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

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SHELCAL K
(Calcium carbonate, Calcitriol and Vitamin K_2)

COMPOSITION

SHELCAL K

Each tablet contain
1250mg calcium carbonate from an organic source (oyster shell) equivalent to
Elemental calcium 500mg
Calcitriol 0.25mcg
Vitamin K_2 (Menatetrenone) 100mcg

DOSAGE FORM

Tablet for oral use

DESCRIPTION

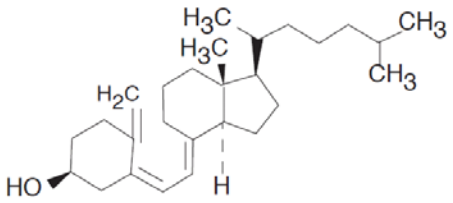
The formulation combines Calcium, Calcitriol and Vitamin K_2.

Calcium Carbonate

Calcium plays a critical role in the body. It is essential for normal functioning of nerves, cells, muscles and bone. Calcium prevents bone loss and is associated with a modest reduction in fracture risk. Calcium and vitamin D preparation are used to prevent or to treat calcium deficiencies. A vitamin D resistant state may exist in uremic patient because of the failure of the kidney to adequately produce calcotriol.

Calcitriol

Calcitriol is the active form of vitamin D_3 (Cholecalciferol). It is produces in the kidney from the vitamin D metabolite 25-hydroxyvitamin D_3 (calcifediol). Vitamin D is important for the absorption of calcium from the stomach and for the functioning of calcium in the body. The known sites of action of calcitriol are intestine, bone, kidney and parathyroid gland. In bone, calcitriol in conjunction with parathyroid hormone stimulates resorption of calcium; and in the kidney, calcitriol increases the tubular reabsorption of calcium.



Vitamin K_2

Vitamin K2 is as essential fat-soluble micronutrient which is needed for a unique post-translational chemical modification in a small group of proteins with calcium binding properties, collectively known as vitamin k-dependent protein or Gia-proteins. Originally discovered as an anti-haemorragic K, vitamin K's activity is now known encompass a variety of physiological processes. Beyond its well-recognized essentiality for activating blood coagulation protein, this

vitamin helps regulate tissue calcium content. The results of recent human and animal studies have suggested that concurrent use of vitamin K and vitamin D may substantially reduce bone loss.

CLINICAL PHACOLOGY

PHARMACODYNAMICS

Calcium Carbonate

Calcium is the most abundant mineral in the human body and is essential for maintaining the functional integrity of nervous and musculoskeletal systems as well as cell membrane and capillary permeability. The majority (99%) of the body calcium is contained in bone with the remainder equally disturbed between intra- and extra cellular fluids. Calcium is an activator in many enzymatic reactions and is necessary for nerve impulse transmission, renal function, respiration and blood coagulation.

Calcitriol

The biological effects of calcitriol are mediated by the vitamin D receptor, a nuclear hormone receptor expressed in most cell types and functioning as a ligand-activated transcription factor that binds to specific DNA sites to modify the expression of target genes.

Calcitriol binds to an intracellular receptor, a member of the steroid receptor super family. The calcitriol receptor complex interacts with specific DNA sequences that regulate transcription and protein synthesis in a variety of cells including osteoblasts, mucosal cells of the intestine, renal tabular cells and parathyroid cells. The changes in protein synthesis induced in these cells by calcitriol are responsible for its profound physiological effects.

The key role calcitriol in the regulation of bone and calcium homeostasis, which includes stimulating effects on osteoblastic activity in the skeleton, provides a sound pharmacological basic for its therapeutic effects in osteoporosis

Vitamin K_2

The biologic role of vitamin K is to act as a colactor for the microsormal y - carboxylase that facilities the post - translational conversion of glutamic acid to y- carboxyglutamyl (Gla) residues. Vitamin K_2 also activities matrix Gla protein (cMGP) in cartilage and smooth muscle layer of the vessel and MGP prevents calcium from binding to the vessel well (inactive MGP, ucMGP). The reaction is catalysed by a microsomal enzyme, vitamin K-dependent carboxilase, which in turn is linked to a cyclic salvage pathway known as the vitamin K epoxide cycle.

PHARMACOKINETICS:

Calcium carbonate

Calcium is actively absorbed, mainly in the duodenum and proximal jejunum. Calcium must be in a soluble, ionized from to be absorbed. Factors such as an acidic intestinal pH, the presence of the Vitamin D, and pregnancy and lactation tend to favour calcium absorption. However, absorption may be impeded in the elderly, or by a deficiency of parathyroid hormone, calcium or Vitamin D, the presence of anions or fatty acids which may precipitate or complex with calcium, or in certain disease states such as achlorhydria, renal oateodystrophy, steatorrhea or ureinia.

