1.5 Product Information: FOLIC ACID TABLETS

1.5.1 Prescribing information (Summary of products characteristics):

1. Name of the Medicinal Product: FOLIC ACID TABLETS
Strength: Each uncoated tablets contains Folic Acid BP 5 mg
Pharmaceutical form: Oral Tablets

2. Qualitative and Quantitative composition:

Qualitative composition:

Sr. No.	Ingredient	Specification	Uses
1.	Lactose	BP	Diluent
2.	Maize starch (mixing)	BP	Diluent
3.	Dicalcium phosphate	BP	Diluent
4.	Maize starch (paste)	BP	Binding agent
5.	Sodium methyl paraben	BP	Preservative
6.	Sodium propyl paraben	BP	Preservative
7.	Folic acid	BP	Active
8.	Purified talc	BP	Glidant
9.	Magnesium stearate	BP	Lubricant

CTD MODULE 1 ADMINISTRATIVE INFORMATION AND PRODUCT INFORMATION	
Product Name :	**FOLIC ACID TABLETS (Folic acid BP 5mg)**

Quantitative composition:

Component and quality standard (and grade, if applicable)	**Function**	**Strength (label claim)**			
		Each uncoated tablets contains Folic Acid BP 5 mg			
		Quantity in mg per tablet	**%**	**Quantity in Kg Per 3,000,000 Tablets**	**%**
Contents of **FOLIC ACID TABLETS**					
Lactose	Diluent	27.000	28.00	81.000	28.00
Maize starch (mixing)	Diluent	27.000	28.00	81.000	28.00
Dicalcium phosphate	Diluent	27.000	28.00	81.000	28.00
Maize starch (paste)	Binding agent	6.000	6.00	18.000	6.00
Sodium methyl paraben	Preservative	0.100	0.00	0.300	0.00
Sodium propyl paraben	Preservative	0.050	0.00	0.150	0.00
Folic acid	Active	5.500	5.00	16.500	5.00
Purified talc	Glidant	2.350	2.00	7.050	2.00
Magnesium stearate	Lubricant	3.000	3.00	9.000	3.00
Total	NA	98.000	100.00	294.000	100.00

3. Pharmaceutical form: Oral Tablets

4. Clinical particular's:

4.1 Therapeutic indication:

In treatment of folate-deficient megaloblastic anaemia.
For prophylaxis in chronic haemolytic states or in renal dialysis.

4.2 Posology and method of administration:

In folate-deficient megaloblastic anaemia
Adults, children over age of 1 year and elderly.
Initially 5 mg daily for 4 months or until a haemotopoietic response has been obtained. Up to 15 mg may be recommended in malabsorption states. Maintenance dose - one 5 mg tablet every 1 - 7 days depending on the underlying disease.
For prophylaxis in chronic haemolytic states or in renal dialysis.
5 mg daily or even weekly, depending on the diet and the rate of haemolysis.
Children up to 1 year of age
500 microgram per kg of body weight daily. Oral administration.

4.3 Contraindication:

• Long-term folate therapy is contraindicated in any patient with untreated cobalamin deficiency. This can be untreated pernicious anaemia or other cause of cobalamin deficiency, including lifelong vegetarians. In elderly people, a cobalamin absorption test should be done before long-term folate therapy. Folate given to such patients for 3 months or longer has precipitated cobalamin neuropathy. No harm results from short courses of folate.
• Folic acid should never be given alone in the treatment of Addisonian pernicious anaemia and other vitamin B_{12} deficiency states because it may precipitate the onset of subacute combined degeneration of the spinal cord.
• Folic acid should not be used in malignant disease unless megaloblastic anaemia owing to folate deficiency is an important complication.
• Known hypersensitivity to the active ingredient or any of the excipients.

