Pr FOLIC ACID

Folic Acid Tablets BP

5 mg

Anemia Therapy

AA PHARMA INC.
1165 Creditstone Road, Unit# 1
Vaughan, Ontario
L4K 4N7

Control No.: 214763

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# Table of Contents

SUMMARY PRODUCT INFORMATION ................................................................. 3  
INDICATIONS AND CLINICAL USE ........................................................................ 3  
CONTRAINDICATIONS ......................................................................................... 4  
WARNINGS AND PRECAUTIONS ......................................................................... 4  
ADVERSE REACTIONS .......................................................................................... 5  
DRUG INTERACTIONS .......................................................................................... 5  
DOSAGE AND ADMINISTRATION .......................................................................... 6  
OVERDOSAGE ..................................................................................................... 7  
ACTION AND PHARMACOLOGY .......................................................................... 7  
STORAGE AND STABILITY .................................................................................. 11  
SPECIAL HANDLING INSTRUCTIONS ................................................................. 11  
DOSAGE FORMS, COMPOSITION, PACKAGING .................................................. 11  
CONTACT INFORMATION ...................................................................................... 11  
REFERENCES ........................................................................................................ 11
SUMMARY PRODUCT INFORMATION

Folic acid

C$_{19}$H$_{19}$N$_7$O$_6$  441.40 g / mol

<table>
<thead>
<tr>
<th>MEDICINAL INGREDIENT</th>
<th>NON-MEDICINAL INGREDIENTS</th>
</tr>
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<tbody>
<tr>
<td>mg / Tablet</td>
<td></td>
</tr>
<tr>
<td>Folic Acid BP 5 mg</td>
<td>croscarmellose sodium, lactose monohydrate, magnesium stearate, microcrystalline cellulose</td>
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</table>

Refer to “Dosage Forms, Composition, Packaging” for additional information.

INDICATIONS AND CLINICAL USE

1. For therapeutic use only

2. For the prevention and treatment of folate deficiency due to inadequate dietary intake, absorption or utilization or increased excretion or need as in tropical sprue (not in all forms of sprue), chronic haemodialysis, chronic haemolytic anaemia, nutritional megaloblastic anaemia, megaloblastic anaemia of pregnancy, infancy, and childhood, and megaloblastic anaemia associated with primary liver disease, alcoholism with cirrhosis, or associated with anticonvulsant therapy.

3. There is strong evidence that prophylactic therapy with folic acid fortified multivitamins, prior to and during pregnancy, can reduce the risk of neural tube defects. Expert groups
recommend that all women of childbearing potential who are planning pregnancy or not should maintain an adequate daily intake of folic acid (see Dosage and Administration).

4. Folic acid is not effective in reversing the effects of folic acid reductase inhibitors such as methotrexate, for which leucovorin calcium (folinic acid) must be used. However, folic acid is used during long term, low-dose methotrexate therapy to prevent methotrexate toxicity, particularly oral ulceration and gastrointestinal irritation, to treat or prevent folate deficiency and to prevent hyperhomocysteinemia.

Taking this medication does not eliminate the need for a balanced nutrition.

CONTRAINdications

1. People who have diseases of the small intestine, especially Crohn’s disease and Sprue, may have trouble absorbing folic acid.

2. Folic acid is contraindicated in patients with hypersensitivity to folic acid products and/or any of the inactive ingredients present in the drug product. (see: Dosage Forms, Composition, Packaging).

WARNINGS AND PRECAUTIONS

1. Do not use if seal is broken

2. Keep out of reach of children. This product contains sufficient drug to seriously harm a child.

3. Megavitamin therapy is a cause of vitamin toxicity (hypervitaminosis) for folic acid (folate).

4. Use only as an adjunct to treatment with vitamin B_{12} whenever pernicious anemia is present or suspected. However, proper diagnosis of the condition of the patient and evaluation of the underlying etiology of the deficiency state is required. The use of folic acid in pernicious anemia patients without adequate vitamin B_{12} therapy may result in hematological improvement, while neurologic manifestations continue to progress. Folate supplementation can mask the early symptoms of vitamin B_{12} deficiency (e.g., chronic malaise, sore tongue, numbness of the fingers), potentially allowing more irreversible symptoms of nerve damage to develop. For this reason, when taking more than 400 mcg daily, it is important to check the level of B_{12}. Signs and symptoms of vitamin B_{12} deficiency (e.g., chronic malaise, sore tongue, numbness of the fingers) should be investigated before starting supplementation with folic acid.

