SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Calcium Folinate 3 mg/mL Injection.

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each vial of 1 ml solution contains 3 mg/ml of folinic acid provided as calcium folinate.

For excipients, see 6.1.

3 PHARMACEUTICAL FORM

Solution for Injection.

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

Calcium folinate is indicated

a) 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 know as “Calcium Folinate Rescue”;

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.

Calcium folinate rescue in methotrexate therapy:
Since the calcium folinate rescue dosage regimen depends heavily on the posology and method of the intermediate-or high-dose methotrexate
administration, the methotrexate protocol will dictate the dosage regimen of calcium folinate rescue. Therefore, it is best to refer to the applied intermediate or high dose methotrexate protocol for posology and method of administration of calcium folinate.

The following guidelines may serve as an illustration of regimens used in adults, elderly and children:

**Calcium folinate rescue has to be performed by parenteral administration in patients with malabsorption syndromes or other gastrointestinal disorders where enteral absorption is not assured. Dosages above 25-50 mg should be given parenterally due to saturable enteral absorption of calcium folinate.**

Calcium folinate rescue is necessary when methotrexate is given at doses exceeding 500 mg/m² body surface and should be considered with doses of 100 mg – 500 mg/m² body surface.

Dosage and duration of calcium folinate rescue primarily depend on the type and dosage of methotrexate therapy, the occurrence of toxicity symptoms, and the individual excretion capacity for methotrexate. As a rule, the first dose of calcium folinate is 15 mg (6-12 mg/m²) to be given 12-24 hours (24 hours at the latest) after the beginning of methotrexate infusion. The same dose is given every 6 hours throughout a period of 72 hours. After several parenteral doses treatment can be switched over to the oral form.

In addition to calcium folinate administration, measures to ensure the prompt excretion of methotrexate (maintenance of high urine output and alkalinisation of urine) are integral parts of the calcium folinate rescue treatment. Renal function should be monitored through daily measurement 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 >0.5µmol/l, calcium folinate dosages should be adapted according to the following table:

<table>
<thead>
<tr>
<th>Residual methotrexate blood level 48 hours after the start of the methotrexate administration:</th>
<th>Additional calcium folinate to be administered every 6 hours for 48 hours or until levels of methotrexate are lower than 0.05 µmol/l:</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt; 0.5 µmol/l</td>
<td>15 mg/m²</td>
</tr>
<tr>
<td>&gt; 1.0 µmol/l</td>
<td>100 mg/m²</td>
</tr>
<tr>
<td>&gt; 2.0 µmol/l</td>
<td>200 mg/m²</td>
</tr>
</tbody>
</table>

**Antidote to the folic acid antagonists trimetrexate, trimethoprim, and pyrimethamine:**

Trimetrexate toxicity:

- Prevention: Calcium folinate should be administered every day during treatment with trimetrexate and for 72 hours after the last dose of trimetrexate. Calcium folinate can be administered either by the intravenous route at a dose of 20 mg/m² for 5 to 10 minutes every 6 hours
for a total daily dose of 80 mg/m², or by oral route with four doses of 20 mg/m² administered at equal time intervals. Daily doses of calcium folinate should be adjusted depending on the haematological toxicity of trimetrexate.

- Overdosage (possibly occurring with trimetrexate doses above 90 mg/m² without concomitant administration of calcium folinate): after stopping trimetrexate, calcium folinate 40 mg/m² IV every 6 hours for 3 days.

Trimethoprim toxicity:
- After stopping trimethoprim, 3-10 mg/day calcium folinate until recovery of a normal blood count.

Pyrimethamine toxicity:
- In case of high dose pyrimethamine or prolonged treatment with low doses, calcium folinate 5 to 50 mg/day should be simultaneously administered, based on the results of the peripheral blood counts.

4.3. Contraindications

- Known hypersensitivity to calcium folinate, or to any of the excipients.
- Pernicious anaemia or other anaemias due to vitamin B₁₂ deficiency.

Regarding the use of calcium folinate with methotrexate during pregnancy and lactation, see section 4.6, “Pregnancy and Lactation” and the summaries of product characteristics for methotrexate – 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 folic acid has been administered intrathecally following intrathecal overdose of methotrexate death has been reported.

General

Calcium folinate should be used with methotrexate 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 B₁₂ 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 Interactions).

**Calcium folinate/methotrexate**

For specific details on reduction of methotrexate toxicity refer to the SPC 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 SPC 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 dose 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 (eg, medications which may interfere with methotrexate elimination or binding to serum albumin) should always be considered when laboratory abnormalities or clinical toxicities are observed.

### 4.5. Interactions 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 the efficacy and toxicity of 5-fluorouracil.

4.6. 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.

Please refer also to the summaries of product characteristics for methotrexate-, other folate antagonists-containing medicinal products.

Lactation

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

Immune system disorders
Very rare (<0.01%): allergic reactions, including anaphylactic reactions and urticaria.

Psychiatric disorders
Rare (0.01-0.1%): insomnia, agitation and depression after high doses.
Gastrointestinal disorders
*Rare* (0.01-0.1%): gastrointestinal disorders after high doses.

Neurological disorders
*Rare* (0.01-0.1%): increases in the frequency of attacks in epileptics (see also section 4.5 Interactions…).

General disorders and administration site conditions
*Uncommon* (0.1-1%): fever has been observed after administration of calcium folinate as solution for injection.

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.

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 reduce 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.

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 ($C_{\text{max}}$) 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 i.v. 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 no preclinical data considered relevant to clinical safety beyond data included in other sections of the SPC.

6. PHARMACEUTICAL PARTICULARS

6.1. List of excipients
Sodium Chloride
Water for Injections
6.2. Incompatibilities

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

Product as packaged for sale: 24 months.

In use: From a microbial point of view, the product should be used immediately. 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 to 8°C.

6.4. Special precautions for storage

Store in a refrigerator (+2°C to +8°C).

Store ampoules in the outer carton in order to protect from light.

6.5. Nature and contents of container
Clear 1ml Type I Glass Ampoules. Presented in packs of 5 ampoules.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

Prior to administration, calcium folinate should be inspected visually. The solution for injection or infusion should be a clear and yellowish solution. If cloudy in appearance or particles are observed, the solution should be discarded. Calcium folinate solution for injection or infusion is intended only for single use. Any unused portion of the solution should be disposed of in accordance with the local requirements.

7 MARKETING AUTHORISATION HOLDER

Hospira UK Limited
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Honey Lane
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SL6 6RJ
United Kingdom

8. MARKETING AUTHORISATION NUMBER

PL 04515/0032.

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORIZATION

08/11/2005

10 DATE OF REVISION OF THE TEXT

01/09/2016