4.4 Special warning and precaution for use:

It is important to establish which deficiency is present and the underlying cause before commencing treatment.
Patients with vitamin B_{12} deficiency should not be treated with folic acid unless administered with adequate amounts of hydroxocobalamin, as it can mask the condition but the subacute irreversible damage to the nervous system will continue. The deficiency can be due to undiagnosed megaloblastic anaemia including in infancy, pernicious anaemia or macrocytic anaemia of unknown aethiology or other cause of cobalamin deficiency, including lifelong vegetarians.

Therefore a full clinical diagnosis should be made before initiating treatment.
Folate should not be routinely used in patients receiving coronary stents
Caution should be exercised when administering folic acid to patients who may have folate dependent tumours.
Folic acid is removed by haemodialysis.
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 medicinal products and other forms of interactions:

Caution should be exercised when administering folic acid to epileptics. It may cause reduction in the plasma concentrations of phenytoin, primidone, phenobarbital, sodium valproate, carbamazepine and the barbiturates.
Trimethoprim or sulfonamides, alone or in combination as co-trimoxazole, may reduce the effect of folic acid and this may be serious in patients with megaloblastic anaemia.
Sulphasalazine and triamterene can reduce the absorption of folic acid.
Folic acid may interfere with the toxic and therapeutic effects of methotrexate.
Methotrexate and trimethoprim are specific anti-folates and the folate deficiency caused by their prolonged use cannot be treated by Folic Acid Tablets. Folinic acid should be used.
Folate supplements enhance the efficacy of lithium therapy. Nitrous oxide anaesthesia may cause an acute folic acid deficiency. Both ethanol and aspirin increase folic elimination.
Concurrent administration with cholestyramine may interfere with folic acid absorption.
Patients on prolonged cholestyramine therapy should take folic acid 1 hour before or 4 to 6 hours after receiving cholestyramine.
Antibiotics may interfere with the microbiological assay for serum and erythrocyte folic acid concentrations and may cause falsely low results.
Fluorouracil toxicity may occur in patients taking folic acid and this combination should be avoided.
Edible clay or antacids containing aluminium or magnesium may reduce folic acid absorption. Patients should be advised to take antacids at least two hours after administration of folic acid.
Folic acid may reduce intestinal absorption of zinc (of particular importance in pregnancy).

Additional information on special populations:

Not Applicable

Pediatric population:

Not Applicable

4.6 Fertility, pregnancy and lactation:

Pregnancy

• There are no known hazards to the use of folic acid in pregnancy, supplements of folic acid are often beneficial.

• Non-drug-induced folic acid deficiency, or abnormal folate metabolism, is related to the occurrence of birth defects and some neural tube defects. Interference with folic acid metabolism or folate deficiency induced by drugs such as anticonvulsants and some antineoplastics early in pregnancy results in congenital anomalies. Lack of the vitamin or its metabolites may also be responsible for some cases of spontaneous abortion and intrauterine growth retardation.

• Imbalance in folate requiring trophoblast cells may also lead to detachment of the placenta.

• Very high doses of folic acid have been shown to cause foetal abnormalities in rats; however, harmful effects in the human foetus, mother or the pregnancy have not been reported following ingestion of folic acid.

Lactation

• Folic acid is actively excreted in human breast milk. Accumulation of folate in milk takes precedence over maternal folate needs. Levels of folic acid are relatively low in colostrum but as lactation proceeds, concentrations of the vitamin rise. No adverse effects have been observed in breast fed infants whose mothers were receiving folic acid.

4.7 Effects on ability to drive and use machines:

None known.

4.8 Undesirable effects:

Folic acid is generally well tolerated although the following side effects have been reported:

Gastrointestinal disorders Rare (≥1/10,000 to <1/1,000)	Anorexia, nausea, abdominal distension and flatulence
Immune system disorders Rare (≥1/10,000 to <1/1,000) Not known	Allergic reactions, comprising erythema, rash, pruritus, urticaria, dyspnoea, and anaphylactic reactions (including shock). Anaphylactic reaction
Blood and lymphatic system disorders	Folic acid may worsen the symptoms of co-existing vitamin B_{12} deficiency and should never be used to treat anaemia without a full investigation of the cause.

