SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Foliumzuur ratiopharm 0,4 mg, tabletten

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 0.4 mg of folic acid hydrate.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Tablet.

Off-white to yellowish in colour, round, convex bevelled-edge tablets of 7 mm in diameter.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Primary prevention of foetal neural tube defects in women who are planning a pregnancy and do not have risk factors that can lead to such defects (see section 4.4).

4.2 Posology and method of administration

Posology
One tablet per day, continuously for 1 month before and up to 3 months after conception.

The daily dose may be doubled in the event of an inadequate folic acid intake.

This dose is not adequate in women with one or more risk factors that can lead to Neural Tube Defects (NTD), such as one or more previous pregnancies where NTD have been observed (see section 4.4).

<PRODUCT NAME> is not effective in preventing the onset of neural tube developmental defects if the treatment is started after the fourth week of pregnancy.

Paediatric population
<PRODUCT NAME> is not indicated in women before menarche. In cases of folic acid deficiency, other formulations with a higher dose are more appropriate.

Method of administration
Oral use.
Take the tablet whole with water, at the same time every day, on an empty stomach.

4.3 Contraindications

- Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.
- Pernicious anaemia not treated or treated insufficiently with vitamin B_{12}.
- Megaloblastic anaemia of unknown origin.

4.4 Special warnings and precautions for use

Before starting treatment with folic acid, the patients should be subjected to a complete diagnosis.

Women with one or more risk factors that can lead to development of neural tube defects should be subjected to a more thorough assessment before starting treatment with <PRODUCT NAME>, as their clinical condition could require the administration of folic acid at higher doses than those contained in <PRODUCT NAME> 0.4 mg. The main established risk factors are:

- Known folic acid deficiency (e.g. women with megaloblastic anaemia caused by a folic acid deficiency);
- One or more previous pregnancies where neural tube defects have been observed (whether or not carried to term);
- Receiving treatment with anti-epileptic medicinal products (e.g., carbamazepine or valproic acid);
- Family history of neural tube defects;
- Receiving treatment with folic acid antagonists (e.g. methotrexate, sulfasalazine) (see section 4.5);
- Having type I or II diabetes mellitus.

Consideration should be given to current national/international recommendations and guidelines on prevention of NTD on other risk factors that can lead to development of neural tube defects.

The administration of folic acid alone is not sufficient for pernicious anaemia and other forms of megaloblastic anaemia associated with vitamin B_{12} deficiency. The treatment of megaloblastic anaemia with folic acid should only be initiated if a vitamin B_{12} deficiency has been ruled out or is being adequately treated. In the case of a vitamin B_{12} deficiency, the administration of folic acid alone leads to a rapid normalization of the blood count; however, the neurological abnormalities resulting from vitamin B_{12} deficiency worsen or are provoked. This masking of the deficiency state can lead to serious neurological damage such as subacute combined degeneration of the spinal cord.

Caution should be exercised when administering folic acid to patients with possible folate-dependent tumours.

Antibiotics may interfere with microbiological tests for the concentrations of folic acid in the serum and the red blood cells, leading to erroneously low results.

This medicinal product contains less than 1 mmol sodium (23 mg) per tablet, that is to say essentially ‘sodium-free’.

4.5 Interaction with other medicinal products and other forms of interaction

Anti-epileptics
Folic acid <PRODUCT NAME> may reduce the plasma concentrations of some anti-epileptic medicinal products, such as phenobarbital, phenytoin and primidone, by increasing their metabolism. If concomitant use occurs, the blood concentration of these anti-epileptic medicinal products must be carefully monitored..

Folic acid antagonists
Methotrexate, sulfasalazine and pyrimethamine may reduce the effectiveness of folic acid due to their antagonist activity.

Very high doses of non-steroidal anti-inflammatory medicinal products may have anti-folate activity but, at the doses normally used, there is no evidence of impaired folate metabolism.

Long-term, continuous use of paracetamol and aspirin, ibuprofen and other non-steroidal anti-inflammatory medicinal products seems to increase the body’s folic acid requirement.

When folic acid is administered concomitantly with folic acid antagonists, the folate status should be monitored. Separating the administration of the folic acid antagonist and folic acid may prevent an interaction.

Antibacterials
Trimethoprim or sulfonamides, alone or in combination, such as with cotrimoxazole, may reduce the effect of folic acid. If administered concomitantly, the folate status should be monitored.

Chloramphenicol use may reduce the efficacy of supplemental folic acid by interfering with the hematopoietic response. Hematologic response should be monitored in patients requiring folic acid if chloramphenicol is administered concomitantly.

Reduced absorption
Cimetidine and antacids, but also bile acid binding resins cholestyramine and colestipol, seem to reduce the absorption of folates.

Anti-tuberculosis medicinal products, alcohol and oral contraceptives may cause low serum and tissue folate concentrations.

When folic acid is administered concomitantly with medicinal products known to reduce the absorption of folic acid and/or to cause low serum and tissue folate concentrations, the folate status should be monitored. Separating the administration of these medicinal products and folic acid may prevent an interaction. Alcohol should be avoided during folic acid treatment.

Green and black tea may cause low serum folate concentrations, therefore they should be avoided during folic acid treatment.

Fluorouracil
Patients who take folic acid and are treated concomitantly with fluorouracil may suffer toxicity reactions. Combination therapy of folic acid and fluorouracil should be administered under the supervision of a physician experienced in the use of antimetabolite cancer chemotherapy.

