CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

Application Number: 018044/S018/S019/S024

Trade Name: ROCALTROL CAPSULES

Generic Name: CALCITRIOL

Sponsor: HOFFMAN-LA ROCHE, INC.

Approval Date: 4/8/91, 3/13/90, 10/22/96

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION: 018044/S018/S019/S024

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CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number: 018044/S018/S019/S024

APPROVAL LETTER

NDA 18-044/S-018

Hoffmann-La Roche Inc.
Attention: Mr. Anthony J. Corrado
Senior Regulatory Specialist
340 Kingsland Street
Nutley, New Jersey 07110-1199

APR 8 1991

Dear Mr. Corrado:

Reference is made to your supplemental new drug application dated November 22, 1988, (S-018) submitted pursuant to section 505(b) of the Federal Food, Drug and Cosmetic Act for Rocaltrol (calcitriol) Capsules.

We also refer to your amendments to S-018 dated August 28, 1990 and February 12, 1991.

The supplement provides for labeling changes in the WARNINGS and OVERDOSAGE sections of the labeling.

We have completed the review of supplemental application S-018 including the final printed labeling submitted August 28, 1990, and it is approved effective on the date of this letter.

We remind you that you must comply with the requirements set forth under 21 CFR 314.80 and 314.81 for approved NDAs.

If you have any questions, please contact Ms. Nancy N. Clagett at (301) 443-3490.

Sincerely yours,

/S/ 4/8/91

Solomon Sobel, M.D.
Director
Division of Metabolism and
Endocrine Drug Products (HFD-510)
Center for Drug Evaluation and Research

cc: NDA Arch /S/ 4/5/91
HFD-510
HFD-80/labeling attached
HFD-500/labeling attached
HFD-600/labeling attached
HFD-730
HFD-510/SDutta/MBennett/AJordan
HFD-511/NClagett4-2-91/FT/MMM/4/5/91/N18044AP.LT2
Concurrences: EGalliers(for)JShort4/2/AJordan/4/3/91
SUPPLEMENT APPROVAL (S-018)

MAR 13 1990

NDA 18-044/S-018/S-019

Hoffmann-La Roche Inc.
Attention:Ms. Mary E. Reilly
Senior Manager Drug Regulatory Affairs
340 Kingsland Street
Nutley, New Jersey 07110-1199

Dear Ms. Reilly:

Reference is made to your supplemental new drug applications (NDAs) dated November 22, 1988 (S-018) and March 8, 1989 (S-019), submitted pursuant to section 505(b) of the Federal Food, Drug and Cosmetic Act for Rocaltrol (calcitriol) Capsules.

The supplemental applications, submitted as "Special Supplements - Changes Being Effected" under 21 CFR 314.70(c), provide for the following:

1. Addition of animal pharmacology data to the labeling (S-018).

2. Revised specifications and directions for testing (S-019).

3. Revised stability testing methodology (S-019).

We have completed the review of supplemental application S-018 including the submitted draft labeling and it is approvable. However, before it may be approved, final printed labeling (FPL) must be submitted. The FPL should be identical to the draft labeling except for the following revisions:

1. In the OVERDOSAGE section, delete "The single dose oral toxicity of calcitriol is as follows:

Species	LD_{50} (mg/kg)
mouse	2.0
rat	>5.0"

2. The statement under ANIMAL PHARMACOLOGY, "Studies in dogs and rats given calcitriol for up to 26 weeks have shown that small increases of calcitriol above endogenous levels can lead to abnormalities of calcium metabolism with the potential for calcification of many tissues in the body." should be placed as the last sentence in the WARNINGS section.

We have also completed our review of supplemental application S-019 and it is approved.

We remind you that you must comply with the requirements set forth under 21 CFR 314.80 and 314.81 for approved NDAs.

In addition, please note that all future NDA submissions should contain a completed form FDA 356h as per 21 CFR 314.50(a)

If you have any questions, please contact Ms. Nancy N. Clagett at (301) 443-3510.

