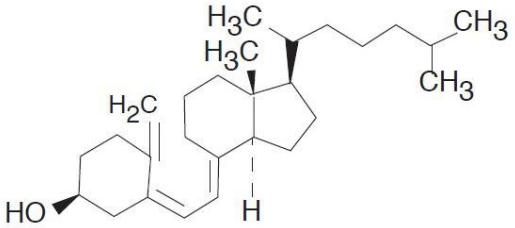
For the use only of a Registered Medical Practitioner or a Hospital or a Laboratory

SHELCAL HD 12
(Calcium with Vitamin D_3 and Vitamin B_{12} tablets)

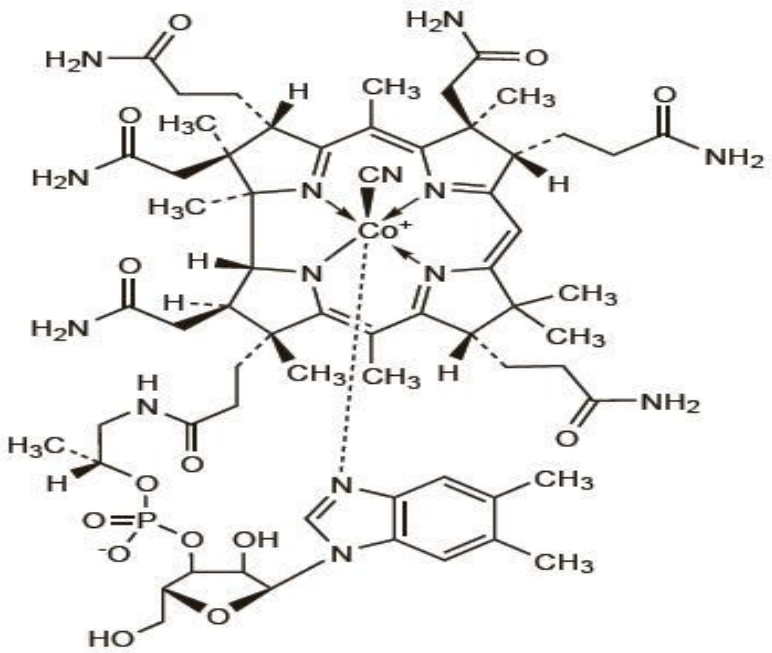
COMPOSITION
SHELCAL HD 12
Each film-coated tablet contains:
1250 mg Calcium Carbonate from an organic source (Powdered Oyster Shell) equivalent to Elemental Calcium 500 mg
Vitamin D_3 I.P. 500 IU
Vitamin B_{12} I.P. (As gelatin triturate) 15 mcg
Colors: Lake of Sunset Yellow FCF and Titanium Dioxide I.P.
Appropriate overages of vitamins added to compensate for loss on storage.

DESCRIPTION
Vitamin D3 (Cholecalciferol)
Cholecalciferol is the naturally occurring form of Vitamin D_3. It is produced from 7-dehydro cholesterol, a sterol present 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.



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 B_{12} (Cyanocobalamin)
Cyanocobalamin is a synthetic form of vitamin B12 with equivalent vitamin B12 activity. The chemical name is 5, 6-dimethyl-benzimidazolyl cyanocobamide. The cobalt content is 4.35%. The molecular formula is $C_{63}H_{88}CoN_{14}O_{14}P$, which corresponds to a molecular weight of 1355.38 and the following structural formula:



CLINICAL PHARMACOLOGY
PHARMACODYNAMIC
Vitamin D_3
Vitamin D3 increases the intestinal absorption of calcium. Administration of calcium and Vitamin D3 counteracts the increase of parathyroid hormone (PTH) which is caused by calcium deficiency and which causes increased bone reabsorption.

