CYNOBAC Tablet

1.Generic name

Lactic acid bacillus, Folic acid and Vitamin B_{12} Tablets

2. Qualitative or Quantitative composition

Each uncoated tablet contains:
Lactic Acid Bacillus - 180 million
[Lactic acid producing bacillus earlier known as Lacobacillus sporogenes]
Folic Acid IP 1500 mcg
Vitamin B_{12} IP 15 mcg
[Adequate overages added]

3. Dosage form and strength

Solid dosage form (Tablet)
Strength – Lactic Acid Bacillus 180 million
Folic Acid IP 1500 mcg
Vitamin B_{12} IP 15 mcg

4.Clinical particulars

a. Therapeutic indications

- Antibiotic associated diarrhea
- Traveler's diarrhea

b. Posology and method of administration

Posology – One tablet daily at least for 30 days or as advised by the physicians.
Method of administration – Through mouth (Orally – Tablet)

c. Contraindications

Not Reported

d. Special warning and precautions

None

e. Drug interaction

None established for the formulation as a whole or for Lactic Acid Bacillus.

In order to function within the body, folic acid must first be reduced by the enzyme dihydrofolate reductase (DHFR) into the cofactors dihydrofolate (DHF) and tetrahydrofolate (THF). This important pathway, which is required for de novo synthesis of nucleic acids and amino acids, is disrupted by anti-metabolite therapies such as methotrexate as they function as DHFR inhibitors to prevent DNA synthesis in rapidly dividing cells, and therefore prevent the formation of DHF and THF.

There are multiple antiepileptic drugs that are associated with reduced serum and red blood cell folate, including Carbamazepine (CBZ), Phenytoin (PHT), or barbiturates.7 Folic acid is therefore often provided as supplementation to individuals using these medications, particularly to women of child-bearing age.

In an uncontrolled study, orally administered folic acid was reported to increase the incidence of seizures in some epileptic patients receiving phenobarbital, primidone, or diphenylhydantoin. Another

investigator reported decreased diphenylhydantoin serum levels in folate-deficient patients receiving diphenylhydantoin who were treated with 5 mg or 15 mg of folic acid daily.

f. Uses in special population (e.g. pregnant women, lactating women, etc.)

Lactobacillus and other probiotics not absorbed through GI tract. Hence probiotics are safe to be administered to pregnant and nursing mother.

Vitamin B12 and Folic acid are essential nutrients for pregnant mothers. Both are important ingredients of human milk. Vitamin B12 has been found distributed into the milk of nursing women in concentrations similar to the maternal blood vitamin B12 concentrations. No adverse effects have been reported to date with intake of recommended doses.

g. Effects on ability to drive and use machines

None

h. Undesirable effect

Folic acid is relatively nontoxic in man. Rare instances of allergic responses to folic acid preparations have been reported and have included erythema, skin rash, itching, general malaise, and respiratory difficulty due to bronchospasm.

Gastrointestinal side effects, including anorexia, nausea, abdominal distention, flatulence, and a bitter or bad taste, have been reported in patients receiving 15 mg folic acid daily for 1 month. Other side effects reported in patients receiving 15 mg daily include altered sleep patterns, difficulty in concentrating, irritability, overactivity, excitement, mental depression, confusion, and impaired judgment. Decreased vitamin B12 serum levels may occur in patients receiving prolonged folic acid therapy.

i. Overdose

Except during pregnancy and lactation, folic acid should not be given in therapeutic doses greater than 0.4 mg daily until pernicious anemia has been ruled out. Patients with pernicious anemia receiving more than 0.4 mg of folic acid daily who are inadequately treated with vitamin B12 may show reversion of the hematologic parameters to normal, but neurologic manifestations due to vitamin B12 deficiency will progress. Doses of folic acid exceeding the Recommended Dietary Allowance (RDA) should not be included in multivitamin preparations; if therapeutic amounts are necessary, folic acid should be given separately.

5. Pharmacological properties

a. Pharmacodynamics

Lactic Acid Bacillus - *Lactobacillus sporogenes* (According to new taxonomic guidelines, the name of the strain is *Bacillus coagulants*) are Gram-positive, spore forming rods, aerobic to microaerophilic and produce L(+) lactic acid homo fermentatively. They have a growth temperature range of 35 to 50 °C and optimum pH range of 5.5 to 6.5. After administration of *Lactobacillus sporogenes*, it crosses the gastric acidity of stomach and bile of duodenum (in duodenum germination of spores takes place). When they reach intestine, germinated spores are transformed into "vegetative cells" which are metabolically quite active. Enzymes and polypeptide activity occurs after spore germination and vegetative cell growth. After reaching intestine, they multiply quickly and inhibit the growth of unwanted bacteria.

Folic acid – Folic acid is a water-soluble B-complex vitamin found in foods such as liver, kidney, yeast, and leafy, green vegetables. Also known as folate or Vitamin B9, folic acid is an essential cofactor for enzymes involved in DNA and RNA synthesis. More specifically, folic acid is required by the body for the synthesis of purines, pyrimidines, and methionine before incorporation into DNA or protein. Folic

acid is the precursor of tetrahydrofolic acid, which is involved as a cofactor for transformylation reactions in the biosynthesis of purines and thymidylates of nucleic acids. Impairment of thymidylate synthesis in patients with folic acid deficiency is thought to account for the defective deoxyribonucleic acid (DNA) synthesis that leads to megaloblast formation and megaloblastic and macrocytic anemias. Folic acid is particularly important during phases of rapid cell division, such as infancy, pregnancy, and erythropoiesis, and plays a protective factor in the development of cancer. As humans are unable to synthesize folic acid endogenously, diet and supplementation is necessary to prevent deficiencies. In order to function properly within the body, folic acid must first be reduced by the enzyme dihydrofolate reductase (DHFR) into the cofactors dihydrofolate (DHF) and tetrahydrofolate (THF).

