PRODUCT MONOGRAPH

ROCALTROL®

(calcitriol)

Capsules 0.25 µg and 0.5 µg

Solution 1.0 µg/mL

VITAMIN D_3 METABOLITE

Hoffmann-La Roche Limited

2455 Meadowpine Boulevard
Mississauga, Ontario
L5N 6L7

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NAME OF DRUG

ROCALTROL®
(calcitriol)

THERAPEUTIC CLASSIFICATION
Vitamin D_3 Metabolite

ACTIONS AND CLINICAL PHARMACOLOGY

The supply of vitamin D in man depends on dietary intake and/or exposure to the ultraviolet rays of the sun for conversion of 7-dehydrocholesterol to vitamin D_3 (cholecalciferol).[1] Vitamin D_3 must be metabolized in the liver and the kidney before it is fully active on its target tissues.[2,3,4] The initial transformation is catalyzed by a vitamin D_3-25-hydroxylase enzyme (25-OHase) present in the liver, and the product of this reaction is 25-hydroxy-vitamin D_3 (25-OH-D_3). The latter undergoes hydroxylation in the mitochondria of kidney tissue. This reaction is activated by the renal 25-hydroxy-vitamin D_3 -1 alphahydroxylase (alpha-OHase) to produce 1,25-$(OH)_2$ D_3 (calcitriol).

The two known sites of action of calcitriol are intestine and bone, but additional evidence suggests that it also acts on the kidney and the parathyroid gland.[5]

In acutely uremic rats calcitriol has been shown to stimulate calcium absorption.[6] It is the most active known form of vitamin D_3 in stimulating intestinal calcium transport. This agent also promotes the intestinal absorption of phosphorus through stimulation of an active transport system distinct from the calcium transport process.[9]

Calcitriol stimulates bone resorption which serves to mobilize calcium for the circulation, when an intestinal source of calcium is absent.[10] This effect is related to the role of vitamin D in maintaining the homeostasis of calcium and phosphorus in plasma. In addition, calcitriol may interact directly with osteoblasts.

The effects of calcitriol on the renal transport of calcium and phosphate appear to be influenced by the presence or absence of the parathyroid glands, vitamin D status, volume expansion and the dose of vitamin D metabolite used.[11] With the available information it is not possible to determine which vitamin D metabolite, if any, influences divalent ion transport by the renal tubule under physiologic conditions or if so, whether an interaction with parathyroid hormone is required.

The presence of a direct negative feedback effect of calcitriol on the parathyroid gland has been suspected. Some investigators have postulated that calcitriol may exert a direct influence on the parathyroids.[12] Although inhibition of PTH secretion by calcitriol has been demonstrated in vitro, the data obtained from in vivo studies is more equivocal.[9]

INDICATIONS AND CLINICAL USE

'Rocaltrol' (calcitriol) is indicated in the management of:

- Hypocalcemia and osteodystrophy in patients with chronic renal failure undergoing dialysis.
- Hypocalcemia and its clinical manifestations associated with:
  - Post-surgical hypoparathyroidism
  - Idiopathic hypoparathyroidism
  - Pseudohypoparathyroidism.
- Vitamin D resistant rickets (familial hypophosphatemia).

CONTRAINDICATIONS

'Rocaltrol' (calcitriol) should not be given to patients with hypercalcemia or with a known hypersensitivity to calcitriol, vitamin D or its analogues and derivatives. It should not be administered if there is evidence of vitamin D overdosage.

WARNINGS

Since 'Rocaltrol' (calcitriol) is a potent cholecalciferol derivative with profound effects on intestinal absorption of dietary calcium and inorganic phosphate, it should not be used concomitantly with other vitamin D products or its derivatives.

Therapy with 'Rocaltrol' should only be considered when adequate laboratory facilities for monitoring of blood and urine chemistries are available. During treatment progressive hypercalcemia either due to hyper-responsiveness or overdosage may become so severe as to require emergency treatment.

Chronic hypercalcemia can lead to generalized vascular calcification, nephrocalcinosis, calcifications of the cornea or other soft tissues. During treatment with 'Rocaltrol' THE SERUM TOTAL CALCIUM (mg/dL) TIMES SERUM INORGANIC PHOSPHATE PRODUCT (Ca x P) SHOULD NOT EXCEED 70 mg^2/dl^2.

