CALCIUM FOLINATE 10 MG/ML SOLUTION FOR INJECTION
PL 05041/0021

UKPAR

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LAY SUMMARY

On 9th June 2010, the MHRA granted Hameln Pharmaceuticals GmbH a Marketing Authorisation (licence) for the medicinal product Calcium Folinate 10mg/ml Solution for Injection (PL 05041/0021). This product is available as a prescription-only medicine (POM) and is used to:
- reduce the harmful effects of some anticancer drugs such as methotrexate.
- increase the effectiveness of the anticancer drug 5-fluorouracil.

Calcium folinate belongs to a group of medicines called detoxifying agents that are used in cancer treatment to reduce the toxic side-effects of some medications, such as methotrexate.

No new or unexpected safety concerns arose from this application and it was, therefore, judged that the benefits of taking Calcium Folinate10mg/ml Solution for Injection outweigh the risks, hence a Marketing Authorisation has been granted.
CALCIUM FOLINATE 10 MG/ML SOLUTION FOR INJECTION
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SCIENTIFIC DISCUSSION

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INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the UK granted a marketing authorisation for the medicinal product Calcium Folinate 10mg/ml Solution for Injection (PL 05041/0021) to Hameln Pharmaceuticals GmbH on 9th June 2010.

This product is prescription-only medicine (POM) to:
- diminish the toxicity and counteract the action of folic acid antagonists such as methotrexate in cytotoxic therapy ("Calcium Folinate Rescue"), and overdose in adults and children,
- in combination with 5-fluorouracil to enhance cytotoxic activity.

This is a national abridged application for Calcium Folinate 10mg/ml Solution for Injection submitted under Article 10(1) of Directive 2001/83/EC, as amended. The application claims to be a generic medicinal product of Lederfolin 10mg/ml Solution for Injection or Infusion (PL 00095/0274), which was originally granted a marketing authorisation to Cyanamid of Great Britain Ltd on 18th June 1993.

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.
PHARMACEUTICAL ASSESSMENT

DRUG SUBSTANCE
Nomenclature
rINN: Calcium folinate
Chemical Name: (2S)-2-[[4-[(6RS)-2-amino-5-formyl-5,6,7,8-tetrahydro-4-hydroxypteridin-6-yl]methylamino]benzamido]glutarate.

Chemical Structure:

![Chemical Structure Image]

Molecular Formula: C_{20}H_{22}CaN_{7}O_{7} \cdot H_{2}O
Molecular Weight: 511.5
CAS No.: 1492-18-8

All aspects of the manufacture and control of the active substance are covered by a European Directorate for the Quality of Medicines (EDQM) certificate of suitability.

Appropriate stability data have been generated, supporting a suitable retest period for active calcium folinate when stored in the proposed packaging.

DRUG PRODUCT
Other ingredients
Other ingredients consist of pharmaceutical excipients, namely sodium chloride, sodium hydroxide, nitrogen and water for injections.

All excipients are controlled to their respective European Pharmacopoeia specifications. Satisfactory Certificates of Analysis have been provided for all excipients.

None of the excipients used contain materials of animal or human origin. No genetically modified organisms (GMO) have been used in the preparation of this product.

Pharmaceutical development
The objective of the product development programme was to produce a stable parenteral single-use product with a high concentration of calcium folinate in liquid form.
**Manufacture**
A description and flow-chart of the manufacturing method has been provided. In-process controls are satisfactory based on process validation data and controls on the finished product. Process validation has been carried out on batches of product. The results appear satisfactory.

**Finished product specification**
The finished product specification is satisfactory. Test methods have been described and have been adequately validated, as appropriate. Batch data have been provided and comply with the release specification. Certificates of Analysis have been provided for any working standards used.

**Container Closure System**
The solution is contained in a Type I glass vial with bromobutyl rubber stopper and aluminium flip-off closure, containing 5 ml, 10 ml, 20 ml, 35 ml, 50 ml or 100 ml solution for injection/infusion. These are packed into cartons in pack sizes of 1, 5 or 10 vials per carton.

Specifications and Certificates of Analysis for all packaging have been provided. These are satisfactory. The primary packaging has been shown to comply with guidelines concerning materials in contact with parenteral products.

**Stability**
Finished product stability studies have been conducted in accordance with current guidelines. Based on the results, a shelf-life of 24 months for unopened vials has been set, with the storage conditions “Store at 2°C–8°C (in a refrigerator)” and “Keep the vial in the outer carton in order to protect from light”.

After first opening, the product is recommended for single-dose use only. Any unused product should be discarded immediately after initial use.

After dilution, from a microbiological viewpoint, 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 be no longer than 24 hours at 2°C–8°C, unless dilution has taken place in controlled and validated aseptic conditions.