4.9 Overdose and Treatment:

No cases of acute over dosage appear to have been reported, but even extremely high doses are unlikely to cause harm to patients.

No special procedure or antidote is likely to be needed, treat symptomatically.

5. Pharmacological Properties:

5.1 Pharmacodynamic properties:

Folic acid is a member of the vitamin B group. Folic acid is reduced in the body to tetrahydrofolate, which is a co-enzyme for various metabolic processes including the synthesis of purine and pyrimidine nucleotides, and hence in the synthesis of DNA; it is also involved in the formation and utilisation of formate.
Deficiency of folic acid leads to megaloblastic anaemia. Deficiency may result from a diminished intake, as in malnutrition, from malabsorption, or from the concomitant use of anticonvulsants or dihydrofolate reductase inhibitors such as pyrimethamine, trimethoprim, or methotrexate.

5.2 Pharmacokinetic properties:

Folic acid is absorbed mainly from the proximal part of the small intestine.
Dietary folates are stated to have about half the bioavailability of crystalline folic acid.Folate polyglutamates are considered to be deconjugated to monoglutamates during absorption.
Folic acid given therapeutically enters the portal circulation largely unchanged, since it is a poor substrate for reduction by dihydrofolate reductases.
Folic acid rapidly appears in the blood, where it is extensively bound to plasma proteins. The principal storage site of folate is in the liver; it is also actively concentrated in the CSF. The amounts of folic acid absorbed from normal diets are rapidly distributed in body tissues and about 4 to 5 ug is excreted in the urine daily.
There is an enterohepatic circulation for folate.
When larger amounts are absorbed a high proportion is metabolised in the liver to other active forms of folate and a proportion is stored as reduced and methylated folate.
Larger amounts of folate are rapidly excreted in the urine. Folic acid is removed by haemodialysis.
Folate is distributed into breast milk.

5.3 Preclinical safety data:

Toxicity studies in animals (rats and rabbits) have shown that massive doses (100mg/kg upwards) produce precipitation of folate crystals in renal tubules, particularly proximal tubules and ascending limb of the loop of Henle.
Tubular necrosis is followed by recovery.

6. Pharmaceutical Particulars:

6.1 List of excipients

Folic acid Tablets contains the following excipients:

Lactose, Maize starch, Dicalcium phosphate, Sodium methyl paraben, Sodium propyl paraben, Purified talc, Magnesium stearate.

6.2 Incompatibilities

None known

6.3 Shelf life

24 Months

6.4 Special precaution for storage

Store in a cool, dry place below 30°C. Keep out of reach of children. Protect from light and moisture.

6.5 Nature and contents of container

Aluminium / amber PVC blister strip of 10x10 tablets in a unit box along with pack insert.

1000 tablets packed in polythene bag and contained in HDPE container with leaflet.

6.6 Special precautions for disposal

No special precaution

7. MARKETING AUTHORISATION HOLDER AND MANUFACTURING SITE ADDRESSES:

Marketing Authorization Holder:
Rene Industries Ltd
Address: PO Box 6034, Plot No.680, Kamuli, Kireka, Kampala, Uganda.

Manufactured by:
Rene Industries Ltd
Address: PO Box 6034, Plot No.680, Kamuli, Kireka, Kampala, Uganda.

8. MARKETING AUTHORISATION NUMBER:

Not Applicable

9. DATE OF FIRST REGISTRATION/RENEWAL OF THE REGISTRATION:

Not Applicable

10. DATE OF REVISION OF THE TEXT:

Not Applicable

11. DOSIMETRY (IF APPLICABLE):

Not Applicable

12. INSTRUCTIONS FOR PREPARATION OF RADIOPHARMACEUTICALS (IF APPLICABLE):

Not Applicable