1. TRADE NAME OF THE PHARMACEUTICAL PRODUCT

FILICINE TABLET

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Drug Substance: FOLIC ACID 5 mg / tablet

3. PHARMACEUTICAL FORM

Tablets

4. CLINICAL CHARACTERISTICS

4.1. Therapeutic indications

Folic acid (pteroglutamic acid) is indicated for the treatment of megaloblastic anemia which is caused by folic acid deficiency.

Pathophysiological conditions that may cause a lack of folic acid and megaloblastic anemia are the following: 1. Dietary deficiencies (vegetarian diet, alcoholism, destruction of the vitamin during cooking, malnutrition) 2. Disturbances related to its absorption by the gastrointestinal tract (chronic diarrheas, celiac sprue, invasive and granulomatous diseases, such as lymphoma and Whipple's disease) 3. Increased needs of the body in folic acid (pregnancy, childhood, hemolytic anemias, hyperthyroidism, infections, hepatic cirrhosis, extensive cutaneous lesions) 4. Lack because of pharmaceutical therapy (anti-epileptics-phenytoin, barbiturates, primidone-contraceptives, alcohol, antagonists of folic acid-methotrexate, aminopterine, trimethoprime-cycloserine) 5. Enzymatic disorders (Dihydrofolic acid reductase and Glutamate forminotransferase). It is also indicated for chronic hemolytic anemias, chronic hemodialysis, usually in combination with iron.

4.2. Posology and mode of administration :

INITIAL THERAPEUTIC DOSE

Adults : The therapeutic dosage for folic acid is the following:

Megaloblastic anemia, adults, children, elderly, usual dose 1 to 5 mg per day orally for 7 to 14 days. In most patients, 5-15 mg of folic acid per day for 7 to 14 days results in a greater improvement of the hematological parameters. Before administering these high doses, it is necessary to exclude the possibility of vitamin B_{12} deficiency. The administration of folic acid when there is a vitamin B_{12} deficiency-malignant anemia aggravates the neurological symptoms that accompany the megaloblastic anemia. An improvement of the hematological parameters is observed 2-3 days after the initiation of the therapy with folic acid and continues until the 4^{th} -7^{th} day. Hemoglobin returns to normal levels within 2 to 6 weeks.

Elderly : Same as in adults.

Children : As in adults.

MAINTENANCE DOSE

Adults : 0,5 -1 mg per day or 5 mg once a week.

Children : 0,3 mg per day.

Neonates : 0,1 mg per day.

The necessary duration of the folic acid regimen has not been determined precisely, however, it is recommended to administer the vitamin for many months until the formation of new colonies of red blood cells. The diet improvement, the treatment of the inflammations and the removal of etiological agents that cause folic acid deficiency will make the complementary administration of the vitamin unnecessary. In other cases, such as the chronic hemolytic anemias or the pharmaceutical treatment with folic acid antagonists, a long-lasting folic acid

maintenance regimen is necessary in order to prevent the manifestation of hematological disorders.

4.3. Contraindications :

The administration of folic acid is contra-indicated for the treatment of megaloblastic anemia due to lack of vitamin B_{12} (malignant anemia) and in those anemias, the character and etiology of which has not been determined. It should not be administered in neoplastic anemias, because it may lead to tumor formation.

4.4. Special warnings and precautions on use :

A therapeutic dose smaller than 1 to 5 mg per day may not always be effective in patients with disturbances in the absorption of folic acid by the gastrointestinal tract. Before administering folic acid in cases of megaloblastic anemia, one should exclude the possibility of a vitamin B_{12} deficiency since the neurological symptoms and lesions do not improve with the administration of folic acid. In epileptics who receive phenytoin, there is the danger of reappearance of spasms. In emergency cases and in cases of inability or delay of an etiological diagnosis, it is necessary to administer vitamin B_{12} and folic acid concomitantly.

Special warnings for excipients

FILICINE contains Lactose Monohydrate. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose–galactose malabsorption should not take this medicine.

4.5. Interactions with other drugs and other forms of interaction

The following drugs cause disturbances in the absorption and the metabolism of folic acid. Oral contraceptives, anti-epileptics (phenytoin, barbiturates, primidone), the anti-tubercular drug cycloserine, the antidiabetic metformin, alcoholic beverages. Also folic acid antagonists (the chemotherapeutic methotrexate, the diuretic triamterene, the antibacterial trimethoprime, the anti-malarial pyrimethamine and others) inhibit the activity of the enzyme Dihydrofolic acid reductase resulting in folic acid deficiency. The folic acid may reduce the activity of folic acid antagonists and the levels of phenytoin in blood.

4.6. Pregnancy and lactation

Use during Pregnancy

In order to satisfy the increased demands in folic acid during pregnancy and prevent the occurrence of anemia, folic acid administration is indicated for prophylactic reasons.

Use during Lactation

The maternal milk contains 25mg folic acid per liter, which satisfies the needs of the developing infant. Dietary problems of the breast-feeding mother, such as a vegetarian diet, infections, and problems of absorption by the gastro-intestinal tract are conditions that require the prophylactic administration of folic acid in the breast-feeding mother in order to prevent the occurrence of megaloblastic anemia in the neonate.

4.7. Effect on the ability to drive and use machines:

The administration of folic acid is not accompanied by side effects and disturbances in the ability to drive and use machines.

