SANIFOLIN

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT
SANIFOLIN tablets
SANIFOLIN powder for injectable solution

2. QUALITATIVE AND QUANTITATIVE COMPOSITION
SANIFOLIN tablets
Each tablet contains:
Active substance: calcium folinate pentahydrate 19.06 mg, equivalent to 15 mg folinic acid, equal to 7.5mg levofolinic acid.
SANIFOLIN powder for injectable solution
Each vial contains in the form of lyophilised powder:
Active substance: calcium folinate 63.51 mg, equivalent to 50 mg folinic acid, equal to 25 mg levofolinic acid.

3. PHARMACEUTICAL FORM
Tablets for oral use.
Lyophilised powder for IM/IV injectable solution.

4. CLINICAL PARTICULARS
4.1 Therapeutic indications
SANIFOLIN is indicated as an antidote to overdoses of folic acid antagonists and to reduce the toxic effects induced by Aminopterin (4-aminopteroyl-glutamic acid) and by Methotrexate (4-amino N 10-methyl-pteroyl-glutamic acid). SANIFOLIN is also used in all the anaemic forms of folate deficiency resulting from increased demand, reduced utilisation or the insufficient dietary introduction of folates.
4.2. Posology and method of administration
SANIFOLIN may be administered orally or parenterally (infusion, intravenous, intramuscular).
Parenteral administration is normally preferred in chemotherapy with folic acid antagonists when the patient is affected by vomit reactions which could prevent the absorption of the medicinal product administered orally.
In the treatment of cancer of the colon-rectum, in combination with fluoropyrimidines, the dosage of calcium folinate is determined in relation to the chemotherapy protocols adopted. The posology most frequently used in combination with 5-fluorouracil is 200 mg/m^2/day (equal to 100 mg/m^2/day levofolinic acid) for 5 consecutive days in slow infusion (10 min.) every 4 weeks or 500 mg/m^2/week (equal to 250 mg/m^2/week levofolinic acid) for 6 weeks followed by a 2 week interval.
SANIFOLIN has proved efficacious in improving the therapeutic index of Methotrexate, at the same time counteracting the increase in toxic effects due to the administration of large doses.
In rescue from high dosages of Methotrexate, calcium folinate is effective in preventing myelosuppression at doses of 200 mg/m^2 (equal to 100 mg/m^2 levofolinic acid) for serum levels of Methotrexate of 10^{-6}M. Dosages may be proportionately increased for higher antiblastic levels in the blood.
In cases of overdose of Methotrexate, SANIFOLIN acts as a specific antidote, neutralising the toxic effects of the antimetabolyte on the hematopoietic system and on the mucus of the digestive system. Depending on the effect to be obtained SANIFOLIN is used at different dosages.
In the case of accidental overdose of Methotrexate, SANIFOLIN should be administered within the first hour, if possible at the same or at a higher dose than the Methotrexate, in that its administration is ineffective after 4 hours. In such cases to achieve a competition effect, administration of up to 100 mg of calcium folinate (equal to 50 mg of levofolinic acid) intravenously within 12 hours is recommended while to achieve a biochemical-metabolic effect a dose of calcium folinate of 15 mg (equal to 7.5 mg of levofolinic acid) every 6 hours in 4 doses by intramuscular, intravenous or oral route is recommended.
In the treatment of megaloblastic anemias resulting from folate deficiency, treatment with SANIFOLIN is orally, one tablet a day for 10/15 days while parenterally the dose is 10 mg (equal to 5 mg levofolinic acid) a day for 10/15 days. In the case of a positive response the dose may be halved continuing until the blood count has normalised and clinical signs have disappeared.
4.3. Contraindications
SANIFOLIN should not be administered in the presence of pernicious anaemia or other megaloblastic anemias resulting from vitamin B_{12} deficiency, except in combination with the same.
Known individual hypersensitivity to calcium folinate.
4.4 Special warnings and precautions for use
The use of SANIFOLIN in the treatment of pernicious anaemia or other megaloblastic anemias resulting from vitamin B_{12}, deficiency my lead to haematological remission without however arresting the progression of neurological symptoms. Treatment should therefore be conducted subject to haematological monitoring.
When treating for overdose of folic acid antagonists SANIFOLIN should be administered within 1 hour, as it generally proves ineffective after a period of 4 hours.
The medicinal product should be administered paying particular attention to the risk of allergic reactions or side effects.
4.5 Interaction with other medicinal products and other forms of interaction