4.6 Fertility, pregnancy and lactation

Pregnancy
There are no known risks for the use of folic acid in pregnancy; folic acid supplements are often useful.
Non-drug-induced folic acid deficiency, or anomalous folate metabolism, is linked to the onset of birth defects and some neural tube defects.
Interference with folic acid metabolism or folic acid deficiency caused by medicinal products such as anticonvulsants and certain antineoplastic medicinal products at the start of pregnancy causes congenital anomalies. Deficiency in the vitamin or its metabolites may also be the cause of certain cases of miscarriage or foetal growth restriction.

Breast-feeding
Folic acid is excreted in human breast milk. No adverse effects have been observed in breast-fed infants whose mothers were receiving treatment with folic acid.

Fertility
No fertility data are available.

4.7 Effects on ability to drive and use machines

<PRODUCT NAME> has no or negligible influence on the ability to drive and use machines.

4.8 Undesirable effects

a) Summary of the safety profile
Folic acid is generally well tolerated. Gastrointestinal disturbances and hypersensitivity reactions have been reported rarely.

b) Tabulated summary of adverse reactions
The undesirable effects that may be associated with <PRODUCT NAME> are listed below according to the MedDRA frequency convention and system organ class database. Safety data is obtained from spontaneous reporting sources.

The frequency of the side effects is defined using the following conventions:
Very common (≥1/10)
Common (≥ 1/100 to < 1/10)
Uncommon (≥ 1/1 000 to < 1/100)
Rare (≥ 1/10 000 to < 1/1 000)
Very rare (<1/10 000)
Not known (cannot be estimated from the available data).

System organ class	Frequency	Adverse reactions
Immune system disorders	Not known	Fever, hypersensitivity, anaphylactic reaction
Nervous system disorders*	Not known	Sleep disorder, agitation, depression
Gastrointestinal disorders*	Not known	Bitter taste, flatulence, loss of appetite, nausea
Skin and subcutaneous tissue disorders	Not known	Rash, pruritus, erythema, urticaria, facial angioedema
*Events observed in patients treated with high doses of folic acid.		

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

Symptoms of overdose:
Folic acid overdose after chronic administration of very high doses (over 15 mg folic acid per day for more than 4 weeks) manifests in the following symptoms: bitter taste, loss of appetite, nausea, flatulence, nightmares, agitation and depression.

Therapeutic measures in case of overdose:
No special actions are required.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Folic acid, Antianemic Preparations, Folic acid and derivatives, ATC code: B03B B01.

Mechanism of action
Folic acid is a B-complex vitamin. It is a coenzyme involved in certain transmethylation processes. Folic acid is converted in the body into 5-10-methylenetetrahydrofolate (5-10-MTHF). 5-10-MTHF can then donate methyl groups, which are necessary for processes such as DNA synthesis and cell division. Deficiency of folic acid, therefore, can disrupt the process of DNA synthesis by limiting the methyl groups available. Folic acid is also needed for the normal production and maturation of the red blood cells and its deficiency is one of the causes of megaloblastic anaemia. The mechanism of action of folate in the prevention of neural tube defects is unknown.

5.2 Pharmacokinetic properties

Absorption
Folic acid is rapidly absorbed by the gastrointestinal tract, primarily by the proximal portion of the small intestine. It has been stated that dietary folates have around half the bioavailability of folic acid in crystal form. The naturally occurring folate polyglutamates normally present are widely unconjugated and reduced to 5-methyltetrahydrofolate (5MTHF) in the intestinal mucosa. Therapeutically administered folic acid enters the portal circulation substantially unmodified, since there is not a good substrate for reduction through dihydrofolate reductase.
Bioavailability is high following oral administration.
Peak plasma concentration is reached in 1 hour.

Distribution
Distribution takes place through portal circulation. The 5MTHF deriving from the folate normally present is extensively bound to plasma. The main folate accumulation site is the liver; it is also actively concentrated in the cerebrospinal fluid.

Folates is distributed to breast milk and the placenta.

Folic acid binds extensively to plasma proteins, and the liver is the main storage organ.

Biotransformation
Therapeutically administered folic acid is converted into the active metabolite 5MTHF in the plasma and liver. The folate is subjected to enterohepatic circulation.
Metabolization is linked to the extent of folate deposits, adjusting according to their saturation homeostasis.

Elimination
Folate metabolites are eliminated in the urine and excess folates above the body's requirements are excreted in an unmodified form in the urine. Folic acid is removed via haemodialysis.
Half-life of folic acid was approx. 1.9 h in healthy volunteers administered with folic acid 0.4 mg tablets.

5.3 Preclinical safety data

Effects in non-clinical studies were observed only at exposures considered sufficiently in excess of the maximum human exposure indicating little relevance to clinical use.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Hydroxypropyl cellulose
Croscarmellose sodium
Cellulose, microcrystalline
Silica, colloidal anhydrous
Stearic acid 50

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

5 years.

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

PVC-PVDC/Al blister packs of 28 and 120 tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements.
Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

Ratiopharm GmbH
Graf-Arco-Strasse 3
89079 Ulm
Duitsland

8. MARKETING AUTHORISATION NUMBER(S)

RVG 131251

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Datum van eerste verlening van de vergunning: 12 november 2024

10. DATE OF REVISION OF THE TEXT