Dialysate calcium level of 7 mg% or above in addition to excessive dietary calcium supplements may lead to frequent episodes of hypercalcemia.

In patients on digitalis, hypercalcemia may precipitate cardiac arrhythmias; in such patients 'Rocaltrol' should be used with extreme caution.

To control serum inorganic phosphate levels and dietary phosphate absorption in patients undergoing dialysis, oral aluminum carbonate or aluminum hydroxide gel must be used. Magnesium containing antacids may contribute towards hypermagnesemia in patients on chronic renal dialysis and should be avoided during therapy with 'Rocaltrol'.

The safety of 'Rocaltrol' in women who are or may become pregnant has not been established; use of 'Rocaltrol' in these cases may be considered only when the potential benefits have been weighed against possible hazards to mother and fetus.

'Rocaltrol' may be excreted in human milk. In view of the potential for hypercalcemia in the mother and for adverse reactions from 'Rocaltrol' in nursing infants, mothers may breastfeed while taking 'Rocaltrol', provided that the serum calcium levels of the mother and infant are monitored.

PRECAUTIONS

Patient Selection and Follow-up: Patients with renal osteodystrophy and hypocalcemia, poorly managed by conventional vitamin D therapy are likely to respond to 'Rocaltrol' (calcitriol). The desired therapeutic margin of 'Rocaltrol' is narrow, therefore, the optimal daily dose must be carefully determined for each patient by dose titration to obtain satisfactory response in the biochemical parameters and clinical manifestations (see **DOSAGE AND ADMINISTRATION**).

Excessive dosage of 'Rocaltrol' induces hypercalcemia and hypercalciuria; therefore, early in treatment during dosage adjustment, serum calcium should be determined at least twice weekly. A fall in serum alkaline phosphatase values may indicate impending hypercalcemia. Should hypercalcemia develop, the drug should be discontinued immediately until the serum calcium level has normalized. This may take several days to a week.

In patients with normal renal function, chronic hypercalcemia may be associated with an increase in serum creatinine. While the elevation of serum creatinine is usually reversible, it is important in such patients to

pay careful attention to those factors which may lead to hypercalcemia. ‘Rocaltrol’ therapy should always be started at the lowest possible dose and increased with careful monitoring of serum calcium concentrations. An estimate of daily dietary calcium intake should be made and the intake adjusted when indicated.

Patients with normal renal function taking ‘Rocaltrol’ should avoid dehydration. Adequate fluid intake should be maintained.

Patients with vitamin D resistant rickets (familial hypophosphatemia) should pursue their oral phosphate therapy. However, the possible stimulation of intestinal phosphate absorption by ‘Rocaltrol’ should be taken into account since this effect may modify the requirement for phosphate supplements.

ESSENTIAL LABORATORY TESTS

Serum calcium, inorganic phosphorus, magnesium, alkaline phosphatase as well as 24-hour urinary calcium and phosphorus should be determined periodically during maintenance therapy with ‘Rocaltrol’. During the initial phase of the medication, serum calcium should be determined more frequently (at least twice weekly). Periodic ophthalmological examinations and radiological evaluation of suspected anatomical regions for early detection of ectopic calcifications are advisable.

DRUG INTERACTIONS

Hypercalcemia in patients on digitalis may precipitate cardiac arrhythmias. Intestinal absorption of ‘Rocaltrol’ may be impaired by resins such as cholestyramine and by use of mineral oil as a laxative. Although the precise mechanism involved is unknown, there is evidence that long-term anticonvulsant treatment, particularly with diphenylhydantoin and barbiturates, may interfere with the actions of vitamin D. Patients under concurrent treatment with such agents may require slightly higher doses of ‘Rocaltrol’.

INFORMATION FOR THE PATIENT

The patient and his or her immediate relatives should be informed about the need for compliance with dosage instructions, strict adherence to prescribed calcium intake, dietary and supplementary, and avoidance of unapproved non-prescription drugs or medications. Patients should also be made aware of the symptoms of hypercalcemia and should seek medical attention if such symptoms are noted (see **ADVERSE REACTIONS**).