**Bioequivalence**
As this is a parenteral solution, bioequivalence data are not necessary to support this application. This is acceptable and in line with the Committee for Proprietary Medicinal Products Notes for Guidance on the Investigation of Bioavailability and Bioequivalence (CPMP/EWP/QWP/1401/98).
Summary of Product Characteristics (SmPC), Patient Information Leaflet (PIL) and Labelling
The SmPC, PIL and labelling are pharmaceutically satisfactory.

The applicant has submitted results of PIL user testing. The results indicate that the PIL is well-structured and organised, easy to understand and written in a comprehensive manner. The test shows that the patients/users are able to act upon the information that it contains.

Marketing Authorisation Application Form
The MAA form is pharmaceutically satisfactory.

Expert Report
The pharmaceutical expert report is written by an appropriately qualified person and is a suitable summary of the pharmaceutical aspects of the dossier.

Conclusion
It is recommended that a Marketing Authorisation is granted for this application.
PRECLINICAL ASSESSMENT

The pharmacodynamic, pharmacokinetic and toxicological properties of calcium folinate are well-known. Thus, the applicant has not provided additional studies and further studies are not required.

A preclinical expert report has been provided, written by an appropriately qualified person. This is satisfactory.
CLINICAL ASSESSMENT

PHARMACOKINETICS
No new data have been submitted and none are required for an application of this type. This application is for a generic medicinal product of Lederfolin 10mg/ml Solution for Injection or Infusion (PL 00095/0274). The use of the reference product is well-established in the UK, and both products contain the same quantitative and qualitative composition of the active substance, calcium folinate.

According to Committee for Proprietary Medicinal Products Notes for Guidance on the Investigation of Bioavailability and Bioequivalence, the applicant is not required to submit a bioequivalence study if the product is to be administered as an aqueous intravenous solution containing the same active substance, in the same concentration as the currently authorised product (CPMP/EWP/1401/98, sub point 5.1.6, Parenteral solution).

PHARMACODYNAMICS
No new data have been submitted and none are required for an application of this type.

EFFICACY
No new data have been submitted and none are required for an application of this type.

SAFETY
No new data have been submitted and none are required for an application of this type.

EXPERT REPORT
The clinical expert report has been written by an appropriately qualified person and is a suitable summary of the clinical aspects of the dossier.

SUMMARY OF PRODUCT CHARACTERISTICS
This is satisfactory.

PATIENT INFORMATION LEAFLET
This is satisfactory.

LABELLING
These are satisfactory.

MAA
This is satisfactory.

CONCLUSION
The grant of a Marketing Authorisation is recommended.
OVERALL CONCLUSION AND BENEFIT/RISK ASSESSMENT

QUALITY
The important quality characteristics of Calcium Folinate 10mg/ml Solution for Injection are well-defined and controlled. The specifications and batch analytical results indicate consistency from batch to batch. There are no outstanding quality issues that would have a negative impact on the benefit/risk balance.

PRECLINICAL
No new preclinical data were submitted and none are required for an application of this type.

EFFICACY
This application is for a generic medicinal product of Lederfolin 10mg/ml solution for injection or infusion. The use of the reference product is well-established in the UK. Both products contain the same quantitative and qualitative composition of the active ingredient, calcium folinate.

According to Committee for Proprietary Medicinal Products Notes for Guidance on the Investigation of Bioavailability and Bioequivalence, the applicant is not required to submit a bioequivalence study if the product is to be administered as an aqueous intravenous solution containing the same active substance, in the same concentration as the currently authorised product (CPMP/EWP/1401/98, sub point 5.1.6, Parenteral solution).

No new safety data are supplied or required for this generic application. Calcium folinate has well-established side-effect profile and is generally well-tolerated.

The SPC, PIL and labelling are satisfactory.

BENEFIT/RISK ASSESSMENT
The quality of the product is acceptable and no new preclinical or clinical safety concerns have been identified. Extensive clinical experience with calcium folinate is considered to have demonstrated the therapeutic value of the compound. The benefit/risk balance is considered to be positive.
## STEPS TAKEN FOR ASSESSMENT