Apart from the known interaction of calcium folinate with fluoropyrimidines, Methotrexate and other anti folates, no interaction with other medicinal products and/or substances has been reported.

4.6 Pregnancy and lactation

The administration of calcium folinate may improve or normalise forms of megaloblastic anaemia in pregnancy resulting from the increased demand for folates. Since there is no evidence of the passage of calcium folinate into breast milk, the medicinal product should be used with caution while breast-feeding.

4.7 Effects on ability to drive and use machines

No effects on the ability to drive and use machines have been found.

4.8 Undesirable effects

Administration of the product may cause allergic sensitisation phenomena such as fever, rash, arterial hypotension, tachychardia, bronchospasm, anaphylactic shock.

4.9 Overdose

No overdose phenomena are known of as at present.

5. CLINICAL INFORMATION

5.1 Pharmacodynamic properties

Calcium folinate in the body is rapidly converted into folinic acid, the active form of folic acid ready to act biochemically in the synthesis and metabolism of nucleic acids and proteins. In fact, folinic acid proves effective in all the anemias resulting from folate deficiency. As such it is also active in the presence of blocked enzymatic activation resulting from the use of antifolic compounds such as Methotrexate.

5.2 Pharmacokinetic properties

Results corresponding to those obtained with the microbiological dosage were achieved with calcium folate marked ^{14}C and ^{3}H: oral administration of SANIFOLIN (15 mg, equal to 7.5 mg of levofolinic acid) is followed by rapid absorption, determining a marked increase in folatemia after 60 minutes.

After intramuscular administration of 15 mg (equal to 7.5 mg of levofolinic acid) its half-life as N5- formyl-tetrahydrofolic is 45 minutes.

Excretion is mainly through the kidneys.

5.3 Preclinical safety data

Orally the LD_{50} is over 7000 mg/kg in mice.

6. PHARMACEUTICAL INFORMATION

6.1 List of excipients

SANIFOLIN tablets

Microcrystalline cellulose, polyvinylpyrrolidone, magnesium stearate.

SANIFOLIN powder for injectable solution

Methyl p-hydroxybenzoate, propyl p-hydroxybenzoate, sodium chloride.

6.2 Incompatibility

None

6.3 Shelf life

36 months for both pharmaceutical formats in correctly stored unopened packages

6.4 Special precautions for storage

None

6.5 Type and contents of the package

SANIFOLIN tablets

10 tablets in heat-sealed Al/PVCD blister pack.

SANIFOLIN powder for injectable solution

Pack with type III neutral glass vial, closed with perforable, pharmaceutical rubber cap and aluminium band.

6.6 Instructions for use, handling and disposal

SANIFOLIN tablets

Swallow with a little water

SANIFOLIN powder for injectable solution

The powder should be dissolved in strictly aseptic conditions with 5 ml of sterile water for injections (each ml contains 10 mg folinic acid equal to 5 mg levofolinic acid); for the infusion use saline solution.

The solution so obtained may be kept for a maximum of up to 12 hours at a temperature of not more than 8°C.

7. MARKETING AUTHORISATION NUMBER

SANIFOLIN tablets

AIC 027683010.

SANIFOLIN powder for injectable solution

AIC 027683046.

8. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

09.03.91/06.2010

9. DATE OF PARTIAL REVISION OF THE TEXT

June 2005