Sincerely yours,

/S/3/12/90

Solomon Sobel, M.D.
Director
Division of Metabolism and
Endocrine Drug Products (HFD-510)
Center for Drug Evaluation and Research

cc: NDA Arch /S/3/12/90
HFD-80
HFD-510
HFD-511/NClagett/2-26-90/ft/dj/3.12.90/N18044AP.LT1
Concurrences: REastep3.9.90/MBennett/YChiu/RPierce/AJordan3.5.90/Dutta3.6.90

SUPPLEMENT APPROVABLE (S-018)
SUPPLEMENT APPROVAL (S-019)

NDA 18,044/S-024

OCT 22 1996

Hoffman-La Roche Inc.
Attention: Ms. Betty C. Holland
340 Kingsland Street
Nutley, NJ 07110-1199

Dear Ms. Holland:

Please refer to your July 9, 1996 supplemental new drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Rocaltrol (calcitriol), 0.25 and 0.5 mcg Capsules.

The supplemental application provides for final printed labeling with an addition to the ADVERSE REACTIONS section of the package insert. The following sentence has been added: "One case of erythema multiforme and one case of allergic reaction (swelling of lips and hives all over the body) were confirmed by rechallenge."

We have completed the review of this supplemental application and have concluded that adequate information has been presented to demonstrate that the drug is safe and effective for use as recommended in the final printed labeling submitted on July 9, 1996. Accordingly, the supplemental application is approved effective on the date of this letter.

The final printed labeling will be retained in our files.

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

APPEARS THIS WAY
ON ORIGINAL

If you have any questions, please contact:

APPEARS THIS WAY
ON ORIGINAL

Randy Hedin, R.Ph.
Consumer Safety Officer
(301) 443-3520

Sincerely yours,

/S/ 10/22/96

APPEARS THIS WAY
ON ORIGINAL

Solomon Sobel, M.D.
Director
Division of Metabolism and
Endocrine Drug Products (HFD-510)
Office of Drug Evaluation II
Center for Drug Evaluation and Research

/S/ 10/22/96

cc:
Original NDA 18,044 S-024
HFD-510/Div. files
HFD-510/CSO/R.Hedin
HFD-510/SDutta/GTroendle/DGWu/SMoore/RSteigerwalt
HFD-102/L.Ripper
HFD-820/Yuan Yuan Chiu
DISTRICT OFFICE
HF-2/Medwatch (with labeling) (+MOR)
HFD-80 (with labeling)
HFD-40/DDMAC (with labeling)
HFD-613 (with labeling)
HFD-735/(with labeling) (+MOR)

drafted: SM/September 27, 1996/n18044ap.lt3
r/d Initials: RHedin 9.26/SDutta/GTroendle/DGWu 10.1/SMoore/
RSteigerwalt 10.7/EGalliers 10.16
final:

APPROVAL OF SUPPLEMENTAL APPLICATION - FPL

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 018044/S018/S019/S024

FINAL PRINTED LABELING

ss ORIGINAL

NDA 18
Rocaltrol® (calcit
Final Printed
Package

Labeling: St-R-024
NDA No: 18044 Rc'd. 7-15-96
Reviewed by: TST 10/22/96
APPROVED OCT 22 1996

elevated serum calcium levels may be corrected by dialysis against a calcium-free dialysate.

Treatment of Accidental Overdosage of Rocaltrol: The treatment of acute accidental overdosage of 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), 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 a low calcium diet are also indicated in accidental overdosage. Due to the relatively short duration of the 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 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 U.S. RDA for calcium in adults is 800 to 1200 mg. 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 proper dietary measures.

Dialysis Patients: The recommended initial dose of Rocaltrol is 0.25 mcg/day. If a satisfactory response in the biochemical parameters and clinical manifestations of the disease state is not observed, dosage may be increased by 0.25 mcg/day at 4- to 8-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.

