Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Folinic Acid (as Calcium Folinate) Hydrate 15mg Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains calcium folinate hydrate equivalent to folinic acid 15 mg.
Excipients: contains lactose monohydrate 145mg

For the full list of excipients, see section 6.1

3 PHARMACEUTICAL FORM

Tablet
A yellowish-white, round, flat, scored, uncoated tablet engraved with 'CF'.
The scoreline is present to facilitate breaking for ease of swallowing and not to divide into equal doses

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

- As an intermediate in folic acid metabolism to reduce or counteract the toxicity of folic acid antagonists such as methotrexate, either in cytotoxic therapy (folinic acid rescue) or in cases of inadvertent overdosage.

- In the treatment of megaloblastic anaemia due to sprue, nutritional deficiency, pregnancy, infancy, liver disease and malabsorption syndrome.

4.2 Posology and method of administration

Posology

Adults and Children:

a) Folinic Acid Rescue
Folinic acid may be used in conjunction with folic acid antagonists, e.g. methotrexate, to reduce their systemic toxicity. It is given 12 to 24 hours after the antineoplastic drug. Doses of up to 120 mg may be given over 12 to 24 hours by intramuscular injection or intravenous injection or infusion, followed by 12 to 15mg intramuscularly, or 15mg orally, every 6 hours for the next 48 hours. With lower doses of methotrexate, folinic acid 15mg orally every 6 hours for 48 to 72 hours may be sufficient.

Treatment should be accompanied by alkalinization of urine with maintenance of urinary output at 2000 ml/m^2/24 hours and should be continued until plasma methotrexate is less than 10^{-7} molar.

b) Treatment of Megaloblastic Anaemia (folate deficiency)

Child over 12 years and adult: 15 mg (one tablet) per day.

c) Treatment of Overdosage of Folic Acid Antagonists
In cases of overdosage of folic acid antagonists, folinic acid may be administered by intravenous infusion in doses of up to 75 mg within 12 hours, followed by 12 mg intramuscularly every 6 hours for 4 doses.

In general, where overdosage is suspected, the dose of folinic acid should be equal to or greater than the offending dose of the folic acid antagonist administered, and should be given as soon as possible; preferably within the first hour and certainly within 4 hours after which it may not be effective.

Method of administration
For oral use.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

Pernicious anaemia or other anaemias due to vitamin B_{12} deficiency.

Regarding the use of calcium folinate hydrate with methotrexate during pregnancy and lactation, see section 4.6, and the summaries of product characteristics for methotrexate-containing medicinal products.

4.4 Special warnings and precautions for use

Folinic acid should only be used with methotrexate under the direct supervision of a clinician experienced in the use of cancer chemotherapeutic agents.

Folinic acid treatment may mask pernicious anaemia and other anaemias resulting from vitamin B_{12} deficiency.

In the treatment of inadvertent overdosage of a folic acid antagonist, folinic acid should be administered as soon as possible; if a period exceeding 4 hours intervenes, the treatment may not be effective.

Parenteral administration of folinic acid 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 folinic acid.

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, 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 hydrate administration and after discontinuation is recommended (see section 4.5).

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.

Calcium folinate hydrate 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.

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 hydrate.

Excipients with known effect

This medicine contains lactose. Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicine.

4.5 Interaction with other medicinal products and other forms of interaction

When calcium folinate hydrate is given in conjunction with a folic acid antagonist (e.g., cotrimoxazole, pyrimethamine, other antibiotics with an antifolate effect, methotrexate) the efficacy of the folic acid antagonist may either be reduced or completely neutralized.

Caution is required during concurrent administration of folinic acid with fluoropyrimidine as this has been associated with seizures and syncope (see section 4.8).

Calcium folinate hydrate 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 section 4.4).

Concomitant administration of calcium folinate hydrate with 5-fluorouracil has been shown to enhance the efficacy and toxicity of 5-fluorouracil.

Concurrent administration of chloramphenicol and folic acid in folate deficient patients may result in antagonism of haematopoietic response to folic acid.