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<td>1</td>
<td>The MHRA received the marketing authorisation applications on 25&lt;sup&gt;th&lt;/sup&gt; March 2002</td>
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<td>2</td>
<td>Following standard checks and communication with the applicant the MHRA considered the applications valid on 10&lt;sup&gt;th&lt;/sup&gt; April 2002</td>
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<td>Following assessment of the application the MHRA requested further information on 27&lt;sup&gt;th&lt;/sup&gt; May 2002, 18&lt;sup&gt;th&lt;/sup&gt; March 2003, 8&lt;sup&gt;th&lt;/sup&gt; February 2006, 20&lt;sup&gt;th&lt;/sup&gt; December 2006, 12&lt;sup&gt;th&lt;/sup&gt; September 2008 and 21st December 2009.</td>
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<td>4</td>
<td>The applicant responded to the MHRA’s requests, providing further information on 14&lt;sup&gt;th&lt;/sup&gt; June 2004, 21&lt;sup&gt;st&lt;/sup&gt; September 2004, 29&lt;sup&gt;th&lt;/sup&gt; August 2006, 24&lt;sup&gt;th&lt;/sup&gt; May 2007, 12&lt;sup&gt;th&lt;/sup&gt; March 2009 and 11 January 2010.</td>
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<td>5</td>
<td>The application was determined on 9&lt;sup&gt;th&lt;/sup&gt; June 2010</td>
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CALCIUM FOLINATE 10 MG/ML SOLUTION FOR INJECTION
PL 05041/0021

STEPS TAKEN AFTER AUTHORISATION - SUMMARY

<table>
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<tr>
<th>Date submitted</th>
<th>Application type</th>
<th>Scope</th>
<th>Outcome</th>
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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 is a mixture of the two enantiomers, the bioactive (S)-folinate and the inactive (R)-folinate.

1 ml of Calcium Folinate 10 mg/ml Solution for Injection contains 10.8 mg of Calcium Folinate, equivalent to 10.0 mg of folinic acid.

5 ml solution contains 54 mg Calcium Folinate, equivalent to 50 mg folinic acid.
10 ml solution contains 108 mg Calcium Folinate, equivalent to 100 mg folinic acid.
20 ml solution contains 216 mg Calcium Folinate, equivalent to 200 mg folinic acid.
35 ml solution contains 378 mg Calcium Folinate, equivalent to 350 mg folinic acid.
50 ml solution contains 540 mg Calcium Folinate, equivalent to 500 mg folinic acid.
100 ml solution contains 1080 mg Calcium Folinate, equivalent to 1000 mg folinic acid.

For a full list of excipients, see section 6.1

3 PHARMACEUTICAL FORM
Solution for injection or infusion.

The solution is a clear yellow solution, practically 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
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 10 mg/ml Solution for Injection may be diluted with 0.9% Sodium Chloride Injection or 5% Glucose Injection 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 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:

<table>
<thead>
<tr>
<th>Residual methotrexate blood level 48 hours after the start of 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>≥ 0.5 µmol/l</td>
<td>15 mg/m²</td>
</tr>
<tr>
<td>≥ 1.0 µmol/l</td>
<td>100 mg/m²</td>
</tr>
<tr>
<td>≥ 2.0 µmol/l</td>
<td>200 mg/m²</td>
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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 200 mg/m² by intravenous infusion over two hours, followed by bolus 400 mg/m² of 5-FU and 22-hour infusion of 5-FU (600 mg/m²) for 2 consecutive days, every 2 weeks on days 1 and 2.

**Weekly regimen**: Calcium folinate 20 mg/m² by bolus i.v. injection or 200 to 500 mg/m² as i.v. infusion over a period of 2 hours plus 500 mg/m² 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/m² by bolus i.v. injection or 200 to 500 mg/m² as i.v. infusion over a period of 2 hours immediately followed by 425 or 370 mg/m² 5-fluorouracil as i.v. bolus injection during five consecutive days.

For the combination therapy with 5-fluorouracil, modification of 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, trimethoprime, 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.

Trimethoprime toxicity:
- After stopping trimethoprime, 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 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

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 or 5-fluorouracil 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, mercaptopurine, thioguanine). Such macrocytosis should not be treated with folinic acid.

In epileptic patients treated with phenobarbital, phenytoine, 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).

The use of diluting infusion fluids containing sodium should be borne in mind when treating patients requiring a restricted sodium intake.

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-FU 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.

**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 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 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.

**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. co-trimoxazole, 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, phenytoine, 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, 4.4 and 4.8).
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 weighted 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 breast-feeding; 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.

**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
**Both therapeutic indications:**

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

**Psychiatric disorders**
Rare (0.01 – 0.1 %): insomnia, agitation and depression after high doses

**Nervous system disorders**
Rare (0.01 – 0.1 %): increase in the frequency of attacks in epileptics (see also section 4.5 Interaction...).

**Gastrointestinal disorders**
Rare (0.01 – 0.1 %): gastrointestinal disorders after high doses.

**General disorders and administration site conditions**
Uncommon (0.1 – 1 %): fever has been observed 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:

**Monthly regimen:**
Gastrointestinal disorders
Very common (>10%): vomiting and nausea
General disorders and administration site conditions
Very common (>10%): (severe) mucosal toxicity.
No enhancement of other 5-fluorouracil induced toxicities (e.g. neurotoxicity).