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

Oral Rocaltrol may normalize plasma ionized calcium in some uremic patients, yet fail to suppress parathyroid hyperfunction. In these individuals with autonomous parathyroid hyperfunction, oral Rocaltrol may be useful to maintain normocalcemia, but has not been shown to be adequate treatment for hyperparathyroidism.

Hypoparathyroidism: The recommended initial dose of Rocaltrol is 0.25 mcg/day given in the morning. If a satisfactory response in the biochemical parameters and clinical manifestations of the disease is not observed, the dose may be increased at 2- to 4-week intervals. During the dosage titration period, serum calcium levels should be obtained at least twice weekly and, if hypercalcemia is noted, Rocaltrol should be immediately discontinued until normocalcemia ensues. Careful consideration should also be given to lowering the dietary calcium intake.

Most adult patients and pediatric patients age 6 years and older have responded to dosages in the range of 0.5 to 2 mcg daily. Pediatric patients in the 1-5 year age group with hypoparathyroidism have usually been given 0.25 to 0.75 mcg daily. The number of treated patients with pseudohypoparathyroidism less than 6 years of age is too small to make dosage recommendations.

HOW SUPPLIED: 0.25 mcg calcitriol in soft gelatin, light orange, oval capsules, imprinted ROCALTROL 0.25 ROCHE; bottles of 30 (NDC 0004-0143-23), and bottles of 100 (NDC 0004-0143-01).

0.5 mcg calcitriol in soft gelatin, dark orange, oblong capsules, imprinted ROCALTROL 0.5 ROCHE; bottles of 100 (NDC 0004-0144-01).

Rocaltrol should be protected from heat and light.

Roche Laboratories
A Member of the Roche Group

Roche Laboratories Inc.
340 Kingsland Street
Nutley, New Jersey 07110-1199

26017550-0696

Revised: June 1996
Printed in U.S.A.

Roche®

ROCALTROL®

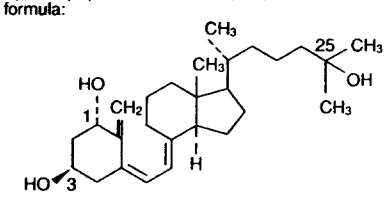
brand of

calcitriol

CAPSULES

DESCRIPTION: Rocaltrol (calcitriol) is a synthetic vitamin D analog which is active in the regulation of the absorption of calcium from the gastrointestinal tract and its utilization in the body. It is available in capsules containing 0.25 mcg or 0.5 mcg calcitriol. Each capsule also contains butylated hydroxyanisole (BHA), butylated hydroxytoluene (BHT) and fractionated triglyceride of coconut oil. Gelatin capsule shells contain glycerin, parabens (methyl and propyl) and sorbitol, with the following dye systems: 0.25 mcg — FD&C Yellow No. 6 and titanium dioxide; 0.5 mcg — FD&C Red No. 3, FD&C Yellow No. 6 and titanium dioxide.

Calcitriol is a white, 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. Chemically, calcitriol is 9,10-seco(5Z,7E)-5,7,10(19)-cholestatriene-1α, 3β, 25-triol and has the following structural formula:



The other names frequently used for calcitriol are 1α,25-dihydroxycholecalciferol, 1,25-dihydroxyvitamin D_3, 1,25-DHCC, 1,25$(OH)_2D_3$ and 1,25-diOHC.

