

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

ELMECOB PLUS

(Methylcobalamin, Alpha Lipoic Acid, Vitamins & Minerals capsules)

COMPOSITION

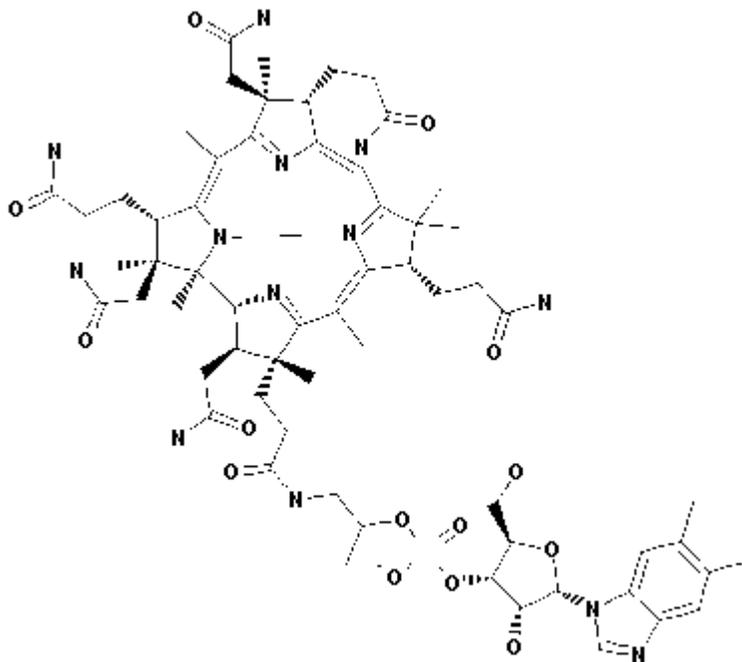
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|--|----------|
| Mecobalamin J.P. | 1500 mcg |
| (Methylcobalamin) | |
| Alpha Lipoic Acid U.S.P. | 100 mg |
| Vitamin B ₆ I.P. | 3 mg |
| Folic Acid I.P. | 1.5 mg |
| Zinc (As Zinc Sulphate I.P.) | 15 mg |
| Chromium (As Chromium Picolinate U.S.P.) | 60 mcg |
| Selenium (As Selenium Dioxide U.S.P.) | 65 mcg |
| Biotin U.S.P. | 100 mcg |
| Inositol U.S.P. | 2 mg |

Approved colours used in hard gelatin capsules shell.

DESCRIPTION

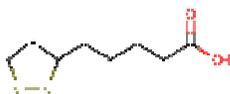
Methylcobalamin

Methylcobalamin or mecobalamin is having molecular weight of 1344.38gram/mol with molecular formula of C₆₃H₉₁CoN₁₃O₁₄. It is having a structural formula as follows:



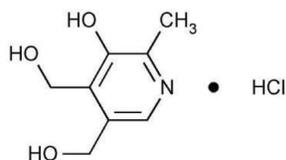
Alpha lipoic acid

Alpha lipoic acid or thioctic acid is a vitamin-like antioxidant and valeric acid derivative having the following structural formula with chemical name of 5-(1,2-Dithiolan-3-yl)valeric acid. The molecular weight is 206.3. The empirical formula is $C_6H_{14}O_2S_2$.



Vitamin B6

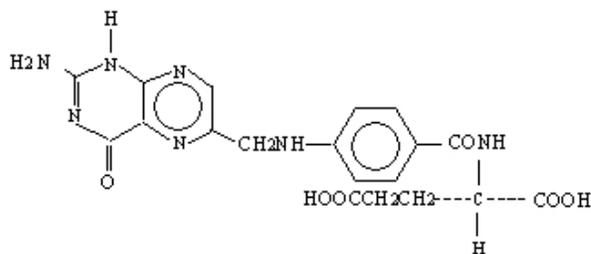
Vitamin B6 or pyridoxine hydrochloride is a vitamin B6 analog. The chemical name for pyridoxine hydrochloride is 3,4-pyridinedimethanol, 5-hydroxy-6-methyl-, hydrochloride. The empirical formula is $C_8H_{11}NO_3 \cdot HCl$ and the molecular mass is 205.64. The structural formula is:



