CALZEM Capsules (Calcitriol + Calcium carbonate + Zinc)

Composition

Each soft gelatin capsule contains:
Calcium Carbonate, IP .................. 500 mg
(from an organic source (Oyster shell) equivalent to elemental Calcium 200 mg)
Calcitriol, BP ...................... 0.25 mcg
Zinc ................ 7.5 mg
(as Zinc Sulphate Monohydrate, USP)

Dosage Form

Capsule for oral use.

Description

This formulation combines calcitriol, calcium and zinc.

Calcitriol is the active from of vitamin D₃ (cholecalciferol). It is produced in the kidney from the vitamin D metabolite, 25-hydroxyvitamin D₃ (25(OH)D₃). 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 the intestines, bone, kidneys and parathyroid gland. In bone, calcitriol in conjunction with the parathyroid hormone stimulates resorption of calcium; in the kidneys, calcitriol increases the tubular reabsorption of calcium.

Calcium plays a critical role in the body. It is essential for the 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 uraemic patients because of the failure of the kidneys to adequately produce calcitriol.

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 oral calcitriol when administered orally. Supplementary zinc not only improves calcitriol response but also helps to arrest bone loss in older postmenopausal women.
Pharmacology

Pharmacodynamics

**Calcium Carbonate**
Calcium administration decreases the elevated rate of bone turnover typically seen in postmenopausal women with osteoporosis. Calcium administration may transiently increase levels of serum calcium, with compensatory reductions in serum parathyroid hormone (PTH) and an increase in urinary calcium. However, urinary and serum calcium levels usually remain within the normal reference range.

**Calcitriol**
The two known sites of action of calcitriol are the intestines and bone. A calcitriol receptor-binding protein appears to exist in the mucosa of the human intestines. Additional evidence suggests that calcitriol may also act on the kidneys and the parathyroid glands. Calcitriol is the most active known form of vitamin D3 in stimulating intestinal calcium transport. The kidneys of uremic patients cannot adequately synthesize calcitriol, the active hormone formed from precursor vitamin D. Resultant hypocalcemia and secondary hyperparathyroidism are a major cause of the metabolic bone disease of renal failure. However, other bone-toxic substances which accumulate in uremia (eg, aluminum) may also contribute. The beneficial effect of calcitriol in renal osteodystrophy appears to result from correction of hypocalcemia and secondary hyperparathyroidism. It is uncertain whether calcitriol produces other independent beneficial effects. Calcitriol treatment is not associated with an accelerated rate of renal function deterioration. No radiographic evidence of extraskeletal calcification has been found in predialysis patients following treatment. The duration of pharmacologic activity of a single dose of calcitriol is about 3 to 5 days.

**Zinc**
Zinc is an integral component of many enzymes and is widely distributed in the body; skeletal tissue, and muscle and soft tissues are rich sources. Zinc has a role in stabilizing macromolecular structure and synthesis.

Pharmacokinetics

**Calcium Carbonate**

**Absorption**
The amount of calcium absorbed through the gastrointestinal tract is approximately 30% of the swallowed dose.

**Distribution and Metabolism**
In the body, 99% of the calcium 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 complexed to citrate, phosphate or other anions, and the remaining 40% being bound to proteins, principally albumin.

**Elimination**
Calcium is eliminated through the faeces, urine and sweat. Renal excretion depends on glomerular filtration and calcium tubular reabsorption.
Calcitriol Absorption
Calcitriol is rapidly absorbed from the intestines. Peak serum concentrations (above basal values) were reached within 3 to 6 hours following oral administration of single doses of 0.25 to 1.0 mcg of calcitriol. Following a single oral dose of 0.5 mcg, mean serum concentrations of calcitriol rose from 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, 44±4.6 at 12 hours, and 41.5±5.1 at 24 hours. Following multiple-dose administration, serum calcitriol levels reached the steady state within 7 days.

Distribution
Calcitriol is approximately 99.9% bound in blood. Calcitriol and other vitamin D metabolites are transported in blood by an alphaglobulin vitamin D-binding protein. There is evidence that maternal calcitriol may enter the foetal circulation. Calcitriol is transferred into human breast milk at low levels (i.e. 2.2 0.1 pg/mL).