5. Folic acid is not effective in the rescue treatment or overdosage of folic acid antagonists such as methotrexate.
6. When cholestyramine and folic acid are administered together, there may be a reduction or delay in the folic acid absorption. If concomitant therapy is required, folic acid should be administered at least 1 hour before and 4 hours after cholestyramine.

7. Pregnancy: Pregnant women are more prone to develop folate deficiency which can lead to complications: foetal abnormalities (see Pharmacology)

8. Lactation: Folic acid is actively excreted in human breast milk. Adverse effects in breast-fed infants have not been documented intake of normal daily requirements of folic acid during lactation.

9. Avoid supplements containing herbs and various other non-medicinal ingredients.

ADVERSE REACTIONS

1. Deficiency can result in fissures and scaling of the lips and corners of the mouth, and dermatitis.

2. Folic acid is relatively non-toxic but has rarely caused allergic reactions including erythema, pruritus, and/or urticaria. High doses (e.g. 15 mg/day) have rarely been associated with various gastrointestinal symptoms such as anorexia, nausea, abdominal distention, flatulence and bitter taste and CNS effects such as altered sleep patterns, difficulty concentrating, irritability, overactivity, excitement, mental depression, confusion, and impaired judgment.

3. Overdose: For overdose contact your regional Poison Control Center.

DRUG INTERACTIONS

1. Phenytoin isoniazid, primidone, barbiturates, sulfasalazine, glutethimide, cycloserine, folic acid antagonists (methotrexate, pyrimethamine, triamterene, diamidine compounds, trimethoprim), anticonvulsants, antacids, cholestyramine, colestipol, H2 blockers, carbamezapine, phenobarbital, valproate, sulfasalazine, nitrous oxide, and oral contraceptives decrease absorption of folic acid. Pregnant and lactating women and people undergoing haemodialysis for kidney disease develop this deficiency because they have an increased need for folic acid.

When cholestyramine and folic acid are administered together, there may be a reduction or delay in folic acid absorption. If concomitant therapy is required, folic acid should be administered at least one hour before or 4 to 6 hours after cholestyramine.

2. Pregnant women are more prone to develop folate deficiency that can lead to complications and foetal abnormalities (see Pharmacology).
3. *Lactation:* Folic acid is actively excreted in human breast milk. Problems in humans have not been documented with intake of normal daily requirements of folic acid during lactation.

4. Alcohol interferes with the absorption and metabolism of folic acid. Those who drink large amounts of alcohol develop this deficiency.

5. Folic acid may interfere with the action of anticonvulsant drugs.

6. Folic acid therapy in folate-deficient individuals may decrease serum levels of phenytoin.

7. Separate the dose of pancreatin from the dose of folate by at least two hours in order to avoid absorption problems.

8. Methotrexate for rheumatoid arthritis, juvenile rheumatoid arthritis, or psoriasis: evidence suggests that folate supplements may reduce side effects of the drug without decreasing its benefits. Nonetheless, physician supervision is highly recommended. If methotrexate is taken for other conditions, folate might decrease the drug’s effectiveness.

   Although folic acid is not effective in the treatment of methotrexate overdose, it is used during long-term methotrexate therapy to prevent or treat associated folate deficiency, prevent methotrexate toxicity and to prevent hyperhomocysteinemia.

**DOSAGE AND ADMINISTRATION**

*To prevent deficiency:* Adequate dietary intake of folic acid is preferred over supplementation whenever possible.

*Treatment of deficiency: Oral:* The usual therapeutic dosage of folic acid for adults and children is 0.25 mg to 1 mg/day, however, some patients may require higher doses. Within the first 48 hours of treatment, the bone marrow begins to become normoblastic. Reticulocytosis begins within 2 to 5 days. To maintain a normoblastic marrow, lower maintenance doses of folic acid are used: adults and children 4 years and over 0.4 mg; children up to 4 years 0.3 mg; infants 0.1 mg. Higher maintenance doses may be required in certain patients such as alcoholics, patients with haemolytic anaemia or chronic infections, renal dialysis patients, pregnant women or patients taking certain anticonvulsants (e.g., valproic acid or carbamazepine).

