SUMMARY OF PRODUCT CHARACTERSTICS

1. NAME OF THE MEDICINAL PRODUCT

LEUCOVORIN 50 mg Lyophilized Powder for Solution for Injection.
FOR INTRAVENOUS OR INTRAMUSCULAR ADMINISTRATION

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Leucovorin powder for solution for injection contains calcium folinate, the formyl derivative of tetrahydrofolic acid in the form of the calcium salt, equivalent to 50 mg folinic acid (leucovorin) as freeze-dried product.

Excipient(s): sodium.
For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Powder for solution for injection.

Yellow-white powder.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

To diminish the toxicity and counteract the action of folic acid antagonists in cytotoxic therapy.
As Leucovorin-Fluorouracil chemotherapy combination for cancer treatment.

4.2 Posology and method of administration

Only for intravenous or intramuscular administration. In 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 an intravenous infusion calcium folinate may be diluted before use with a 0.9% sodium chloride solution or with a 5% glucose solution. Se also sections 6.3 and 6.6

Calcium folinate rescue with treatment of methotrexate:
As the dosage schedule of the rescue treatment with calcium folinate is strongly dependent on the dose and the method of administration of methotrexate in intermediate or high dose, the methotrexate protocol will determine the dosage schedule of the rescue treatment with calcium folinate. It is therefore best to refer to the applied protocol of methotrexate to intermediate or high dose for determining the dose and method of administration of calcium folinate.

The following guidelines can serve as illustration for treatments used in adults and the elderly.

Calcium folinate rescue should occur via parenteral administration in patients with malabsorption syndromes or other gastro-intestinal disorders in which the intestinal resorption is not guaranteed. Doses larger than 25-50 mg must be administered parenterally due to the saturatable intestinal resorption of calcium folinate.

Calcium folinate rescue is needed if methotrexate is administered in doses of more than 500mg/m^2 of body surface and must be considered with doses of 100 mg - 500 mg/m^2 of body surface.

The dose and the duration of the calcium folinate rescue is mainly dependent on the nature and the dose of the treatment of methotrexate, the occurrence of toxicity symptoms and the individual excretion capacity for methotrexate. Generally the first dose of calcium folinate is 15 mg (6-12 mg/m^2), administered 12 to 24 hours (at the latest 24 hours) after the start of the infusion of methotrexate. The same dose is administered every 6 hours for a period of 72 hours. After the administration of several parenteral doses can be switched to the oral form.

In addition to the administration of calcium folinate measures for securing the rapid excretion of methotrexate (maintaining a high urine flow and alkalinisation of the urine) are an integral part of the calcium-folinate rescue treatment. The renal function must be followed through daily assessments of the serum creatinine.

48 hours after the initiation of the methotrexate infusion the residual concentration of methotrexate should be determined. If the residual concentration of methotrexate is greater than 0.5 µmol/l the doses of calcium folinate must be adjusted in accordance with the following table:

Rest concentration of methotrexate in the blood 48 hours after the initiation of the administration of methotrexate:	Additional calcium folinate to be administered every 6 hours for 48 hours or until the concentration of methotrexate is 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 for a cytotoxic treatment:
Various schedules and different doses were used, without a specific dosage appearing to be the optimal dose.

Antidote for the folic acid antagonists trimetrexate, trimethoprim and pyrimethamine:
Toxicity of trimetrexate:
- Prevention: calcium folinate must be administered every day during the treatment with trimetrexate and for 72 hours after the last dose of trimetrexate. Calcium folinate can be administered either intravenously in a dose of 20 mg/m^2 for 5 to 10 minutes every 6 hours up to a total daily dose of 80 mg/m^2, or orally with 4 doses of 20mg/m^2 administered at equal time intervals. The daily doses of calcium folinate must be adjusted on the basis of the haematological toxicity of trimetrexate
- Overdose (possibly occurring with doses of trimetrexate above 90 mg/m^2 without concomitant administration of calcium folinate): after the discontinuation of trimetrexate, calcium folinate of 40 mg/m2 every 6 hours for 3 days.