Once absorbed into the bloodstream, most calcium is rapidly incorporated into skeletal muscle; the remainder is equally distributed between intra- and extra cellular fluids. Normal total serum calcium concentrations range from 2.2 to 2.6 mmol/L, although only the ionized fraction is physiologically active. Of the total serum calcium, 50% is ionized, 5% is complexed with anions such as phosphates or citrates and 45% is protein bound. Hyperproteinemia is associated with an increase in total scrum calcium; hypoprotienemia has the opposite effect. Acidosis favors an increase in ionic calcium concentration, while alkalosis leads to a decrease in the ionized fraction. CSF calcium concentrations tend to be similar to the serum concentration of ionized calcium, i. e., approximately 50% of total serum calcium. Calcium crosses the placenta, reaching higher levels in fatal blood than in the mother. Calcium is excreted in breast milk.

Calcium is excreted mainly in the faces, either as a result of passing through the gut unabsorbed or through biliary or pancreatic secretion into gut lumen. Very small amounts of calcium are excreted in the urine as most filtered calcium is reabsorbed. Urinary excretion of calcium is promoted by growth hormone, Vitamin D, thiazide diuretics or a decrease in ionizes calcium concentration tend to decrease the amount of calcium excreted in the urine, Calcium is also excreted in sweat.

Calcitriol

Calcitriol is rapidly absorbed from the intestine. Peak scrum concentrations (above basal values) were reached within 3 to 6 hours following oral administration of single doses of 0.25 to 1.0 microgram of calcitriol. Following a single oral dose of 0.5 microgram mean serum concentrations of calcitriol rose a baseline value of 40.0 + 4.4 (S.D) pg/ml to 60.0 + 4.4 pg/ml at 2 hours and declined to 53.0 + 6.9 at 4 hours, 50+ 7.0 at 8 hours and 44 + 4.4 at 12 hours and 41.5 + 5.1 at 24 hours. Calcitriol and other vitamin D metabolites are transported approximately 99.9% bound to specific plasma proteins in the blood. Calcitriol is hydroxyated and oxidized by CYP24A1.

The elimination half-life of calcitriol from serum was found to range from 3 to 6 hours. However, the pharmacological effect of a single dose of calcitriol lasts about three to five days. Enterohepatic recycling and biliary excretion occur. Cumulative excretion of radio activity on the on the sixth day following intravenous administration of radio labeled calcitriol averaged 16% in urine and 49% in faces. There is evidence that maternal calcitriol may enter the fetal circulation.

Vitamin K_7

The intestinal absorption of vitamin k follows a well-established pathway that applies to most dietary lipids, which includes bile salt-and pancreatic-dependent solubilization, uptake of mixed micelles into the enterocyics, the packaging of concentrations of phylloquinone and MK-7 reached a plateau after 3 and 20 d, respectively, with MK-7 attaining serum concentrations that were 7 -to 8- fold higher than those for phylloquinone. These higher concentrations MK-7 were associated with a greater tissue uptake and biological activity in bone as evidenced by an increased proportion of serum g-carboxilated osteocalcin that plateaued after 3 d. In the phylloquinone arm but continued to rise for at least 40 d in the MK-7 arm. Humans excrete phylloquinone and MK by a common degradative path way where by the polyisoprenold side chain is first shortened to major carboxylic acid metabolites with 7- and 5- carbon side chains,

respectively, the metabolites are then conjugated, mainly with glucuronic acid, and excreted in to the bile and urine.

INDICATION

For the prevention and treatment of osteoporosis in the elderly especially those with or predisposed to vertebral fractures.

CONTRAINDICATIONS

SHELCAL K should not be given to patients with hypercalcaemia or evidence of vitamin D toxicity. It should be noted that the anticoagulant effect of warfarin (Coumodin), functioning by its interference with the clotting effect of vitamin K, can be offset with as little as 1 mg vitamin K. Therefore, use of vitamin K is contraindicated in individuals on anticoagulant therapy.

WARNING AND PRECAUTIONS

Since calcitriol is the most potent metabolite of vitamin D available, vitamin D and its derivatives should be withheld during treatment. In patients undergoing dialysis, who have serum phosphorus levels, appropriate serum phosphate binders should be used.

DRUG INTERACTIONS

Concomitant use of magnesium containing antacids and calcitriol may to the development of hypermagneseaemia.

SHELCAL K should be avoided in patients on digitalis because hypercalcaemia in such patients may precipitate cardiac arrhythmias.

