CALCITRIOL
RENTROL

0.25 mcg Softgel Capsule
VITAMIN

Rx

FORMULATION:
Each softgel capsule contains:
Calcitriol ..... 0.25 µg

PRODUCT DESCRIPTION:
An oval ivory white soft capsule containing pale yellow oil content. (print: BKC)

PHARMACOLOGICAL PROPERTIES:
Pharmacodynamic Properties:
Calcitriol is the most active known form of vitamin D 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 mineralization. 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 functions as a ligand-activated transcription factor that binds to DNA sites to modify the expression of target genes.
This is a synthetic preparation of calcitriol. Oral administration of Calcitriol to patients with chronic renal failure compensates for impaired endogenous production of calcitriol which is decreased when the glomerular filtration rate falls below 30 mL/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 increases calcium absorption, elevates circulating levels of calcitriol and reduces vertebral fracture frequency.
The onset and reversal of the effects of Calcitriol are more rapid than those of other compounds with vitamin D activity and adjustment of the dose can be achieved sooner and more precisely. The effects of inadvertent overdosage can also be reversed more readily.

Pharmacokinetic Properties:
Absorption
Calcitriol is rapidly absorbed from the intestine. Peak serum concentrations following a single oral dose of 0.25-1 µg Calcitriol in healthy subjects were found within 2-6 hours.
After a single oral dose of 0.5 mcg of Calcitriol in healthy subjects, the average serum concentrations of calcitriol rose from a baseline value of 40.0 ± 4.4 pg/mL to 60.0 ± 4.4 pg/mL after two hours, and then fell to 53.0 ± 6.9 after four hours, to 50.0 ± 7.0 after eight hours, to 44 ± 4.6 after twelve hours and to 41.5 ± 5.1 pg/mL after 24 hours.
Distribution
During transport in the blood at physiological concentrations, calcitriol is mostly bound to a specific vitamin D binding protein (DBP), but also, to a lesser degree, to lipoproteins and albumin. At higher blood calcitriol concentrations, DBP appears to become saturated and increased binding to lipoproteins and albumin occurs.
Metabolism
Calcitriol is hydroxylated and oxidized in the kidney and in the liver by a specific cytochrome P450 enzyme: CYP24A1.
Several metabolites with different degrees of vitamin D activity have been identified.
Elimination
The elimination half-life of calcitriol in plasma ranges between 5 to 8 hours. However, the pharmacological effect of a single dose of calcitriol lasts at least 4 days. The elimination and absorption kinetics of calcitriol remain linear in a very broad dose range and up to 165 µg single oral dose. Calcitriol is excreted in the bile and may undergo an enterohepatic circulation.

Preclinical safety data
Subchronic toxicity studies in rats and dogs indicated that calcitriol at an oral dose of 20 ng/kg/day (twice the usual human dosage) for up to 6 months produced no or minimal adverse effects. A dose of 80 ng/kg/day (8 times the usual human dosage) for up to 6 months produced moderate adverse effects; changes seen appeared to be primarily the result of prolonged hypercalcemia. Reproductive toxicity studies in rats indicated that oral doses up to 300 ng/kg/day (30 times the usual human dose) did not adversely affect reproduction. In rabbits, multiple fetal abnormalities were observed in two litters at an oral maternally toxic dose of 300 ng/kg/day and one litter at 80 ng/kg/day, but not at 20 ng/kg/day (twice the usual human dose). Although there were no statistically significant differences between treated groups and controls in the number of litters or fetuses showing abnormalities, the possibility that these findings were due to calcitriol administration could not be discounted.

INDICATIONS:
Calcitriol is indicated for the correction of the abnormalities of calcium and phosphate metabolism in patients with renal osteodystrophy.
Calcitriol is also indicated for the treatment of established post-menopausal osteoporosis.