Folic acid

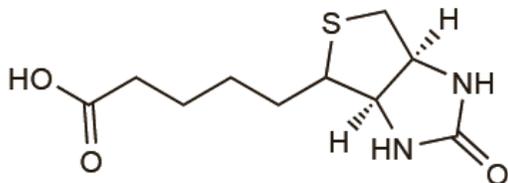
Folic acid, N-[p-[[[(2-amino-4-hydroxy-6-pteridinyl) methyl]-amino]benzoyl]-L-glutamic acid, is a B complex vitamin containing a pteridine moiety linked by a methylene bridge to para-aminobenzoic acid, which is joined by a peptide linkage to glutamic acid. Conjugates of folic acid are present in a wide 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:



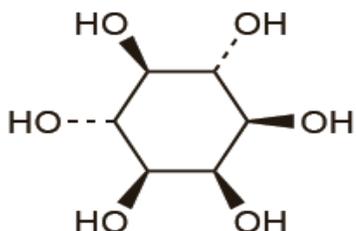
Biotin

Biotin or Vitamin H is chemically *cis*-5-(Hexahydro-2-oxo-1*H*-thieno[3,4-*d*]imidazol-4-yl)valeric acid with an empirical formula $C_{10}H_{16}N_2O_3S$ and molecular weight 244.3. It is having structural formula as follows:



Inositol

Inositol is an isomer of glucose having an empirical formula of $C_6H_{12}O_6$ and molecular weight of 180.2. The structural formula is



Zinc

Zinc is an element. Its molecular weight is 65.38.

Chromium

Chromium is an element. Its molecular weight is 51.99.

Selenium

It is an element. Its molecular weight is 78.96.

CLINICAL PHARMACOLOGY

Pharmacodynamics

Methylcobalamin

Methylcobalamin is one of the biologically active form of vitamin B12. It acts as coenzymes in nucleic acid synthesis. Methylcobalamin is also closely involved with folic acid in several important metabolic pathways. Methylcobalamin (CH_3B_{12}) supports the methionine synthetase reaction, which is essential for normal metabolism of folate.

Alpha-lipoic acid

Lipoic acid is used for its antioxidant effects in the treatment of diabetic neuropathy. It has been tried in the treatment of liver dysfunction and in subacute necrotising encephalopathy. Beneficial results have been claimed in amanitin poisoning after ingestion of the mushroom *Amanita phalloides*, but such use is controversial.

Vitamin B6

It is converted to pyridoxal phosphate which is the co-enzyme for a variety of metabolic transformations. It is essential for human nutrition.

Folic acid

Folic acid is a member of the vitamin B group. Folic acid is reduced in the body to tetrahydrofolate, which is a coenzyme for various metabolic processes including the synthesis of purine and pyrimidine nucleotides, and hence in the synthesis of DNA; it is also involved in some amino-acid conversions, and in the formation and utilisation of formate.

Biotin

Biotin is vitamin B substance, an essential coenzyme in fat metabolism and in other carboxylation reactions. A holocarboxylase synthetase acts on a lysine residue of the apoenzymes of acetyl-CoA carboxylase, pyruvate carboxylase, propionyl-CoA carboxylase, or methylcrotonyl-CoA carboxylase to react with free biotin to form the biocytin residue of the holoenzyme. The reactive intermediate is 1-N-carboxybiocytin, formed from bicarbonate in an ATP-dependent reaction. The carboxyl group is then transferred to the substrate for carboxylation.

Inositol

Inositol appears to be involved physiologically in lipid metabolism.

Zinc

It is a constituent of many enzyme systems and is present in all tissues.

Chromium

Chromium is an essential trace element that potentiates insulin action and thus influences carbohydrate, lipid, and protein metabolism.

