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

GEMITROL

Calcitriol, Calcium Carbonate And Zinc Capsules

COMPOSITION

Each soft gelatin capsule contains :

Calcitriol I.P.	0.25 mcg
Calcium Carbonate I.P.	500 mg
(equivalent to elemental Calcium 200 mg)	
Zinc (as Zinc sulphate monohydrate I.P.)	7.5 mg
Excipients	q.s.

Approved colours used in capsule shell.

Appropriate overage of Vitamin is added to compensate loss on storage

DESCRIPTION

Gemitrol soft gelatin capsule is a combination of Calcitriol, elemental Calcium which is derived from Calcium Carbonate and Zinc.

CLINICAL PHARMACOLOGY

Pharmacodynamics

Calcitriol

Calcitriol stimulates intestinal absorption of Calcium. It exerts negative feedback control on the parathyroid gland through both direct and indirect mechanisms. It directly inhibits parathyroid hormone (PTH) secretion and indirectly it increases serum Ca^{2+} which has negative effect on PTH secretion. Calcitriol is the active form of vitamin D3 (cholecalciferol). It is produced in the kidney from the vitamin D metabolite 25-hydroxyvitamin D3 (calciferol). 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. Calcitriol in conjunction with parathyroid hormone stimulates mobilization of calcium in bone and in the kidney, calcitriol increases the tubular reabsorption of calcium. Calcitriol increases intestinal absorption of Calcium, thus giving supplemental Calcium helps in achieving maximum effect of Calcitriol. Calcium as such prevents bone loss in postmenopausal women and is associated with a modest reduction in fracture risk.

Calcium

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

Zinc

Zinc is a nutritional supplement important for normal growth and tissue repair. Urinary elimination of zinc is increased in osteoporotic women. Zinc depletion is shown to diminish the response of calcitriol when administered orally. Supplementary zinc not only improves calcitriol response but also helps to arrest bone loss in old postmenopausal women.

Pharmacokinetics

Calcitriol

Calcitriol is fat-soluble and upto 100% absorption normally takes place. Calcitriol is rapidly distributed throughout the body. Peak plasma levels are achieved within 3-6h. Calcitriol metabolism involves multiple metabolic pathways. The largest fraction undergoes side chain oxidation to calcitroic acid, which is biologically inactive. A fraction undergoes hydroxylation at 24^{th} position to calcitriol, which has less biological activity than Calcitriol. A number of minor catabolic routes like 26-hydroxylation, 23 -oxidation and lactonization at the 26 and 23 position are also involved. The elimination half life of Calcitriol in serum is 9-10 hours. The duration of pharmacologic activity of a single dose of calcitriol is about 3 to 5 days.Bile is the main excretory route for Calcitriol metabolites. Very little intact Calcitriol is excreted. Calcitriol passes freely across placenta.

Following multiple administration, serum calcitriol levels reached a steady state with in 7 days, with a relationship to the dose of calcitriol administered.

Calcium Carbonate

Calcium carbonate is converted to Calcium chloride by gastric hydrochloric acid in stomach. 39% of Calcium is absorbed from 0.5-1.4gm dose of Calcium Carbonate. Absorption of Calcium depends upon previous intake of Calcium, other nutrients, pregnancy, lactation, overall Calcium balance and availability of vitamin D or its analogues. Calcium carbonate is absorbed as free Calcium and not metabolised. Approximately half the Calcium in serum is protein bound, 5-10 % complexed in the form of small readily diffusible organic salts and the remaining as free ions.

Zinc

20% to 30% of dietary Zinc is absorbed from the GI tract. The main excretion route is through the intestine. Only minor amounts are lost in urine (~2%).

INDICATIONS

For the treatment of hypocalcaemia and/or osteoporosis.

CONTRAINDICATIONS

Gemitrol should not be given to patients with hypercalcaemia or evidence of vitamin D toxicity. Use of Gemitrol Capsules in patients with known hypersensitivity to Gemitrol Capsules or any of the inactive ingredients is contraindicated.

WARNINGS AND PRECAUTIONS

- Since calcitriol is the most potent metabolite of vitamin D available, other preparations of vitamin D and its derivatives should be withheld during treatment.
- Excessive dosage of this combination may induce hypercalcaemia and in some instances hypercalciuria.Chronic hypercalcemia can lead to generalized vascular calcification, nephrocalcinosis and other soft-tissue calcification. Therefore early in the treatment during dosage adjustment, serum Calcium should be determined periodically at regular intervals.
- Calcitriol increases inorganic phosphate levels in serum. While this is desirable in patients with hypophosphatemia, caution is called for in patients with renal failure because of the danger of ectopic calcification. A non-aluminum phosphate - binding compound and a low-phosphate diet should be used to control serum phosphorus levels in patients undergoing dialysis.
- Magnesium - containing preparations (eg, antacids) and calcitriol should not be used concomitantly in patients on chronic renal dialysis because such use may lead to the development of hypermagnesemia.
- Studies in dogs and rats given calcitriol for up to 26 weeks have shown that small increases of calcitriol above endogenous levels can lead to abnormalities of calcium metabolism with the potential for calcification of many tissues in the body.
- Excessive intake of Zinc may lead to overdosage symptoms like nausea, severe vomiting, dehydration, restlessness and sideroblastic anaemia (secondary to Zinc induced copper depletion).
- This combination should be avoided in patients on digitalis because hypercalcaemia in such patients may precipitate cardiac arrhythmias.

