous infusion, L-folinic acid (as calcium levofolinate) may be diluted with 0.9% sodium chloride solution or 5% glucose solution before use. See also sections 6.3 and 6.6.

Posology

L-folinic acid (as calcium levofolinate) rescue in methotrexate therapy
Since the L-folinic acid (as calcium levofolinate) 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 L-folinic acid (as calcium levofolinate) rescue. Therefore, it is best to refer to the applied intermediate or high dose methotrexate protocol for posology and method of administration of L-folinic acid (as calcium levofolinate).

The following guidelines may serve as an illustration of the regimens:

L-folinic acid (as calcium levofolinate) 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 12.5 - 25 mg should be given parenterally due to the saturable enteral absorption of L-folinic acid (as calcium levofolinate).

L-folinic acid (as calcium levofolinate) rescue in methotrexate therapy: After high-dose methotrexate for osteosarcoma: age 6 years and older, 7.5 mg (approximately 5 mg/m(2) IV every 6 hr for 10 doses starting 24 hr after beginning of methotrexate infusion, rescue dose is based on a methotrexate dose of 12 grams/m(2) IV infusion over 4 hr; hydration and urinary alkalinization (pH 7 or higher) are suggested; continue until methotrexate level less than 5 x 10(-8) M (0.05 micromolar).

L-folinic acid (as calcium levofolinate) rescue is necessary when methotrexate is given in doses exceeding 500 mg/m^2 body surface and should be considered with doses of 100 mg to 500 mg/m^2 body surface.

The dosage and duration of L-folinic acid (as calcium levofolinate) 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 L-folinic acid (as calcium levofolinate) is 7.5 mg (3 - 6 mg/m^2) and it should be given 12-24 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 the L-folinic acid (as calcium levofolinate) administration, measures to ensure the prompt excretion of methotrexate (maintenance of a high urine output and alkalinisation of urine) are integral components of the L-folinic acid (as calcium levofolinate) rescue treatment. The kidney function should be monitored through daily measurements of the serum creatinine.

The residual methotrexate level should be measured 48 hours after the start of the methotrexate infusion. If the residual methotrexate level is >0.5µmol/l, the L-folinic acid (as calcium levofolinate) dosages should be adjusted according to the following table:

Residual methotrexate blood level 48 hours after the start of the methotrexate administration:	Additional L-folinic acid (as calcium levofolinate) to be administered every 6 hours for 48 hours or until the methotrexate level is lower than 0.05 µmol/l:
≥ 0.5 µmol/l	7.5 mg/m^2
≥ 1.0 µmol/l	50 mg/m^2
≥ 2.0 µmol/l	100 mg/m^2

Where overdose of methotrexate is suspected, the dose of L-folinic acid (as calcium levofolinate) should be at least 50% of the offending dose of methotrexate and should be administered in the first hour.

In combination with 5-fluorouracil in cytotoxic therapy

Different regimens and different dosages are used, without any of the dosages 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:

Biweekly regimen
L-folinic acid (as calcium levofolinate) with 100 mg/m^2 by intravenous infusion over 2 hours, followed by bolus 400 mg/m^2 of 5-fluorouracil and a 22-hour infusion of 5-FU (600 mg/m^2) for 2 consecutive days, every 2 weeks on days 1 and 2.

Weekly regimen
L-folinic acid (as calcium levofolinate) in a dose of 10 mg/m^2 administered as intravenous bolus injection or 100 – 250 mg/m^2 administered as intravenous infusion over 2 hours with 500 mg/m^2 of 5-fluorouracil administered as intravenous bolus injection in the middle of or at the end of the L-folinic acid (as calcium levofolinate) infusion.

Monthly regimen
L-folinic acid (as calcium levofolinate) 10 mg/m^2 administered as intravenous bolus injection or 100 to 250 mg/m^2 as intravenous infusion over a period of 2 hours, immediately followed by 425 or 370 mg/m^2 of 5-fluorouracil as intravenous bolus injection during 5 consecutive days.