CLINICAL PHARMACOLOGY: Man's natural supply of vitamin D depends mainly on exposure to the ultraviolet rays of the sun for conversion of 7-dehydrocholesterol in the skin to vitamin D_3 (cholecalciferol). Vitamin D_3 must be metabolically activated in the liver and the kidney before it is fully active as a regulator of calcium and phosphorus metabolism at target tissues. The initial transformation of vitamin D_3 is catalyzed by a vitamin D_3-25-hydroxylase enzyme (25-OHase) present in the liver, and the product of this reaction is 25-hydroxyvitamin D_3 [25-$(OH)D_3$]. Hydroxylation of 25-$(OH)D_3$ occurs in the mitochondria of kidney tissue, activated by the renal 25-hydroxyvitamin D_3-1 alpha-hydroxylase (alpha-OHase), to produce 1,25-$(OH)_2D_3$ (calcitriol), the active form of vitamin D_3. Several metabolites of calcitriol have been identified which include:

1α, 25, $(OH)_2$-24-oxo-D_3
1α, 23,25$(OH)_3$-24-oxo-D_3
1α, 24R,25$(OH)_3D_3$
1α, 25R$(OH)_2$-26-23S-lactone D_3
1α, 25S,26$(OH)_3D_3$
1α, 25$(OH)_2$-23-oxo-D_3
1α, 25R,26$(OH)_3$-23-oxo-D_3
1α, (OH)24,25,26,27-tetranor-COOH-D_3

The two known sites of action of calcitriol are intestine and bone. A calcitriol receptor-binding protein appears to exist in the mucosa of human intestine. Additional evidence suggests that calcitriol may also act on the kidney and the parathyroid glands. Calcitriol is the most active known form of vitamin D_3 in stimulating intestinal calcium transport. In acutely uremic rats calcitriol has been shown to stimulate intestinal calcium absorption. 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 Rocaltrol in renal osteodystrophy appears to result from correction of hypocalcemia and secondary hyperparathyroidism. It is uncertain whether Rocaltrol produces other independent beneficial effects.

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 doses of 0.25 to 1.0 mcg of Rocaltrol. The half-life of calcitriol elimination from serum was found to range from 3 to 6 hours. 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. The duration of pharmacologic activity of a single dose of calcitriol is about 3 to 5 days.

Calcitriol and other vitamin D metabolites are transported in blood, bound to specific plasma proteins. Enterohepatic recycling and biliary excretion of calcitriol occurs. Following intravenous administration of radiolabeled calcitriol in normal subjects, approximately 27% and 7% of the radioactivity appeared in the feces and urine, respectively, within 24 hours. When a 1-mcg oral dose of radiolabeled 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 radiolabeled calcitriol averaged 16% in urine and 49% in feces.

There is evidence that maternal calcitriol may enter the fetal circulation. Calcitriol may be excreted in human milk.

INDICATIONS AND USAGE: Rocaltrol is indicated in the management of hypocalcemia and the resultant metabolic bone disease in patients undergoing chronic renal dialysis. In these patients, Rocaltrol administration enhances calcium absorption, reduces serum alkaline phosphatase levels and may reduce elevated parathyroid hormone levels and the histological manifestations of osteitis fibrosa cystica and defective mineralization.

Rocaltrol is also indicated in the management of hypocalcemia and its clinical manifestations in patients with postsurgical hypoparathyroidism, idiopathic hypoparathyroidism, and pseudohypoparathyroidism.

CONTRAINDICATIONS: Rocaltrol should not be given to patients with hypercalcemia or evidence of vitamin D toxicity.

WARNINGS: Since Rocaltrol is the most potent metabolite of vitamin D available, pharmacologic doses of vitamin D and its derivatives should be withheld during Rocaltrol treatment to avoid possible additive effects and hypercalcemia.

Both appropriate oral phosphate-binders and a low phosphate diet should be used to control serum phosphate levels in patients undergoing dialysis.

Magnesium-containing antacids and Rocaltrol should not be used concomitantly in patients on chronic renal dialysis because such use may lead to the development of hypermagnesemia.

Overdosage of any form of vitamin D is dangerous (see also OVERDOSAGE). Progressive hypercalcemia due to overdosage of vitamin D and its metabolites may be so severe as to require emergency attention. Chronic hypercalcemia 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.** Radiographic evaluation of suspect anatomical regions may be useful in the early detection of this condition.