Vitamin B_{12}
Vitamin B_{12} is essential for growth, cell reproduction, hematopoiesis, and nucleoprotein and myelin synthesis. Rapidly dividing cells (e.g., epithelial cells, bone marrow, myeloid cells) have the greatest requirement for vitamin B_{12}. In tissues, vitamin B_{12} is essential for the conversion of methylmalonate to succinate and for the synthesis of methionine from homocysteine. In the absence of vitamin B_{12}, tetrahydrofolate cannot be regenerated from 5-methyl tetrahydrofolate, and functional folate deficiency occurs. Vitamin B_{12} also may be involved in sulfhydryl-activated enzyme systems associated with fat and carbohydrate metabolism and protein synthesis.

An elevated serum homocysteine concentration appears to be a risk factor for osteoporotic fractures in older men and women. Treatment with vitamin B_{12} and folate can reduce plasma homocysteine concentrations. In a placebo-controlled study of patients with hemiplegia following stroke (and at increased risk of hip fracture), those given folate and vitamin B_{12} were found to have a significantly reduced risk of hip fracture despite a lack of effect on bone mineral density. Vitamin B_{12} status has been associated with bone health in a number of studies and it was suggested that the observed effects on fracture might be due to increased concentrations of vitamin B_{12} rather than the lowering of plasma homocysteine.

PHARMACOKINETIC

Vitamin D

Absorption: Vitamin D_3 is absorbed in the small intestine.

Distribution and metabolism: Cholecalciferol and its metabolites circulate in the blood bound to a specific globulin. Cholecalciferol is converted in the liver by hydroxylation to the active form 25-hydroxy Cholecalciferol. It is then further converted in the kidneys to 1,25 hydroxy Cholecalciferol. 1, 25 hydroxy Cholecalciferol is the metabolite responsible for increasing calcium absorption. Vitamin D which is not metabolized is stored in adipose and muscle tissues.

Elimination: Vitamin D is excreted in feces and urine.

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 ionized form with approximately 10% being complexes to citrate, phosphate or other anions, the remaining 40% being bound to proteins, principally albumin.

Elimination: Calcium is eliminated through feces, urine and sweat. Renal excretion depends on glomerular filtration and calcium tubular reabsorption.

Vitamin B_{12}

Vitamin B_{12} substances 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. 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.

Gastrointestinal absorption of vitamin B12 depends on the presence of sufficient intrinsic factor and calcium ions. Intrinsic factor deficiency causes pernicious anemia, which may be associated with sub-acute combined degeneration of the spinal cord. Prompt parenteral administration of vitamin B_{12} prevents progression of neurologic damage.

The average diet supplies about 4 to 15 mcg/day of vitamin B12 in a protein-bound form that is available for absorption after normal digestion. Vitamin B_{12} is not present in foods of plant origin, but is abundant in foods of animal origin. In people with normal absorption, deficiencies have been reported only in strict vegetarians who consume no products of animal origin (including no milk products or eggs).

Vitamin B_{12} is bound to intrinsic factor during transit through the stomach; separation occurs in the terminal ileum in the presence of calcium, and vitamin B_{12} enters the mucosal cell for absorption. It is then transported by the transcobalamin binding proteins. A small amount (approximately 1% of the total amount ingested) is absorbed by simple diffusion, but this mechanism is adequate only with very large doses. Oral absorption is considered too undependable to rely on in patients with pernicious anemia or other conditions resulting in malabsorption of vitamin B_{12}. Colchicine, para-aminosalicylic acid, and heavy alcohol intake for longer than 2 weeks may produce malabsorption of vitamin B_{12}.

The absorption of cobalamins from the gut is dependent upon the glycoprotein intrinsic factor. Cobalamins are transported rapidly into the blood bound to protein, known as transcobalamins. Cobalamins are stored in the liver and excreted in the bile. They are known to cross the placenta.

INDICATION

Shelcal HD 12 is indicated in the management of associated deficiencies of calcium, vitamin B_{12} and vitamin D in pregnancy, as well as chronic disease.
FOR THERAPEUTIC USE.

