For the use of a Registered Medical Practitioner or a Hospital or a Laboratory only

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B Long F Tablets
(Pyridoxine hydrochloride sustained release and Folic Acid tablets)

COMPOSITION

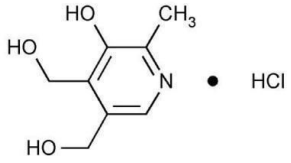
Each sustained release tablets contains

Pyridoxine hydrochloride (as sustained release)	IP	100mg
Folic acid	IP	5mg

DESCRIPTION

Pyridoxine hydrochloride

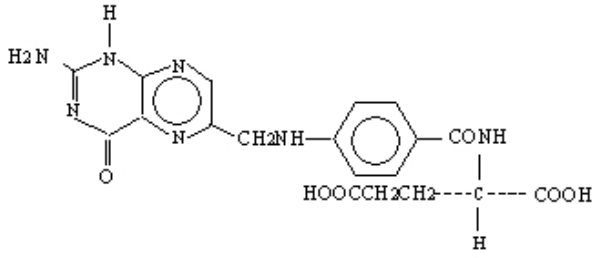
Pyridoxine hydrochloride is a vitamin B6 analog. The chemical name for pyridoxine hydrochloride is 3,4-pyridinedimethanol, 5-hydroxy-6-methyl-, hydrochloride. The empirical formula is $C_8H_{11}NO_3$ • HCl and the molecular mass is 205.64. The structural formula is:



Folic acid

Folic acid, N-[ρ-[[(2-amino-4-hydroxy-6-pteridinyl) methyl]-amino]benzoyl]-L-glutamic acid, is a B complex vitamin containing a pteridine moiety linked by a methylene bridge to para-aminobenzoic acid, which is joined by a peptide linkage to glutamic acid. Conjugates of folic acid are present in a wide variety of foods, particularly liver, kidneys, yeast, and leafy green vegetables. Commercially available folic acid is prepared synthetically. Folic acid occurs as a yellow or yellowish-orange crystalline powder and is very slightly soluble in water and insoluble in alcohol. Folic acid is readily soluble in dilute solutions of alkali hydroxides and carbonates and solutions of the drug may be prepared with the aid of sodium hydroxide or sodium carbonate, thereby forming the soluble sodium salt of folic acid (sodium folate). Aqueous solutions of folic acid are heat sensitive and rapidly decompose in the presence of light and/or riboflavin; solutions should be stored in a cool place protected from light.

The structural formula of folic acid is as follows:



$C_{19}H_{19}N_7O_6$ M.W. 441.40

CLINICAL PHARMACOLOGY

Pyridoxine hydrochloride

Pharmacodynamics

Natural substances that have vitamin B6 activity are pyridoxine in plants and pyridoxal or pyridoxamine in animals. All 3 are converted to pyridoxal phosphate by the enzyme pyridoxal kinase. The physiologically active forms of vitamin B6 are pyridoxal phosphate (codecarboxylase) and pyridoxamine phosphate. Riboflavin is required for the conversion of pyridoxine phosphate to pyridoxal phosphate.

Vitamin B6 acts as a coenzyme in the metabolism of protein, carbohydrate, and fat. In protein metabolism, it participates in the decarboxylation of amino acids, conversion of tryptophan to niacin or to serotonin (5-hydroxtryptamine), deamination, and transamination and transulfuration of amino acids. In carbohydrate metabolism, it is responsible for the breakdown of glycogen to glucose-1-phosphate.

The total adult body pool consists of 16 to 25 mg of pyridoxine. Its half-life appears to be 15 to 20 days. Vitamin B6 is degraded to 4-pyridoxic acid in the liver. This metabolite is excreted in the urine.

Pharmacokinetic

Pyridoxine readily absorbed from the gastrointestinal tract after oral dose and converted to the active forms pyridoxal phosphate and pyridoxamine phosphate. They are stored mainly in the liver where there is oxidation to 4-pyridoxic acid and other inactive metabolites which are excreted in the urine. As the dose increases, proportionally greater amounts are excreted unchanged in the urine. Pyridoxal crosses the placenta and is distributed into breast milk.