Toxicity of trimethoprim:
- After the discontinuation of trimethoprim, 3-10 mg/day of calcium folinate until the recovery of a normal blood picture.

Toxicity of pyrimethamine:
- In cases of a high dose of pyrimethamine or a long-term treatment with low doses, 5 to 50 mg/day of calcium folinate must be administered concomitantly, depending on the results of the blood picture of the peripheral blood.

4.3 Contra-indications

- Known hypersensitivity to calcium folinate or to one of the excipients.
- The combination with fluorouracil is not indicated in:
  - - existing contraindications against fluorouracil, in particular pregnancy and lactation,
  - - severe diarrhoea.
- Therapy in combination with fluorouracil must not be initiated or continued in patients who have symptoms of gastrointestinal toxicity of any severity until those symptoms have completely resolved. Patients with diarrhoea must be monitored with particular care until the diarrhoea has resolved, as rapid clinical deterioration leading to death can occur.
- Pernicious anaemia or other anaemias as a result of a vitamin B_{12} deficiency.

Concerning the use of calcium folinate and methotrexate or 5-fluorouracil during the pregnancy or during the period of lactation, see section 4.6 "Pregnancy and lactation" as well as the summary of product characteristics of methotrexate and 5-fluorouracil containing medicinal products.

4.4 Special warnings and special precautions for use

Calcium folinate may only be injected intramuscularly or intravenously, and may not be administered intrathecally. Death was reported when folinic acid was administered intrathecally after an intrathecal overdose of methotrexate.

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

A treatment with calcium folinate can mask a pernicious anaemia or other anaemias as a result of a vitamin B_{12} deficiency.

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

In epileptic patients, who are treated with phenobarbital, phenytoin, primidone and succinimides, the risk of an increased frequency of attacks exists due to a reduction of the plasma concentrations of the anti-epileptic products. Clinical monitoring, possibly monitoring of the plasma concentrations and, if needed, adjustment of the dose of the anti-epileptic product during the administration of calcium folinate and after the discontinuation, is recommended (see also section 4.5 “Interactions”).

In the treatment of accidental overdose of folic acid antagonists, leucovorin should be administered as promptly as possible. With increasing time interval between antifolate administration (e.g. methotrexate) and leucovorin rescue the effectiveness of leucovorin in counteracting toxicity decreases. Monitoring of the serum methotrexate concentration is essential in determining the optimal dose and duration of treatment with leucovorin. Delayed methotrexate excretion may be caused by third space fluid accumulation (i.e., ascites, pleural effusion), renal insufficiency, inadequate hydration or non steroidal anti inflammatory or salicylates drug administration. Under such circumstances, higher doses of leucovorin or prolonged administration may be indicated.

Leucovorin has no effect on non-haematological toxicities of methotrexate such as the nephrotoxicity resulting from drug and/or metabolite precipitation in the kidney.

Calcium folinate / 5-fluorouracil

Calcium folinate can potentiate the toxicity profile of 5-fluorouracil, especially in elderly or weakened patients. The most frequent symptoms are leucopenia, mucositis, stomatitis and/or diarrhoea, which can be dose limiting. If calcium folinate and 5-fluorouracil are used in combination, the dose of 5-fluorouracil, in case of toxicity, must be reduced more than if only 5-fluorouracil is used.

A combination therapy of 5-fluorouracil / calcium folinate may not be started or continued in patients with symptoms of gastro-intestinal toxicity, regardless of the severity, until all these symptoms are completely resolved.

Because diarrhoea can be a sign of gastro-intestinal toxicity, patients with diarrhoea must be carefully monitored until the symptoms have disappeared completely, because a rapid clinical decline, possibly lethal, can occur. If diarrhoea and/or stomatitis occur it is recommended to reduce the dose of 5-fluorouracil until the symptoms have disappeared completely. Especially elderly patients and patients with a low degree of physical functioning due to their illness are susceptible for this toxicity. For that reason extreme caution is needed for the treatment of these patients. .(See also Contraindications)

It is recommended to start with a reduced dose of 5-fluorouracil in elderly patients and in patients who have undergone a preliminary radio-therapy.

