CALCITRIOL

RENATROL

0.25mcg Softgel Capsule

Vitamin

FORMULATION:

Each softgel capsule contains:

Active ingredient:

Calcitriol (Vitamin D).....0.25 mcg

Inactive ingredients:

Soy bean oil, gelatin, glycerin, methyl p-hydroxybenzoate, propyl p-hydroxybenzoate, 70% D-Sorbitol, yellow ferric oxide, titanium dioxide.

PRODUCT DESCRIPTION:

Orange oval softgel capsule containing light yellow substance.

INDICATIONS:

* Treatment and prevention of Vitamin D deficiency states and hypocalcemia in disorders such as hypoparathyroidism and secondary hyperparathyroidism associated with chronic renal failure.

* Treatment of established post-menopausal osteoporosis.

PHARMACODYNAMICS:

Calcitriol is the most active known form of Vitamin D_3 in stimulating intestinal calcium transport. It is normally formed in the kidneys from its immediate precursor, 25-hydroxycholecalciferol. In physiological amounts it augments the intestinal absorption of calcium and phosphate and plays a significant part in the regulation of bone mineralisation. The defective production of calcitriol in chronic renal failure contributes to the abnormalities of mineral metabolism found in that disorder.

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 DNA sites to modify the expression of target genes.

Calcitriol (Renatrol) is a synthetic preparation of calcitriol.

Oral administration of Calcitriol (Renatrol) to patients with chronic renal failure compensates for impared endogenous production of calcitriol which is decreased when the glomerular filtration rate falls below 30ml/min. Consequently, intestinal malabsorption of calcium and phosphate and the resulting hypocalcemia are improved, thereby reversing the signs and symptoms of bone disease.

In patients with established post-menopausal osteoporosis, Calcitriol (Renatrol) increases calcium absorption, elevates circulating levels of calcitriol and reduces vertebral fracture frequency.

The onset and reversal of the effects of Calcitriol (Renatrol) are more rapid than those of other compounds with vitamin D activity and an adjustment of the dose can be achieved sooner and more precisely. The effects of inadvertent overdosage can also be reversed more readily.

PHARMACOKINETICS:

Vitamin D substances are well absorbed from the gastrointestinal tract. The presence of bile is essential for adequate intestinal absorption; absorption may be decreased in patients with decreased fat absorption.

Vitamin D and its metabolites circulate in the blood bound to a specific a-globulin. Vitamin D can be stored in adipose and muscle tissue for long periods of time. It is slowly released from storage sites and from the skin where it is formed in the presence of sunlight or ultraviolet light, Ergocalciferol and cholecalciferol have a slow onset and a long duration of action; calcitriol and its analogue alfacalcidol however, have a more rapid action and shorter half-lives.

Cholecalciferol and ergocalciferol are hydroxylated in the liver by the enzyme vitamin D 25-hydroxylase to form 25-hydroxycholecalciferol (calcifediol) and 25-hydroxyergocalciferol respectively. These compounds undergo further hydroxylation in the kidneys by the enzyme vitamin D1-hydroxylase to form the active metabolites 1,25-dihydroxycholecalciferol (calcitriol) and 1,25-dihydroxyergocalciferol, respectively. Further metabolism also occurs in the kidneys, including the formation of 1,24,25-trihydroxy derivatives of the synthetic analogues, alfacalcidol, dihydrotachysterol, and doxercalciferol are converted directly in the liver to their active metabolites (calcitriol, 25-hydroxydihydrotachysterol, and 1,25-dihydroxyergocalciferol respectively).

Vitamin D compounds and their metabolites are excreted mainly in the bile and feces with only small amounts appearing in urine; there is some enterohepatic recycling but it is considered to have a negligible contribution to vitamin D status. Certain vitamin D substances may be distributed into breast milk.

DOSAGE AND ADMINISTRATION:

The usual initial adult oral dose is 0.25 mcg (1 capsule) daily or on alternate days are given, increased if necessary, in steps of 0.25 mcg (1 capsule) at intervals of 2 to 4 weeks, to a usual dose of 0.5 mcg (2 capsules) to 1 mcg (4 capsules) daily.

For moderate to severe secondary hyperparathyroidism in dialysis patients, initial doses of 0.5 mcg (2 capsules) to 4 mcg (8 capsules) have been given three times a week, increased if necessary in steps of 0.25 mcg (1 capsule) to 1 mcg (4 capsules) at intervals of 2 to 4 weeks to a maximum of 8 mcg (16 capsules) given three times a week.

In established postmenopausal osteoporosis, a dose of 0.25 mcg (1 capsule) twice daily is recommended.

When vitamin D substances are given in pharmacological doses, dosage must be individualized for each patient, and should be based on regular monitoring of plasma-concentrations (initially once or twice weekly), to optimize clinical response and avoid hypercalcaemia.

CONTRAINDICATIONS:

1.All kinds of diseases related to hypercalcemia.