**Weekly regimen:**
Gastrointestinal disorders
Very common (>10%): diarrhoea with higher grades of toxicity, and dehydration, resulting in hospital admission for treatment and even death.
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.

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.

Calcium folinate is also frequently used in the biochemical modulation of fluoropyridine (5-FU) to enhance its cytotoxic activity. 5-FU 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 5FU-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

Absorption

Following intramuscular administration of the aqueous solution, systemic availability is comparable to an intravenous administration. However, lower peak serum levels (Cmax) 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-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 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
Sodium hydroxide (for pH-adjustment)
Water for injections
Nitrogen

6.2 Incompatibilities
All forms of mixed infusions should be avoided. Calcium folinate solution should not be mixed with any other drug, unless compatibility has been satisfactorily demonstrated.

In particular, calcium folinate solution should not be mixed in the same infusion as fluorouracil because a precipitate may form.

Incompatibilities have been reported between injectable forms of calcium folinate and injectable forms of droperidol, fluorouracil, foscarnet, methotrexate and sodium bicarbonate.

6.3 Shelf life
Unopened vials: 24 months
After first opening: For Single Dose Use Only. Discard any unused solution immediately after initial use.

After dilution:
When diluted according to directions with 0.9% Sodium Chloride Injection or 5% Glucose Injection, chemical and physical in-use stability has been demonstrated when protected from light.

Chemical and physical in-use stability of Calcium Folinate Solution for Injection after dilution to 1.5 mg/ml with either 0.9% Sodium Chloride Injection or 5% Glucose Injection was demonstrated for up to 96 hours, at both room temperature and 2-8° C, when protected from light.

Chemical and physical in-use stability of Calcium Folinate Solution for Injection after dilution to 0.2 mg/ml with 0.9% Sodium Chloride Injection was demonstrated for up to 24 hours at 2-8° C, when protected from light.

From a microbiological 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 2-8° C, unless dilution has taken place in controlled and validated aseptic conditions.

6.4 Special precautions for storage
Store at 2° C – 8° C (in a refrigerator).
Keep the vial in the outer carton in order to protect from light.
6.5 Nature and contents of container
Colourless, neutral, Ph Eur Type I glass vial, with bromobutyl rubber stopper and aluminium flip-off closure, containing 5 ml, 10 ml, 20 ml, 35 ml, 50 ml or 100 ml solution for injection/infusion.

Original pack containing 1 (5 / 10) vial(s) of 5 ml (each).
Original pack containing 1 (5 / 10) vial(s) of 10 ml (each).
Original pack containing 1 (5 / 10) vial(s) of 20 ml (each).
Original pack containing 1 (5 / 10) vial(s) of 35 ml (each).
Original pack containing 1 (5 / 10) vial(s) of 50 ml (each).
Original pack containing 1 (5 / 10) vial(s) of 100 ml (each).

Not all pack sizes may be marketed.

6.6 Special precautions for disposal
Calcium Folinate Solution for Injection or Infusion is intended only for single use. Discard any unused solution immediately after initial use and also if precipitation occurs following dilution.

Prior to administration, Calcium Folinate Injection should be visually inspected. 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.

The administration of calcium folinate depends on the individual dosage regime.

For slow intravenous infusion, Calcium Folinate Injection may be diluted with 0.9% Sodium Chloride Injection to give a final concentration within the range of 1.5 mg/ml to 0.2 mg/ml folinic acid, and with 5% Glucose Injection to give a final concentration of 1.5 mg/ml. The infusion rate should not exceed 160 mg of calcium folinate per minute. (For further instructions please see also section 4.2.).

For in-use stability of the prepared infusion solutions, please see section 6.3.

Any unused product or waste material should be disposed of in accordance with local requirements.
UKPAR Calcium Folinate 10mg/ml Solution for Injection PL 05041/0021

PATIENT INFORMATION LEAFLET (PIL)

PACKAGE LEAFLET: INFORMATION FOR THE USER
Calcium Folinate 10 mg/ml Solution for Injection

Important Information about your medicine
- Your doctor or nurse will give you the injection.
- If the injection causes you any problems talk to your doctor, nurse or pharmacist.
- Please tell your doctor or pharmacist, if you have any other medical conditions or have an allergy to any of the ingredients of this medicine.
- Please tell your doctor or pharmacist, if you are taking any other medicines.

Read all of this leaflet carefully before you start using this medicine.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you. Do not pass it on to others. It may harm them, even if their symptoms are the same as yours.
- If any of the side effects becomes serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

The name of your medicine is Calcium Folinate 10 mg/ml Solution for Injection, which will be referred to as Calcium Folinate throughout this leaflet.

