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

Elmecob D

(Alpha lipoic acid, Pyridoxine hydrochloride, Methylcobalamin, Folic acid & Vitamin D3 Tablets)

COMPOSITION

Each film coated tablets contains
Alpha lipoic acid USP…….100mg
Pyridoxone hydrochloride I.P……. 3mg
Mecobalamin I.P (Methylcobalamin)……1500 mcg
Folic acid I.P…….. 1.5mg
Vitamin D_3 I.P……... 1000 IU
Colors: Red oxide of iron & Yellow oxide of iron & Titanium dioxide IP.
Appropriate Overages of Vitamins Added to Compensate for Loss of Storage

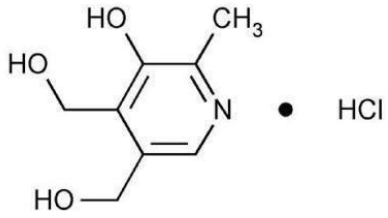
DESCRIPTION

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 $C_6H_{14}O_2S_2$.

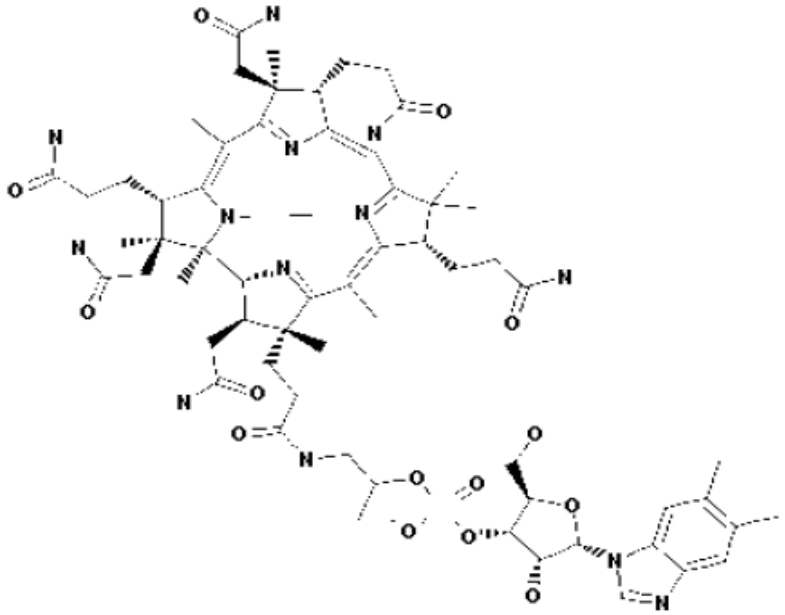
Pyridoxine hydrochloride

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 $C_8H_{11}NO_3 \bullet HCl$ and the molecular mass is 205.64. The structural formula is:



Methylcobalamin

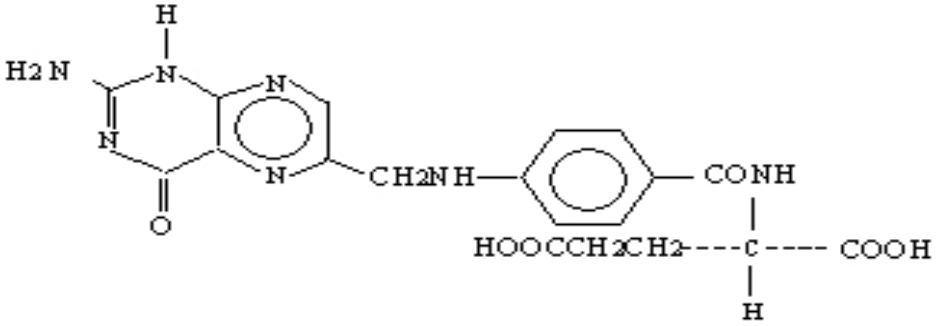
Methylcobalamin or mecobalamin is having molecular weight of 1344.38gram/mol with molecular formula of $C_{63}H_{91}CoN_{13}O_{14}$. It is having a structural formula as follows:



Folic acid

Folic acid, N-[ρ-[[(2-amino-4-hydroxy-6-pteridinyl) methyl]-amino]benzoyl]-L-glutamicacid, 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:

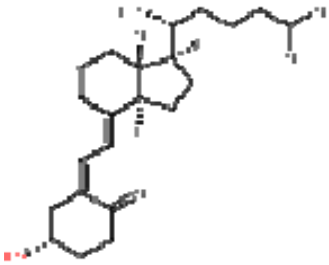


$C_{19}H_{19}N_7O_6$ M.W. 441.40

Vitamin D3

Cholecalciferol is the naturally occurring form of vitamin D. It is produced from 7-dehydrocholesterol, a sterol present in mammalian skin, by ultraviolet irradiation. The

chemical name of cholecalciferol is (5Z,7E)-(3S)-9,10-secocholesta -5,7,10(19)-triene-3-ol. The empirical formula of cholecalciferol is $C_{27}H_{44}O$ and its molecular weight is 384.6. The structural formula is:



CLINICAL PHARMACOLOGY

The clinical pharmacology data for the combination constituents are not available. The individual constituent's properties are enumerated below:

Pharmacodynamics

Alpha lipoic acid

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

Pyridoxone hydrochloride

Pyridoxine hydrochloride is 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.