2.Patients with history of hypersensitivity to this drug or any components of this drug.

3.Patient with evidence of vitamin D toxicity.

PREGNANCY AND LACTATION:

The safety of Calcitriol (Renatrol) during pregnancy has not been established.

Calcitriol (Renatrol) should be used during pregnancy only if the benefits outweigh the potential risk to the fetus.

It should be assumed that exogenous calcitriol passes into breast milk. In view of the potential for hypercalcemia in the mother and for adverse reactions from Calcitriol (Renatrol) in nursing infants, mothers may breastfeed while taking Calcitriol (Renatrol), provided that the serum calcium levels of the mother and infant are monitored.

WARNING:

1.Pregnant women: since it had not yet been established that this drug is safe in pregnant women or women suspected of being pregnant, administration to these kind of people should be carried out after comparing possible risks which can occur in a mother and fetus with therapeutic benefits following medication.

2.Infants below 3 years and being taken hemodialysis: it should be administered to these patients after comparing risks which can be able to occur individually with therapeutic benefits because of lack experience about using this drug in such cases.

ADVERSE REACTIONS:

Excessive intake of vitamin D leads to the development of hyperphosphatemia or hypercalcemia. Associated effects of hypercalcemia include hypercalciuria, ectopic calcification, and renal and cardiovascular damage.

Symptoms of overdosage include anorexia, lassitude, nausea and vomiting, constipation or diarrhea, nocturia, sweating, headache, thirst, somnolence, and vertigo. Interindividual tolerance to vitamin D varies considerably; infants and children are generally more susceptible to its toxic effects. The vitamin should be withdrawn if toxicity occurs. It has been stated that vitamin D dietary supplementation may be detrimental in persons already receiving an adequate intake through diet and exposure to sunlight, since the difference between therapeutic and toxic concentrations is relatively small.

Hypersensitivity reactions have occurred.

Inform your doctor in case of any adverse reactions related to drug use.

GENERAL PRECAUTIONS:

Vitamin D should not be given to patients with hypercalcemia. It should be used with caution in infants, who may have increased sensitivity to its effects, and patients with renal impairment or calculi, or heart disease, who might be at increased risk of organ damage if hypercalcemia occurred. Plasma phosphate concentrations should be controlled during vitamin D therapy to reduce the risk of ectopic calcification.

It is advised that patients receiving pharmacological doses of vitamin D should have their plasma-calcium concentration monitored at regular intervals, especially initially or if symptoms suggest toxicity. Similar monitoring is recommended in infants if they are breastfed by mothers receiving pharmacological doses of vitamin D.

DRUG INTERACTIONS:

There is an increase risk of hypercalcemia if vitamin D is given with thiazide diuretics, calcium, or phosphate. Plasma-calcium concentrations should be monitored in such situations. Some antiepileptics may increase vitamin D requirements (e.g. Carbamazepine, Phenobarbital, Phenytoin, and Primidone). Rifampicin and Isoniazid may reduce the effectiveness of vitamin D. Corticosteroids may counteract the effect of vitamin D. Ketoconazole may inhibit the metabolism of Paricalcitol and these drugs should be used with caution together; care should be taken when using Paricalcitol with other potent inhibitors of the cytochrome P450 isoenzyme CYP3A4.

OVERDOSE AND TREATMENT:

overdose are the same as for an overdose of vitamin D. Intake of high doses of calcium and phosphate together with Calcitriol (Renatrol) may give rise to similar symptoms. the serum calcium times phosphate (Ca x P) product should not be allowed to exceed 70 mg^2/dl^2. A high calcium level in the dialysate may contribute to the development of hypercalcemia.

Acute symptoms of vitamin D intoxication: anorexia, headache, vomiting, constipation.

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

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.

Hypercalcemia at higher levels (>3.2 mmol/L) may lead to renal insufficiency particularly if blood phosphate levels are normal or elevated due to impaired renal function.

Should hypercalcemia occur following prolonged treatment, Calcitriol (Renatrol) should be discontinued until plasma calcium levels have returned to normal. A low-calcium diet will speed this reversal. Calcitriol (Renatrol) can then be restarted at a lower dose or given in the same dose but at less frequent intervals than previously.

In patients treated by intermittent hemodialysis, a low concentration of calcium in the dialysate may also be used. However, a high concentration of calcium in the dialysate may contribute to the development of hypercalcemia.

STORAGE CONDITION:

Store at temperatures not exceeding 30°C.

CAUTION:

Foods, Drugs, Devices and Cosmetics Act prohibits dispensing without prescription.

AVAILABILITY:

Alu/Clear PVC Blister Pack x 10's (Box of 100's)

Alu/Clear PVC blister Pack x 10's (Box of 30's)

For suspected adverse drug reaction, report to the FDA: www.fda.gov.ph

Seek medical attention immediately at the first sign of any adverse drug reaction.

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