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

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SHELCAL-XT

(Calcium, Vitamin D3, Methylcobalamin, L-methylfolate calcium & Pyridoxal-5-phosphate Tablets)

COMPOSITION

Each film coated tablet contains:

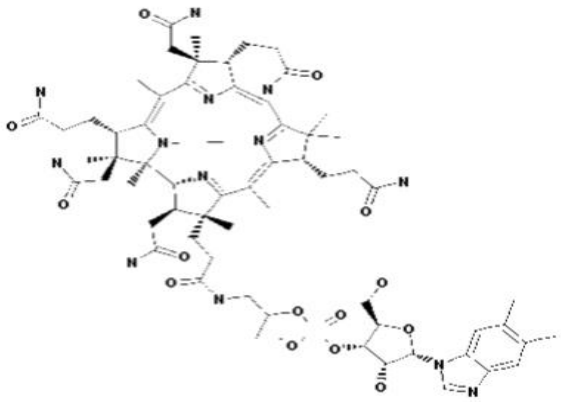
Calcium carbonate IP	1250 mg
Eq. to Elemental Calcium	500 mg
Vitamin D3 IP	2000 IU
Mecobalamin JP (Methylcobalamin)	1500 mcg
L - Methylfolate Calcium	1 mg
Pyridoxal - 5 - Phosphate	20 mg

Colours: Red Oxide of Iron & Titanium Dioxide IP

DESCRIPTION

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:



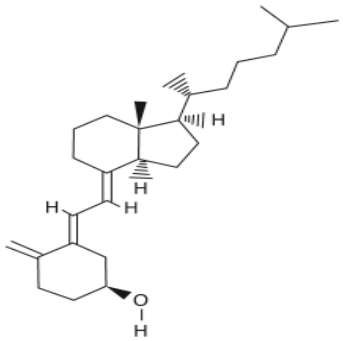
Calcium

Calcium is a mineral that is present naturally in the food. It is necessary for many normal functions of body mainly, bone formation and maintenance

Vitamin D3

Vitamin D3 (Cholecalciferol) is the naturally occurring form of Vitamin D3. It is produced from 7-dehydrocholesterol, a sterol presents in mammalian skin, by ultraviolet irradiation. It's empirical

formula is $C_{27}H_{44}O$, and molecular weight is 384.6. It is chemically as (5Z,7E)-(3S)-9,10-secocholesta-5,7,10(19)-triene-3-ol.



INDICATIONS
- Hyperhomocysteinemia induced osteoporosis
- Senile osteoporosis
- Bone fracture Hypocalcemia
- Post menopausal osteoporosis

POSOLOGY AND METHOD OF ADMINISTRATION
1-2 tablet daily or as directed by the physician.

CONTRAINDICATION
Calcium and Vitamin D3
Diseases and/or conditions resulting in
- hypercalcaemia and/or hypercalciuria
- Nephrolithiasis
- Hypervitaminosis D
- Hypersensitivity to the active substances or to any of the excipients

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

L-methylfolate calcium and Pyridoxal-5-phosphate
Contraindicated in patients with known hypersensitivity to any of the components.

SPECIAL WARNINGS AND PRECAUTIONS FOR USE
Calcium:
During long-term treatment, serum calcium levels should be followed and renal function should be monitored through measurement of serum creatinine. Monitoring is especially important in elderly patients on concomitant treatment with cardiac glycosides or diuretics and in patients with a high tendency to calculus formation. In case of hypercalcaemia or signs of impaired renal function, the dose should be reduced or the treatment discontinued.