4.8. Undesirable effects:

The administration of folic acid is not accompanied by undesirable effects. One should mention however the possibility of very rare allergic reactions.

4.9. Overdosage:

The administration and intake of a vitamin complex concomitantly with iron in very large doses is accompanied by the side effects of the rest of the ingredients in the complex and especially of the iron. In cases of mixed overdosage, such as the combination of a vitamin complex and iron, the rapid evacuation of the stomach is recommended and a specific and symptomatic treatment for the overdosage.

5. PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamics

General characteristics

Folic acid is necessary for DNA synthesis and the function of the cell nucleus. Lack of folic acid results in the non simultaneous maturing and function of the nucleus in comparison to DNA synthesis and the cytoplasmic proteins. Megaloblastic cell lesions follow, which are not limited in the erythrocytes but also in other cells such as those of the gastrointestinal mucosa, the vagina and the cervix of the uterus among others. The megaloblasts are nucleated erythrocytes that manifest lack of synchronization in the maturing between the nucleus and the cytoplasm. In addition a DNA and chromatin disturbance in synthesis may occur. The size of the erythrocytes (MCV) is of the order of 105-165 μ^3 and their shape is oval. Their lifetime is reduced to 16-21 days. Lesions are also observed in the leucocytes and the blood platelets. The administration of folic acid improves the hematological picture and the megaloblastic anemia clinical syndrome as long as there is no vitamin B_{12} deficiency.

Recent clinico-laboratory studies examine the role of folic acid (pteroglutamic acid) in the metabolism and plasma concentration of homocysteine. The increased homocysteine in plasma is a graduated independent risk factor, which undoubtedly aggravates the already known predisposing factors for cardiovascular and cerebrovascular disease and is an especially determinant factor of the respective mortality. There are reports that the intake of folic acid and other vitamins reduce the levels of homocysteine in plasma.

Persons with mild to intermediate increase of homocysteine in the serum have a higher risk of thromboembolic incidents in comparison to those for which the plasma homocysteine is within normal limits. The concentration of homocysteine in plasma depends on the genetically determined enzymes of its metabolism and increases with age as well as in cases of renal insufficiency, when there is lack of folic acid, pyridoxine, covalamine, or with the administration of medicinal agents that cause a reduction of folic acid such as the contraceptives, the alcoholic beverages and the chemotherapeutic drugs.

5.2. Pharmacokinetics:

a. General characteristics:

Folic acid is found in foods in the form of polyglutamates and is degraded into monoglutamates in order to be absorbed by the gastrointestinal tract. The monoglutamates are mainly absorbed by the first part of the small intestine although they are also absorbed by the whole surface of the small intestine. In the intestinal mucosa, the various forms of the absorbed folic acid are converted into N-methyl tetrahydrofolate which is introduced into the cells by a specific carrier and re-forms polyglutamate compounds which remain inside the cell. Before the reassociation of monoglutamates and the formation of polyglutamates inside the cell, the removal of the methyl and the N5-methyl tetrahydrofolate takes place with the catalytic action of the homocystane methyltransferase with the formation of Tetrahydrofolate, which is used as it is or in the form of N10-formyl in the various reactions of the cell that require folic acid as a synergistic factor but, in this reaction, it is oxidized by two electrons and gives dihydrofolate. The dihydrofolate can be transformed again into tetrahydrofolate in order to be able to act again as a carbon atom carrier (cofactor). A disturbance in this reaction is the basic reason for the megaloblastic lesions and the anemia. The composition of deoxythimidine is very sensitive to the lack of N5, 10-methylene H4PteGlu which is due to

the lack of folic acid. An inhibition of this reaction leads to a disturbance in the synthesis of folic acid, abnormalities of the chromosomes in the dividing cells, the appearance of megaloblasts and finally the death of the cells.

b. Characteristics in patients:

The administration of folic acid in patients with malignant anemia caused by vitamin B_{12} deficiency improves the hematological picture, but does not influence the neurological symptoms of the disease. In these patients, parenteral administration of vitamin B_{12} is necessary.

5.3. Preclinical evidence concerning the safety (toxicological evidence)

Acute toxicity:

It is possible to observe allergic reactions both by the oral and the parenteral administration of folic acid.

Chronic toxicity:

Allergic reactions due to the sensitization of the patient to the administration folic acid.

Mutagenic activity – carcinogenesis:

Not reported

Toxicity during reproduction:

Not reported

6. PHARMACEUTICAL PARTICULARS

6.1. List of excipients

Lactose Monohydrate, Starch Maize, Magnesium Stearate.

6.2. Incompatibilities

None Known

6.3. Shelf life

The expiration date is printed on the internal and external package. Do not use past the expiration date.

6.4. Special Procautions for the storage of the medicinal product

Keep at room temperature, below 25ºC in a dry place, protected from light, out of reach and sight of children.

6.5. Nature and contents of the container

PACKAGE: Box x 30 Aluminum and PVC blister 3 x 10 tabs
Box x 1000 Aluminum and PVC blister 100 x10 tabs

6.6. Instructions for use and handling

Not required

7. MARKETING AUTHORIZATION HOLDER

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8. MARKETING AUTHORIZATION NUMBER

MA072/00201

9. INITIAL AUTHORIZATION

26th December 2005

10. DATE OF THE (PARTIAL) REVISION OF THE TEXT

July 2014