Metabolism
In vivo and in vitro studies indicate the presence of two pathways of metabolism for calcitriol. The first pathway involves the 24-hydroxylase as the first step in catabolism of calcitriol. There is definite evidence of 24-hydroxylase activity in the kidneys; this enzyme is also present in many target tissues that have the vitamin D receptor, such as the intestine. The end product of this pathway is a side chain, shortened metabolite, calcitroic acid. The second pathway involves the conversion of calcitriol via the stepwise hydroxylation of carbon-26 and carbon-23, and further cyclization to yield, ultimately, 1a, 25R(OH)2-26, 23S-lactone D3. The lactone appears to be the major metabolite circulating in humans, with mean serum concentrations of 131±17 pg/mL. In addition, several other metabolites of calcitriol have been identified: 1a, 25(OH)2-24-oxo-D3; 1a , 23,25(OH)3-24-oxo-D3; 1a, 24R,25(OH)2-D3; 1a,25S,26(OH)2-D3; 1a, 25(OH)2-23-oxo-D3; 1a, 25R,26(OH)2-23-oxo-D3; and 1a, (OH)24,25,26,27-tetranor-COOH-D3.

Excretion
Enterohepatic recycling and biliary excretion of calcitriol occur. The metabolites of calcitriol are excreted primarily in the faeces. Following intravenous administration of radiolabelled calcitriol in normal subjects, approximately 27% and 7% of the radioactivity appeared in the faeces and urine, respectively, within 24 hours. When a 1 mcg oral dose of radiolabelled calcitriol was administered to normal subjects, approximately 10% of the total radioactivity appeared in urine within 24 hours. Cumulative excretion of radioactivity on the sixth day following intravenous administration of radiolabelled calcitriol averaged 16% in the urine and 49% in faeces. The elimination half-life of calcitriol in serum after single oral doses is about 5 to 8 hours in normal subjects.

Zinc
The bioavailability of oral zinc sulphate is 20% to 30%. Absorption of dietary zinc is nearly twice as high during lactation as before conception. Zinc malabsorption occurs in rheumatoid arthritis and, perhaps, in other inflammatory diseases. Food and beverages reduce the uptake of zinc. The major stores of zinc are in skeletal muscle, skin, hair, nails, spermatozoa, choroid of the eyes and bone, and the pancreas. Zinc is excreted through the kidneys and faeces. The major route of excretion of zinc is secretion into the duodenum and jejunum. Excretion is influenced by levels of dietary nitrogen and phosphorus.

Indications
- Management of hypocalcaemia in patients undergoing dialysis for chronic renal failure. It has been
shown to significantly reduce elevated PTH levels. Reduction of PTH has been shown to result in an improvement in renal osteodystrophy.

- Postmenopausal osteoporosis.
- Hypocalcaemia in hypoparathyroidism.
- Parathyroidectomy.
- Vitamin D-dependent rickets.
- Renal tubular osteocalcaemia.
- Sporadic and oncogenic hypophosphataemic osteomalacia.
- X-linked hypophosphatemic osteomalacia.
- Osteomalacia in malabsorption syndrome.
- Hypocalcaemia and hypomagnesaemia after small bowel resection.
- Osteoporosis in males.
- Psoriasis.

**Dosage And Administration**

The optimal dose must be carefully determined for each patient. The recommended initial dose is one capsule of **CALZEM** daily. If a satisfactory response in the biochemical parameters and clinical manifestations of the disease state is not observed, the dose may be increased by an increment of 1 to 2 capsules at 2- to 4-week intervals. In patients undergoing dialysis, the dose may be increased by an increment of one capsule at 4- to 8-week intervals. During this titration period, serum calcium and phosphorus levels should be obtained at least twice weekly and if hypercalcaemia is noted, the drug should be immediately discontinued until normocalcaemia ensues. In patients undergoing dialysis, phosphorus, magnesium and alkaline phosphatase should be determined periodically. Patients should be informed of the symptoms of hypercalcaemia.

**Contraindications**

**CALZEM** should not be given to patients under following conditions:

- 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 (including soya or peanut).

**Warnings And Precautions**

**General**

**Calcium Carbonate**

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 impairment, 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 carbonate 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 carbonate should be used with caution in immobilized patients with osteoporosis due to increased risk of hypercalcaemia. Calcium carbonate should be used with caution in other patients with increased risk of hypercalcaemia, e.g. those suffering from malignancies. The content of vitamin D 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.