ADVERSE REACTIONS

The following adverse reactions, based on clinical studies, have been reported in association with 'Rocaltrol' treatment:

a) Most frequent: hypercalcemia (20-30%).

b) Less frequent: headache, nausea, vomiting, constipation, abdominal cramp, pruritis, conjunctivitis, agitation, extremity pain, apprehension, polyuria, insomnia, elevated SGOT and/or SGPT, elevated alkaline phosphatase, hypercalciuria, hypermagnesemia, hyperphosphatemia, elevated lymphocytes, elevated hematocrit, elevated neutrophils, elevated hemoglobin.

The number of adverse effects reported from clinical use of 'Rocaltrol' 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

Hypersensitivity reactions (pruritis, rash, urticaria, and very rarely severe erythematous skin disorders) may occur in susceptible individuals.The adverse effects of 'Rocaltrol' (calcitriol) are, in general, similar to those encountered with excessive vitamin D intake. The early and late signs and symptoms associated with vitamin D intoxication and hypercalcemia are:

a) Early: weakness, headache, somnolence, nausea, cardiac arrhythmias, excessive thirst, vomiting, dry mouth, constipation, muscle pain, bone pain, metallic taste, abdominal pain or stomach ache.

b) Late: polyuria, polydipsia, urinary tract infections, anorexia, weight loss, nocturia, conjunctivitis (calcific), pancreatitis, photophobia, rhinorrhea, pruritus, hyperthermia, decreased libido, elevated BUN, albuminuria, hypercholesterolemia, elevated SGOT and SGPT, ectopic calcification, hypertension, cardiac arrhythmias, and rarely, overt psychosis.

SYMPTOMS AND TREATMENT OF OVERDOSAGE

Administration of 'Rocaltrol' (calcitriol) to patients in excess of their daily requirements can cause hypercalcemia, hypercalciuria and hyperphosphatemia. Conversely, high intake of calcium and phosphate concomitantly with therapeutic doses of 'Rocaltrol' may cause similar abnormalities. In dialysis patients, high levels of calcium in the dialysis bath may contribute to hypercalcemia. The serum calcium times phosphate (Ca x P) product should not be allowed to exceed $70mg^2/dl^2$.

TREATMENT OF HYPERCALCEMIA AND OVERDOSAGE

General treatment of hypercalcemia (more than 1 mg/dL or 0.25 mmol/L above the upper limit of the normal range) or serum creatinine is more than 120 µmol/L, consists of immediate discontinuation of 'Rocaltrol' therapy, institution of a low calcium diet and withdrawal of calcium supplements. Serum calcium and phosphate levels should be determined daily until normocalcemia ensues. Hypercalcemia frequently resolves in two to seven days. When serum calcium levels have returned to within normal limits, 'Rocaltrol' therapy may be reinstituted at a dose of 0.25 µg/day less than prior therapy. Serum calcium levels should be carefully monitored (at least twice weekly) during this period of dosage adjustment and subsequent dosage titration. In dialysis patients, persistent or markedly elevated serum calcium levels may be corrected by dialysis against a calcium-free dialysate.

TREATMENT OF ACCIDENTAL OVERDOSAGE

The treatment of acute accidental overdosage with 'Rocaltrol' should consist of general supportive measures. If drug ingestion is discovered within a relatively short time, induction of emesis or gastric lavage may be of benefit in preventing further absorption. If the drug has passed through the stomach, the administration of mineral oil may promote its fecal elimination. Serial serum electrolyte determinations (especially calcium ion) rate of urinary calcium excretion and assessment of electrocardiographic abnormalities due to hypercalcemia should be obtained. Such monitoring is critical in patients receiving

digitalis. Discontinuation of supplemental calcium and low calcium diet are also indicated in accidental overdosage. Due to the relatively short pharmacological action of calcitriol, further measures are probably unnecessary. Should, however, 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 optimal daily dose of 'Rocaltrol' (calcitriol) must be carefully determined for each patient. The effectiveness of 'Rocaltrol' therapy is predicated on the assumption that each patient is receiving an adequate daily intake of calcium. The recommended daily intake for calcium is in the order of 800 mg for adults and 350 mg for infants during the first six months of life.

To ensure that each patient receives an adequate daily intake of calcium, the physician should either prescribe a calcium supplement or instruct the patient in appropriate dietary measures.

However, because of improved calcium absorption from the gastrointestinal tract, some patients on 'Rocaltrol' may be maintained on a lower calcium intake or no supplementation at all.

