Calcium carbonate, Calcitriol and Vitamin K2-7

Gemcal DS

1. NAME OF THE MEDICINAL PRODUCT

Gemcal DS

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each formulation contains:
Calcium Carbonate……. 1250mg
(Equivalent to elemental calcium ……...500mg)
Calcitriol……..0.25 mcg
Vitamin K2-7……...45mcg

3. PHARMACEUTICAL FORM

Soft gel capsule

4. CLINICAL PARTICULARS

4.1 Therapeutic Indications

Gemcal DS is indicated in treatment of osteoporosis.

4.2 Posology and Method of Administration

For adults, orally 1 capsule once or twice a day or as directed by physician.

Dose Modification

Safety and tolerability

Renal Impairment

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

Hepatic Impairment

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

Paediatric Use

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

Geriatric 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.

4.3 Contraindications

Gemcal DS 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.

4.4 Special Warnings and Special Precautions for Use

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 high serum phosphorus levels, appropriate serum phosphate binders should be used.

4.5 Interaction with Other Medicinal Products and Other Forms of Interaction

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

4.6 Fertility, Pregnancy and Lactation

Pregnancy

Pregnancy Category C

There are no adequate and well-controlled studies in pregnant women, Gemcal DS should be used during pregnancy only if the potential benefit justifies the potential risk to the foetus.

Lactation

Calcitriol may be excreted in human milk. A mother should not nurse while taking Gemcal DS.

4.7 Effects on Ability to Drive and Use Machines

None known.

4.8 Undesirable Effects

Table 1. Adverse Reactions Reported in Clinical Trials

System organ class	Very common ≥1/10	Common ≥1/100 to <1/10	Uncommon ≥1/1,000 to <1/100	Rare ≥1/10,000 to <1/1,000

4.9 Overdose

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

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. Hypercalcaemia 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 peritoneal dialysis against a calcium free dialysis has also been reported.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic Properties

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 K2-7

The biologic role of vitamin K is to act as a cofactor for the microsormal gamma - carboxylase that facilities the post - translational conversion of glutamic acid to gamma- carboxyglutamyl residues. Vitamin K2 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 carboxylase, which in turn is linked to a cyclic salvage pathway known as the vitamin K epoxide cycle.

Clinical Studies

5.2 Pharmacokinetic Properties

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 uraemia.

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 favours 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 9 to 10 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 foetal circulation.

Vitamin K2-7
The intestinal absorption of vitamin k follows a well-established pathway that applies to most dietary lipids, which includes bile salt-and pancreatic-dependent solubilisation, uptake of mixed micelles into the enterocytes, 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 gamma-carboxylated 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 pathway 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.

5.3 Preclinical Safety Data

6. PHARMACEUTICAL PARTICULARS

6.1 List of Excipients

6.2 Incompatibilities

6.3 Shelf-life

6.4 Special Precautions for Storage

6.5 Nature and Contents of Container

6.6 Special Precautions for Disposal

Manufactured & Marketed By: Details