In the case of a combination therapy with 5-fluorouracil, the adjustment of the 5-fluorouracil dose and of the treatment-free period may be necessary, depending on the patient's condition, the responsiveness to the treatment and/or the occurrence of dose-limiting toxicity. It is not necessary to reduce the L-folinic acid (as calcium levofolinate) dose.

The number of the repeat cycles is at the discretion of the treating physician.

Antidote to the folic acid antagonists trimetrexate, trimethoprim and pyrimethamine

Trimetrexate toxicity

Prevention
L-folinic acid (as calcium levofolinate) should be administered every day during treatment with trimetrexate and for 72 hours after the last dose of trimetrexate. L-folinic acid (as calcium levofolinate) can be administered either intravenously at a dose of 10 mg/m^2 for 5 to 10 minutes every 6 hours for a total daily dose of 40 mg/m^2 or orally in 4 doses for a total daily dose of 10 mg/m^2 administered at equal time intervals. The daily L-folinic acid (as calcium levofolinate) doses should be adjusted depending on the haematological toxicity of trimetrexate.

Overdose
(possibly occurring with trimetrexate doses above 90 mg/m^2 without concomitant administration of L-folinic acid (as calcium levofolinate):
after stopping trimetrexate:
administration of 20 mg/m^2 L-folinic acid (as calcium levofolinate) intravenously every 6 hours for 3 days.

Trimethoprim toxicity
after stopping trimethoprim:
administration of 1.5 - 5 mg/day of L-folinic acid (as calcium levofolinate) until recovery of a normal blood count.

Pyrimethamine toxicity
In case of a high dose pyrimethamine treatment or in case of a longer treatment with low doses, 2.5 to 25 mg/day of L-folinic acid (as calcium levofolinate) should be administered simultaneously, based on the results of the peripheral blood counts.

Paediatric population
There are insufficient data on the use in children and adolescents.

4.3 Contraindications

- Known hypersensitivity to L-folinic acid (as calcium levofolinate) or to any of the excipients listed in section 6.1.
- Pernicious anaemia or other anaemias due to vitamin B12 deficiency.

Regarding the use of levofolinic acid with methotrexate or 5-fluorouracil during pregnancy and lactation, see section 4.6, “Pregnancy and Lactation” and the summaries of product characteristics for methotrexate and 5-fluorouracil containing medicinal products.

4.4 Special warnings and precautions for use

L-folinic acid (as calcium levofolinate) may only be given by intramuscular or intravenous injection and must not be administered intrathecally. When folinic acid has been administered intrathecally following intrathecal methotrexate overdose, death has been reported.

In general
L-folinic acid (as calcium levofolinate) should be used in combination with folic acid antagonists, such as for example methotrexate, or fluoropyrimidines, such as for example 5-fluorouracil, only under the direct supervision of a physician experienced in the use of chemotherapeutic agents in cancer patients.

Treatment with L-folinic acid (as calcium levofolinate) can disguise pernicious anaemia or other anaemias caused by vitamin B_{12} deficiency.

Many cytotoxic medicinal products - direct or indirect DNA synthesis inhibitors – lead to macrocytosis (hydroxcarbamide, cytarabine, mercaptopurine, thioguanine). Such macrocytosis should not be treated with folinic acid.

In epileptic patients treated with phenobarbital, phenytoin, primidone and succinimides, there is a risk of increase in the frequency of seizures due to a decrease of the plasma concentrations of anti-epileptic drugs. During the administration and after the discontinuation of L-folinic acid (as calcium levofolinate), clinical monitoring, possibly the monitoring of the plasma concentrations and, if necessary, a dose adjustment of the anti-epileptic drug is recommended (see also section 4.5).

L-folinic acid (as calcium levofolinate)/5-fluorouracil
L-folinic acid (as calcium levofolinate) may enhance the toxicity risk of 5-fluorouracil, particularly in elderly and debilitated patients. The most common manifestations that may be dose-limiting are leucopoenia, mucositis, stomatitis and/or diarrhoea. When, in cases of toxicity, L-folinic acid (as calcium levofolinate) and 5-fluorouracil are used in combination, the 5-fluorouracil dosage has to be reduced more than when 5-fluorouracil is used alone.