DIALYSIS PATIENTS

Adults

Titration: The recommended initial dose of 'Rocaltrol' is 0.25 µg/day. If a satisfactory response in the biochemical parameters and clinical manifestations of the disease state are not observed, dosage may be increased by 0.25 µg/day at two to four week intervals. During this titration period, serum calcium levels should be obtained at least twice weekly, and if hypercalcemia is noted, the drug should be immediately discontinued until normocalcemia ensues.

Maintenance: Patients with normal or only slightly reduced serum calcium levels may respond to 'Rocaltrol' doses of 0.25 µg every other day. Most patients undergoing hemodialysis respond to between 0.5 and 1 µg/day.

In order to decrease the risk of hypercalcemic episodes, a downward adjustment of the dose of 'Rocaltrol' may be advisable once a reduction in serum alkaline phosphatase has been achieved.

HYPOPARATHYROIDISM AND VITAMIN D RESISTANT RICKETS

Adults

The recommended initial dose of 'Rocaltrol' is 0.25 µg/day. If a satisfactory response in the biochemical parameters and clinical manifestations of the disease are not observed, the dose may be increased by 0.25 µg/day at two to four-week intervals. During the dosage titration period, serum calcium levels should be measured at least twice weekly and, if hypercalcemia is present, 'Rocaltrol' should be immediately discontinued until normocalcemia ensues. Consideration should also be given to lowering the calcium intake.

Malabsorption is occasionally noted in patients with hypoparathyroidism; hence, larger doses of 'Rocaltrol' may be needed.

Children

Initiation of Treatment

X-linked hypophosphatemic rickets:	0.01 - 0.02 µg/kg/day (mean 0.018 µg/kg/day)
Vitamin D dependency rickets type 1:	0.010 - 0.025 µg/kg/day (mean 0.017 µg/kg/day)
Hypoparathyroidism:	0.03 - 0.05 µg/kg/day (mean 0.04 µg/kg/day)

Response is checked after two weeks to ascertain that the dose has not produced hypercalcemia. Biochemical evaluation should include serum calcium (total and ionized if available), phosphate, alkaline phosphatase, and creatinine. If satisfactory biochemical improvement has not occurred, the dose is increased by about 25% and the effect re-evaluated in two weeks. Until the desired response to treatment is achieved, the dose is gradually increased or decreased in this manner. Improvement in the radiographic lesions of rickets takes several weeks to become apparent.

For severely hypocalcemic or symptomatic patients, an initial dose as high as 0.05 µg/kg/day may be used to treat the hypocalcemia. In this situation, the serum calcium concentration should be monitored very closely (hospitalization recommended), and as soon as the patient is out of danger from hypocalcemia, the dose reduced.

Maintenance

X-linked hypophosphatemic rickets:	0.01 - 0.05 µg/kg/day (mean 0.022 µg/kg/day)
Vitamin D dependency rickets type 1:	0.0046 - 0.015 µg/kg/day
Hypoparathyroidism:	0.014 - 0.040 µg/kg/day (mean 0.025 µg/kg/day)

Assessment of serum calcium (total and ionized), phosphate, alkaline phosphatase and creatinine should be made at 3-4 month intervals once treatment has been established and for as long as the medication is administered.

Hypercalcemia can occur at any time while the patient is treated with ‘Rocaltrol’ (even if the dose has not been changed). Patients with rachitic or osteomalacic bone changes may become hypercalcemic as the bones become remineralized and therefore take up less calcium from the blood. To decrease the risk of hypercalcemia, a downward adjustment of the ‘Rocaltrol’ dose may be advisable once a reduction in serum alkaline phosphatase has been achieved.

The single most important indicator of calcitriol overdose appears to be hypercalcemia as determined by accurate and frequent measurement of the serum calcium concentration. Signs of hypercalcemia such as polyuria, nocturia, polydipsia, nausea, vomiting, anorexia, weight loss, and constipation should be watched for but are less sensitive indicators of toxicity. Most hypercalcemic patients are asymptomatic.

If hypercalcemia occurs, ‘Rocaltrol’ is discontinued for 1-2 weeks or until hypercalcemia disappears. Hypercalcemia frequently resolves in 2-7 days. Therapy is then resumed with a dose about 25% lower than that which caused intoxication. If the dose has been increased or decreased for any reason, the calcium level should be re-evaluated at 2-week intervals.