Selenium

Selenium is an essential trace element. It is an integral part of the enzyme system glutathione peroxidase, which protects intracellular structures against oxidative damage.

Pharmacokinetic

Methylcobalamin

It binds to intrinsic factor; a glycoprotein secreted by the gastric mucosa, and is 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. Absorption from the gastrointestinal tract can also occur by passive diffusion; little of the vitamin present in food is absorbed in this manner although the process becomes increasingly important with larger amounts such as those used therapeutically. After intranasal dosage, peak plasma concentrations of cyanocobalamin have been reached in 1 to 2 hours. The bioavailability of the intranasal preparation is about 7 to 11% of that by intramuscular injection.

It is extensively bound to specific plasma proteins called transcobalamins; transcobalamin II appears to be involved in the rapid transport of the cobalamins to tissues. A parent form -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, most of it in the first 8 hours; urinary excretion, however, accounts for only a small fraction in the reduction of total body stores acquired by dietary means. Vitamin B12 diffuses across the placenta and also appears in breast milk.

Alpha lipoic acid

It is reported that alpha-lipoic acid 600 mg was administered orally once daily for 4 days, and the pharmacokinetic parameters were measured on days 1 and 4 revealed the mean

percentage of the administered dose excreted in urine as parent compound was 0.2 (which is 0.67% with assumption of 30% bioavailability).

Vitamin B6

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

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.

Inositol

Inositol phospholipids are important in signal transduction.

Zinc

Absorption of zinc from the gastrointestinal tract is incomplete, and is reduced in the presence of some dietary constituents such as phytates. Bioavailability of dietary zinc varies widely between different sources, but is about 20 to 30%. Zinc is distributed throughout the body with the highest concentrations found in muscle, bone, skin, eye, and prostatic fluids. It is primarily excreted in the faeces, and regulation of faecal losses is important in zinc homeostasis. Small amounts are lost in urine and perspiration.

Chromium

Chromium is an essential trace element that potentiates insulin action and thus influences carbohydrate, lipid, and protein metabolism.

Selenium

Selenium compounds are generally readily absorbed from the gastrointestinal tract. Selenium is stored in red blood cells, the liver, spleen, heart, and nails. It is converted in tissues to its metabolically active forms. Selenium is excreted in the urine, and to a lesser extent in the faeces.

INDICATIONS

Useful as a co-prescription in the management of chronic diseases: Diabetic Neuropathy Alcohol-induced neuropathy Vitamin-deficiency related neuropathy Vitamin B12 induced neuropathy Fibromyalgia Postherpetic neuropathy Drug and Toxin-induced neuropathy.

CONTRAINDICATION

Elmecob PG is contraindicated in patients with known hypersensitivity to active constituents or any of its components.

WARNINGS AND PRECAUTIONS

If symptoms persist or worsen, seek medical advice. Do not exceed the stated dose.

Methylcobalamin

If symptoms persist or worsen, seek medical advice. Do not exceed the stated dose.

Should be given with caution in patients suffering from folate deficiency.

The treatment of vitamin B12 (parent compound of methylcobalamin) deficiency can unmask the symptoms of polycythemia vera.

Megaloblastic anemia is sometimes corrected by treatment with vitamin B12. But this can have very serious side effects. Don't attempt vitamin B12 therapy without close supervision by your healthcare provider.

Do not take vitamin B12 if Leber's disease, a hereditary eye disease. It can seriously harm the optic nerve, which might lead to blindness.

Patients with vitamin B12 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 aetiology or other cause of cobalamin deficiency, including lifelong vegetarians.

Vitamin B6

Women taking oral contraceptives may exhibit increased pyridoxine requirements.

Patients treated with levodopa should avoid supplemental vitamins that contain more than 5 mg pyridoxine in the daily dose.

Folic acid

Patients with vitamin B12 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 aetiology or other cause of cobalamin deficiency, including lifelong vegetarians.

Caution should be exercised when administering folic acid to patients who may have folate dependent tumours.