DOSAGE AND ADMINISTRATION:
The dose of Calcitriol should be carefully adjusted for each patient according to the biological response so as to avoid hypercalcemia. The effectiveness of treatment depends in part on an adequate daily intake of calcium, which should be augmented by dietary changes or supplements if necessary. The capsules should be swallowed with a little water.
Adults
Renal Osteodystrophy
The initial daily dose is 0.25 mcg of Calcitriol. In patients with normal or only slightly reduced 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 daily dosage may be increased by 0.25 mcg at 2 - 4 week intervals. During this period, serum calcium levels should be determined at least twice weekly. Should the serum calcium levels rise to 1 mg/100 mL (250 µmol/L) above normal (9 to 11 mg/100 mL or 2250 – 2750 µmol/L), or serum creatinine rises to > 120 µmol/L, treatment with Calcitriol should be stopped immediately until normocalcaemia ensues. Most patients respond to between 0.5 mcg and 1.0 mcg daily.
An oral Calcitriol pulse therapy with an initial dosage of 0.1 mcg/kg/week split into two or three equal doses given at the end of the dialysis is effective in patients with osteodystrophy refractory to continuous therapy. A maximum total cumulative dosage of 12 mcg per week should not be exceeded.
Post-menopausal Osteoporosis
The recommended dose of Calcitriol is 0.25 mcg twice daily.
Serum calcium and creatinine levels should be determined at 1, 3, and 6 months and at 6 monthly intervals thereafter.
Elderly
Clinical experience with Calcitriol in elderly patients indicates that the dosage recommended for use in younger adults may be given without apparent ill consequences.
Pediatric Population
The safety and efficacy of calcitriol capsules in children have not been sufficiently investigated to enable dosing recommendations. Limited data are available for the use of calcitriol capsules in pediatric patients.
Calcitriol capsules are for oral administration only.

CONTRAINDICATIONS:
Calcitriol is contraindicated:
- in all diseases associated with hypercalcemia;
- in patients with evidence of metastatic calcification;
- in patients with known hypersensitivity to calcitriol (or drugs of the same class) and any of the constituent excipients;
- if there is evidence of vitamin D toxicity.

WARNINGS AND PRECAUTIONS:
There is a close correlation between treatment with calcitriol and the development of hypercalcemia.
All other vitamin D compounds and their derivatives, including proprietary compounds or foodstuffs that may be "fortified" with vitamin D, should be withheld during treatment with Calcitriol.
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 hypercalcemia. Patients and their families should be advised that strict adherence to the prescribed diet is mandatory and they should be instructed on how to recognize the symptoms of hypercalcemia.
As soon as the serum calcium levels rise to 1 mg/100 mL (250 µmol/L) above normal (9-11 mg/100 mL or 2250-2750 µmol/L), or serum creatinine rises to >120 µmol/L, treatment with Calcitriol should be stopped immediately until normocalcaemia ensues.
Immobilized patients, e.g., 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. In such cases, the plasma phosphate level should be maintained at the normal level (2-5 mg/100 mL or 0.65-1.62 mmol/L) by the oral administration of appropriate phosphate-binding agents and low phosphate diet.
The serum calcium times phosphate (Ca x P) product should not be allowed to exceed 70 mg2/dl2.
Patients with vitamin D-resistant rickets(familial hypophosphatemia) who are being treated with 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 that the development of hypervitaminosis D is avoided.
If the patient is switched from a long-acting vitamin D preparation (e.g. ergocalciferol(vitamin D) or cholecalciferol) to calcitriol, it may take several months for the ergocalciferol level in the blood to return to the baseline value, thereby increasing the risk of hypercalcemia.
Patients with normal renal function who are taking Calcitriol should avoid dehydration. Adequate fluid intake should be maintained.
In patients with normal renal function, chronic hypercalcemia may

be associated with an increase in serum creatinine.
Calcitriol capsules contain sorbitol. Patients with rare hereditary problems of fructose intolerance should not take Calcitriol capsules.

DRUG INTERACTIONS:
Dietary instructions, especially concerning 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 analogs, which promote calcium absorption, and corticosteroids, which inhibit it.
Magnesium-containing drugs (e.g., antacids) may cause hypermagnesaemia and should therefore not be taken during therapy with Calcitriol by patients on chronic renal dialysis.
Since 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.
Bile acid sequestrants including cholestyramine and sevelamer can reduce intestinal absorption of fat-soluble vitamins and therefore may impair intestinal absorption of calcitriol.