In this leaflet:
1. WHAT CALCIUM FOLINATE IS AND WHAT IT IS USED FOR
2. BEFORE YOU RECEIVE CALCIUM FOLINATE
3. HOW TO USE CALCIUM FOLINATE
4. POSSIBLE SIDE EFFECTS
5. HOW TO STORE CALCIUM FOLINATE
6. FURTHER INFORMATION

1. WHAT CALCIUM FOLINATE IS AND WHAT IT IS USED FOR

Calcium Folinate belongs to a group of medicines called folate-replenishing agents that are used in cancer treatment to reduce the toxic side effects of some medications such as methotrexate.

Calcium Folinate is used:
- to reduce the harmful effects of some anti-cancer drugs such as methotrexate.
- to increase the effectiveness of the anti-cancer drug 5-fluorouracil.

2. BEFORE YOU RECEIVE CALCIUM FOLINATE

You should NOT be given Calcium Folinate:
- If you are allergic (hypersensitive) to Calcium Folinate or any of its ingredients. An allergic reaction may include rash, itching, difficulty of breathing or swelling of the face, lips, throat or tongue.
- If you have a blood disease called anaemia that is caused by too little vitamin B12 in the body.

Take special care with Calcium Folinate:
- If you are taking medication for treatment of epilepsy.
- If you are currently suffering from diarrhoea.
- If elderly patients and weak patients are receiving combination therapy with the anticancer drug 5-fluorouracil, the toxicity risk of 5-fluorouracil is enhanced especially with gastrointestinal disorders.
- If you are receiving anticancer drugs such as hydroxyurea, cytarabine, melphalan and thiotepa because Calcium Folinate will not reduce their harmful effects.
- If your kidney function is impaired because higher doses or prolonged use of Calcium Folinate may be necessary.

Using other medicines
Please tell your doctor or pharmacist if you are taking or have recently taken any other medicines, including medicines you can get without a prescription.

This is especially important with the following medicines as Calcium Folinate may influence their effect:
- Calcium Folinate may reduce the effect of medications for the treatment of epilepsy such as phenytoin, primidone, phenobarbital, and some sulphonamides and may increase the frequency of seizures in susceptible patients.
- Calcium Folinate given together with some anti-cancer drugs such as cotrimoxazole and pyrimethamine may reduce or completely neutralize the effect of the anticancer drug.
- Calcium Folinate may enhance the effect of 5-fluorouracil.

It may still be all right for you to receive Calcium Folinate and your doctor will be able to decide what is suitable for you.

Important information about some of the ingredients of Calcium Folinate
Calcium Folinate contains 3.1 mg sodium per ml solution for injection. That has to be taken into account, if you are on a controlled sodium diet.

Children
For the treatment with Calcium Folinate in combination with 5-fluorouracil there are no data available on the use in children.

Ask your doctor if you have any further questions.

Pregnancy and breast-feeding
This medicine should only be used during pregnancy where the advantages to the individual outweigh the potential risks. Always inform your doctor if you are pregnant or planning a pregnancy before using any medicine.

It is not known if this medicine passes into breast milk.

It should be used with caution in nursing mothers, and only if the benefits to the mother outweigh any risks to the nursing infant. Ask your doctor or pharmacist for advice before taking any medicine.

Driving and using machines
There is no evidence that calcium folinate has an effect on the ability to drive or use machines.

3. HOW TO USE CALCIUM FOLINATE

Calcium Folinate must only be given by a doctor or nurse.

It can be given:
- as slow injection into a vein
- as injection into a large muscle
- as continuous infusion into a vein.

It must not be given as an injection into your spine.
The following information is intended for medical or healthcare professionals only:

**Calcium Folinate 10 mg/ml Solution for Injection**

**Instructions for use, handling**

1. 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.

2. For intravenous infusion, calcium folinate may be administered with 0.9% Sodium Chloride or 5% Glucose Injection before use. Chemical and physical in-use stability of Calcium Folinate after dilution to 1.5 mg/ml with either 0.9% Sodium Chloride Injection or 5% Glucose Injection was demonstrated for up to 96 hours, at both room temperature and 2-8°C, when protected from light. Chemical and physical in-use stability of Calcium Folinate after dilution to 0.2 mg/ml was demonstrated with 0.9% Sodium Chloride Injection over an in-use shelf life of 24 hours at 2-8°C, when protected from light. From a microbiological 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, unless dilution has taken place in controlled and validated aseptic conditions.

3. Calcium folinate solutions should not be mixed with any other drug, unless compatibility has been satisfactorily demonstrated. Due to chemical incompatibility with other calcium folinate solutions, should not be mixed with injectable forms of droperidol, fluorouracil, foscarin or methotrexate and sodium bicarbonate.