Studies in dogs and rats given calcitriol for up to 26 weeks have shown that small increases of calcitriol above endogenous levels can lead to abnormalities of calcium metabolism with the potential for calcification of many tissues in the body.

PRECAUTIONS: *General:* Excessive dosage of Rocaltrol induces hypercalcemia and in some instances hypercalciuria; therefore, early in treatment during dosage adjustment, serum calcium should be determined twice weekly. In dialysis patients, a fall in serum alkaline phosphatase levels usually antedates the appearance of hypercalcemia and may be an indication of impending hypercalcemia. Should hypercalcemia develop, the drug should be discontinued immediately. Rocaltrol should be given cautiously to patients on digitalis, because hypercalcemia in such patients may precipitate cardiac arrhythmias.

In patients with normal renal function, chronic hypercalcemia 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 hypercalcemia. Rocaltrol 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 Rocaltrol should avoid dehydration. Adequate fluid intake should be maintained.

Information for the Patient: The patient and his or her parents or spouse should be informed about compliance with dosage instructions, adherence to instructions about diet and calcium supplementation and avoidance of the use of unapproved nonprescription drugs. Patients should also be carefully informed about the symptoms of hypercalcemia (see ADVERSE REACTIONS section).

ROCALTROL® (calcitriol)

Laboratory Tests: For dialysis patients, serum calcium, phosphorus, magnesium and alkaline phosphatase should be determined periodically. For hypoparathyroid patients, serum calcium, phosphorus and 24-hour urinary calcium should be determined periodically.

Drug Interactions: Cholestyramine has been reported to reduce intestinal absorption of fat-soluble vitamins; as such it may impair intestinal absorption of Rocaltrol. (Also see WARNINGS and PRECAUTIONS [General] sections.)

Carcinogenesis, Mutagenesis, Impairment of Fertility: Long-term studies in animals have not been conducted to evaluate the carcinogenic potential of Rocaltrol. There was no evidence of mutagenicity as studied by the Ames method. No significant effects of Rocaltrol on fertility and/or general reproductive performances were reported.

Pregnancy: Teratogenic Effects: Pregnancy Category C. Rocaltrol has been found to be teratogenic in rabbits when given in doses 4 and 15 times the dose recommended for human use. All 15 fetuses in 3 litters at these doses showed external and skeletal abnormalities. However, none of the other 23 litters (156 fetuses) showed significant abnormalities compared with controls. Teratogenicity studies in rats showed no evidence of teratogenic potential. There are no adequate and well-controlled studies in pregnant women. Rocaltrol should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nonteratogenic Effects: In the rabbit, dosages of 0.3 mcg/kg/day administered on days 7 to 18 of gestation resulted in 19% maternal mortality, a decrease in mean fetal body weight and a reduced number of newborn surviving to 24 hours. A study of peri- and postnatal development in rats resulted in hypercalcemia in the offspring of dams given Rocaltrol at doses of 0.08 or 0.3 mcg/kg/day, hypercalcemia and hypophosphatemia in dams at doses of 0.08 or 0.3 mcg/kg/day, and increased serum urea nitrogen in dams given Rocaltrol at a dose of 0.3 mcg/kg/day. In another study in rats, maternal weight gain was slightly reduced at a dose of 0.3 mcg/kg/day administered on days 7 to 15 of gestation.

The offspring of a woman administered 17 to 36 mcg/day of Rocaltrol (17 to 144 times the recommended dose) during pregnancy manifested mild hypercalcemia in the first 2 days of life which returned to normal at day 3.

Nursing Mothers: 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 Rocaltrol in nursing infants, a mother should not nurse while taking this drug.

Pediatric Use: Safety and efficacy of Rocaltrol in children undergoing dialysis have not been established.

ADVERSE REACTIONS: Since Rocaltrol is believed to be the active hormone which exerts vitamin D activity in the body, adverse effects are, in general, similar to those encountered with excessive vitamin D intake. The early and late signs and symptoms of vitamin D intoxication associated with hypercalcemia include:

Early: Weakness, headache, somnolence, nausea, vomiting, dry mouth, constipation, muscle pain, bone pain and metallic taste.