Combined 5-fluorouracil and L-folinic acid (as calcium levofolinate) 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 can be a sign of gastrointestinal toxicity, patients with diarrhoea must be carefully monitored until the symptoms have completely disappeared since a rapid clinical deterioration can occur which can also lead to death. If diarrhoea and/or stomatitis occur, it is advisable to reduce the dose of 5-FU until the symptoms have entirely disappeared. Especially the elderly and patients with poor general health as a result of their illness are at an increased risk of these toxicities. Therefore, particular care should be taken when treating these patients.

In case of elderly patients and patients who have undergone preliminary radiotherapy, it is recommended to begin treatment with a reduced dosage of 5-fluorouracil.

L-folinic acid (as calcium levofolinate) may not be mixed with 5-fluorouracil in the same intravenous injection or infusion.

Calcium levels should be monitored in patients receiving a combined 5-fluorouracil/L-folinic acid (as calcium levofolinate) treatment and calcium supplements should be provided if calcium levels are low.

L-folinic acid (as calcium levofolinate)/methotrexate
For specific details regarding the reduction of methotrexate toxicity, please refer to the summary of the product characteristics of the medicinal product (SmPC) of methotrexate.

L-folinic acid (as calcium levofolinate) has no effect on non-haematological toxicities of methotrexate, such as nephrotoxicity resulting from methotrexate and/or metabolite precipitation in the kidney. Patients who experience delayed early methotrexate elimination are highly likely to develop reversible renal failure and any of the toxicities associated with methotrexate (please refer to the SPC for methotrexate). The presence of pre-existing or methotrexate-induced renal insufficiency is potentially associated with a delayed excretion of methotrexate and may increase the need for higher doses or more prolonged use of L-folinic acid (as calcium levofolinate).

Excessive L-folinic acid (as calcium levofolinate) doses must be avoided since this may impair the anti-tumour activity of methotrexate. This is especially the case with CNS tumours where L-folinic acid (as calcium levofolinate) accumulates after repeated treatment cycles.

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

An accidental overdose with a folate antagonist, such as methotrexate, should be treated as a medical emergency. As the time interval between the administration of methotrexate and the L-folinic acid (as calcium levofolinate) rescue increases, the effectiveness of L-folinic acid (as calcium levofolinate) in counteracting toxicity decreases.

The possibility that the patient is taking other medications that interact with methotrexate (e.g. medications which may interfere with the elimination of methotrexate or bind to serum albumin) should always be considered when laboratory abnormalities or clinical toxicities are observed. Levofolinic Acid Ebewe 10 mg/ml solution for injection or infusion contains less than 1 mmol (23 mg) of sodium per ml.

4.5 Interaction with other medicinal products and other forms of interaction

When L-folinic acid (as calcium levofolinate) is administered in conjunction with a folic acid antagonist (e.g. cotrimoxazole, pyrimethamine), the efficacy of the folic acid antagonist may either be reduced or completely neutralized.

L-folinic acid (as calcium levofolinate) may decrease the efficacy of anti-epileptic drugs (phenobarbital, primidone, phenytoin and succinimide), and may thus increase the frequency of seizures (a decrease of the 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 sections 4.4. and 4.8).

The simultaneous use of L-folinic acid (as calcium levofolinate) with 5-fluorouracil increases the toxicity of 5-fluorouracil (see sections 4.2, 4.4 and 4.8) tegafur and capecitabine.

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 L-folinic acid (as calcium levofolinate) 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 folic acid antagonists take place despite pregnancy or lactation, there are no limitations with respect to the use of L-folinic acid (as calcium levofolinate) to diminish toxicity or to counteract the effects.

The use of 5-fluorouracil and Methotrexate is generally contraindicated during pregnancy and lactation; this also

applies to the combined use of L-folinic acid (as calcium levofolinate) with 5-fluorouracil or Methotrexate. Please refer also to the Summaries of Product Characteristics for methotrexate, other folate antagonists and 5-fluorouracil containing medicinal products

Breastfeeding
It is not known whether L-folinic acid (as calcium levofolinate) is excreted into the human breast milk. L-folinic acid (as calcium levofolinate) can be used during lactation if this is considered necessary according to the therapeutic indications.