4. Prior to administration, Calcium Folinate Injection should be visually inspected. 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.

5. Calcium Folinate solution is for single dose use only. Discard any unused solution immediately after initial use and also if precipitation occurs following dilution.

6. Store the unopened vial at 2°C - 8°C in a refrigerator. Keep it in the outer carton in order to protect from light.

**Dosage**

**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 measurements of serum creatinine.

Fifteen 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:

<table>
<thead>
<tr>
<th>Residual methotrexate blood level</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>≥ 0.5 μmol/l</td>
<td>15 mg/m²</td>
</tr>
<tr>
<td>≥ 1.0 μmol/l</td>
<td>100 mg/m²</td>
</tr>
<tr>
<td>≥ 2.0 μmol/l</td>
<td>200 mg/m²</td>
</tr>
</tbody>
</table>

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 200 mg/m² by intravenous infusion over two hours, followed by bolus 400 mg/m² of 5-fluorouracil and 22-hour infusion of 5-FU (600 mg/m²) for 2 consecutive days, every 2 weeks on days 1 and 2.

**Weekly regimen**: Calcium folinate 20 mg/m² by bolus i.v. injection or 200 to 500 mg/m² as i.v. infusion over a period of 2 hours plus 500 mg/m² 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/m² by bolus i.v. injection or 200 to 500 mg/m² as i.v. infusion over a period of 2 hours immediately followed by 425 or 370 mg/m² 5-fluorouracil as i.v. bolus injection during five consecutive days.
UKPAR Calcium Folinate 10mg/ml Solution for Injection

For intravenous infusion, Calcium Folinate may be diluted according to directions with the recommended infusion fluids, 0.9% w/v Sodium Chloride Intravenous Infusion or 5% w/v Glucose Intravenous Infusion, before administration. Prior to administration, the sterile solution for injection should be visually inspected for clarity, particulate matter, discoloration and the integrity of the container. The solution should only be used if it is clear and the container is undamaged.

**Dosage.**

Your doctor will decide your correct dose of Calcium Folinate. It can be different from patient to patient (depending for example on body size and patient condition). When used in combination with anticancer drugs, the dose depends on the dose of the anticancer drug you received.

**What to do if you have received too much Calcium Folinate (overdose)**

As a doctor or nurse will be giving you your medicine, it is unlikely that you will receive an overdose. However, if you suspect an overdose warn a doctor immediately.

If you have any further questions on the use of this medicine, ask your doctor or pharmacist.

**4. POSSIBLE SIDE EFFECTS**

Like all medicines, Calcium Folinate can cause side effects, although not everybody gets them.

The frequency of side effects is classified into the following categories:

<table>
<thead>
<tr>
<th>Side Effect</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Very common</td>
<td>in more than 1 in 10 patients</td>
</tr>
<tr>
<td>Common</td>
<td>in more than 1 in 100 patients, but less than 1 in 10 patients</td>
</tr>
<tr>
<td>Uncommon</td>
<td>in more than 1 in 1,000 patients, but less than 1 in 100 patients</td>
</tr>
<tr>
<td>Rare</td>
<td>in more than 1 in 10,000 patients, but less than 1 in 1,000 patients</td>
</tr>
<tr>
<td>Very rare</td>
<td>in less than 1 in 10,000 patients, including isolated reports</td>
</tr>
<tr>
<td>Not known</td>
<td>cannot be estimated from the available data</td>
</tr>
</tbody>
</table>

The following side effects have been reported:

- Uncommon
  - fever
- Rare
  - difficulty in sleeping
  - agitation
  - depression
  - symptoms of the gastrointestinal tract caused by high doses (such as loss in appetite, nausea, distension, flatulence, bad taste in the mouth)
  - increased occurrence of epileptic seizures
- Very rare
  - allergic reactions including nettle rash (urticaria)
  - severe allergic reactions including shock, altered heart rhythms and complete airway obstruction (blockage of the breathing tubes)

**Possible side effects if you are taking Calcium Folinate to increase the effectiveness of 5-fluorouracil:**

Calcium Folinate may increase the side effects of 5-fluorouracil.

- vomiting
- nausea (being or feeling sick)
- sore mouth or lips
- diarrhoea

If you are taking 5-fluorouracil and Calcium Folinate weekly

- Very common
  - diarrhoea
  - dehydration

The above side effects may require medical intervention and some may be life-threatening or fatal.

If any of the side effects becomes serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

**5. HOW TO STORE CALCIUM FOLINATE**

Keep out of the reach of children.

Your doctor and pharmacist are responsible for the correct storage, use and disposal of Calcium Folinate.

