For Malaysia
Artwork of insert **"OSTEOCAP"** HLM (PCL) code ***RI-C038-H14-00-09***

OSTEOCAP

(Calcitriol BP 0.25 micrograms)

For the use of the registered medical practitioner or a phamacist or a hospital

COMPOSITION:
Each softgel capsule contains :
Calcitriol BP ..... 0.25 micrograms

PRODUCT DESCRIPTION:
3 minim, oval shaped, red and white, opaque soft gelatin capsule.

MECHANISM OF ACTION:
Calcitriol is one of the most important active metabolites of vitamin D3. It is normally formed in the kidneys from its precursor, 25-hydroxycholecalciferol (25-HCC).

Calcitriol promotes intestinal absorption of calcium and regulates bone mineralization. The plasma half-life of calcitriol lasts about 3-5 days. The key role of calcitriol in the regulation of calcium homeostasis, which includes stimulating effects on osteoblastic activity in the skeleton, provides a sound pharmacological basis for its therapeutic effects in osteoporosis.

DESCRIPTION:
Synthetic calcitriol is the biologically active form of vitamin D3 which regulates absorption of calcium from the gastrointestinal tract and its utilization in the body. Calcitriol is a colourless, crystalline compound which occurs naturally in humans. It has a calculated molecular weight of 416.65 and is soluble in organic solvents but relatively insoluble in water.

INDICATIONS:
Established postmenopausal osteoporosis; renal osteodystrophy in patients with chronic renal failure, particularly those undergoing hemodialysis; post-surgical hypoparathyroidism; idiopathic hypoparathyroidism, pseudohypoparathyroidism; vitamin D dependent rickets; hypophosphatemic vitamin D-resistant rickets.

CONTRAIDICATIONS:
In all diseases associated with hypercalcemia. Use in patients with known hypersensitivity to calcitriol (for drugs of the same class) and any of the constituent is contraindicated. It is contraindicated if there is evidence of vitamin D toxicity.

PHARMACOKINETICS

Absorption:
Calcitriol is rapidly absorbed from the intestine. Peak serum concentrations (above basal values) were reached within 3 to 6 hours following oral administration of single dosed of 0.25 to 1.0 microgram.

Following a single oral dose of 0.5 microgram 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 declines 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.

Distribution:
Calcitriol and other vitamin D metabolites are transported approximately 99.9% bound to specific plasma proteins in the blood.

Metabolism:
Several metabolites of calcitriol, each exerting different vitamin D activities, have been identified : 1α,25-dihydroxy-24-oxo-cholecalciferol, 1α,23,25-trihydroxy-24-oxo-cholecalciferol, 1α,24R, 25-trihycroxycholecalciferol, 1α,25R-dihydroxycholecalciferol-26, 23S-lactone, 1α,25S,26-trihydroxycholecalciferol, 1α,25-dihydroxy-23-oxo-cholecalciferol, 1α,25R,26-trihydroxy-23-oxo-cholecalciferol and 1α-hydroxy-23-carboxy-24, 25, 26, 27-tetranorcholecalciferol.1α,25R-dihydroxycholecalciferol-26, 23S-lactone is the major metabolite in humans.

Excretion:
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. 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 microgram oral dose of radiolabelled calcitriol was administered to normals, 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 urine and 49% in faeces.

There is evidence that maternal calcitriol may enter the fetal circulation.

PRECAUTIONS:
There is a close correlation between treatment with calcitriol and the development of hypercalcemia.

In patients with normal renal function, chronic hypercalcemia may be associated with an increase in serum creatine.

Immobilized patients, eg. those who have undergone surgery, are particularly exposed to the risk of hypercalcemia.

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.

Patients with vitamin D-resistant rickets (familial hypophosphatemia) who are being treated wih calcitriol must continue their oral phosphate therapy. However, possible stimulation of intestinal absorption of phosphate by calcitriol should be taken into account since this effect may modify the need for phosphate supplementation. Since calcitriol is the most effective vitamin D metabolite available, no other vitamin D preparation should be prescribed during treatment with calcitriol, thereby ensuring the development of hypervitaminosis D in avoided.

If the patient is switched from ergocalciferol (vitamin D2) to calcitriol, it may take several months for the ergocalciferol level in the blood to return to the baseline values.

Patients with normal renal function who are taking calcitriol should avoid dehydration. Adequate fluid intake should be maintained.

Hypersensitivity reactions may occur in susceptible individuals.

Effects on the Ability to Drive or Operate Machinery : On the basis of the pharmacodynamic profile of reported adverse events, calcitriol is presumed to be safe or unlikely to produce an effect.

Use in Pregnancy & Lactation : Studies of reproductive toxicology in animals have not yielded unequivocal findings, and no controlled studies on the effect of exogenous calcitriol on pregnancy and fetal development have been performed in human subjects. Consequently, calcitriol should be administered only if the benefits outweigh the potential risk to the fetus.

It should be assumed that exogenous calcitriol passes into the breast milk. In view of the possible adverse effects on the infant, mothers shold not breastfeed while taking calcitriol.

ADVERSE REACTIONS:
Since calcitriol exerts vitamin D activity, adverse effects may occur which are similar to those found when an excessive dose of vitamin D is taken, i.e. hypercalcemia syndrome or calcium intoxication (depending on the severity and duration of hypercalcemia). Occasional acute symptoms include anorexia, headache, vomiting and constipation. Chronic effects may include dystrophy, sensory disturbances, fever with thirst, polyuria, apathy, arrested growth and urinary tract infections.

In concurrent hypercalcemia and hyperphosphatemia of >6 mg/100 ml or >1.9 mmol/L, soft tissue calcification may occur; this can be seen radiographically. In patients with normal renal, function, chronic hypercalcemia may be associated with an increase in serum creatinine.