Fasting urine samples for measurement of calcium/creatinine ratio may be used to monitor the development of hypercalciuria.

Kidney ultrasounds may be indicated yearly during ‘Rocaltrol’ therapy. However, the clinical significance of the finding of nephrocalcinosis is not known.

'Rocaltrol' solution must be measured accurately and can be administered directly into the mouth of the infant. The bottle should be closed tightly each time after use, and when stored between 15 and 30°C and protected from light, the solution is stable for six weeks after opening.

Intermittent (pulse) therapy

Oral intermittent (pulse) therapy with 'Rocaltrol' two or three times weekly has been shown to be effective even in patients refractory to continuous therapy. Serum calcium levels should be monitored during therapy.

PHARMACEUTICAL INFORMATION

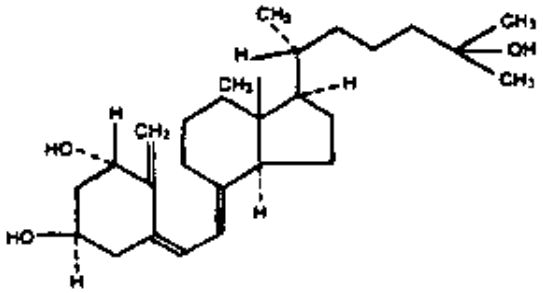
CHEMISTRY

TRADE NAME: 'Rocaltrol'

PROPER NAME: Calcitriol

CHEMICAL NAME: 1α,25-dihydroxycholecalciferol; (5Z,7E)-9, 10-secocholesta-5,7,10(19)-triene-1α,3β, 25-triol.

STRUCTURAL FORMULA:



MOLECULAR FORMULA: $C_{27}\ H_{44}\ O_3$

MOLECULAR WEIGHT: 416.65

DESCRIPTION: Calcitriol is a practically white crystalline compound with a melting range of 111-115°C. It is soluble in organic solvents, but relatively insoluble in water.

DOSAGE FORM

AVAILABILITY:

'Rocaltrol' is supplied as follows:

Capsules 0.25 µg:	brown-orange to red-orange, opaque (first-half)/white to grey-yellow or grey-orange, opaque (second half) oval soft gelatin capsules in blister packages of 100.
Capsules 0.50 µg:	brown-orange to red-orange, opaque oval soft gelatin capsules in blister packages of 100.
Solution 1.0 µg/mL:	clear, colourless oily solution in bottles of 10 mL.

Non-medicinal ingredients:

Capsules:	butylated hydroxyanisole, butylated hydroxytoluene, fractioned coconut oil, gelatin, glycerol 85%, hydrogenated products of partially hydrolysed starch, red iron oxide, titanium dioxide E 171, yellow iron oxide.
Oral Solution:	butylated hydroxyanisole, butylated hydroxytoluene, medium chain triglyceride.

STORAGE:

'Rocaltrol' solution should be stored at 15-30°C, store in the original container. Protect from light.

Capsules should be stored a 15-25°C, store in the original container. Protect from light and moisture. Keep blister in the outer carton.

PHARMACOLOGY

The relative biological activity between the parent vitamin D_3 and its metabolites is summarized in Table 1.[5,13,14] Most studies of vitamin D metabolism have utilized naturally occurring cholecalciferol or vitamin D_3, as the comparison standard.

TABLE 1

RELATIVE BIOLOGICAL EFFECTIVENESS OF VITAMIN D_3, 25-OH-D_3 AND CALCITRIOL

Biological Response	Species	Vitamin D_3	Relative Activity*	
			25-OH-D_3	Calcitriol
Intestinal Ca^{2+} Transport	Chick	1.0	2.0	13
Bone Ca^{2+} Mobilization	Chick	1.0	1.5	5-6
Rat Line Test	Rat	1.0	1.5	2-3
Percent Bone Ash	Chick	1.0	1.6	2
	Chick	1.0	-	7-8
Body Growth	Chick	1.0	1.0	5

* *In each instance the response obtained with vitamin D_3 was set equal to 1.0 and the responses obtained from an equal molar quantity of the other vitamin D_3 metabolites calculated accordingly.*

A single dose of calcitriol was administered orally to chicks. It was found to be at least 13 times as effective as D_3 in stimulating the intestinal absorption of calcium and 5 to 6 times as effective as D_3 in elevating the serum calcium level (bone calcium mobilization). In experiments where calcitriol was administered daily to chickens and rats it was equally, if not more, active than vitamin D_3 bone ash, serum calcium levels and rate of growth tests.