Higher doses have been recommended for the treatment of tropical sprue: 3 to 15 mg daily.

*Prophylaxis of Neural Tube Defects (NTD):* Health Canada’s 2002 statement on folic acid recommends that women who could become pregnant should take a multivitamin containing 0.4 mg to 1 mg of folic acid every day, in addition to their dietary folate intake. Supplementation should start at least 2 to 3 months before conception and continue throughout pregnancy, 4 to 6 weeks postpartum and as long as breastfeeding continues [*J Obstet Gynaecol Can*]
The critical time for formation of the neural tube is shortly after conception.

Women with a history of pregnancy complicated by NTD are considered at high risk for recurrence and are advised to take 5 mg folic acid daily under physician supervision while not using reliable birth control (or 3 months prior to conception), continuing for 10 to 12 weeks after the last menstrual period. Thereafter, supplementation with 0.4 mg to 1 mg daily throughout pregnancy and 4 to 6 weeks postpartum or as long as breastfeeding continues is recommended. Higher doses (4 to 5 mg daily) should not be taken with a multivitamin because of the risk of intake of harmful amounts of other components such as vitamins A and D.

Some women with no previous history of NTD-affected pregnancy may be at increased risk due to a 1st degree relative (child, sibling or parent) with NTD, belonging to a high-risk group (e.g., Celtic, northern Chinese, Sikh heritage), or certain medical conditions (e.g., type I diabetes, therapy with valproic acid or carbamazepine, BMI >35 kg/m², malabsorption disorders). Such women should consider taking folic acid 5 mg daily under physician supervision when not using reliable birth control (or 3 months prior to conception), continuing until 10 to 12 weeks after the last menstrual period.

Prevention of methotrexate toxicity: (see Indications): 0.4 to 1 mg daily.

Missed dose: Women should not take more than the prescribed daily dose. If a dose is missed, for one or more days, do not try to ‘catch up’ by taking the missed dose(s) all at one time. Contact your doctor or pharmacist for more information.

OVERDOSAGE

For management of a suspected drug overdose, contact your regional Poison Control Centre.

ACTION AND PHARMACOLOGY

Pharmacology

Folic acid deficiency can lead to megaloblastic and macrocytic anemias, as a result of impairment of thymidylate synthesis.

Folic acid occurs in a variety of foods in the form of polyglutamate complexes. Folic acid found in pharmaceutical preparations is synthetically derived.

Many plant and animal tissues contain folic acid (pteroylglutamic acid, folacin, vitamin B₂) as reduced methyl or formyl polyglutamates. In the tetrahydro form, folates act as coenzymes for processes in which there is a transfer of a one-carbon unit (e.g., in purine and pyrimidine nucleotide biosynthesis), amino acid conversions (e.g., histidine to glutamic acid through formiminoglutamic
acid), generation and use of formate, maturation of RBCs, neural function, DNA synthesis related to folate coenzyme, and methionine synthesis.

Folic acid is a water soluble B complex vitamin and is essential in the body for the formation of new cells. It is involved in the metabolism of DNA and RNA, deoxyribonucleic acid and ribonucleic acid respectively, and is required for normal growth, development and functioning of the foetus, nervous system and bone marrow.

Folates act as coenzymes for two sets of cellular reactions. The first involves methylation reactions that are central to amino acid metabolism. For example, folate plays an important role in the conversion of homocystine to methionine. (Vitamin B₁₂ is also a coenzyme for this reaction) Methionine in turn a central building block for proteins. It plays a further role in phospholipids synthesis and creatine- phosphate synthesis, two reactions vital to the survival of the cell and the organism. Folate’s second important function as a coenzyme is in the synthesis of nucleic acids, i.e., of DNA and RNA. In this capacity, folate is essential to normal cell replication and embryonic development.