Folic acid

Pharmacodynamics

Folic acid acts on megaloblastic bone marrow to produce a normo-blastic marrow. In man, an exogenous source folate is required for nucleo-protein synthesis and the maintenance of normal erythropoiesis. 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 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. After intravenous administration, the drug is rapidly cleared from the plasma. Cerebrospinal fluid levels of folic acid are several times greater than serum levels of the drug. Folic acid is metabolized in the liver to 7,8-dihydrofolic acid and eventually to 5,6,7,8-tetrahydrofolic acid with the aid of reduced diphospho-pyridine nucleotide (DPNH) and folate reductases. Tetrahydrofolic acid is linked in the N5 or N10 positions

with formyl, hydroxymethyl, methyl, or formimino groups. N5-formyltetrahydrofolic acid is leucovorin. Tetrahydrofolic acid derivatives are distributed to all body tissues but are stored primarily in the liver. Normal serum levels of total folate have been reported to be 5 to 15 ng/mL; normal cerebro-spinal fluid levels are approximately 16 to 21 ng/mL. Normal erythrocyte folate levels have been reported to range from 175 to 316 ng/mL. In general, folate serum levels below 5 ng/mL indicate folate deficiency, and levels below 2 ng/mL usually result in megalo-blastic anemia.
After a single oral dose of a 100 μg 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 μg/kg of body weight in another study resulted in approximately 50% of the dose appearing in the urine. After a single 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.
Pharmacokinetic
Folic acid is rapidly absorbed from the gastrointestinal tract, mainly from the duodenum and jejunum. Dietary folates are stated to have about half the bioavailability of crystalline folic acid. The naturally occurring folate polyglutamates are largely deconjugated, and then reduced by dihydrofolate reductase in the intestines to form 5-methyltetrahydrofolate, which appears in the portal circulation, where it is extensively bound to plasma proteins. Folic acid given therapeutically enters the portal circulation largely unchanged, since it is a poor substrate for reduction by dihydrofolate reductase. It is converted to the metabolically active form 5- methyltetrahydrofolate in the plasma and liver. The principal storage site of folate is the liver; it is also actively concentrated in the CSF. Folate undergoes enterohepatic circulation. Folate metabolites are eliminated in the urine and folate in excess of body requirements is excreted unchanged in the urine. Folate is distributed into breast milk. Folic acid is removed by haemodialysis.

INDICATIONS
Treatment of pyridoxine and folic acid deficiency in pregnancy.

i) Unexplained infertility
ii) Female infertility due to Hyperprolactinemia
iii)Hyperhomocysteinemia
iv) Prophylaxis for neural tube defect.

CONTRAINDICATION
Pyridoxine hydrochloride
A history of sensitivity to pyridoxine or to any of the ingredients of formulation.

Folic acid
Folic acid is contraindicated in patients who have shown previous intolerance to the drug. Long term folate therapy is contraindicated in any patients with intreated cobalamin deficiency. This can be untreated pernicious anaemia or other cause of cobalamin deficiency, including lifelong vegetarians. No harm results from short course of folate.

WARNINGS AND PRECAUTIONS

Pyridoxine hydrochloride

WARNINGS

WARNING: This product contains aluminum that may be toxic. Aluminum may reach toxic levels with prolonged parenteral administration if kidney function is impaired. Premature neonates are particularly at risk because their kidneys are immature, and they require large amounts of calcium and phosphate solutions, which contain aluminum.

Research indicates that patients with impaired kidney function, including premature neonates, who receive parenteral levels of aluminum at greater than 4 to 5 mcg/kg/day accumulate aluminum at levels associated with central nervous system and bone toxicity. Tissue loading may occur at even lower rates of administration.

PRECAUTIONS

General

Single deficiency, as of pyridoxine alone, is rare. Multiple vitamin deficiency is to be expected in any inadequate diet. Patients treated with levodopa should avoid supplemental vitamins that contain more than 5 mg pyridoxine in the daily dose.

Women taking oral contraceptives may exhibit increased pyridoxine requirements.

Folic acid

WARNINGS

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

PRECAUTIONS

General

Folic acid in doses above 0.1 mg daily may obscure pernicious anemia in that hematologic remission can occur while neurologic manifestations remain progressive.