This product is not intended for healthy pregnant women where lower doses are recommended, but for pregnant women with folic acid deficiency or women at risk for the reoccurrence of neural tube defects.

No data are available for inositol, zinc, chromium, and selenium.

DRUG INTERACTION

Methylcobalamine

The data are unavailable for methylcobalamine drug interaction, however evidences for parent drug – vitamin B12 are as follows.

Absorption from the gastrointestinal tract may be reduced by neomycin, aminosalicylic acid, histamine H₂-antagonists, omeprazole, and colchicine.

Serum concentrations may be decreased by use of oral contraceptives.
Many of these interactions are unlikely to be of clinical significance but should be taken into account when performing assays for blood concentrations.
Parenteral chloramphenicol may attenuate the effect in anaemia.
Potassium supplements can reduce absorption of vitamin B12 in some people and might contribute to vitamin B12 deficiency.
Folic acid, particularly in large doses, can cover up vitamin B12 deficiency, and cause serious health effects. Be sure that your healthcare provider checks your vitamin B12 levels before you start taking folic acid.
Early research suggests that vitamin C supplements can destroy dietary vitamin B12. It isn't known whether this interaction is important, but to stay on the safe side, take vitamin C supplements at least 2 hours after meals.
Heavy drinking for at least a two-week period can decrease vitamin B12 absorption from the gastrointestinal tract.

Vitamin B6

Many drugs may alter the metabolism or bioavailability of pyridoxine, including isoniazid, penicillamine and oral contraceptives, which may increase the requirements for pyridoxine. Pyridoxine hydrochloride may reduce the effect of levodopa, a drug used in the treatment of Parkinsons Disease unless a dopa decarboxylase inhibitor is also given
Pyridoxine reduces the activity of altretamine.
It has also been reported to decrease serum concentrations of phenobarbital and phenytoin.

Folic acid

Antiepileptics – if folic acid supplements are given to treat folate deficiency, which can be caused by the use of antiepileptics (phenytoin, phenobarbital and primidone), the serum antiepileptic levels may fall, leading to decreased seizure control in some patients.
Antibacterials – chloramphenicol and co-trimoxazole may interfere with folate metabolism.
Sulfasalazine - can reduce the absorption of folic acid.
Folic acid may interfere with the toxic and therapeutic effects of methotrexate.

Biotin

Data are not available.

Inositol

Data are not available.

Zinc

The absorption of zinc may be reduced by iron supplements, penicillamine, phosphorus-containing preparations, and tetracyclines. Zinc supplements reduce the absorption of copper, fluoroquinolones, iron, penicillamine, and tetracyclines.

Chromium

Data are not available.

Selenium

Data are not available.

ADVERSE EFFECTS

Methylcobalamin

- Pulmonary edema and congestive heart failure early in treatment; peripheral vascular thrombosis.
- Polycythemia vera may also be seen.
- Mild transient diarrhea has been seen.
- Rarely itching; transitory exanthema.
- Other adverse effects reported with vitamin B12 are diarrhea, blood clots, itching, serious allergic reactions.

Vitamin B6

Long-term use of large doses of pyridoxine is associated with the development of severe peripheral neuropathies (including severe sensory neuropathy).

Folic acid

Gastrointestinal disorders: Anorexia, nausea, abdominal distention and flatulence

Immune system disorders: Allergic reactions, comprising erythema, rash, pruritus, urticaria, dyspnea, and anaphylactic reactions (including shock).

No data available for the alpha lipoic acid use.

Biotin

Life-threatening eosinophilic pleuropericarditis have been reported.

Inositol

No data are available.

Zinc

The most frequent adverse effects of zinc salts (the gluconate and sulfate) given orally are gastrointestinal and include abdominal pain, dyspepsia, nausea, vomiting, diarrhoea, gastric irritation, and gastritis. These are particularly common if zinc salts are taken on an empty stomach, and may be reduced by giving them with meals.

Isolated cases reported of anaemia, leucopenia, and neutropenia in patients consuming excessive amounts of zinc supplements.