Absorption occurs in the gastrointestinal tract (duodenum and upper jejunum). Folic acid is converted in the liver into tetrahydrofolic acid that is a cofactor in the biosynthesis of purines and thymidylates of nucleic acids. An exogenous source of folic acid necessary for the synthesis of nucleoproteins and maintenance of normal erythropoiesis. In the epithelial cells, food polyglutamates are reduced to dihydrofolates and tetrahydrofolates. They are bound to protein and transported as methyltetrahydrofolate. Serum levels vary from 4 to 21 ng/mL (9 to 48 nmol/L) and closely reflect dietary intake. RBC folate (normal, 225 to 640 ng/mL whole blood [510 to 1450 nmol/L] corrected to packed cell volume of 45%) is a better indicator of folate tissue status. Total body folate is about 70 mg, of which 1/3 is found in the liver. About 20% of ingested folate is secreted unabsorbed together with 60 to 90 mcg/day not reabsorbed from bile.

Alcohol interferes with its intermediate metabolism, intestinal absorption, and enterohepatic salvage. Hence marginal dieters and chronic alcoholics are prone to macrocytic anaemia from folate deficiency, as are those with chronic liver disease. Because the foetus obtains folate from maternal supplies, pregnant women are susceptible to megaloblastic anaemia. In tropical sprue, malabsorption is secondary to the atrophy of intestinal mucosa resulting from the lack of folate, so even minute doses usually correct both anaemia and steatorrhea. Folate deficiency may develop in patients taking long-term anticonvulsant therapy or oral contraceptives, due to decreased absorption, or in patients taking antimetabolites (methotrexate) and antimicrobial drugs (e.g., trimethoprim-sulfa- methoxazole) that interfere with folate metabolism. Increased demand for folate occurs in pregnant and lactating patients with chronic (especially congenital) haemolytic anaemias or psoriasis and in patients on long-term dialysis.
### CAUSES OF FOLATE DEFICIENCY

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<thead>
<tr>
<th>CAUSE</th>
<th>SOURCE</th>
</tr>
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<tbody>
<tr>
<td>Inadequate intake</td>
<td>Diet lacking fresh, slightly cooked food; chronic alcoholism; TPN</td>
</tr>
<tr>
<td>Inadequate absorption</td>
<td>Malabsorption syndromes (especially celiac disease, sprue), drugs (phenytoin, primidone, barbiturates, cycloserine, oral contraceptives), folic acid malabsorption (congenital, acquired), blind loop syndrome.</td>
</tr>
<tr>
<td>Inadequate utilization</td>
<td>Folic acid antagonists (methotrexate, pyrimethadine, triamterene, diamidine compounds, trimethoprim), anticonvulsants, enzyme deficiency (congenital, acquired), vitamin B$_{12}$ deficiency, alcoholism, scurvy</td>
</tr>
<tr>
<td>Increased requirement</td>
<td>Pregnancy, lactation, infancy, malignancy (especially lymphoproliferative), increased haemopoiesis (especially β-thalassemia major), increased metabolism</td>
</tr>
<tr>
<td>Increased excretion</td>
<td>Renal dialysis (peritoneal or haemodialysis); vitamin B$_{12}$ dependency, liver disease</td>
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Deficiency of folic acid is quite common and can be caused by inadequate intake, problems with absorption and metabolism or increased requirements. Symptoms of severe deficiency include:

- Loss of appetite
- Abdominal pain
- Sickness
- Diarrhoea
- Ulcers in the mouth
- In pregnancy: premature birth and/or malformation
- In children: growth retardation

1. Folic acid is a B complex vitamin, which after conversion to tetrahydrofolic acid, is necessary for normal erythropoiesis and nucleoprotein synthesis. It is important for carbohydrate metabolism and healthy mucous membranes.

2. Because Folic Acid is a water-soluble vitamin, it is not stored in the body in appreciable amounts and as a result a daily supply is essential to prevent depletion.

