SUMMARY OF PRODUCT CHARACTERISTICS

1  NAME OF THE MEDICINAL PRODUCT

Calcium Folinate 15mg Tablets

2.  QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains Calcium Folinate (Calcium Leucovorin) equivalent to folinic acid (leucovorin) 15mg.

For excipients, see 6.1

3.  PHARMACEUTICAL FORM

Tablet.

Light yellow, round, convex, uncoated tablets. The tablets are scored and marked “CF” on one side.

4.  CLINICAL PARTICULARS

4.1  Therapeutic indications

Leucovorin (folinic acid) is the formyl derivative of tetrahydrofolic acid which is a metabolite and active form of folic acid.

Calcium Folinate is indicated in:

a)  Neutralising the immediate toxic effects of folic acid antagonists, e.g. Methotrexate.

b)  Calcium Folinate Rescue - a treatment technique using Calcium Folinate in conjunction with folic acid antagonists, e.g. methotrexate, to minimise systemic toxicity.

c)  The treatment of megaloblastic anaemias due to sprue, nutritional deficiency, pregnancy, infancy, liver disease and malabsorption syndrome.
4.2 **Posology and method of administration**

To be given orally.

Although calcium folinate may also be available as a solution for injection, Calcium Folinate should not be administered intrathecally.

**Adults and children:**

Calcium folinate rescue: Depending upon the dose of methotrexate administered, dosage regimens of calcium folinate vary. Up to 120 mg calcium folinate are generally given, usually in divided doses over 12-24 hours by intramuscular injection, bolus intravenous injection or intravenous infusion in normal saline. This is followed by 12-15 mg intramuscularly or 15 mg orally every 6 hours for 48 hours. Rescue therapy is usually started 24 hours after the commencement of methotrexate administration.

Neutralising the immediate toxic effects of folic acid antagonists: If overdosage of methotrexate is suspected, the dose of calcium folinate should be equal to or greater than the dose of methotrexate and should be administered within one hour of the methotrexate administration.

Megaloblastic anaemia (folate deficiency): One tablet of calcium folinate per day.

4.3 **Contra-indications**

Calcium Folinate is contraindicated in patients who have previously shown hypersensitivity to folinate or any of the excipients.

Calcium Folinate Injection is contraindicated in the treatment of pernicious anaemia or other megaloblastic anaemias where vitamin B12 is deficient. Its use can lead to an apparent response of the haematopoietic system, but neurological damage may occur or progress if already present.

Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take calcium folinate tablets.

4.4 **Special warnings and special precautions for use**

Calcium Folinate should only be used with methotrexate or 5-FU under the direct supervision of a clinician experienced in the use of cancer chemotherapeutic agents.

In the treatment of inadvertent overdosage of a folic acid antagonist, folinate should be administered as soon as possible; if a period exceeding 4 hours intervenes, the treatment may not be effective.
In general, Calcium Folinate should not be given simultaneously with folic acid antagonists, e.g. methotrexate, to abort clinical toxicity as the therapeutic effect of the antagonist may be nullified. However, Calcium Folinate given concurrently with folate antagonists, such as pyrimethamine and trimethoprim does not inhibit their antibacterial activity.

Parenteral administration of folinate is preferable to oral dosing following chemotherapy with folic acid antagonists if there is a possibility that the patient may vomit and not absorb the folinate.

Measures to ensure the prompt excretion of methotrexate are important as part of Calcium Folinate Rescue Therapy. These measures include:

1) Alkalinisation of urine so that the urinary pH is greater than 7.0 before methotrexate infusion (to increase solubility of methotrexate and its metabolites)

2) Maintenance of urine output of 1800-2000 cc/m²/24 hr by increased oral or intravenous fluids on days 2, 3 and 4 following methotrexate therapy.

3) Plasma methotrexate concentration, BUN and creatinine should be measured on days 2, 3 and 4.

These measures must be continued until the plasma methotrexate level is less than $10^{-7}$ molar (0.1μM).

4.5 Interaction with other medicinal products and other forms of interaction

Folinates given in large amounts may counteract the antiepileptic effect of phenobarbitone, phenytoin and primidone and increase the frequency of seizures in susceptible patients.

Caution is required during concurrent administration of Calcium Folinate with fluoropyrimidine as this has been associated with seizures and syncope (see Section 4.8).

4.6 Pregnancy and lactation

Reproduction studies have been performed in rats and rabbits at doses of at least 50 times the human dose. These studies have revealed no evidence of harm to the foetus due to Calcium Folinate. There are, however, no adequate and well-controlled studies in pregnant women. Because animal studies are not always predictive of human response, Calcium Folinate should only be used in pregnant women if the potential benefit justifies the potential risk to the foetus.

Since it is not known if Folinate is distributed into milk, the drug should be used with caution in nursing women.

4.7 Effects on ability to drive and use machines
4.8 Undesirable effects

Adverse reactions to calcium folinate are rare, but following intravenous and intramuscular administration occasional pyrexial reactions have been reported.