Calcitriol

Overdosage is dangerous. Progressive hypercalcaemia due to overdosage of vitamin D and its metabolites may be so severe as to require emergency attention. Chronic hypercalcaemia can lead to generalized vascular calcification, nephrocalcinosis and other soft-tissue calcification. The serum calcium times phosphate (Ca x P) product should not be allowed to exceed 70 mg2/dL2. Radiographic evaluation of suspect anatomical regions may be useful in the early detection of this condition.

Calcitriol is the most potent metabolite of vitamin D available. The administration of calcitriol to patients in excess of their daily requirements can cause hypercalcaemia, hypercalciuria and hyperphosphataemia. Therefore, pharmacologic doses of vitamin D and its derivatives should be withheld during calcitriol treatment to avoid possible additive effects and hypercalcaemia. Calcitriol increases inorganic phosphate levels in serum. While this is desirable in patients with hypophosphataemia, caution is called for in patients with renal failure because of the danger of ectopic calcification. A non-aluminium, phosphate-binding compound and a low-phosphate diet should be used to control serum phosphorus levels in patients undergoing dialysis. Magnesium-containing preparations (e.g. antacids) and calcitriol should not be used concomitantly in patients on chronic renal dialysis because such use may lead to the development of hypermagnesaemia.

Excessive dosage of calcitriol induces hypercalcaemia and, in some instances, hypercalciuria; therefore, during dosage adjustment early in treatment, serum calcium should be determined twice weekly. In dialysis patients, a fall in serum alkaline phosphatase levels usually antedates the appearance of hypercalcaemia and may be an indication of impending hypercalcaemia. An abrupt increase in calcium intake as a result of changes in diet (e.g. increased consumption of dairy products) or uncontrolled intake of calcium preparations may trigger hypercalcaemia. Should hypercalcaemia develop, treatment with calcitriol should be stopped immediately. During periods of hypercalcaemia, serum calcium and phosphate levels must be determined daily. When normal levels have been attained, treatment with calcitriol can be continued at a daily dose of 0.25 mg lower than that previously used. An estimate of daily dietary calcium intake should be made and the intake adjusted when indicated. Calcitriol should be given cautiously to patients on digitalis, because hypercalcaemia in such patients may precipitate cardiac arrhythmias. Immobilized patients, e.g. those who have undergone surgery, are particularly exposed to the risk of hypercalcaemia. In patients with normal renal function, chronic hypercalcaemia may be associated with an increase in serum creatinine. While this is usually reversible, it is important in such patients to pay careful
attention to those factors which may lead to hypercalcaemia. Calcitriol therapy should always be started at the lowest possible dose and should not be increased without careful monitoring of the serum calcium. An estimate of daily dietary calcium intake should be made and the intake adjusted when indicated. Patients with normal renal function taking calcitriol should avoid dehydration. Adequate fluid intake should be maintained.

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**Calcium Carbonate**
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 digitalized patients.

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

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

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.

Calcium carbonate may interfere with the absorption of concomitantly administered tetracycline preparations. For this reason, tetracycline preparations should be administered at least 2 hours before, or 4 to 6 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+ vitamin D, these medicinal products should be administered at least 3 hours before the intake of calcium+ vitamin D since gastrointestinal absorption may be reduced.

Calcium salts may decrease the absorption of iron, sodium fluoride, zinc or strontium. Consequently, the iron, zinc or strontium preparation should be taken at a distance of 3 hours from the calcium preparation.

The absorption of quinolone antibiotics may be impaired if administered concomitantly with calcium. Quinolone antibiotics should be taken two hours before or six hours after intake of calcium.

Calcium salts may reduce the absorption of the estramustin or thyroid hormones.

Oxalic acid (found in spinach, sorrel and rhubarb) and phytic acid (found in whole cereals) may inhibit calcium absorption through the formation of insoluble compounds with calcium ions. The patient should not take calcium products within 2 hours of eating foods high in oxalic acid and phytic acid.

**Calcitriol**

**Cholestyramine**
Cholestyramine has been reported to reduce intestinal absorption of fat-soluble vitamins; as such, it may impair intestinal absorption of calcitriol.