Because of the short biological half-life of calcitriol, pharmacokinetic investigations have shown normalization of elevated serum calcium within a few days of treatment withdrawal of a dosage reduction, i.e. much faster than in treatment with vitamin D3 preparations.

INTERACTIONS:
Since calcitriol is one of the most important active metabolites of vitamin D3, pharmacological doses of vitamin D and its derivatives should be withheld during treatment with calcitriol to avoid possible additive effects and hypercalcemia. Dietary instructions, especially calcium supplements, should be strictly observed, and uncontrolled intake of additional calcium-containing preparations avoided.

Concomitant treatment with a thiazide diuretic increases the risk of hypercalcemia. Calcitriol dosage must be determined with care in patients undergoing treatment with digitalis, as hypercalcemia in such patients may precipitate cardiac arrhythmias.

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

Magnesium-containing drugs (eg. Antacids) may cause hypermagnesemia and should therefore not be taken during thereby with calcitriol by patients on chronic renal dialysis. Calcitriol also has an effect on phosphate transport in the intestine, kidneys and bones, the dosage of phosphate binding agents must be adjusted in accordance with the serum phosphate concentration (normal values: 2-5 mg/100 ml, or 0.65-1.62 mmol/l).

Patients with vitamin D - resistant rickets (familial hypophosphatemia) should continue their oral phosphate therapy.

However, possible stimulation of intestinal phosphate absorption by calcitriol should be taken into account since this effect may modify the requirement for phosphate supplements.

Administration of enzyme inducers, e.g. phenytoin or phenobarbital may lead to increases metabolism and, hence, reduced serum concentrations of calcitriol. Therefore, higher dosed of calcitriol may be necessary if these drugs are administered simultaneously.

Cholestyramine can reduce intestinal absorption of fat soluble vitamins and therefore may impair intestinal absorption of calcitriol.

OVERDOSAGE:
Since calcitriol is a derivative of vitamin D, the symptoms of overdose are the same as for an overdose of vitamin D. Intake of high doses of calcium and phosphate together with calcitriol may give rise to similar symptoms. A high calcium level in the dialysate may contribute to the development of hypercalcemia.

Acute Symptoms of Vitamin D Intoxication : Anorexia, headache, vomiting and constipation.

Chronic Symptoms : Dystrophy (weakness, loss of weight). Sensory disturbances, possibly fever thirst, polyuria, dehydration, apathy, arrested growth and urinary tract infections. Hypercalcemia ensues with metastatic calcification of the renal cortex, myocardium, lungs and pancreas.

Treatment : The following measures should be considered in treatment of accidental overdosage; immediate gastric lavage or induction of vomiting to prevent further absorption.

Administration of liquid paraffin to promote fecal excretion.

Repeated serum calcium determinations are advisable. If elevated calcium levels persist in the serum, phosphates and corticosteroids may be administered and measures instituted to bring about adequate diuresis.

DOSAGE & ADMINISTRATION:
Standard Dosage: The optimal daily dose of calcitriol must be carefully determined for each patient on the basis of the serum calcium level. Calcitriol therapy should always be started at lowest possible dose and should not be increased without careful monitoring of serum calcium.

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. As soon as the serum calcium levels rise to 1 mg/100 ml above normal, or serum creatinine rises to >120 µmol/L the dosage of calcitriol should be substantially reduced or treatment stopped altogether until normocalcemia ensues.

During the periods of hypercalcemia, 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 0.25 mcg lower than that previously used. An estimate of daily dietary calcium intake should be made and the intake adjusted when indicated.

A prerequisite for optimal efficacy of calcitriol is adequate but not excessive calcium intake (in adults: Approximately 800 mg daily) at the beginning of therapy. Calcium supplements may be necessary.

Bacause of improved calcium absorption from the gastrointestinal tract, some patients on calcitriol may be maintained on a lower calcium intake. Patients who tend to develop hypercalcemia may require only low doses of calcium or not supplementation at all.

The total daily calcium intake (i.e. from food and where applicable from drugs) should average approximately 800 mg and should not exceed 1000 mg.

Special Dosage Instruction:
Postmenopausal Osteoporosis: The recommended dosage is 0.25 mcg twice daily. Serum calcium and creatinine levels should be determined at 4 week, 3 and 6 months and a 6 monthly intervals thereafter.

Renal Osteodystrophy (Dialysis Patients): Initial daily dose should be 0.25 mcg. In patients with normal or only slightly reduced serum calcium levels, doses of 0.25 mcg every other day are sufficient. If no satisfactory response in the biochemical parameters and clinical manifestations of the disease is observed within 2-4 weeks, the dosage may be increased by 0.25 mcg/day for 2 to 4 weeks intervals. During this period, serum calcium levels should be determined at least twice weekly. Most patients respond to between 0.5 and 1 mcg daily.

Hypoparathyroidism and Rickets: Recommended initial dose should be 0.25 mcg/day given in the morning. If a satisfactory response in the biochemical parameters and clinical manifestations of the disease are not observed, the dose may be increased at 2 to 4 week intervals. During this period, serum calcium levels should be determined at least twice weekly.

Malabsorption is occasionally noted in patients with hypoparathroidism; hence, larger doses of calcitriol may be needed.

Elderly: No specific dosage modifications are required in elderly patients. The general recommendations for monitoring serum calcium and creatinine should be observed.

Route of administration: Oral

STORAGE:
Store below 30°C in a dry place, away from direct sunlight.

PRESENTATION:
Osteocap 0.25 micrograms - Box containing 10 strips of 10 capsules each.
Osteocap 0.25 micrograms - Box containing 3 strips of 10 capsules each.

Manufactured by :
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