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

In clinical studies on hypoparathyroidism and pseudohypoparathyroidism, hypercalcemia was noted on at least one occasion in about 1 in 3 patients and hypercalciuria in about 1 in 7. Elevated serum creatinine levels were observed in about 1 in 6 patients (approximately one half of whom had normal levels at baseline).

One case of erythema multiforme and one case of allergic reaction (swelling of lips and hives all over the body) were confirmed by rechallenge.

OVERDOSAGE: Administration of Rocaltrol to patients in excess of their daily requirements can cause hypercalcemia, hypercalciuria and hyperphosphatemia. High intake of calcium and phosphate concomitant with Rocaltrol may lead to similar abnormalities. High levels of calcium in the dialysate bath may contribute to the hypercalcemia.

Treatment of Hypercalcemia and Overdosage: General treatment of hypercalcemia (greater than 1 mg/dL above the upper limit of the normal range) consists of immediate discontinuation of Rocaltrol therapy, institution of a low calcium diet and withdrawal of calcium supplements. Serum calcium levels should be determined daily until normocalcemia ensues. Hypercalcemia frequently resolves in 2 to 7 days. When serum calcium levels have returned to within normal limits, Rocaltrol therapy may be reinstituted at a dose of 0.25 mcg/day less than prior therapy. Serum calcium levels should be obtained at least twice weekly after all dosage changes and subsequent dosage titration. In dialysis patients, persistent or markedly

patients, persistent or markedly elevated serum calcium levels may be corrected by dialysis against a calcium-free dialysate.

Treatment of Accidental Overdosage of Rocaltrol: The treatment of acute accidental overdosage of 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), 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 a low calcium diet are also indicated in accidental overdosage. Due to the relatively short duration of the 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 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 U.S. RDA for calcium in adults is 800 to 1200 mg. 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 proper dietary measures.

Dialysis patients: The recommended initial dose of Rocaltrol is 0.25 mcg/day. If a satisfactory response in the biochemical parameters and clinical manifestations of the disease state is not observed, dosage may be increased by 0.25 mcg/day at four- to eight-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.

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

Oral Rocaltrol may normalize plasma ionized calcium in some uremic patients, yet fail to suppress parathyroid hyperfunction. In these individuals with autonomous parathyroid hyperfunction, oral Rocaltrol may be useful to maintain normocalcemia, but has not been shown to be adequate treatment for hyperparathyroidism.

Hypoparathyroidism: The recommended initial dose of Rocaltrol is 0.25 mcg/day given in the morning. If a satisfactory response in the biochemical parameters and clinical manifestations of the disease is not observed, the dose may be increased at two- to four-week intervals. During the dosage titration period, serum calcium levels should be obtained at least twice weekly and, if hypercalcemia is noted, Rocaltrol should be immediately discontinued until normocalcemia ensues. Careful consideration should also be given to lowering the dietary calcium intake.

Most adult patients and pediatric patients age 6 years and older have responded to dosages in the range of 0.5 to 2 mcg daily. Pediatric patients in the 1-5 year age group with hypoparathyroidism have usually been given 0.25 to 0.75 mcg daily. The number of treated patients with pseudohypoparathyroidism less than 6 years of age is too small to make dosage recommendations.

HOW SUPPLIED: 0.25 mcg calcitriol/Roche in soft gelatin, light orange, oval capsules, imprinted ROCALTROL 0.25 ROCHE; bottles of 30 (NDC 0004-0143-23), and bottles of 100, (NDC 0004-0143-01).

0.5 mcg calcitriol/Roche in soft gelatin, dark orange, oblong capsules, imprinted ROCALTROL 0.5 ROCHE; bottles of 100, (NDC 0004-0144-01).

Rocaltrol should be protected from heat and light.