In the intestinal cell, calcitriol and its cytoplasmic protein receptor become bound to the chromatin fraction of the cell nucleus.[15,16,17] Thus, calcitriol directs the synthesis of new proteins or alters membrane structure in such a way as to facilitate the transcellular movement of calcium. Calcitriol also promotes resorption of bone[18] and leads to calcium mobilization. The mechanism by which calcitriol produces mineralization of osteoids in the skeleton is uncertain but it is known that calcitriol becomes localized in the nuclei of bone cells.[19] The mechanism whereby calcitriol acts on the kidney and parathyroid gland is obscure. It is believed that calcitriol may enhance the tubular reabsorption of calcium and phosphate.[20] It may also have a negative feedback effect on the secretion of PTH by the parathyroid gland.[21]

CLINICAL PHARMACOLOGY

In human studies, calcitriol is rapidly absorbed from the intestine. After an oral dose of tritiated calcitriol, the peak concentration of radioactivity in the serum was reached after 4 hours.[22] The half-life of calcitriol elimination from serum was found to range from 9 to 10 hours. However, the duration of pharmacologic activity of a single dose of calcitriol lasts about 3-5 days. Vitamin D metabolites are known to be transported in blood, bound to a specific $alpha_2$ globulin.[23,24,25]

Results from clinical studies[26] indicate that treatment with calcitriol does not affect serum magnesium levels which are already elevated in the majority of patients with severe chronic renal failure.

It has been suggested that a vitamin D resistant state exists in uremic patients because of the failure of the kidney to adequately convert precursors to the active compound, calcitriol.[7,8]

A number of recent reports[27,28,29] have indicated that vitamin D analogues may cause a deterioration of renal function in chronic renal failure patients who are not on renal dialysis. One controlled study[29] was conducted in 18 non-dialysed patients with creatinine clearances of less than 35 mL/min and mild osteodystrophy, who received daily doses of approximately 4,000 I.U. of vitamin D_3 or 0.25 - 1.0 µg of calcitriol for 6 months. Results indicated that the percentage fall in creatinine clearance was greater during treatment than during the preceding 6 months in all patients receiving calcitriol and in 7 out of 9 patients on vitamin D_3. Therefore, before vitamin D analogues are used prophylactically, additional trials are necessary to show whether the benefits outweigh any hazard that may emerge.

TOXICOLOGY

ACUTE TOXICITY

Acute LD_{50} studies have been performed on both mice and rats.

Acute toxicity studies in mice and rats indicated that the approximate oral lethal dose of calcitriol ranged from 1.35 to 3.9 mg/kg. These values are several orders of magnitude higher than the proposed clinical dose of 0.25 μg twice daily (approximately 8-10 ng/kg/day).

Species	Route	LD_{50} Calcitriol mg/kg
Mice	p.o. i.p. s.c. i.v.	2.0 1.0 0.5 1.6
Rats	p.o.	> 5.0

Calcitriol (100 µg/mL) was administered intramuscularly to rabbits. Volumes of 0.1 and 1.0 mL produced only very slight irritation (minor hemorrhage and necrosis). No hemolysis was produced following an intravenous injection of 0.2 mL/kg (20 µg) in dogs, and no evidence of venous irritation was found 24 hours after injection.

CHRONIC TOXICITY

Rats

Charies River CD rats received calcitriol by oral intubation daily for 26 weeks at dose levels of 0 (vehicle only), 0.02, 0.08 and 0.30 µg/kg. A 5th group was sham intubated daily.

All rats were observed daily for signs of toxicity. Dose related changes occurred in groups receiving calcitriol. Reduction in body weight and food consumption, increased serum calcium, as well as slight changes other clinical chemistry values and organ weights were noted in the high and mid-dose groups; these were either absent or less extensive in the low-dose group. Histologic examination of tissues from rats of all groups given calcitriol revealed calcification in kidney tubules and cardiac myofibers, as well as bone changes; in the low-dose group the changes consisted only of focal calcification and less severe bone changes. The bone changes in rats of the high-dose group consisted of alterations of the epiphyseal plate with disorganization of chondmcytes and evidence of bone resorption; there was thickening of the periosteum due to increased connective tissue.