The most common dose-limiting adverse reaction occurring in patients receiving combination of calcium folinate and 5-fluorouracil are stomatitis and diarrhoea. In addition, haematological adverse reactions, such as leucocytopenia and thrombocytopenia, may occur. These adverse reactions are dose-dependent and their occurrence can usually be decreased by reducing the dosage of cytotoxic drugs. These adverse reactions can be controlled by close monitoring of haematological values, e.g. blood leucocyte and thrombocyte levels, and serum electrolyte (e.g. Na, K, Ca) and creatinine levels.

Anaphylactoid and urticaria allergic reactions have also been reported with the use of calcium folinate.

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 via:

Yellow Card Scheme
Website: www.mhra.gov.uk/yellowcard

By reporting side effects you can help provide more information on the safety of this medicine.

4.9 Overdose

There is no specific antidote to calcium folinate overdose. In cases of overdosage patients should be given appropriate supportive care.

Should overdosage of the combination of 5-FU with Calcium Folinate occur, the overdosage instruction for 5-FU should be followed.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic Properties

Folinate is a derivative of tetrahydrofolic acid, the reduced form of folic acid, which is involved as a cofactor for 1-carbon transfer reactions in the biosynthesis of purine and pyrimidines of nucleic acids.
Impairment of thymidylate synthesis in patients with folic acid deficiency is thought to account for the defective DNA synthesis that leads to megaloblast formation and megaloblastic and macrocytic anemias. Because of its ready conversion to other tetrahydrofolic acid derivatives, Folinate is a potent antidote for both hematopoietic and reticuloendothelia toxic effects of folic acid antagonists, (e.g. Methotrexate, Pyrimethamine, Trimethoprim). It is postulated that in some cancers, Folinate enters and "rescues" normal cells from the toxic effects of folic acid antagonists, in preference to tumour cells, because of a difference in membrane transport mechanisms; this principle is the basis of high-dose Methotrexate therapy with "Folinate rescue".

5.2. Pharmacokinetic Properties

**ABSORPTION AND DISTRIBUTION**

In vivo, Calcium Folinate is rapidly and extensively converted to other tetrahydrofolic acid derivatives including 5-methyl tetrahydrofolate, which is the major transport and storage form of folate in the body.

Normal total serum folate concentrations have been reported to range from 0.005-0.015 µg/mL. Folate is actively concentrated in CSF, and normal CSF concentrations are reported to be about 0.016-0.021 µg/mL. Normal erythrocyte folate concentrations range from 0.175-0.316 µg/mL.

In general, serum folate concentrations less than 0.005 µg/mL indicate folate deficiency and concentrations less than 0.002 µg/mL usually result in megaloblastic anemia. Following I.M. administration of a 15mg (7.5mg/m²) dose in healthy men, mean peak serum folate concentrations of 0.241 µg/mL occur within about 40 minutes. Following oral administration of a 15mg (7.5mg/m²) dose in healthy men, mean peak serum folate concentrations of 0.268 µg/mL occur within about 1.72 hours. Areas under the serum folate concentration-time curves (AUCs) are reported to be about 8% less following I.M. injection in the gluteal region than in the deltoid region and about 12% less following I.M. injection in the gluteal region than following I.V. or oral administration.

Tetrahydrofolic acid and its derivatives are distributed to all body tissues; the liver contains about one-half of total body folate stores. In a small number of patients, biliary concentration of folates was about 4.5 times the plasma folate concentration after oral administration of a 2mg dose of Folinate; this is believed to represent the hepatic folate pool rather than excretion of the administered dose.

**ELIMINATION**

Folinate is excreted in urine, mainly as 10-formyl tetrahydrofolate and 5, 10-methenyl tetrahydrofolate. There is some evidence that 5-methyl tetrahydrofolate may be conserved by the kidneys in preference to 5-formy
tetrahydrofolate (Folinate). Loss of folate in the urine becomes approximately logarithmic as the amount of Folinate administered exceeds 1mg.

5.3. Pre-clinical Safety Data

There is no preclinical data of relevance to the prescriber which are additional to that already included in other sections of the SPC.

6. PHARMACEUTICAL PARTICULARS

6.1. List of Excipients

Microcrystalline cellulose
Magnesium Stearate
Lactose

There is no overage included in the formulation.

6.2. Incompatibilities

Immediate precipitation results when combined with Droperidol in syringe.

6.3. Shelf life

Product as packaged for sale: 3 years

6.4. Special Precautions for Storage

Do not store above 25°C.

Keep container in outer carton

6.5. Nature and Content of Container

White polyethylene bottle with high density polyethylene screw closure containing 10 tablets.

6.6. Instructions for Use, Handling and Disposal

Not applicable.
7. MARKETING AUTHORIZATION HOLDER

Hospira UK Limited
Horizon
Honey Lane
Hurley
Maidenhead
SL6 6RJ
United Kingdom

8. MARKETING AUTHORISATION NUMBER

PL 04515/0017

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

08/11/2005

10. DATE OF REVISION OF THE TEXT

02/09/2016