Information for the Patients

Patients should be informed for dietary restrictions and adverse effect of overdosage of this combination.

Drug Interactions

- Concomitant use of magnesium containing antacids and calcitriol may lead to the development of hyper-magnesaemia.
- Gemitrol 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. Ketoconazole may inhibit both synthetic and catabolic enzymes of calcitriol. Reductions in serum endogenous calcitriol concentrations have been observed following the

administration of 300 mg/day to 1200 mg/day ketoconazole for a week to healthy men. However, in vivo drug interaction studies of ketoconazole with calcitriol have not been investigated

- Concurrent use of calcium containing formulations may reduce the response of verapamil and other calcium channel blockers.
- Oestrogens may increase calcium absorption. Calcium may prevent absorption of etidronate. Calcium carbonate may reduce absorption of fluoroquinolones
- The effects of gallium may be antagonized in presence of calcium.
- Concurrent use with phenytoin decreases the bioavailability of both phenytoin and calcium. Calcium may also decrease the absorption of tetracyclines.
- Bran products (including brown bread) and some foods (e.g. proteins, phytates, some minerals) may decrease zinc absorption.
- Thiazides are known to induce hypercalcaemia by the reduction of Calcium excretion in urine. Concomitant administration of thiazides with Calcitriol may cause hypercalcaemia.
- The dosage of phosphate binding agents must be adjusted based on serum phosphate concentrations as phosphate transport in the intestine, kidneys and bones may be affected.

Renal Insufficiency

Lower predose and peak calcitriol levels in serum were observed in patients with nephrotic syndrome and in patients undergoing hemodialysis compared with healthy subjects. The elimination half-life of calcitriol increased by at least twofold in chronic renal failure and hemodialysis patients compared with healthy subjects. Peak serum levels in patients with nephrotic syndrome were reached in 4 hours. For patients requiring hemodialysis peak serum levels were reached in 8 to 12 hours; half-lives were estimated to be 16.2 and 21.9 hours, respectively.

Hepatic insufficiency

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

Pregnancy

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

Nursing Mother

Calcitriol from ingested calcitriol capsules may be excreted in human milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions from calcitriol in nursing infants, a mother should not nurse while taking Gemitrol capsules.

Pediatric use

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

Geriatric use

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

ADVERSE REACTIONS

Adverse effects are in general similar to those encountered with excessive vitamin D intake. The early and late signs and symptoms of vitamin D intoxication associated with hypercalcaemia include :

Early-Weakness, headache, somnolence, nausea, vomiting, dry mouth, constipation, muscle pain, bone pain,anorexia, abdominal pain or stomach ache and metallic taste and metallic taste.

Late - Polyuria, polydipsia, anorexia, weight loss, nocturia, conjunctivitis (calcific), pancreatitis, photophobia, rhinorrhea, pruritus, hyperthermia, decreased libido, elevated BUN, albuminuria, hypercholesterolaemia, elevated SGOT and SGPT, ectopic calcification, hypertension, cardiac arrhythmias, nephrocalcinosis, dystrophy, sensory disturbances, dehydration, apathy, arrested growth, urinary tract infections, and rarely, overt psychosis.

OVERDOSAGE

Administration of this formulation to patients in excess of their requirements can cause hyper-calcaemia, hypercalciuria and hyper phosphataemia. Overdosage of any form of vitamin D is dangerous. Progressive hypercalcaemia due to overdosage 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 $70mg^2/dl^2$. Radiographic evaluation of suspect anatomical regions may be useful in the early detection of this condition. Excessive intake of zinc may lead to overdosage symptoms like nausea, severe vomiting, dehydration, restlessness and sideroblastic anaemia (secondary to zinc induced copper depletion).

General treatment of hypercalcaemia (greater than 1mg/dl above the upper limit of normal range) consists of immediate discontinuation of therapy. Serum calcium levels should be determined daily until normocalcaemia (8.5 to 10.5 mg/dl) ensues. Hypercalcaemia usually resolves 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 overdosage 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 the 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 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 dialysate has also been reported.

DOSAGE AND ADMINISTRATION

The recommended dose is one capsule of Gemitrol daily. Gemitrol Capsules should be administered orally. The optimal daily dose of calcitriol must be carefully determined for each patient. Calcitriol therapy should always be started at the lowest possible dose and should not be increased without careful monitoring of serum calcium.During the titration period of treatment with calcitriol, serum calcium levels should be checked at least twice weekly. When the optimal dosage of calcitriol has been determined, serum calcium levels should be checked every month. Samples for serum calcium estimation should be taken without a tourniquet.

EXPIRY DATE

Do not use later than expiry date.

STORAGE

Store in a cool, dry and dark place below $25^{o}C$ or in air conditioned area.

Keep out of reach of children.

PRESENTATION

GEMITROL is available in blister strips of 15 capsules.

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Manufactured by :
TORRENT PHARMACEUTICALS LTD.
Indrad- 382 721, Dist. Mehsana, INDIA.

at : 197/2, Athiyawad,
Dabhel-Village, Daman-396 210