3. Folic acid dependency results from a genetic defect in the metabolism of the vitamin or in the binding of the vitamin-related coenzyme to its apoenzyme. In some instances, doses much higher than the recommended dietary allowance (RDA) improve the function of the altered metabolic pathway. Patients on long-term dialysis commonly receive multivitamin supplements (to replace estimated dialytic loss of the water-soluble vitamins B-complex, folic acid and vitamin C).
4. Folic acid and vitamin B\textsubscript{12} function interdependently in the formation of normal red blood cells and in the production of DNA, and thymidine. A deficiency of either of these vitamins results in a serious anaemia (such as pernicious anaemia), in which the red blood cells are few in number but large in size. Symptoms include paleness, weakness, reduced acid secretion in the stomach, and nerve damage (neuropathy). Nerve damage occurs mainly in vitamin B\textsubscript{12} deficiency. Folic acid deficiency can lead to megaloblastic and macrocytic anaemias as a result of impairment of thymidylate synthesis. Within 48 hours of beginning treatment with folic acid, the bone marrow of patients with megaloblastic anaemia due to folate deficiency begins to become normoblastic. In megaloblastic anaemias due to folate deficiency, the megaloblastic erythropoiesis disappears within 48 hours of initiation of treatment and the reticulocyte count begins to increase within 2 to 5 days, reaching a maximum at 5 to 7 days.

5. Studies have provided strong scientific support for periconceptual prophylaxis with folic acid in reducing the risk of foetal neural tube defects. Folic acid deficiency may occur in pregnant women on diets that lack green leafy vegetables and legumes that contain folic acid. Infants may develop folic acid deficiency when the folic acid content of their formula is low. Treatment of folic acid deficiency consists of folic acid taken orally. Infants may have neurological abnormalities, and this deficiency in a pregnant woman can cause spinal cord defects and other malformations of the foetus.

6. Folic acid polyglutamates from food sources are enzymatically hydrolized in the gastrointestinal tract to monoglутamates prior to absorption, which occurs mainly in the proximal small intestine. In the presence of malabsorption syndrome, folic acid from oral supplements will still be absorbed whereas absorption of folic acid from food sources may be impaired.

**Pharmacokinetics**

Following absorption of 1 mg or less, folic acid is converted in the liver and plasma into its metabolically active form tetrahydrofolic acid, which is then distributed into all body tissues. The liver contains about 50% of total body folate stores. Larger doses of folic acid may escape metabolism by liver and appear in the blood mainly as folic acid.

Following oral administration of single 0.1 to 0.2 mg doses of folic acid in healthy adults, only a trace amount of the drug appears in urine. Following administration of large doses, the renal tubular reabsorption maximum is exceeded, and excess folate is excreted unchanged in urine. After doses of about 2.5 to 5.0 mg, about 50% of a dose is excreted in urine and after a 15 mg dose, up to 90% may be recovered in urine. Small amounts of orally administered folic acid have been recovered from feces.
STORAGE AND STABILITY

Store at room temperature 15°C to 30°C, Protect from light.

SPECIAL HANDLING INSTRUCTIONS

No special handling required.

DOSAGE FORMS, COMPOSITION, PACKAGING

FOLIC ACID tablet is a yellow, round, flat-faced, bevelled-edge tablet. Scored and engraved 5 on one side, other side plain. Available in bottles of 100 and 1000 tablets.

Refer to “Summary Product Information” for composition.

CONTACT INFORMATION

For questions or concerns regarding the use of this product, please call: 1-877-998-9097.

REFERENCES

1. The Food and Drugs Act and Regulations
4. US Pharmacopoeia, USP 28/NF23, official 8/1/05 to 12/31/05; Folic Acid monograph P.869, Pharmacopeial Forum: Volume No. 29(2) Page 409; Folic Acid Tablets monograph P.870, Pharmacopeial Forum: Volume No.29(2) Page 409; Staff Liaison Lawrence Evans, III, PhD
10. CPhA Monograph – Pr Folic Acid (folic acid) Tablets 0.4 mg, 1 mg, 5 mg, and Injectable solution 5 mg/mL. Date of Revision: July 2012.

**Reporting Side Effects**

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting ([https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada/adverse-reaction-reporting.html](https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada/adverse-reaction-reporting.html)) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

*NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.*

AA Pharma Inc.
1165 Creditstone Road, Unit #1
Vaughan, Ontario, Canada L4k 4N7

Questions or Concerns: 1-877-998-9097

This leaflet was prepared by AA Pharma Inc.

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