Methylcobalamin

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

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.

Vitamin D3

The *in vivo* synthesis of the major biologically active metabolites of vitamin D occurs in two steps. The first hydroxylation takes place in the liver (to 25-hydroxy vitamin D) and the second in the kidneys (to 1, 25-dihydroxy- vitamin D). Vitamin D metabolites promote the active absorption of calcium and phosphorus by the small intestine, thus elevating serum calcium and phosphate levels sufficiently to permit bone mineralization. Vitamin D metabolites also mobilize calcium and phosphate from bone and probably increase the reabsorption of calcium and perhaps also of phosphate by the renal tubules. There is a time lag of 10 to 24 hours between the administration of vitamin D and the initiation of its action in the body due to the necessity of synthesis of the active metabolites in the liver and

kidneys. Parathyroid hormone is responsible for the regulation of this metabolism in the kidneys.

Pharmacokinetic

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).

Pyridoxine hydrochloride

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.

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.

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.

Vitamin D3

Vitamin D substances are well absorbed from the gastrointestinal tract. The presence of bile is essential for adequate intestinal absorption; absorption may be decreased in patients

with decreased fat absorption. Vitamin D and its metabolites circulate in the blood bound to a specific α-globulin. Vitamin D can be stored in adipose and muscle tissue for long periods of time. It is slowly released from such storage sites and from the skin where it is formed in the presence of sunlight or ultraviolet light. Cholecalciferol has a slow onset and a long duration of action; calcitriol and its analogue alfacalcidol, however, have a more rapid action and shorter half-lives. Cholecalciferol is hydroxylated in the liver by the enzyme vitamin D 25 - hydroxylase to form 25-hydroxycholecalciferol (calcifediol). These compounds undergo further hydroxylation in the kidneys by the enzyme vitamin D 1-hydroxylase to form the active metabolites 1, 25-dihydroxycholecalciferol (calcitriol). Further metabolism also occurs in the kidneys, including the formation of the 1, 24, 25-trihydroxy derivatives. Vitamin D compounds and their metabolites are excreted mainly in the bile and faeces with only small amounts appearing in urine; there is some enterohepatic recycling but it is considered to have a negligible contribution to vitamin D status. Certain vitamin D substances may be distributed into breast milk.

INDICATIONS

For the treatment of diabetic neuropathy.

CONTRAINDICATION

It is contraindicated in the patients who are having hypersensitivity to active constituents or any of the formulation ingredients.

In patients with hypercalcemia, malabsorption syndrome, abnormal sensitivity to the toxic effects of vitamin D and hypervitaminosis D.

WARNINGS AND PRECAUTIONS

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 aethiology 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.

Vitamin D should not be given to patients with hypercalcaemia. It should be used with caution in infants, who may have increased sensitivity to its effects, and patients with renal impairment or calculi, or heart disease, who might be at increased risk of organ damage if

hypercalcaemia occurred. Plasma phosphate concentrations should be controlled during vitamin D therapy to reduce the risk of ectopic calcification.
It is advised that patients receiving pharmacological doses of vitamin D should have their plasma-calcium concentration monitored at regular intervals, especially initially or if symptoms suggest toxicity. Similar monitoring is recommended in infants if they are breast fed by mothers receiving pharmacological doses of vitamin D.

DRUG INTERACTION

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 H_2-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 gast
rointestinal tract.
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.
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.
There is an increased risk of hypercalcaemia if vitamin D is given with thiazide diuretics, calcium, or phosphate. Plasma-calcium concentrations should be monitored in such situations. Some antiepileptics may increase vitamin D requirements (e.g. carbamazepine, phenobarbital, phenytoin, and primidone). Rifampicin and isoniazid may reduce the effectiveness of vitamin D. Corticosteroids may counteract the effect of vitamin D.
Ketoconazole may inhibit the metabolism of paricalcitol and these drugs should be used with caution together; care should be taken when using paricalcitol with other potent inhibitors of the cytochrome P450 isoenzyme CYP3A4. Mineral oil interferes with the absorption of fat-soluble vitamins, including vitamin D preparations.

ADVERSE EFECTS

Methylcobalamine

• Pulmonary edema and congestive heart failure early in treatment; peripheral vascular thrombosis.

• Polycythemia vera, mild transient diarrhea, rarely itching; transitory exanthema.

• Other adverse effects reported with vitamin B12 are diarrhea, blood clots, itching, serious allergic reactions.

Pyridoxine hydrochloride

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).