Dogs

Calcitriol was administered orally to beagle dogs (6 dogs/group) at daily doses of 0 (vehicle only), 0.02 and 0.08 µg/kg for 26 weeks. A 0.30 µg/kg dosage was also included at the beginning of the study but had to be discontinued because of toxicity after 39 days.

Two dogs of the 0.30 µg/kg/day group were sacrificed after 39 days and the remaining 4 dogs were observed for an additional 21 weeks. In these dogs, body weight loss slowly reversed and general condition improved but clinical laboratory measurements did not completely regress and soft tissue calcification was noted at autopsy. Two of the 6 dogs of the 0.08 µg/kg/day group died. Marked anorexia, severe weight loss, deterioration of physical condition, increased serum calcium and urea nitrogen, as well as other alterations in clinical laboratory measurements, calcification of soft tissue, bone resorption with replacement by fibrous tissue and irregular calcium deposits in the epiphyseal cartilage plates were observed in the high and mid-dose group.

In the low-dose group (0.02 µg/kg/day) inconsistent alterations in clinical laboratory measurements and pathological changes of limited extent were observed. Histopathologic changes in low-dose dogs were limited to a single calcified focus in the kidney of 1 dog, a calcified urinary bladder artery in a second and a slight bone abnormality in a third animal.

Subchronic toxicity studies in rats and dogs indicated that calcitriol at an oral dose of 20 ng/kg/day (twice daily 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 STUDIES

Fertility and General Reproductive Performance

Calcitriol was administered orally to rats at dose levels of 0, 0.02, 0.08 and 0.30 µg/kg/day. No adverse effects on fertility, implantation, length of gestation, litter size, viability or lactation indices were noted in rat reproduction studies in which males were pretreated for 61 days and females for 14 days prior to mating and through sacrifice on either day 13 of gestation or through lactation day 21. Treatment of females resulted in a statistically significant greater weight gain. One pup from the 0.30 µg/kg/day group appeared jaundiced. In the clinical laboratory measurements, increased serum calcium levels in the 0.30 µg/kg dams, decreased serum phosphate levels in the 0.08 µg/kg dams and increased blood urea nitrogen in the 0.02 µg/kg pups were statistically significant.

TERATOLOGY

Calcitriol was administered orally to rabbits and rats at dose levels of 0, 0.02, 0.08 and 0.30 µg/kg/day. Rabbits treated with 0.30 µg/kg/day from day 7 through day 18 of gestation exhibited marked weight loss. Three of these fifteen animals died, two exhibiting tissue lesions suggestive of hypervitaminosis D. In the 0.30 µg/kg/day group there was also a decreased litter size, an increased resorption rate, reduced fetal body weight and viability index, as well as increased neonatal mortality during the first postnatal day. Two litters of the 0.3 µg/kg/day (7 fetuses) and one at the 0.08 µg/kg/day (9 fetuses) dose levels had multiple external malformations, accompanied by skeletal visceral abnormalities. These anomalies (16/177 fetuses) occurred at doses 4 to 15 times the dose recommended for human use.

In the rat, pregnant females were intubated from day 7 through day 15 of gestation. Maternal weight gain and average number of implantation sites were slightly reduced in the 0.30 µg/kg/day group. A small number of isolated fetal abnormalities were seen in all groups. However, no significant differences were observed in the frequency and nature of abnormalities or skeletal variations between control and treated groups.

PERINATAL AND POSTNATAL STUDIES

Calcitriol was administered orally to rats at dose levels of 0, 0.02, 0.08, 0.30 µg/kg/day. No adverse effects on average litter size, viability and lactation indices were noted in litters from female rats treated from day 15 of gestation through day 21 of lactation. One female of the 0.08 µg/kg/day group became moribund and had to be sacrificed prior to delivery, a second had a mammary tumor, and 1 female of the 0.30 µg/kg/day group had urinary calculi. Dams at 0.08 and 0.30 µg/kg/day exhibited hypercalcemia and hypophosphatemia. Elevated blood urea nitrogens were noted only at 0.30 µg/kg/day dose. Only elevated

serum calcium was found in pups at 0.08 and 0.30 µg/kg, and a slight elevation in bone ash only at 0.30 µg/kg.

MUTAGENICITY

There was no evidence of mutagenicity as studied by the Ames Method.

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