Hypersensitivity reactions, like palmoplantar pustulosis also reported.

Chromium

There have been rare reports of cutaneous reactions to oral chromium tripicolinate, including of acute generalised exanthematous pustulosis.

Selenium

Limited data are available.

OVERDOSAGE

Vitamin B6

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

No special procedures or antidote are likely to be needed.

Evidences are un-available for overdose experience of methylcobalamine or alpha lipoic acid.

Zinc

In acute overdosage zinc salts are corrosive, due to the formation of zinc chloride by stomach acid; treatment consists of giving milk or alkali carbonates and activated charcoal. The use of emetics or gastric lavage should be avoided.

Prolonged use of high doses of zinc supplements, orally or parenterally, leads to copper deficiency with associated sideroblastic anaemia and neutropenia; full blood counts and serum cholesterol should be monitored to detect early signs of copper deficiency. Zinc toxicity has occurred after the use of contaminated water in haemodialysis solutions. High serum zinc concentrations may be reduced by using a chelating drug such as sodium calcium edetate.

Chromium

Cases of renal failure were attributed to ingestion of excessive doses of chromium tripicolinate in women with no history of renal dysfunction. Acute renal failure with features of acute tubular necrosis, and requiring haemodialysis, has been reported after ingestion of a chromium picolinate- containing supplement. The amount of chromium in the supplement could not be determined.

Selenium

Overdosage of selenium has been associated with loss of hair, nail changes, diarrhoea, dermatitis, metallic taste, garlic odour of breath, irritability, fatigue, and peripheral neuropathy.

Chronic exposure to high amounts of selenium has been reported to cause toxic effects on endocrine function, hepatotoxicity, gastrointestinal disturbances, and dermatological effects such as nail and hair loss and dermatitis. There has been some suggestion also of neurotoxicity, and a possible increased risk of amyotrophic lateral sclerosis. Studies have had conflicting results, and different inorganic and organic forms may vary greatly in biological activity, toxicity, and nutritional importance.

Acute toxicity has also been reported; characteristic symptoms of selenium toxicity are garlicky or sour breath odour, vomiting and gastrointestinal disturbances, restlessness, hypersalivation, muscle spasms, haemolysis, liver necrosis, cerebral and pulmonary oedema, coma, and death. A man who had taken vitamin tablets containing between 500 and 1000 times the amount of selenium labelled on the bottle developed generalised alopecia, changes in nail colour, diarrhoea, worsening fatigue, and paraesthesias. Two weeks after stopping the vitamins, early regrowth of hair and yellowish-white and red transverse lines on his nails were noted. In another case, an elderly man who was concerned that he might have prostate cancer ingested 10 g of sodium selenite. He developed significant abdominal pain, vomiting and diarrhoea, hypotension, and ventricular tachycardia. Blood tests showed acidosis, hypokalaemia and an excessive selenium concentration. Despite symptomatic therapy, he suffered a cardiac arrest and died.

Limited data are available for biotin, inositol.

DOSAGES AND ADMINISTRATION

1-2 capsules daily OR as directed by the physician.

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

Methylcobalamin

No data available for use of methylcobalamin in special population.

Vitamin B6

Data on exposed pregnancies indicate no adverse effects of pyridoxine in therapeutic doses on pregnancy or the health of the foetus or newborn child, or during lactation.

Animal studies are insufficient with respect to effects on pregnancy, embryonal/foetal development, parturition or postnatal development.

Caution should be exercised when prescribing to pregnant women.

Folic Acid

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.

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.

Limited data are available for the alpha lipoic acid, biotin, inositol, chromium, and selenium.

Zinc

Zinc requirements are increased in pregnancy.

EXPIRY DATE

Do not use later than expiry. 18 Months from the date of manufacturing.

STORAGE

Store in a cool, dry place. Protect from light. Keep out of reach of children.

PRESENTATION

Blister pack of 10 capsule.

MARKETED BY



Torrent Pharmaceuticals Ltd.

Indrad-382 721, Dist Mehsana, India.