Calcium folinate may not be mixed with 5-fluorouracil in the same intravenous injection or infusion.

The calcium concentrations must be followed in patients treated with the combination 5-fluorouracil / calcium folinate, and calcium supplements must be administered if the calcium concentrations are low.

Calcium folinate / methotrexate

See the SmPC of methotrexate for the specific details on the reduction of the toxicity of methotrexate.

Calcium folinate does not have an effect on the non-haematological toxicity of methotrexate, like the nephrotoxicity as a result of methotrexate and/or a metabolic deposit in the kidneys. Reversible renal failure and all toxicities associated with methotrexate can occur in patients with a delayed premature elimination of methotrexate (see Module 1.3.1 of methotrexate). The presence of a pre-existing or by methotrexate induced renal insufficiency can involve a delayed excretion of methotrexate and may require higher doses or a more long-term use of calcium folinate.

Excessive doses of calcium folinate must be avoided as this can reduce the anti-tumoral activity of methotrexate, especially in tumours of the central nervous system where calcium folinate accumulates after repeated administration.

Resistance to methotrexate as a result of a reduced membrane transport also implies resistance against a rescue treatment with folinic acid, as both products make use of the same transport system.

An accidental overdose with a folate antagonist like methotrexate must be treated like a medical emergency. As the time interval between the administration of methotrexate and the calcium folinate rescue becomes greater, the effect of calcium folinate to counteract the toxicity is reduced.

The possibility that the patient takes other medicines that interact with methotrexate (for instance medicinal products that interfere with the elimination of methotrexate or its binding to serum albumin) should always be considered if abnormal laboratory values or clinical toxicity are observed.

This medicinal product contains 0.16 mmol (= 3.6 mg) of sodium per ml after dilution. Caution is needed in patients with a controlled sodium diet.

4.5 Interactions with other medicinal products and other forms of interaction

Leucovorin is an antidote of folic acid antagonists - e.g. methotrexate. Following the use of methotrexate, leucovorin overdose may lead to a loss of the effect of methotrexate therapy ("over-rescue").

Concomitant use of leucovorin counteracts the antineoplastic activity of methotrexate and increases the cytotoxic effects of fluorouracil.

If calcium folinate is administered in combination with a folic acid antagonist (for instance cotrimoxazole, pyrimethamine) the efficacy of the folic acid antagonist may be reduced or completely neutralised.

Calcium folinate can reduce the effect of anti-epileptics like phenobarbital, primidone, phenytoin and succinimides and can increase the frequency of the attacks (a reduction of the plasma concentrations of enzyme inducing anti-convulsants can be observed because the liver metabolism is increased as folates are one of the co-factors)(see also sections 4.4 and 4.8).

Concomitant administration of calcium folinate and 5-fluorouracil appeared to increase the efficacy and the toxicity of 5-fluorouracil (see sections 4.2, 4.4 and 4.8).

4.6 Pregnancy and lactation

Pregnancy
No adequate and well-controlled clinical studies were performed in pregnant or breast-feeding women. No formal toxicity studies with calcium folinate were performed on the reproduction in animals. There are no indications that folic acid has toxic effects in case of administration during the pregnancy.
During pregnancy methotrexate may only be administered in strict indications, whereby the benefit of the product for the mother must be weighed against the possible risks to the foetus. If a treatment with methotrexate or other folate antagonists takes place despite a pregnancy or breast-feeding, there are no limits on the use of calcium folinate to reduce the toxicity or counteract the effects.

The use of 5-fluorouracil is generally contra-indicated during the pregnancy and is contra-indicated during the period of breast-feeding; this is also applicable for the combined use of calcium folinate and 5-fluorouracil.
See also the Summary of Product Characteristics of medicinal products that contain methotrexate, other folate antagonists and 5-fluorouracil.