Roche Laboratories
a division of Hoffmann-La Roche Inc.

340 Kingsland Street
Nutley, New Jersey 07110-1199

13-20-78503-0690

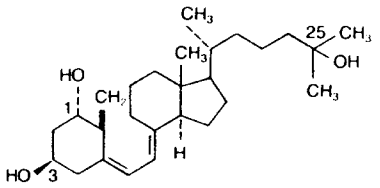
Revised: June 1990
Printed in U.S.A.

A.H.F.S. Category 88:16

ROCALTROL®
(calcitriol/Roche)
CAPSULES

DESCRIPTION: Rocaltrol (calcitriol/Roche) is a synthetic vitamin D analog which is active in the regulation of the absorption of calcium from the gastrointestinal tract and its utilization in the body. It is available in capsules containing 0.25 mcg or 0.5 mcg calcitriol/Roche. Each capsule also contains butylated hydroxyanisole (BHA), butylated hydroxytoluene (BHT) and fractionated triglyceride of coconut oil. Gelatin capsule shells contain glycerin, parabens (methyl and propyl) and sorbitol, with the following dye systems: 0.25 mcg—FD&C Yellow No. 6 and titanium dioxide; 0.5 mcg—FD&C Red No. 3, FD&C Yellow No. 6 and titanium dioxide.

Calcitriol is a colorless, 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. Chemically, calcitriol is 9,10-seco(5Z,7E)-5,7,10(19)-cholestatriene-1α, 3β, 25-triol and has the following structural formula:



The other names frequently used for calcitriol are 1α,25-dihydroxycholecalciferol, 1,25-dihydroxyvitamin D_3, 1,25-DHCC, 1,25$(OH)_2D_3$ and 1,25-diOHC.

CLINICAL PHARMACOLOGY: Man's natural supply of vitamin D depends mainly on exposure to the ultraviolet rays of the sun for conversion of 7-dehydrocholesterol in the skin to vitamin D_3 (cholecalciferol). Vitamin D_3 must be metabolically activated in the liver and the kidney before it is fully active as a regulator of calcium and phosphorus metabolism at target tissues. The initial transformation of vitamin D_3 is catalyzed by a vitamin D_3-25-hydroxylase enzyme (25-OHase) present in the liver, and the product of this reaction is 25-hydroxyvitamin D_3 [25-$(OH)D_3$]. Hydroxylation of 25-$(OH)D_3$ occurs in the mitochondria of kidney tissue, activated by the renal 25-hydroxyvitamin D_3-1 alpha-hydroxylase (alpha-OHase), to produce 1,25-$(OH)_2D_3$ (calcitriol), the active form of vitamin D_3. Several metabolites of calcitriol have been identified which include:

1α, 25, $(OH)_2$-24-oxo-D_3
1α, 23,25$(OH)_3$-24-oxo-D_3
1α, 24R,25$(OH)_3D_3$
1α, 25R$(OH)_2$-26-23S-lactone D_3
1α, 25S,26$(OH)_3D_3$
1α, 25$(OH)_2$-23-oxo-D_3
1α, 25R,26$(OH)_3$-23-oxo-D_3
1α, (OH)24,25,26,27-tetranor-COOH-D_3

The two known sites of action of calcitriol are intestine and bone. A calcitriol receptor-binding protein appears to exist in the mucosa of human intestine. Additional evidence suggests that calcitriol may also act on the kidney and the parathyroid glands. Calcitriol is the most active known form of vitamin D_3 in stimulating intestinal calcium transport. In acutely uremic rats calcitriol has been shown to stimulate intestinal calcium absorption. 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 (*e.g.*, aluminum) may also contribute.

The beneficial effect of Rocaltrol in renal osteodystrophy appears to result from correction of hypocalcemia and secondary hyperparathyroidism. It is uncertain whether Rocaltrol produces other independent beneficial effects.