FERTILITY, PREGNANCY, AND LACTATION:
The safety of Calcitriol during pregnancy has not been established. Supravalvular aortic stenosis has been produced in fetuses by near-fatal oral doses of vitamin D in pregnant rabbits.
There is no evidence to suggest that vitamin D is teratogenic in humans even at very high doses. Calcitriol should be used during pregnancy only if the benefits outweigh the potential risks 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 in nursing infants, mothers may breastfeed while taking Calcitriol, provided that the serum calcium levels of the mother and infant are monitored.

Effects on the ability to drive and use machines
On the basis of the pharmacodynamic profile of reported adverse events, this product is presumed to be safe or unlikely to adversely affect such activities.

ADVERSE DRUG REACTIONS:
The adverse drug reactions listed below reflect the experience from investigational studies of Calcitriol, and the postmarketing experience.
The most commonly reported adverse reaction was hypercalcemia.
The ADRs listed in Table 1 are presented by system organ class and frequency categories, defined using the following convention: 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); very rare (<1/10,000); not known (cannot be estimated from the available data). Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

Table 1 Summary of ADRs Occurring in Patients Receiving Calcitriol

System organ class	Very common	Common	Uncommon	Not known
Immune system disorders	-	-	-	Hypersensitivity, urticaria
Metabolism and nutrition disorders	Hypercalcaemia	-	Decreased appetite	Polydipsia, dehydration, weight decreased
Psychiatric disorders	-	-	-	Apathy, psychiatric disturbances
Nervous system disorders	-	Headache	-	Muscular weakness, sensory disturbance, somnolence
Cardiac disorders	-	-	-	Cardiac arrhythmias
Gastrointestinal disorders	-	Abdominal pain, Nausea	Vomiting	Constipation, abdominal pain upper, Paralytic ileus
Skin and subcutaneous tissue disorders	-	Rash	-	Erythema, pruritus
Musculoskeletal and connective tissue disorders	-	-	-	Growth retardation
Renal and urinary disorders	-	Urinary tract infection	-	Polyuria, nocturia
General disorders and administration site conditions	-	-	-	Calcinosis, pyrexia, thirst
Investigations	-	-	Blood creatinine increased	-

Since calcitriol exerts vitamin D activity, adverse effects may occur that 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 decreased appetite, headache, nausea, vomiting, abdominal pain or upper abdominal pain and constipation.
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, i.e., much faster than in treatment with vitamin D3 preparations.
Chronic effects may include muscular weakness, weight decreased, sensory disturbances, pyrexia, thirst, polydipsia, polyuria, dehydration, apathy, growth retardation, and urinary tract infections.
In concurrent hypercalcemia and hyperphosphataemia of > 6 mg/100 mL or > 1.9 mmol/L, calcinosis may occur; this can be seen radiographically.
Hypersensitivity reactions including rash, erythema, pruritus, and urticaria may occur in susceptible individuals.
Laboratory Abnormalities
In patients with normal renal function, chronic hypercalcemia may be associated with a blood creatinine increase.
Post Marketing
The number of adverse effects reported from the clinical use of Calcitriol over a period of 15 years in all indications is very low with each individual effect, including hypercalcemia, occurring at a rate of 0.001 % or less.

OVERDOSE AND TREATMENT:
Treatment of asymptomatic hypercalcemia.
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. The serum calcium times phosphate (Ca x P) product should not be allowed to exceed 70 mg2/dl2. 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. Hypercalcaemia ensues, with metastatic calcification of the renal cortex, myocardium, lungs, and pancreas.
The following measures should be considered in the 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 should be discontinued until plasma calcium levels have returned to normal. A low-calcium diet will speed this reversal. Calcitriol can then be restarted at a lower dose or given at 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.

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

ADR REPORTING STATEMENT:
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.

STORAGE CONDITION:
Store at temperatures not exceeding 30°C. Protect from light and moisture.

KEEP ALL MEDICINES OUT OF REACH OF CHILDREN.

AVAILABILITY:
Alu/PVDC Blister Pack x 10's (Box of 6 blister packs x 10 softgel capsules)
DRP-13353-01
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YUYU PHARMA, INC.
94, Bio Valley 1-Ro, Jecheon-Si,
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104-A Residencia 8888 Condominium Bldg.,
Pearl Drive cor. Amethyst St.,
Ortigas Center, Pasig City, Metro Manila

Read the insert paper carefully before using; ask your doctor for information.