**Phenytoin/Phenobarbital**
The co-administration of phenytoin or phenobarbital will not affect plasma concentrations of calcitriol, but may reduce endogenous plasma levels of 25(OH)D3 by accelerating metabolism. Since blood level of calcitriol will be reduced, higher doses of calcitriol may be necessary if these drugs are administered simultaneously.

**Thiazides**
Thiazides are known to induce hypercalcaemia by the reduction of calcium excretion in urine. Some reports have shown that the concomitant administration of thiazides with calcitriol causes hypercalcaemia. Therefore, precaution should be taken when co-administration is necessary.

**Digitalis**
Calcitriol dosage must be determined with care in patients undergoing treatment with digitalis, as hypercalcaemia in such patients may precipitate cardiac arrhythmias.

**Ketoconazole**
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 1,200 mg/day ketoconazole for a week to healthy men. However, in vivo drug interaction studies of ketoconazole with calcitriol have not been investigated.

**Corticosteroids**
A relationship of functional antagonism exists between vitamin D analogues, which promote calcium absorption, and corticosteroids, which inhibit calcium absorption.

**Phosphate-Binding Agents**
Since calcitriol also has an effect on phosphate transport in the intestines, kidneys and bones, the dosage of phosphate-binding agents must be adjusted in accordance with the serum phosphate concentration.

**Vitamin D**
Since calcitriol is the most potent active metabolite of vitamin D3, pharmacological doses of vitamin D and its derivatives should be withheld during treatment with calcitriol to avoid possible additive effects and hypercalcaemia.

**Calcium Supplements**
Uncontrolled intake of additional calcium-containing preparations should be avoided.

**Magnesium**
Magnesium-containing preparations (e.g. antacids) may cause hypermagnesaemia and should, therefore, not be taken during therapy with calcitriol by patients on long-term renal dialysis.

**Zinc**
**Cinoxacin**
Zinc may interfere with the gastrointestinal absorption of cinoxacin. Decreased absorption may result in lower systemic levels than desired, thereby compromising the efficacy of the quinolone. Cinoxacin should be administered at least 2 hours before or 2 hours after the administration of zinc or a multiple-ingredient product containing zinc.

**Ciprofloxacin**
In a four-way crossover design, the concurrent use of ciprofloxacin and multivitamins with zinc resulted in a decreased absorption of ciprofloxacin by up to 24%. Avoid concurrent use of ciprofloxacin and products containing zinc.

**Copper**
Concomitant administration of copper and zinc may decrease gastrointestinal zinc or copper absorption. Optimal dosage separation time has not been determined. Space the administration of zinc and copper as far apart as possible.

**Enoxacin**
Concurrent use of enoxacin and multivitamins containing zinc results in a reduction in the bioavailability of enoxacin. Enoxacin should not be administered with zinc due to the formation of chelates, which interfere with drug absorption and may result in sub-therapeutic plasma and tissue enoxacin concentrations. Advise patients not to take multivitamins containing zinc for 8 hours prior to enoxacin administration or for 2 hours after enoxacin administration.

**Gatifloxacin**
The co-administration of gatifloxacin and zinc, or any product containing zinc, may result in substantially decreased gatifloxacin absorption, resulting in lower systemic gatifloxacin concentrations. Gatifloxacin should be administered at least 4 hours before zinc or any product containing zinc.

**Gemifloxacin**
Quinolones form chelates with alkaline earth and transition metals. The absorption of oral gemifloxacin is significantly reduced by the concomitant administration of a zinc-containing product. Products containing zinc should not be taken within 3 hours before or 2 hours after gemifloxacin.

**Grepafloxacin**
Quinolones form chelates with metal cations, including zinc. The co-administration of zinc and grepafloxacin may substantially reduce the absorption of grepafloxacin, resulting in lower systemic concentrations. Separate the administration of grepafloxacin and zinc supplements or zinc-containing products by at least 4 hours.

**Iron**
Prenatal supplements containing iron and folate reduced zinc absorption in women in their third trimester of pregnancy (O’Brien et al., 2000a). Compared to iron and zinc administered individually, statistically significant impairments in physical and cognitive development have occurred when iron and zinc were concurrently administered over a 6-month period to infants. Separate the administration of zinc and iron by at least 2 hours.