Breast-feeding
It is not known if calcium folinate is excreted in the breast milk. Calcium folinate can be used during the period of breast-feeding if it is deemed necessary according to therapeutic indications.

4.7 Ability to drive and use machines

There are no indications that calcium folinate has an effect on the ability to drive or operate machines.

4.8 Undesirable effects

Both therapeutic indications:
Immune system disorders
Very rarely, including incidental reports (0.01% and less)
Allergic reactions, including anaphylactoid reactions and urticaria.

Psychic disorders
Rarely (0.1% or less, but more than 0.01%)
Insomnia, agitation and depression after high doses.

Gastro-intestinal system disorders
Rarely (0.1% or less, but more than 0.01%)
Gastro-intestinal complaints after high doses.

Nervous system disorders
Rarely (0.1% or less, but more than 0.01%)
Increased frequency of attacks in epileptics (see also section 4.5 "Interactions with other medicinal products and other forms of interaction").

General disorders and administration site disorders
Uncommon (1% or less, but more than 0.1%)
Fever has been reported after the administration of calcium folinate as a solution for injection.

Combination therapy with 5-fluorouracil:
The safety profile is generally dependent on the applicable administration schedule of 5-fluorouracil due to the increase of the toxicity induced by 5-fluorouracil.

Monthly schedule:

Gastro-intestinal system disorders
Very common (more than 10%)
Nausea and vomiting.

General disorders and administration site disorders
Very common (more than 10%)
(Severe) toxicity at the level of the mucous membranes.

No increase of other toxicities induced by 5-fluorouracil (like neurotoxicity).

Weekly schedule:

Gastro-intestinal system disorders
Very common (more than 10%)
Diarrhoea with high degrees of toxicity, and dehydration, leading to hospitalisation 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 to the Ministry of Health according to the National Regulation by using an online form (http://forms.gov.il/globaldata/getsequence/getsequence.aspx?formType=AdversEffectMedic@moh.health.gov.il) or by email (adr@MOH.HEALTH.GOV.IL).

4.9 Overdose

No sequelae were reported in patients who had received significantly more calcium folinate than the recommended dose. Excessive amounts of calcium folinate can neutralise the chemotherapeutic effect of folic acid antagonists though.

In case of an overdose of the combination 5-fluorouracil and calcium folinate, the guidelines for an overdose with 5-fluorouracil must be followed.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: agents for detoxification of anti-neoplastic treatments.
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 the synthesis of nucleic acids.

Calcium folinate is frequently used for the reduction of the toxicity and the counteracting of the activity of folate antagonists like methotrexate. Calcium folinate and folate antagonists share the same membrane transport carrier and are in competition for transport in the cells, through which the outflow of folate antagonist is stimulated. It also protects the cells from the effects of folate antagonists through repletion of the reduced folate pool. Calcium folinate functions as pre-reduced source of H4-folate, thus it can also bypass the blockage of folate antagonists and form a source for the various co-enzyme forms of folic acid.

Calcium folinate is also frequently used in the biochemical modulation of fluoropyridine (5-FU) for increasing the cytotoxic activity. 5-FU inhibits thymidylate synthase (TS) an essential enzyme involved in the biosynthesis of pyrimidine, and calcium folinate increases the inhibition of TS by increasing the intracellular folate pool, through which the complex 5-FU-TS is stabilised and the activity increased.

Finally calcium folinate can be administered intravenously for the prevention and the treatment of a folate deficiency if it cannot be prevented or corrected by the administration of folic acid via the oral route. This may be the case with a total parenteral nutrition and with severe malabsorption disorders. It is also indicated for the treatment of megaloblastic anaemia as a result of folic acid deficiency if an oral administration is not possible.