Vitamin B12 – This ingredient corrects vitamin B12 deficiency and improves the symptoms and laboratory abnormalities associated with pernicious anemia (megaloblastic indices, gastrointestinal lesions, and neurologic damage). This drug aids in growth, cell reproduction, hematopoiesis, nucleoprotein, and myelin synthesis. It also plays an important role in fat metabolism, carbohydrate metabolism, as well as protein synthesis. Cells that undergo rapid division (for example, epithelial cells, bone marrow, and myeloid cells) have a high demand for vitamin B12. It serves as a cofactor for methionine synthase and L-methylmalonyl-CoA mutase enzymes. Methionine synthase is essential for the synthesis of purines and pyrimidines that form DNA. L-methylmalonyl-CoA mutase converts L-methylmalonyl-CoA to succinyl-CoA in the degradation of propionate 24, an important reaction required for both fat and protein metabolism. It is a lack of vitamin B12 cofactor in the above reaction and the resulting accumulation of methylmalonyl CoA that is believed to be responsible for the neurological manifestations of B12 deficiency 10. Succinyl-CoA is also necessary for the synthesis of hemoglobin.

b. Pharmacokinetics

Lactic Acid Bacillus – It is non-systemic and is not absorbed in intestine and therefore does not reach circulation.

Folic acid – It is absorbed rapidly from the small intestine, primarily from the proximal portion. Naturally occurring conjugated folates are reduced enzymatically to folic acid in the gastrointestinal tract prior to absorption. Folic acid appears in the plasma approximately 15 to 30 minutes after an oral dose; peak levels are generally reached within 1 hour. THF derivatives are distributed to all body tissues but are stored primarily in the liver. There is high binding to plasma proteins. Folic acid is metabolized in the liver into the cofactors DHF and THF by the enzyme dihydrofolate reductase (DHFR). After a single oral dose of 100 mcg of folic acid in a limited number of normal adults, only a trace amount of the drug appeared in the urine. An oral dose of 5 mg in 1 study and a dose of 40 mcg/kg of body weight in another study resulted in approximately 50% of the dose appearing in the urine. After a single oral dose of 15 mg, up to 90% of the dose was recovered in the urine. A majority of the metabolic products appeared in the urine after 6 hours; excretion was generally complete within 24 hours. Small amounts of orally administered folic acid have also been recovered in the feces. Folic acid is also excreted in the milk of lactating mothers.

Vitamin B12 – Cyanocobalamin and other Vitamin B12 derivatives bind to intrinsic factor, a glycoprotein secreted by the gastric mucosa, and are then actively absorbed from the gastrointestinal tract. Absorption is impaired in patients with an absence of intrinsic factor, with a malabsorption syndrome or with disease or abnormality of the gut, or after gastrectomy. Vitamin B12 is extensively bound to specific plasma proteins called transcobalamin; transcobalamin II appears to be involved in the rapid transport of the cobalamins to tissues. Vitamin B12 is stored in the liver, excreted in the bile, and undergoes extensive enterohepatic recycling; part of a dose is excreted in the urine.

Passive diffusion through the intestinal wall can occur, however, high doses of vitamin B12 are required in this case (i.e. >1 mg). After the administration of oral doses less than 3 mcg, peak plasma concentrations are not reached for 8 to 12 hours, because the vitamin is temporarily retained in the wall of the lower ileum. Cobalamin is distributed to tissues and stored mainly in the liver and bone marrow.

After absorption into enterocytes, intrinsic factor is broken down in the lysosome, and cobalamin is then released into the bloodstream. The transporter ABCC1, found in the basolateral membrane of intestinal epithelial and other cells, exports cobalamin bound to transcobalamin out of the cell. Cyanocobalamin then passes through the portal vein in the liver, and then reaches the systemic circulation. In the process it is converted to active forms like methylcobalamin and S-adenosylcobalamin. Vitamin B12 is partially excreted in the urine. A small amount is also secreted into the gastrointestinal tract daily via the bile. In patients with adequate levels of intrinsic factor, all except approximately 1 mcg is reabsorbed. When vitamin B12 is administered in higher doses that saturate the binding capacity of plasma proteins and the liver, the unbound vitamin B12 is eliminated rapidly in the urine. The body storage of vitamin B12 is dose-dependent.

6. Product description

Yellow color flat circular tablet with STRASSENBURG engraved on upper face.

7. Pharmaceutical particulars

a. Incompatibility – not reported

b. Shelf life – 30 months from the month of manufacture

c. Packaging information – 20x10's packed in amber color blister

d. Storage – Store in a cool place, protected from light & moisture

8. Patient counselling information

CONTRAINDICATIONS : Folic acid and Vitamin B12 are contraindicated in patients who have shown previous intolerance to the drug.

WARNINGS : Administration of folic acid alone is improper therapy for pernicious anemia and other megaloblastic anemias in which vitamin B12 is deficient.

9. Details of manufacturer: **Strassenburg Pharmaceuticals Ltd.**
D. H. Road, 24 Parganas (S), West Bengal - 743503

10. Details of license no.: **DL-632-MB**