The medicine should be stored in a refrigerator (2°C - 8°C).

Keep the vial in the outer carton in order to protect from light.

The medicine is for single use only. Any unused solution has to be discarded immediately after initial use.

For intravenous infusion, when diluted with the recommended infusion fluids, the solution should be used immediately.

This medicine must not be used after the expiry date which is stated on the packaging after „EXP“. The expiry date refers to the last day of that month.

**6. FURTHER INFORMATION**

**What Calcium Folinate contains**

Each 1 ml of Calcium Folinate contains 10.8 mg calcium folinate, equivalent to 10 mg folinic acid.

The other ingredients are water for injections, sodium hydroxide, sodium chloride, and nitrogen.

**What Calcium Folinate looks like and contents of the pack**

Calcium Folinate is a sterile, clear yellow solution, practically free from particles. It is supplied in colourless glass vials.

Each single-dose vial contains either 54 mg, 108 mg, 216 mg, 378 mg, 540 mg or 1080 mg of calcium folinate equivalent to 50 mg in 5 ml, 100 mg in 10 ml, 200 mg in 20 ml, 350 mg in 35 ml, 500 mg in 50 ml and 1000 mg in 100 ml of folinic acid, respectively.

Pack sizes:

1 (5 / 10) vial(s) containing 5 ml, 10 ml, 20 ml, 35 ml, 50 ml, or 100 ml.

Not all pack sizes may be marketed.

**Marketing Authorisation Holder and Manufacturer**

**Marketing Authorisation Holder**

haneh Pharmaceuticals GmbH,
Langes Feld 13,
31789 Hameln, Germany

**Manufacturer**

Haupt Pharma Wolfatshausen GmbH,
Pfaffendorfer Str. 5,
82615 Wolfatshausen, Germany

haneh rds a.s.,
Hrné 36,
900 01 Modra, Slovak Republic

This leaflet was last approved in 04/2010.
UKPAR Calcium Folinate 10mg/ml Solution for Injection PL 05041/0021

100 mg in 10 ml
1 x 10 ml vial
For intravenous or intramuscular administration.

1 ml solution for injection contains:
Calcium Folinate: 10.8 mg equivalent to folic acid 10.5 mg
Other ingredients:
Water for injections, sodium chloride, sodium hydroxide for pH adjustment.

Store at 2°C - 8°C in a refrigerator.
Keep the container in the outer carton in order to protect from light.

Keep out of the reach and sight of children.
Read package insert before use. Use as directed by a physician.

Batch no.
Exp. date.

Marketing authorisation holder:
hameln pharmaceuticals gmbh
Langs Feld 13, 51789 Hameln
Germany

PL 05041/0021
UKPAR Calcium Folate 10mg/ml Solution for Injection

1000 mg in 100 ml
1 x 100 ml vial
For intravenous or intramuscular administration.

1 ml solution for injection contains:
Calcium Folate: 10.8 mg equivalent to folic acid 10.0 mg
Other ingredients:
Water for injections, sodium chloride, sodium hydroxide for pH adjustment.

Store at 2°C - 8°C (in a refrigerator).
Keep the container in the outer carton in order to protect from light.
Keep out of reach and sight of children.
Read package insert before use.
Use as directed by a physician.

Batch no.: XXXXXXXX
Exp. date: 04

hameln pharmaceuticals

For single use only. Discard any unused solution immediately after initial use and also if precipitation occurs. Following dilution:

PL 05041/0021

Marketing authorisation holder:
hameln pharmaceuticals gmbh
Langes Feld 13, 31792 Hameln, Germany
UKPAR Calcium Folinate 10mg/ml Solution for Injection

PL 0541/0021

Calcium Folinate 10 mg/ml Solution for Injection

Store at 2°C - 8°C in a refrigerator. Keep the container in the outer carton until just before use; protect from light.

Keep out of the reach and sight of children.

For veterinary use only. Not for human use. Not for injection by the intramuscular route.

For veterinary use only. Not for human use. Not for injection by the intramuscular route.

Calcium Folinate 10 mg/ml Solution for Injection

10 vials containing 20 ml solution
20 ml contains 200 mg folinic acid.

For human use: intravenous/parenteral administration.

1 ml solution for injection contains: Calcium Folinate equivalent to folinic acid 10.0 mg

Other ingredients:

Water for Injections, sodium chloride, sodium hydroxide for pH adjustment.

Calcium Folinate 10 mg/ml Solution for Injection

10 vials containing 20 ml solution
20 ml contains 200 mg folinic acid.

For veterinary use only. Not for human use. Not for injection by the intramuscular route.

For veterinary use only. Not for human use. Not for injection by the intramuscular route.