5.2 Pharmacokinetic properties

Absorption
After an intramuscular administration of the watery solution, the systemic availability is equivalent to an intravenous administration. Lower peak serum concentrations (Cmax) are reached though.

Metabolism
Calcium folinate is a racemic mixture in which the L-form (L-5-formyl tetrahydrofolate, L-5-formyl-THF) is the active enantiomer.
The most important metabolite of folinic acid is 5-methyl-tetrahydrofolic acid (5-methyl-THF) which is primarily produced in the liver and in the intestinal mucous membrane.

Distribution
The distribution volume of folinic acid is unknown.
Peak serum concentrations of the parent substance (D/L-5-formyl tetrahydrofolic acid, folinic acid) are reached 10 minutes after the intravenous administration.
The AUC for L-5-formyl-THF and 5-methyl-THF were resp. 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 concentrations than the L-5-formyl tetrahydrofolate.

Elimination
The elimination half-life is resp. 32-35 minutes for the active L-form and 352-485 minutes for the inactive D-form.
The total terminal half-life of the active metabolites is approximately 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 no preclinical data considered relevant to the clinical safety, aside from the data included in other parts of the SmPC text.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium chloride, sodium hydroxide (for pH adjustment), hydrochloric acid (for pH adjustment)

6.2 incompatibilities:
Leucovorin 50mg should not be mixed with other medicinal products, unless compatibility has satisfactory been shown.

Incompatibilities were reported between injectable forms of calcium folinate and injectable forms of droperidol, fluorouracil, foscarnet and methotrexate,

Droperidol
1. Droperidol 1.25mg/0.5ml and calcium folinate 5mg/0.5ml, immediate deposit with direct mixing in syringe for 5 minutes at 25^0C, followed by 8 minutes of centrifuging.
2. Droperidol 2.5mg/0.5ml with calcium folinate 10mg/0.5ml, immediate deposit if the products are injected sequentially in a Y-form site without flushing the Y-branch between injections.

Fluorouracil
Calcium folinate may not be mixed in the same infusion with 5-fluorouracil because a deposit can occur. Fluorouracil 50mg/ml and calcium folinate 20mg/ml, with or without dextrose 5% in water, appear incompatible with mixing with different quantities and stored at 4^0C, 23^0C or 32^0C in containers in polyvinyl chloride.

Foscarnet
Foscarnet 24mg/ml and calcium folinate 20mg/ml: formation of a yellow cloudy solution has been reported.

6.3 Shelf life after the first opening of the bottle (vial)
Only for single administration. Any unused portion of the reconstituted solution must be discarded immediately after the first use.

The reconstituted product with water for injections is physical-chemically stable for 24 hours at 15-25^{0}C.

From a microbiological point of view, unless the method of opening/reconstitution/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 the user.

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 15-25^{0}C.

From a microbiological point of view, unless the method of opening/reconstitution/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 the user.

Normally the term in the last case is no longer than 24 hours at 2-8^{0}C, unless dilution took place under controlled and validated aseptical conditions.

6.4 Special precautions for storage

Store below 25°C. Protect from light (Keep in original container). Do not refrigerate.

6.5 Nature and contents of container

Clear glass injection bottles (vials) provided with bromobutyl rubber stopper, with an aluminium seal provided with a polypropylene disc.

Leucovorin powder for solution for injection contains calcium folinate equivalent to 50 mg of folinic acid.

Leucovorin powder for solution for injection is packed in a vials of 13.5 ml in packs of 1 or 50 vials.

Not all mentioned package sizes are marketed.

6.6 instructions for use and handling
Leucovorin 50mg should be dissolved by adding 12 to 50 ml of sterile water for injections to a concentration of 10mg folinic acid per ml. Further dilution with 0.9% NaCl solution to a concentration of 0.5mg of folinic acid per ml is possible.

7. DRUG REGISTRATION No.:
032 59 22206 05

7. MANUFACTURER
Pharmachemie B.V.,
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For
Abic Ltd Teva Group

8. LICENCE HOLDER
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