Higher doses of calcitriol may be required in patients taking barbiturates or anticonvulsants. The effect of calcitriol may be counteracted by corticosteroids.

Cholestyramine may impair intestinal absorption of calcitriol.

Concurrent use of calcium containing formulations may reduce the response of verapamil and other calcium channel blockers.

Oestrogens may increase calcium absorption and calcium may prevent absorption of etidronate.

Calcium carbonate may reduce absorption of fluoroquinoloes and the effects of gallium may be antagonized.

Concurrent use with phenytoin decreased the bioavailability of both phenytoin and calcium.

Calcium may also decrease the absorption of tetracyclines.

Extended use of broad spectrum antibiotics may decrease vitamin K synthesis by intestinal bacteria. Use of cephalosporins and salicylates may adversely affect vitamin K recycling inhibiting vitamin K expose reductase. Furthermore absorption of vitamin K may be decreased with the use of drugs such as cholestyramine, colestipol, orlistat, and substances such as mineral oil and the fat substitute, olestra.

Renal Impairment
The elimination half-life of calcitriol increased by at least two fold in chronic renal failure and hemodialysis patients compared to healthy subjects.

Hepatic Impairment
Controlled studies examining the influence of hepatic disease on calcitriol have not been conducted.

Pregnancy
Pregnancy Category C
There are no adequate and well-controlled studies in pregnant women, **SHELCAL K** should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Lactation
Calcitriol may be excreted in human milk. A mother should not nurse while taking SHELCAL K.

Prediatric Use
Safety and efficacy of this drug has not been established in children.

Geratric Use
The dose selection for an elderly patient should be cautions, usually starting at the lower end of the dose range, reflecting the greater frequency of decreased hepatic, real or cardiac function and of concomitant disease or other drug therapy.

UNDESIRABLE EFFECTS
Adverse effects are of vitamin D intoxication with hypercalcaemia include weakness, headache, somnolence, nausea, vomiting, dry mouth, constipation, muscle pain bone pain and metabolic taste.

Late signs include polyuria, polysipsia, anorexia, weigh loss, nocturia, conjunctivitis (calcific),pancreatitis, photophobia, rhinorrhea, pruritus, hyperthermia, decreased libido, elevated BUN, albuminuria, hypercholesterolaemia, elevated SGOT and SGPT, ectopic calcification, hypertension, cardiac arrhythmias and rarely, overt psychosis.

Although allergic reaction is possible, there is no known toxicity associated with high doses of the phylloquinone (vitamin K_1 or menaquinone (vitamin K_2) forms of vitamin K.

OVERDOSAGE
Administration of this formulation to patients in excess of their requirements can cause hypercalcaemia, hypercalciuria and hyperphosphateemia.

Over dosage of any form of vitamin D is dangerous. Progressive hypercalcaemia due to over dosage of this formulation may be so severe as to require emergency attention. Sometimes hypercalciuria can also occur. Chronic hypercalcaemia can lead to generalized vascular calcification, nephrocalcinosis and other soft tissue calcification. The serum calcium times phosphate product (Ca x P) should not be allowed to exceed 70. Radiographic evaluation of suspect anatomical regions may be useful in the early detection of this condition.

General treatment of hypercalcaemia (greater than 1 mg /dl above the upper limits of normal range) consist of immediate discontinuation of therapy. Serum calcium levels should be determined daily until normocalcaemia (8.5 to 10.5 mg /dl) ensues. Hypervalcaemia usually resolved in two to seven days. When serum calcium levels have returned to within normal limits, drug may be reinstituted at a dose lower than the prior therapy. Serum calcium levels should be obtained at least twice weekly after all dosage changes. Persistent or markedly elevated serum calcium levels may be corrected by dialysis against a calcium free dialysate.

The treatment of acute accidental over dosage of the drug should consist of general supportive measures. Serial serum electrolyte determinations (especially calcium), rate of urinary calcium excretion and assessment of electrocardiographic abnormalities due to hypercalcaemia should be obtained. Such monitoring is critical in patients receiving digitalis. Due to pharmacological action of calcitriol lasting only 3-5 days, further measures are probably unnecessary. However, should persistent and markedly elevated serum calcium levels occur, there are a variety of the therapeutic alternatives, which may be considered, depending on the patient's underlying condition. These include the use of drugs such as phosphates and corticosteroids as well as measures to induce an appropriate forced diuresis. The use of peritoncal dialysis against a calcium free dialysis has also been reported.

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

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

PACKAGING INFORMATION
Shelcal K is available in blister strip of 15 tablets.

MARKETED BY:
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TORRENT PHARMACEUTICALS LTD.
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Ahmedabad-380 009, INDIA