4.6 Fertility, pregnancy and lactation

Pregnancy
There are no adequate and well-controlled clinical studies conducted in pregnant or breast-feeding women. Animal studies are insufficient with respect to reproductive toxicity (see section 5.3). However, 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 hydrate to diminish toxicity or counteract the effects.

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

Breast-feeding
It is not known whether calcium folinate hydrate is excreted into human milk. Calcium folinate hydrate can be used during breast-feeding when considered necessary according to the therapeutic indications.

Fertility
Calcium folinate hydrate is an intermediate product in the metabolism of folic acid and occurs naturally in the body. No fertility studies have been conducted with calcium folinate hydrate in animals.

4.7 Effects on ability to drive and use machines

Not relevant.

4.8 Undesirable effects

Immune system disorders
Very rare (<0.01%): allergic reactions, including anaphylactoid / 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%): increase in the frequency of attacks in epileptics (see also section 4.5). Seizures and/or syncope have been reported in cancer patients receiving folinic acid, usually in association with fluoropyrimidine administration and most commonly in those with CNS metastases or other predisposing factors; however, a causal relationship has not been established.

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

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 HPRA Pharmacovigilance. Website: www.hpra.ie.

4.9 Overdose

There have been no reported sequelae in patients who have received significantly more calcium folinate then the recommended dosage. However, excessive amounts of calcium folinate may nullify the chemotherapeutic effect of folic acid antagonists.

There is no specific antidote to folinic acid overdose. In cases of overdosage, patients should be given appropriate supportive care.

Should overdosage of the combination of 5-flourouracil with folinic acid occur, the overdosage instructions for 5-flourouracil 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 anaemias. Because of its ready conversion to other tetrahydrofolic acid derivatives, folinic acid 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, folinic acid 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 "folinic acid rescue".

5.2 Pharmacokinetic properties

Absorption and Distribution:
In vivo, calcium folinate hydrate 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 microgram/mL. Folate is actively concentrated in CSF, and normal CSF concentrations are reported to be about 0.016-0.021 microgram/mL. Normal erythrocyte folate concentrations range from 0.175-0.316 microgram/mL.

In general, serum folate concentrations less than 0.005 microgram/mL indicate folate deficiency and concentrations less than 0.002 microgram/mL usually result in megaloblastic anaemia.

Following I.M. administration of a 15 mg (7.5mg/m^2) dose in healthy men, mean peak serum folate concentrations of 0.241 microgram/mL occur within about 40 minutes. Following oral administration of a 15 mg (7.5 mg/m^2) dose in healthy men, mean peak serum folate concentrations of 0.268 microgram/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 2 mg 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-formyl tetrahydrofolate (folinate). Loss of folate in the urine becomes approximately logarithmic as the amount of folinate administered exceeds 1 mg.

5.3 Preclinical safety data

Genotoxicity, carcinogenicity, fertility and pre-/postnatal development studies have not been conducted with calcium folinate hydrate.

Embryo-foetal reproduction toxicity studies have been performed in rats and rabbits. Rats were dosed up to 1800 mg/m^2 which is 9 times the maximum recommended human dose, and rabbits were dosed up to 3600 mg/m^2 which is 18 times the maximum recommended human dose. There was no embryo-foetal toxicity noted in rats. At the maximum dose in rabbits, there was an increase in embryonic resorptions and no other adverse effects on embryo-foetal development. No resorptions were noted in dose groups at 6 times the maximum recommended human dose.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Microcrystalline cellulose
Magnesium stearate
Lactose

6.2 Incompatibilities

Not applicable

6.3 Shelf life

3 years

6.4 Special precautions for storage

Do not store above 25°C.
Keep container in the outer carton in order to protect from light

6.5 Nature and contents of container

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

6.6 Special precautions for disposal of a used medicinal product or waste materials derived from such medicinal product and other handling of the product

No special requirements

6.6 Special precautions for disposal and other handling

No special requirements.

7 MARKETING AUTHORISATION HOLDER

Pfizer Healthcare Ireland
9 Riverwalk
National Digital Park
Citywest Business Campus
Dublin 24
Ireland

8 MARKETING AUTHORISATION NUMBER

PA0822/198/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 28 July 1986

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10 DATE OF REVISION OF THE TEXT

November 2023