DOSAGES AND ADMINISTRATION

One tablet a day or as directed by the physician.

CONTRAINDICATIONS

Diseases and/or conditions resulting in hypercalcaemia and/or hypercalciuria (e.g. myeloma, bone metastases, primary hyperparathyroidism).

- Nephrolithiasis/nephrocalcinosis
- Renal failure
- Hypervitaminosis D
- Hypersensitivity to the active substances or to any of the excipients
- Sensitivity to cobalt and/or vitamin B12 or any component of the medication is a contraindication.

WARNING AND PRECAUTION

During long-term treatment, serum and urinary calcium levels should be followed and renal function should be monitored through measurements 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.

Patients with mild to moderate impairment of renal function should be supervised carefully 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 D

in the form of Cholecalciferol is not metabolized normally and other forms of vitamin D should be used.

In patients with a history of renal stones urinary calcium excretion should be measured to exclude hypercalciuria.

Calcium and Vitamin D_3 Tablets should be prescribed with caution to patients suffering from sarcoidosis, due to the risk of increased metabolism of vitamin D into its active form. These patients should be monitored with regard to the calcium content in serum and urine.

Calcium and Vitamin D_3 Tablets should be used with caution in immobilized patients with osteoporosis due to increased risk of hypercalcaemia.

Calcium and Vitamin D_3 Tablets should be used with caution in other patients with increased risk of hypercalcaemia e.g. those suffering from malignancies.

The content of vitamin D (500 IU) in Shelcal tablets should be considered when prescribing other medicinal products containing vitamin D. Additional doses of calcium or vitamin D should be taken under close medical supervision. In such cases it is necessary to monitor serum calcium levels and urinary calcium excretion frequently.

Caution should be exercised while prescribing Cholecalciferol and other medicinal products containing Vitamin D_3 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.

Patients with early Leber's disease (hereditary optic nerve atrophy) who were treated with vitamin B_{12} suffered severe and swift optic atrophy.

Hypokalemia and sudden death may occur in severe megaloblastic anemia which is treated intensely with vitamin B_{12}. Folic acid is not a substitute for vitamin B12 although it may improve vitamin B_{12}-deficient megaloblastic anemia. Exclusive use of folic acid in treating vitamin B_{12}-deficient megaloblastic anemia could result in progressive and irreversible neurologic damage.

Blunted or impeded therapeutic response to vitamin B_{12} may be due to such conditions as infection, uremia and drugs having bone marrow suppressant properties such as chloramphenicol, and concurrent iron or folic acid deficiency.

Doses of vitamin B_{12} exceeding 10 mcg daily may produce hematologic response in patients with folate deficiency. Indiscriminate administration may mask the true diagnosis.

The validity of diagnostic vitamin B_{12} or folic acid blood assays could be compromised by medications, and this should be considered before relying on such tests for therapy.

Vitamin B_{12} is not a substitute for folic acid and since it might improve folic acid deficient megaloblastic anemia, indiscriminate use of vitamin B_{12} could mask the true diagnosis.

Hypokalemia and thrombocytosis could occur upon conversion of severe megaloblastic to normal erythropoiesis with vitamin B_{12} therapy. Therefore, serum potassium levels and the platelet count should be monitored carefully during therapy.

Vitamin B_{12} deficiency may suppress the signs of polycythemia vera. Treatment with vitamin B_{12} may unmask this condition.

DRUG INTERACTION

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. Hypercalcaemia must be avoided in digitalised patients.

Systemic corticosteroids reduce calcium absorption. During concomitant use, it may be necessary to increase the dose of Calcium and Vitamin D_3 Tablets.

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

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.

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

If a bisphosphonate or sodium fluoride is used concomitantly with Calcium and Vitamin D_3 Tablets, these medicinal products should be administered at least three hours before the intake of Calcium and Vitamin D_3 Tablets since gastrointestinal absorption may be reduced.

Rifampicin, phenytoin or barbiturates may reduce the activity of vitamin D_3, since they increase the rate of its metabolism.