Vitamin D3
Vitamin D3 should be used with caution in patients with impairment of renal function and the effect on calcium and phosphate levels should be monitored. The risk of soft tissue calcification should be taken into account. In patients with severe renal insufficiency, Vitamin D3 in the form

of Cholecalciferol is not metabolised normally and other forms of Vitamin D3 should be used. Should be prescribed with caution to patients suffering from sarcoidosis because of the risk of increased metabolism of Vitamin D3 to its active form. These patients should be monitored with regard to the calcium content in serum and urine. Used with caution in immobilised patients with osteoporosis due to the increased risk of hypercalcaemia. Caution should be exercised while prescribing Cholecalciferol and other medicinal products containing Vitamin D3 or nutrients (such as milk). Additional doses of calcium or Vitamin D3 increase the risk of hypercalcaemia with subsequent kidney function impairment and milk-alkali syndrome; therefore they should be taken under close medical supervision. In such cases it is necessary to monitor serum calcium levels and urinary calcium excretion frequently.

L-methylfolate calcium

L-methylfolate calcium is not interchangeable with folic acid. Folic acid is not effective in some patients in impacting cerebral folate levels due to low rates of folic acid transport across the blood-brain barrier and/or low brain levels of the enzyme required to convert folic acid into a biological and functional form. Patients at risk for vitamin B12 deficiency should consult with their physician prior to taking L-methylfolate calcium.

Methylcobalamin

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

The following warnings and precautions suggested with parent form – vitamin B12

• The treatment of vitamin B12 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.

DRUG INTERACTION

Calcium and vitamin D3:

Thiazide diuretics reduce the urinary excretion of calcium. Due to increased risk of hypercalcaemia, serum calcium should be regularly monitored during concomitant use of thiazide diuretics.

Systemic corticosteroids reduce calcium absorption. During concomitant use, it may be necessary to increase the dose of dosage form.

Calcium carbonate may interfere with the absorption of concomitantly administered tetracycline preparations. For this reason, tetracycline preparations should be administered at least two hours before, or four to six hours after, oral intake of calcium.

Simultaneous treatment with ion exchange resins such as cholestyramine or laxatives such as paraffin oil may reduce the gastrointestinal absorption of Vitamin D3.

Hypercalcaemia may increase the toxicity of cardiac glycosides during treatment with calcium and Vitamin D3. Patients should be monitored with regard to electrocardiogram (ECG) and serum calcium levels.

If a bisphosphonate or sodium fluoride is used concomitantly, this preparation should be administered at least three hours before the intake of tablet(s) since gastrointestinal absorption may be reduced.

The efficacy of levothyroxine can be reduced by the concurrent use of calcium, due to decreased levothyroxine absorption. Administration of calcium and levothyroxine should be separated by at least four hours.
The absorption of quinolone antibiotics may be impaired if administered concomitantly with calcium. Quinolone antibiotics should be taken two hours before or after intake of calcium.
Oxalic acid (found in spinach and rhubarb) and phytic acid (found in whole cereals) may inhibit calcium absorption through formation of insoluble calcium salts. The patient should not take calcium products within two hours of eating foods high in oxalic acid and phytic acid.

Methylcobalamin

The data are unavailable for methylcobalamin drug interaction, however evidences for parent drug, vitamin B_{12} are as follows:

• 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 of vitamin B12 in anaemia.
• Folic acid, particularly in large doses, can cover up vitamin B12 deficiency, and cause serious health effects.
• Early research suggests that vitamin C supplements can destroy dietary vitamin B_{12}. 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.

Pyridoxal-5-phosphate

Pyridoxal-5-phosphate should not be given to patients receiving the drug levodopa, because the action of levodopa is antagonized by pyridoxal-5-phosphate. However, pyridoxal-5-phosphate may be used concurrently in patients receiving a preparation containing both carbidopa and levodopa.

FERTILITY, PREGNANCY AND LACTATION

Calcium and vitamin D3:

Pregnancy

During pregnancy the daily intake should not exceed 1500 mg calcium and 600 IU Vitamin D3. Studies in animals have shown reproductive toxicity with high doses of Vitamin D3. In pregnant women, overdoses of calcium and Vitamin D3 should be avoided as permanent hypercalcaemia has been related to adverse effects on the developing foetus. There are no indications that Vitamin D3 at therapeutic doses is teratogenic in humans. Calcium and Vitamin D3 tablets can be used during pregnancy, in case of a calcium and Vitamin D3 deficiency.

