SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Folsyra Evolan 5 mg tablet

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Folic Acid 5 mg

Excipient: lactose monohydrate 97.1 mg.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Tablet

Yellow to yellow-orange, dotted, round, planoconvex tablets with a score line on one side, diameter 7 mm.
The tablet can be divided into two equal halves.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Megaloblastic anaemia with folic acid deficiency. Alcoholism and haemolytic anaemia with high folate metabolization. Malabsorption (celiac disease, sprue, etc.). Inadequate folate intake. As a prophylactic before and during pregnancy, especially in case of increased risk of neural tube defects. In case of drug treatments that inhibit folate absorption or folate metabolization, such as phenytoin antiepileptics and long-term sulphonamide treatment.

4.2 Posology and method of administration

At these levels, folic acid may mask pernicious anaemia and thereby delay diagnosis. In case of B_{12} deficiency, adequate doses of vitamin B_{12} must be administered. Individual posology.

Adults: For remission treatment in megaloblastic anaemia: 1 tablet of 5 mg a day for approximately two weeks. *Maintenance therapy:* 1 tablet of 1 mg a day, the dose may be increased if folate deficiency persists. Since <Invented name> is not compatible with this posology, another product must be selected.
As a prophylactic before pregnancy with an increased risk of neural tube defects: 1 tablet of 5 mg a day for a minimum of 4 weeks prior to conception and a minimum of 12 weeks thereafter.
As a prophylactic before pregnancy: ½ tablet every other to every third day.
Children: In case of folate deficiency in children age 10–18, 1 tablet of 1 mg a day. Since <Invented name> is not compatible with this posology, another product must be selected.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients.

4.4 Special warnings and precautions for use

Folic acid treatment may mask a concurrent vitamin B_{12} deficiency or the development of B_{12} deficiency, which may result in serious neurological damage. In case of cobalamin malabsorption, cobalamin deficiency or methylmalonic acid elevation, an adequate dose of B_{12} must be administered.

<Invented name> contains lactose monohydrate. Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not use this medicine.

4.5 Interaction with other medicinal products and other forms of interaction

Folate metabolization and folate action may be affected by a number of drugs. In many cases, the mechanism and clinical relevance is unclear. Folate deficiency or folate antagonism has been reported in long-term treatment with antiepileptics, phenothiazines, tricyclic antidepressants, contraceptives, biguanides, cholestyramine, tuberculostatic agents and folic acid antagonists, including trimethoprim and sulfonamides.

4.6 Pregnancy and lactation

Pregnancy: There are no known risks associated with the use of <Invented name> during pregnancy.
Lactation: Excreted in human milk, but at therapeutic dosage no effects on the child are anticipated.

4.7 Effects on ability to drive and use machines

<Invented name> does not affect the ability to drive or use machines.

4.8 Undesirable effects

Rare (<1/1000) *Skin and subcutaneous tissue disorders*: Pruritus, erythema, urticaria.

Not known *Immune system disorders*: anaphylactic reaction
(cannot be estimated from the available data)

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 the national reporting system listed in Appendix V.

4.9 Overdose

The acute toxicity is low. Overdosage does not generally result in any symptoms and symptomatic overdose treatment should only be required in exceptional cases.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Folic acid and derivatives, ATC code: B03BB01

Upon absorption by the cells by means of receptor-mediated endocytosis, methyltetrahydrofolate acts as the methyl donor to methylcobalamine. Tetrahydrofolate acts as the base for other products, such as methylenetetrahydrofolate, formyltetrahydrofolate and formiminotetrahydrofolate, which are important for single carbon movements, including the synthesis of purines and pyrimidines. Folic acid deficiency causes the same type of megaloblastic anaemia as in vitamin B_{12} deficiency. Long-term folic acid treatments may mask the concurrent development of vitamin B_{12} deficiency. Despite hematologic remission, neurological damage may develop due to the vitamin B_{12} deficiency, which may be revealed by methylmalonic acid analysis.
Homocysteine is a sulphur-containing amino acid normally formed by the metabolization of methionine. Homocysteine in turn is metabolized via two pathways, by remethylation and transsulfuration. In remethylation, methionine is reformed through a reaction catalysed by methionine synthase. Vitamin B_{12} is an essential enzyme co-factor, and N5-methyltetrahydrofolate acts as the methyl donor. N5, N10-methylenetetrahydrofolate reductase acts as the catalyst during the remethylation. The transsulfuration to cystathionine is catalysed by the vitamin B_6-dependent enzyme cystathionine-beta-synthase. The deficiency of any of these essential vitamins will affect the homocysteine metabolization. Therefore, homocysteine assessments expand and improve the diagnostic options when investigating vitamin B_{12} deficiency and folic acid deficiency.

Due to genetic mutations, the effect of the methyltetrahydrofolate reductase enzyme may be impaired, which disrupts the homocysteine-folic acid metabolization, this may however be normalized using folic acid treatment. These mutations are more prevalent in families with neural tube defects.
Studies show that a combination of folic acid and vitamin B_{12} normalizes elevated homocysteine levels. Elevated homocysteine levels have been proven to be an independent risk factor in cardiovascular diseases.

5.2 Pharmacokinetic properties

Folic acid is quickly and efficiently absorbed through oral administration, including in case of mucosal tissue damage. Dietary folate amounts to approximately 0.2 mg, primarily in the form of reduced polyglutamates, and is hydrolysed in the proximal intestinal brush border by folate conjugase, a zinc-containing enzyme, to monoglutamate (monofolate), which is absorbed by the mucosa by means of a specific process. The dihydrofolate reductase enzyme reduces dihydrofolate to tetrahydrofolate, and the methylation also occurs in the mucosa. The liver absorbs the 5-methyltetrahydrofolate from the portal vein for storage, distribution or excretion through the gall bladder and reabsorption in the enterohepatic circulation.

5.3 Preclinical safety data

There are no relevant preclinical data for the safety assessment in addition to that already mentioned in the summary of product characteristics.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Lactose monohydrate, powdered cellulose, talc, anhydrous colloidal silica, magnesium stearate.

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years.

6.4 Special precautions for storage

Do not store above 25 °C.

6.5 Nature and contents of container

Blister: 100, 105 pcs
Plastic bottle: 1000 pcs

6.6 Special precautions for disposal and other handling

No special requirements.

7 MARKETING AUTHORISATION HOLDER

<To be completed nationally>

8 MARKETING AUTHORISATION NUMBER(S)

22776

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

07/08/2009/ 07/08/2014

10 DATE OF REVISION OF THE TEXT

2019-10-01