Calcium salts may decrease the absorption of iron, zinc or strontium. Consequently, the iron, zinc or strontium preparation should be taken at a distance of two hours from the calcium preparation.

Calcium salts may reduce the absorption of the estramustin or thyroid hormones. It is recommended that taking Calcium and Vitamin D_3 Tablets be spaced at least 2 hours from these medicines.

Oxalic acid (found in spinach, sorrel and rhubarb) and phytic acid (found in whole cereals) may inhibit calcium absorption through formation of insoluble compounds with calcium ions. The patient should not take calcium products within two hours of eating foods high in oxalic acid and phytic acid.

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.

Persons taking most antibiotics, methotrexate or pyrimethamine invalidate folic acid and vitamin B_{12} diagnostic blood assays.

Colchicine, para-aminosalicylic acid and heavy alcohol intake for longer than 2 weeks may produce malabsorption of vitamin B_{12}.

USE IN SPECIFIC POPULATION

Pregnancy

Calcium and Vitamin D_3 Tablets may be given during pregnancy in cases of calcium and vitamin D_3 deficiency.

During pregnancy the daily dose should not exceed 1500 mg of calcium and 600 IU of vitamin D. Animal studies have shown toxic effects on reproduction at high doses of vitamin D. In pregnant women, all calcium or vitamin D overdoses must be avoided as prolonged hypercalcaemia in pregnancy may lead to retardation of physical and mental development, supravalvular aortic stenosis and retinopathy in the child. There are no indications that Vitamin D_3 at therapeutic doses is teratogenic in human.

Pregnancy Category C: Animal reproduction studies have not been conducted with vitamin B_{12}. It is also not known whether vitamin B_{12} can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. Adequate and well-controlled studies have not been done in pregnant women. However, vitamin B_{12} is an essential vitamin and requirements are increased during pregnancy.

Breast-feeding

Calcium and Vitamin D_3 can be used during breast-feeding. Calcium and vitamin D pass into breast milk. This should be considered when giving additional vitamin D to the child.

Vitamin B_{12} appears in the milk of nursing mothers in concentrations which approximate the mother's vitamin B_{12} blood level.

ADVERSE REACTION

Adverse reactions are listed below, by system organ class and frequency. Frequencies are defined as: uncommon (>1/1,000 to <1/100) or rare (>1/10,000 to <1/1,000).
Metabolism and nutrition disorders
Uncommon: Hypercalcaemia and hypercalciuria.
Gastrointestinal disorders
Rare: Constipation, flatulence, nausea, abdominal pain, and diarrhoea.
Skin and subcutaneous disorders
Rare: Pruritus, rash and urticaria.

Vitamin B_{12}
Sensitisation to this medicine is rare, but may present as an itching exanthema, and exceptionally as anaphylactic shock.

Acne form and bullous eruptions have been reported rarely.

Patients who have become sensitized to this medicine by injection are often able to tolerate the oral route without trouble.

OVERDOSE

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, renal calculi 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.

Treatment of hypercalcaemia: The treatment with calcium and vitamin D must be discontinued. Treatment with thiazide diuretics, lithium, vitamin A, vitamin D and cardiac glycosides must also be discontinued. Gastric lavage in patients with impaired consciousness. Rehydration, and, according to severity, isolated or combined treatment with loop diuretics, bisphosphonates, calcitonin and corticosteroids. Serum electrolytes, renal function and diuresis must be monitored. In severe cases, ECG and CVP should be followed.

EXPIRY DATE

Do not use later than the date of expiry.

STORAGE

Store in a cool and dry place

PRESENTATIONS

Shelcal HD 12 is available in blister pack of 15 Tablets

MARKETED BY:

TORRENT PHARMACEUTICALS LTD.
Torrent House, Off Ashram Road,
Ahmedabad-380 009, INDIA

IN/SHELCAL HD 12/APR-16/02/PI