Lactation

Calcium and Vitamin D3 tablets can be used during breast-feeding. Calcium and Vitamin D3 pass into breast milk. This should be considered when giving additional Vitamin D3 to the child.

Methylcobalamin

Vitamin B12 is likely safe for pregnant or breast-feeding women when taken by mouth in the amounts recommended. Don’t take larger amounts. The safety of larger amounts is unknown.
No data available for use of methylcobalamin in special population.

L-methylfolate calcium

Pregnancy

L-methylfolate calcium has not been formally assigned a pregnancy risk category; there are no controlled studies in humans or animals

At recommended doses, folic acid is pregnancy risk category A [adequate, well controlled studies in pregnant women have failed to demonstrate risk to the fetus]

At high doses, folic acid is pregnancy risk category C [no controlled studies in humans]

Because pregnant women are advised to take folic acid or prenatal vitamins that contain folic acid, it is important to ask the patient about any supplements or vitamins she may be taking and consider this when deciding whether to prescribe L-methylfolate calcium.

Breast Feeding

Some drug is found in mother's breast milk.

Pyridoxal-5-phosphate

Pyridoxal-5-phosphate is the active form of Pyridoxine

Pyridoxine

Pregnancy and lactation

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.

EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

No data is available regarding the effects on ability to drive and use machines.

UNDESIRABLE EFFECTS

Calcium and vitamin D3:

Adverse reactions are listed below, by system organ class and frequency. Frequencies are defined as: uncommon (1/1,000, to < 1/100); rare (1/10,000 to < 1/1,000) or very rare (1/10,000) Metabolism and nutrition disorders Uncommon: Hypercalcaemia and hypercalciuria. Very rare: Seen usually only in overdose : Milk-alkali syndrome Gastrointestinal disorders Rare: Constipation, dyspepsia, flatulence, nausea, abdominal pain and diarrhoea. Skin and subcutaneous disorders Rare: Pruritus, rash and urticaria.

Methylcobalamin

Generally, methylcobalamin is well tolerated. No toxicity reactions have been reported.

• 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

L-methylfolate calcium

Allergic reactions have been reported following the use of oral L-methylfolate calcium.

Pyridoxal-5-phosphate
Paresthesia, somnolence, nausea and headaches have been reported with pyridoxal-5-phosphate.

OVERDOSE

Calcium and vitamin D3:
Overdose can lead to hypervitaminosis D and hypercalcaemia. Symptoms of hypercalcaemia may include anorexia, thirst, nausea, vomiting, constipation, abdominal pain, muscle weakness, fatigue, mental disturbances, polydipsia, polyuria, bone pain, nephrocalcinosis, nephrolithiasis and in severe cases, cardiac arrhythmias. Extreme hypercalcaemia may result in coma and death. Persistently high calcium levels may lead to irreversible renal damage and soft tissue calcification. Milk-alkali syndrome (frequent urge to urinate; continuing headache; continuing loss of appetite; nausea or vomiting; unusual tiredness or weakness; hypercalcaemia, alkalosis and renal impairment). The milk-alkali syndrome of hypercalcaemia, alkalosis and renal impairment still occur in patients who ingest large amounts of calcium and absorbable alkali; it is not uncommon as a cause of hypercalcaemia requiring hospitalisation. The syndrome has also been reported in a patient taking recommended doses of antacids containing discomfort, and in a pregnant woman taking high, but not grossly excessive, doses of calcium (about 3 g of elemental calcium daily). Metastatic calcification can develop. Treatment of hypercalcaemia The treatment with Calcium and Vitamin D3 must be discontinued. Treatment with thiazide diuretics, lithium, vitamin A and cardiac glycosides must also be discontinued. Treatment is rehydration, and, according to severity of hypercalcaemia, isolated or combined treatment with loop diuretics, bisphosphonates, calcitonin and corticosteroids should be considered. Serum electrolytes, renal function and diuresis must be monitored. In severe cases, ECG and CVP should be followed.

Methylcobalamine, L-methylfolate calcium, Pyridoxal-5-Phosphate
Evidences are not available for overdose.