**Levofloxacin**
Levofloxacin is capable of forming chelate complexes with zinc, potentially reducing the gastrointestinal absorption of levofloxacin. Decreased absorption may result in lower systemic levels than desired, thereby compromising the efficacy of the quinolone. Levofloxacin should be administered at least 2 hours before or 2 hours after the administration of zinc or a multiple-ingredient product containing zinc.

**Moxifloxacin**
The co-administration of moxifloxacin and zinc, or any product containing zinc, may result in substantially decreased moxifloxacin absorption, resulting in lower systemic moxifloxacin concentrations. Moxifloxacin should be administered at least 4 hours before or 8 hours after zinc.
**Norfloxacin**
Zinc interferes with absorption, resulting in reduced serum levels of norfloxacin. Avoid concurrent use. However, if used concurrently, the dose of the zinc salt should be given at least 6 hours before or 4 hours after the norfloxacin dose.

**Ofloxacin**
Quinolones form chelates with metal cations, including zinc. The co-administration of zinc and ofloxacin may substantially reduce the absorption of ofloxacin, resulting in lower systemic concentrations. Separate the administration of ofloxacin and zinc supplements or zinc-containing products by at least 2 hours.

**Penicillamine**
Concomitant administration of penicillamine might decrease gastrointestinal zinc absorption and enhance zinc excretion. Optimal dosage separation time has not been determined. Space the administration of zinc and penicillamine as far apart as possible.

**Sparfloxacin**
The absorption of quinolones, including sparfloxacin, is reduced when given concurrently with preparations containing zinc. If sparfloxacin and a product containing zinc must be taken concurrently, administer the zinc-containing preparation 4 hours after sparfloxacin is given.

**Tetracycline**
Polyvalent cations such as calcium, iron, magnesium, zinc and aluminium have a high affinity to form complexes, when given concurrently with tetracycline, thus altering the gastrointestinal absorption. Zinc may decrease tetracycline absorption by as much as 50%. Administer tetracycline at least 2 hours before or 3 hours after zinc.

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### Renal Impairment

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 haemodialysis patients, compared to 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 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. Calcitriol 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. 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 calcitriol.

**Paediatric**

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

**Geriatric**

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.

**Undesirable Effects**

Adverse effects are in general similar to those encountered with excessive vitamin D intake.

The early symptoms of vitamin D intoxication associated with hypercalcaemia include weakness, headache, somnolence, nausea, vomiting, dry mouth, constipation, flatulence, diarrhoea, urticarial, muscle pain and weakness, mental disturbances, abdominal pain, thirst, nephrocalcinosis, renal calculi, bone pain and metallic taste.

Late signs include 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, dystrophy, sensory disturbances, apathy, arrested growth, urinary tract infections and, rarely, overt psychosis. Extreme hypercalcaemia may result in coma and death. Persistently high calcium levels may lead to irreversible renal damage and soft-tissue calcification.

In clinical studies on hypoparathyroidism and pseudo-hypoparathyroidism, hypercalcaemia was noted on at least one occasion in about 1 in 3 patients and hypercalciuria in about 1 in 7 patients. Elevated serum creatinine levels were observed in about 1 in 6 patients (approximately half of whom had normal levels at baseline). In concurrent hypercalcaemia and hyperphosphataemia, soft-tissue calcification may occur; this can be seen radiographically.

In patients with normal renal function, chronic hypercalcaemia may be associated with an increase in serum creatinine. Hypersensitivity reactions (pruritus, rash, urticaria and, very rarely, severe erythematous skin disorders) may occur in susceptible individuals. One case of erythema multiforme and one case of allergic reaction (swelling of the lips and hives all over the body) were confirmed by rechallenge.

**Overdosage**

Administration of this formulation to patients in excess of their requirements can cause hypercalcaemia, hypercalciuria and hyperphosphataemia.
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 70 mg^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 1 mg/dl above the upper limit of normal range) consists of immediate discontinuation of calcium and vitamin D supplements. Serum calcium levels should be determined daily until normocalcaemia (8.5 to 10.5 mg/dl) ensues. Hypercalcaemia usually resolves in 2 to 7 days. When serum calcium levels have returned to within normal limits, the 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. Gastric lavage should be considered in patients with impaired consciousness. Rehydration according to severity, 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.

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 to 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.

### Storage And Handling Instructions

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

### Packaging Information

**CALZEM**

Blister strip pack of 10 capsules

Last updated: November 2013

Last reviewed: November 2013

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