4.7 Effects on ability to drive and use machines

There is no indication that L-folinic acid (as calcium levofolinate) has an effect on the ability to drive and use machines.

4.8 Undesirable effects

The frequencies of undesirable effects have been listed according to the following convention:
Very common (≥ 1/10)
Common (≥ 1/100 to <1/10)
Uncommon (≥ 1/1,000 to <1/100)
Rare (≥ 1/10,000 to <1/1,000)
Very rare (≥ 1/10,000)
Not known (cannot be estimated from the available data)

All therapeutic indications

Immune system disorders
Very rare: anaphylactoid/anaphylactic reactions (including shock)
Not known: Allergic reactions, urticaria

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

Nervous system disorders
Rare: increase in the frequency of attacks in epileptics (see also section 4.5), seizures and/or syncope

Gastrointestinal disorders
Rare: gastrointestinal disorders after high doses

General disorders and administration site conditions
Uncommon: fever

Cases of Stevens-Johnson Syndrome (SJS) and Toxic Epidermal Necrolysis (TEN), some fatal, have been reported in patients receiving L-folinic acid (as calcium levofolinate) in combination with other agents known to be associated with these disorders. A contributory role of L-folinic acid (as calcium levofolinate) in these cases cannot be excluded.

Combination therapy with 5-fluorouracil

Gastrointestinal disorders
Very common: vomiting, nausea and diarrhoea
Diarrhoea with higher grades of toxicity and dehydration may result in hospitalization for treatment and may even lead to death.

Hepatobiliary disorders
Not known: Hyperammonemia

Skin and subcutaneous tissue disorders
Not known: Palmar-Plantar Erythrodysaesthesia

General disorders and administration site conditions
Very common: (severe) toxic effect on the mucosa: mucositits, including stomatitis and chelitis

Fatalities have occurred as a result of gastrointestinal toxicity (predominantly mucositis and diarrhoea) and myelosuppression.
Cases of allergic reactions and anaphylactoided reactions have been reported in patients receiving L-folinic acid (as calcium levofolinate) in combination with 5 FU.

4.9 Overdose

There have been no reports about effects in patients who have received significantly more L-folinic acid (as calcium levofolinate) than the recommended dose. However, excessive amounts of L-folinic acid (as calcium levofolinate) may neutralize the chemotherapeutic effect of folic acid antagonists.

In case of an overdose of the combination of 5-fluorouracil and L-folinic acid (as calcium levofolinate), the overdose instructions for 5-fluorouracil should be followed.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Detoxifying agents for antineoplastic treatment

ATC code: V03AF04

L-folinic acid (as calcium levofolinate) is the active l-isomer of 5-formyl tetrahydrofolic acid (folinic acid) and an essential co-enzyme of the nucleic acid synthesis in cytotoxic treatment.

L-folinic acid (as calcium levofolinate) is frequently used in order to diminish and counteract the action of folate antagonists, such as methotrexate. L-folinic acid (as calcium levofolinate) and folate antagonists share the same membrane transport carrier and compete for transport into the cells, stimulating folate antagonist efflux. It also protects the cells from the effects of the folate antagonists by filling up the reduced folate pool. L-folinic acid (as calcium levofolinate) serves as a pre-reduced source of H4 folate; it can, therefore, bypass a folate antagonist blockage and provide a source for the various coenzyme forms of folic acid.

L-folinic acid (as calcium levofolinate) is also frequently used in the biochemical modulation of fluoropyridine (5-FU) to enhance its cytotoxic activity. 5-FU inhibits the thymidilate synthase (TS), a key enzyme involved in pyrimidine biosyntheses and L-folinic acid (as calcium levofolinate) enhances TS inhibition by increasing the intracellular folate pool, thus stabilising the 5-FU/TS complex and increasing its activity.