Vitamin D3

Excessive intake of vitamin D leads to the development of hyperphosphataemia or hypercalcaemia. Associated effects of hypercalcaemia include hypercalciuria, ectopic calcification, and renal and cardiovascular damage. Symptoms of overdosage include anorexia, lassitude, nausea and vomiting, constipation or diarrhoea, polyuria, nocturia, sweating, headache, thirst, somnolence, and vertigo. Interindividual tolerance to vitamin D varies considerably; infants and children are generally more susceptible to its toxic effects. The vitamin should be withdrawn if toxicity occurs. It has been stated that vitamin D dietary supplementation may be detrimental in persons already receiving an adequate intake through diet and exposure to sunlight, since the difference between therapeutic and toxic concentrations is relatively small.

The most potent forms of vitamin D, such as alfacalcidol and calcitriol, might reasonably be expected to pose a greater risk of toxicity; however, their effects are reversed rapidly on withdrawal. Hypersensitivity reactions have occurred. Skin irritation or contact dermatitis has been reported with topical preparations.

Hypercalcaemia. Vitamin D is the most likely of all vitamins to cause overt toxicity.

Doses of 60000 units daily can cause hypercalcaemia, with muscle weakness, apathy, headache, anorexia, nausea and vomiting, bone pain, ectopic calcification, proteinuria, hypertension, and cardiac arrhythmias. Chronic hypercalcaemia can lead to generalized vascular calcification, nephrocalcinosis, and rapid deterioration of renal function.

Hypercalcaemia has been reported in a patient after brief industrial exposure to colecalciferol.

Another such study has suggested that vitamin D has nephrotoxic properties independent of the degree of induced hypercalcaemia, and that the decline in renal function may be more marked with calcitriol.

Topical calcitriol may affect calcium homoeostasis, and hypercalcaemia has been reported in some studies.

Hypervitaminosis D is characterized by effects on the following organ system: Renal: Impairment of renal function with polyuria, nocturia, polydipsia, hypercalciuria, reversible azotemia, hypertension, nephrocalcinosis, generalized vascular calcification, or irreversible renal insufficiency which may result in death. CNS: Mental retardation. Soft Tissues: Widespread calcification of the soft tissues, including the heart, blood vessels, renal tubules, and lungs. Skeletal: Bone demineralization (osteoporosis) in adults occurs concomitantly. Decline in the average rate of linear growth and increased mineralization of bones in infants and children (dwarfism), vague aches, stiffness, and weakness.

Gastrointestinal: Nausea, anorexia, constipation. Metabolic: Mild acidosis, anemia, weight loss.

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

No special procedures or antidote are likely to be needed

Vitamin D3

The effects of administered vitamin D can persist for two or more months after cessation of treatment.

Hypervitaminosis D is characterized by yypercalcemia with anorexia, nausea, weakness, weight loss, vague aches and stiffness, constipation, mental retardation, anemia, and mild acidosis, impairment of renal function with polyuria, nocturia, polydipsia, hypercalciuria, reversible azotemia, hypertension, nephrocalcinosis, generalized vascular calcification, or irreversible renal insufficiency which may result in death. Widespread calcification of the soft tissues, including the heart, blood vessels, renal tubules, and lungs. Bone demineralization (osteoporosis) in adults occurs concomitantly. Decline in the average rate of linear growth and increased mineralization of bones in infants and children (dwarfism).

The treatment of hypervitaminosis D with hypercalcemia consists of immediate withdrawal of the vitamin, a low calcium diet, generous intake of fluids, along with symptomatic and supportive treatment. Hypercalcemic crisis with dehydration, stupor, coma, and azotemia requires more vigorous treatment. The first step should be hydration of the patient. Intravenous saline may quickly and significantly increase urinary calcium excretion. A loop diuretic (furosemide or ethacrynic acid) may be given with the saline infusion to further increase renal calcium excretion. Other reported therapeutic measures include dialysis or the administration of citrates, sulfates, phosphates, corticosteroids,

EDTA (ethylenediaminetetraacetic acid), and mithramycin via appropriate regimens.

With appropriate therapy, recovery is the usual outcome when no permanent damage has occurred. Deaths via renal or cardiovascular failure have been reported.

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

DOSAGES AND ADMINISTRATION

1 tablet daily OR as directed by the physician.

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

Pyridoxine hydrochloride

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.

Vitamin D3

Pregnancy

Hypercalcaemia during pregnancy may produce congenital disorders in the offspring, and neonatal hypoparathyroidism. However, the risks to the fetus of untreated maternal hypoparathyroidism are considered greater than the risks of hypercalcaemia due to vitamin D therapy.

Breast feeding

Vitamin D is distributed into breast milk, and its concentration appears to correlate with the amount of vitamin D in the serum of exclusively breast-fed infants. The infant be closely monitored for hypercalcaemia or clinical manifestations of vitamin D toxicity if the mother is taking pharmacological doses of vitamin D.

No data available for use of methylcobalamin, alpha lipoic acid use in special population.

EXPIRY DATE

Do not use later than expiry.

STORAGE

Store in cool dry place, protect from light.

PRESENTATION

10x10 Tablets.

MANUFACTURED BY

Akums drugs & Pharmaceuticals Ltd
19,20,21 Sector – 6A, IIE;
SIDCUL, Ranipur, Haridwar-249403, India.

MARKETED BY

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