There is a potential danger in administering folic acid to patients with undiagnosed anemia, since folic acid may obscure the diagnosis of pernicious anemia by alleviating the hematologic manifestations of the disease while allowing the neurologic complications to progress. This may result in severe nervous system damage before the correct diagnosis is made. Adequate doses of vitamin B12 may prevent, halt, or improve the neurologic changes caused by pernicious anemia.

DRUG INTERACTION

Pyridoxine hydrochloride

Pyridoxine supplements should not be given to patients receiving levodopa, because the action of the latter drug is antagonized by pyridoxine. However, this vitamin may be used concurrently in patients receiving a preparation containing both carbidopa and levodopa.

Pyridoxine reduces the activity of altretamine.

It has also been reported to decrease serum concentrations of phenobarbital and phenytoin.

Folic acid

There is evidence that the anticonvulsant action of phenytoin is antagonized by folic acid. A patient whose epilepsy is completely controlled by phenytoin may require increased doses to prevent convulsions if folic acid is given.
Folate deficiency may result from increased loss of folate, as in renal dialysis and/or interference with metabolism (e.g. folic acid antagonists such as methotrexate); the administration of anticonvulsants, such as diphenylhydantoin, primidone, and barbiturates; alcohol consumption and, especially alcoholic cirrhosis; and the administration of pyrimethamine and nitrofurantoin.
False low serum and red cell folate levels may occur if the patient has been taking antibiotics, such as tetracycline, which suppress the growth of *Lactobacillus casei.*

ADVERSE EFECTS
Pyridoxine hydrochloride
Paresthesia, somnolence, and low serum folic acid levels have been reported.
Symptoms of dependence have been noted in adults given only 200 mg daily, followed by withdrawal.
Long-term use of large doses of pyridoxine is associated with the development of severe peripheral neuropathies (including severe sensory neuropathy); the dose at which these occur is controversial.

Folic acid
Allergic sensitization has been reported following both oral and parenteral administration of folic acid.
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.
One patient experienced symptoms suggesting anaphylaxis following injection of the drug. 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.
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.

OVERDOSAGE
Pyridoxine hydrochloride
Pyridoxine given to animals in amounts of 3 to 4 g/kg of body weight produces convulsions and death. In man, a dose of 25 mg/kg of body weight is well tolerated.

Folic acid

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.

DOSAGES AND ADMINISTRATION

B Long F one tablet once daily or as prescribed by the physician.

USE IN PREGNANCY, NURSING MOTHER, USE IN CHILDREN AND OLDER PATIENTS

Pyridoxine hydrochloride

Pregnancy

Pregnancy Category A-The requirement for pyridoxine appears to be increased during pregnancy. Pyridoxine is sometimes of value in the treatment of nausea and vomiting of pregnancy.

Nursing Mothers

The need for pyridoxine is increased during lactation. It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when pyridoxine hydrochloride is administered to a nursing woman.

Usage in Children

Safety and effectiveness in children have not been established.

Geriatric patient

Data are not available.

Folic acid

Pregnancy

Teratogenic Effects

Pregnancy Category A

Folic acid is usually indicated in the treatment of megaloblastic anemias of pregnancy. Folic acid requirements are markedly increased during pregnancy, and deficiency will result in fetal damage.

Studies in pregnant women have not shown that folic acid increases the risk of fetal abnormalities if administered during pregnancy. If the drug is used during pregnancy, the possibility of fetal harm appears remote. Because studies cannot rule out the possibility of harm, however, folic acid should be used during pregnancy only if clearly needed.

Nursing mothers

Folic acid is excreted in the milk of lactating mothers. During lactation, folic acid requirements are markedly increased; however, amounts present in human milk are adequate to fulfill infant requirements, although supplementation may be needed in low birth-weight infants, in those who are breast-fed by mothers with folic acid deficiency (50 μg daily), or in those with infections or prolonged diarrhea.

EXPIRY DATE
Do not use later than expiry date.

STORAGE
Store in cool and dry place. Protect from light.

PRESENTATION
Blister pack (1x30 tablets)

MANUFACTURED BY
Elder Pharmaceuticals Ltd.
Plot No. C-11/1, Industrial are,
Selaqui, Dehradun -248 197
Uttarakhand, India.

MARKETED BY


Torrent Pharmaceuticals Ltd.
Indrad-382 721, Dist Mehsana, India.