5.2 Pharmacokinetic properties

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

Metabolism
L-folinic acid (as calcium levofolinate) (L-5-formyl tetrahydrofolic acid, L-5-formyl-THF) is the active enantiomer of folinic acid. The major metabolic product of folinic acid is 5-methyl-tetrahydrofolic acid (5-methyl-THF) which is predominantly produced in the liver and the intestinal mucosa.

Distribution
The distribution volume of folinic acid in tissue and body fluids and protein binding have not been determined and is not known.

The peak serum levels of the parent substance (D/L-5-formyl-tetrahydrofolic acid, folinic acid) are reached 10 minutes after intravenous administration.

AUC for L-5-formyl-THF and 5-methyl-THF were 28.4.4±3.5mg.min/l and 129±112mg.min/l after a dose of 25 mg. The inactive D-isomer is present in higher concentrations than L-5-formyl-tetrahydrofolate is.

Elimination
The elimination half-time for L-folinic acid (as calcium levofolinate) is 32 - 35 minutes.

The total terminal elimination half life value for the active metabolites is about 6 hours (after intravenous or intramuscular administration).

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

Due to the inherent lack of levofolinate toxicity, the influence of impaired renal or hepatic function on levofolinate disposition was not evaluated.

5.3 Preclinical safety data

There are no preclinical data that are considered relevant to clinical safety beyond the data included in other sections of the SmPC.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium chloride
Water for injection
Hydrochloric acid (for the adjustment of pH value)
Sodium hydroxide (for the adjustment of pH value)

6.2 Incompatibilities

Incompatibilities have been reported between the injectable forms of L-folinic acid (as calcium levofolinate) and the injectable forms of 5-fluorouracil and methotrexate.

5-fluorouracil
L-folinic acid (as calcium levofolinate) must not be mixed in the same infusion with 5-fluorouracil because a precipitate may form. Fluorouracil 50 mg/ml with L-folinic acid (as calcium levofolinate) 20 mg/ml, with or without dextrose 5% in water, has been shown to be incompatible when mixed in different quantities and stored at 4 °C, 23 °C or 32 °C in polyvinyl chloride containers.

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

6.3 Shelf life

Before opening: 18 months

After opening: the product should be used immediately

After dilution:
Chemical and physical in-use stability has been demonstrated on diluted solutions under light protection:

Concentration mg/ml	**Dilution with**	**Shelf life**	
		2 – 8°C	**Ambient temperature**
0.2 – 4.0	0.9 % sodium chloride	28 days	28 days
0.2	5 % glucose	7 days	1 day
4.0	5 % glucose	28 days	28 days

From a microbiological point of view, the product should be used immediately after dilution. 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 - 8°C unless dilution has taken place in controlled and validated aseptic conditions.

Discard the leftover product after initial use!

6.4 Special precautions for storage

Store in a refrigerator (2°C - 8°C).

Keep the ampoule(s)/vial(s) 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

Vial made from brown glass of hydrolytic class I in accordance with Ph. Eur., sealed with a chlorobutyl rubber stopper with Teflon coating or ampoule from brown glass.

Original packages with:
5 ml (50 mg) ampoules: pack size of 1
10 ml (100 mg) ampoules: pack size of 1 or 5
17.5 ml (175 mg) ampoules: pack size of 1
20 ml (200 mg) ampoules: pack size of 1 or 5
5 ml (50 mg) vial: pack sizes of 1 or 5 or 10

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

Prior to administration, L-folinic acid (as calcium levofolinate) should be visually inspected. The solution for injection or infusion should be a clear and yellowish solution. If it is cloudy in appearance or particles are observed, the solution should be discarded.
Levofolinic Acid Ebewe 10 mg/ml solution for injection or infusion can be diluted with the following solutions for infusion when necessary: 5 % glucose solution or 0.9 % sodium chloride solution.
The medicinal product is intended for single use only.
Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7 MARKETING AUTHORISATION HOLDER

Ebewe pharma G.e.s.m.b.H Nfg.KG,
Mondseestraβe 11,
4866 Unterach,
Austria

8 MARKETING AUTHORISATION NUMBER

PA0789/024/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 28th September 2012

10 DATE OF REVISION OF THE TEXT