PHARMACOLOGICAL PROPERTIES

Calcium:
Absorption: The amount of calcium absorbed through the gastrointestinal tract is approximately 30% of the swallowed dose. Distribution and metabolism: 99% of the calcium in the body is concentrated in the hard structure of bones and teeth. The remaining 1% is present in the intra - and extracellular fluids. About 50% of the total blood-calcium content is in the physiologically active ionised form with approximately 10% being complexed to citrate, phosphate or other anions, the remaining 40% being bound to proteins, principally albumin. Elimination: Calcium is eliminated through faeces, urine and sweat. Renal excretion depends on glomerular filtration and calcium tubular reabsorption.

Vitamin D3:
Absorption: Vitamin D3 is easily absorbed in the small intestine. Distribution and metabolism: Vitamin D3 and its metabolites circulate in the blood bound to a specific globulin. Vitamin D3 is converted in the liver by hydroxylation to the active form 25-hydroxycholecalciferol. It is then further converted in the kidneys to 1,25 hydroxycholecalciferol; 1,25 hydroxycholecalciferol is the metabolite responsible for increasing calcium absorption. Vitamin D3 which is not metabolised is stored in adipose and muscle tissues. Elimination: Vitamin D3 is excreted in faeces and urine.

Methylcobalamin:

Pharmacodynamics

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.

Pharmacokinetic

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.

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.

L-methylfolate calcium

Pharmacodynamics

L-methylfolate calcium or 6(S)-5-methyltetrahydrofolate [6(S)-5-MTHF], is the primary biologically active diastereoisomer of folate and the primary form of folate in circulation. It is also the form which is transported across membranes into peripheral tissues,3 particularly across the blood brain barrier.4 In the cell, 6(S)-5-MTHF is used in the methylation of homocysteine to form methionine and tetrahydrofolate (THF). THF is the immediate acceptor of one carbon units for the synthesis of thymidine-DNA, purines (RNA and DNA) and methionine. About 70% of food folate and cellular folate is comprised of 6(S)-5-MTHF. Folic acid, the synthetic form of folate, must undergo enzymatic reduction by methylenetetrahydrofolate reductase (MTHFR) to become biologically active.6 Genetic mutations of MTHFR result in a cell's inability to convert folic acid to 6(S)-5-MTHF.

Pharmacokinetics

Absorption and Elimination: L-methylfolate calcium is a water soluble molecule which is primarily excreted via the kidneys. Reportedly, in a study of subjects with coronary artery disease (n=21), peak plasma levels were reached in 1-3 hours following oral/parenteral administration. Peak concentrations of L-methylfolate calcium were found to be more than seven times higher than folic acid (129 ng/ml vs. 14.1 ng/ml) following oral/parenteral administration. The mean elimination half-life is approximately 3 hours for L-methylfolate calcium after the administration of 5mg of oral D,Lmethylfolate. The mean values for Cmax, Tmax, and AUC_{0-12} were 129 ng/ml, 1.3 hr., and 383 respectively.

Distribution: Red blood cells (RBCs) appear to be the storage depot for folate, as RBC levels remain elevated for periods in excess of 40 days following discontinuation of supplementation. Plasma protein binding studies showed that L-methylfolate calcium is 56% bound to plasma proteins.

Pyridoxal-5-phosphate:
Pyridoxal-5'-phosphate (PLP) is the active form of vitamin B6 and is used as the prosthetic group for many of the enzymes where this vitamin is involved. PLP is readily absorbed by the intestine by a process which is preceded by dephosphorylation to form pyridoxal. The phosphate group is regained during passage through the intestine. Pyridoxine, the parent compound of PLP and the most frequently used form of vitamin B6, requires reduction and phosphorylation before becoming biologically active.

PRECLINICAL SAFETY DATA
No data on animal studies of safety pharmacology available.

EXPIRY DATE
Do not use later than the date of expiry.

STORAGE
Store protected from light & moisture, at a temperature not exceeding 30°C.

PRESENTATION
Blister strip of 15 tablets

MARKETED BY
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