Calcium Folinate 10 mg/ml Solution for Injection

10 vials containing 20 ml solution
20 ml contains 200 mg folinic acid.

For human use: intravenous/parenteral administration.

1 ml solution for injection contains: Calcium Folinate equivalent to folinic acid 10.0 mg

Other ingredients:

Water for Injections, sodium chloride, sodium hydroxide for pH adjustment.

Calcium Folinate 10 mg/ml Solution for Injection

10 vials containing 20 ml solution
20 ml contains 200 mg folinic acid.

For veterinary use only. Not for human use. Not for injection by the intramuscular route.

For veterinary use only. Not for human use. Not for injection by the intramuscular route.

Calcium Folinate 10 mg/ml Solution for Injection

10 vials containing 20 ml solution
20 ml contains 200 mg folinic acid.

For human use: intravenous/parenteral administration.

1 ml solution for injection contains: Calcium Folinate equivalent to folinic acid 10.0 mg

Other ingredients:

Water for Injections, sodium chloride, sodium hydroxide for pH adjustment.

Calcium Folinate 10 mg/ml Solution for Injection

10 vials containing 20 ml solution
20 ml contains 200 mg folinic acid.

For veterinary use only. Not for human use. Not for injection by the intramuscular route.

For veterinary use only. Not for human use. Not for injection by the intramuscular route.

Calcium Folinate 10 mg/ml Solution for Injection

10 vials containing 20 ml solution
20 ml contains 200 mg folinic acid.

For human use: intravenous/parenteral administration.

1 ml solution for injection contains: Calcium Folinate equivalent to folinic acid 10.0 mg

Other ingredients:

Water for Injections, sodium chloride, sodium hydroxide for pH adjustment.

Calcium Folinate 10 mg/ml Solution for Injection

10 vials containing 20 ml solution
20 ml contains 200 mg folinic acid.

For veterinary use only. Not for human use. Not for injection by the intramuscular route.

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10 vials containing 20 ml solution
20 ml contains 200 mg folinic acid.

For human use: intravenous/parenteral administration.

1 ml solution for injection contains: Calcium Folinate equivalent to folinic acid 10.0 mg

Other ingredients:

Water for Injections, sodium chloride, sodium hydroxide for pH adjustment.

Calcium Folinate 10 mg/ml Solution for Injection

10 vials containing 20 ml solution
20 ml contains 200 mg folinic acid.

For veterinary use only. Not for human use. Not for injection by the intramuscular route.

For veterinary use only. Not for human use. Not for injection by the intramuscular route.

Calcium Folinate 10 mg/ml Solution for Injection

10 vials containing 20 ml solution
20 ml contains 200 mg folinic acid.

For human use: intravenous/parenteral administration.

1 ml solution for injection contains: Calcium Folinate equivalent to folinic acid 10.0 mg

Other ingredients:

Water for Injections, sodium chloride, sodium hydroxide for pH adjustment.
UKPAR Calcium Folinate 10mg/ml Solution for Injection

Calcium Folinate 10 mg/ml
Solution for Injection
50 mg in 5 ml
For i.v. or i.m. administration
For single dose use only. Discard any unused solution immediately after initial use and also if precipitation occurs following dilution.
Store at 2°C - 8°C. Keep the container in the outer carton.

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Calcium Folinate 10 mg/ml
Solution for Injection
100 mg in 10 ml
For i.v. or i.m. administration
For single dose use only. Discard any unused solution immediately after initial use and also if precipitation occurs following dilution.
Store at 2°C - 8°C. Keep the container in the outer carton.

hameln pharmaceuticals gmbh

Calcium Folinate 10 mg/ml
Solution for Injection
200 mg in 20 ml
For i.v. or i.m. administration
For single dose use only. Discard any unused solution immediately after initial use and also if precipitation occurs following dilution.
Store at 2°C - 8°C. Keep the container in the outer carton.

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PL 05041/0021
Calcium Folinate 10 mg/ml
Solution for Injection

350 mg in 35 ml
For i.v. or i.m. administration
For single dose use only. Discard any unused solution immediately after initial use and also if precipitation occurs following dilution. Store at 2°C - 8°C. Keep the container in the outer carton.

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Calcium Folinate 10 mg/ml
Solution for Injection

500 mg in 50 ml
For i.v. or i.m. administration
For single dose use only. Discard any unused solution immediately after initial use and also if precipitation occurs following dilution. Store at 2°C - 8°C. Keep the container in the outer carton.

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Calcium Folinate 10 mg/ml
Solution for Injection

1000 mg in 100 ml
For i.v. or i.m. administration
For single dose use only. Discard any unused solution immediately after initial use and also if precipitation occurs following dilution. Store at 2°C - 8°C. Keep the container in the outer carton.

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