Calcitriol is rapidly absorbed from the intestine. Peak serum concentrations (above basal values) were reached within 3 to 6 hours following oral administra-

tion of single doses of 0.25 to 1.0 mcg of Rocaltrol. The half-life of calcitriol elimination from serum was found to range from 3 to 6 hours. 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. The duration of pharmacologic activity of a single dose of calcitriol is about 3 to 5 days.

Calcitriol and other vitamin D metabolites are transported in blood, bound to specific plasma proteins. Enterohepatic recycling and biliary excretion of calcitriol occurs. Following intravenous administration of radiolabeled calcitriol in normal subjects, approximately 27% and 7% of the radioactivity appeared in the feces and urine, respectively, within 24 hours. When a 1-mcg oral dose of radiolabeled 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 radiolabeled calcitriol averaged 16% in urine and 49% in feces.

There is evidence that maternal calcitriol may enter the fetal circulation. Calcitriol may be excreted in human milk.

INDICATIONS AND USAGE: Rocaltrol is indicated in the management of hypocalcemia and the resultant metabolic bone disease in patients undergoing chronic renal dialysis. In these patients, Rocaltrol administration enhances calcium absorption, reduces serum alkaline phosphatase levels and may reduce elevated parathyroid hormone levels and the histological manifestations of osteitis fibrosa cystica and defective mineralization.

Rocaltrol is also indicated in the management of hypocalcemia and its clinical manifestations in patients with postsurgical hypoparathyroidism, idiopathic hypoparathyroidism, and pseudohypoparathyroidism.

CONTRAINDICATIONS: Rocaltrol should not be given to patients with hypercalcemia or evidence of vitamin D toxicity.

WARNINGS: Since Rocaltrol is the most potent metabolite of vitamin D available, pharmacologic doses of vitamin D and its derivatives should be withheld during Rocaltrol treatment to avoid possible additive effects and hypercalcemia.

Both appropriate oral phosphate-binders and a low phosphate diet should be used to control serum phosphate levels in patients undergoing dialysis.

Magnesium-containing antacids and Rocaltrol should not be used concomitantly in patients on chronic renal dialysis because such use may lead to the development of hypermagnesemia.

Overdosage of any form of vitamin D is dangerous (see also OVERDOSAGE). Progressive hypercalcemia due to overdosage of vitamin D and its metabolites may be so severe as to require emergency attention. Chronic hypercalcemia 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.** Radiographic evaluation of suspect anatomical regions may be useful in the early detection of this condition.

Studies in dogs and rats given calcitriol for up to 26 weeks have shown that small increases of calcitriol above endogenous levels can lead to abnormalities of calcium metabolism with the potential for calcification of many tissues in the body.

PRECAUTIONS: *General:* Excessive dosage of Rocaltrol induces hypercalcemia and in some instances hypercalciuria; therefore, early in treatment during dosage adjustment, serum calcium should be determined twice weekly. In dialysis patients, a fall in serum alkaline phosphatase levels usually antedates the appearance of hypercalcemia and may be an indication of impending hypercalcemia. Should hypercalcemia develop, the drug should be discontinued immediately. Rocaltrol should be given cautiously to patients on digitalis, because hypercalcemia in such patients may precipitate cardiac arrhythmias.

In patients with normal renal function, chronic hypercalcemia 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 hypercalcemia. Rocaltrol 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 Rocaltrol should avoid dehydration. Adequate fluid intake should be maintained.

Information for the patient: The patient and his or her parents or spouse should be informed about compliance with dosage instructions, adherence to instructions about diet and calcium supplementation and avoidance of the use of unapproved nonprescription drugs. Patients should also be carefully informed about the symptoms of hypercalcemia (see ADVERSE REACTIONS section).

Laboratory tests: For dialysis patients, serum calcium, phosphorus, magnesium and alkaline phosphatase should be determined periodically. For hypoparathyroid patients, serum calcium, phosphorus and 24-hour urinary calcium should be determined periodically.

Drug interactions: Cholestyramine has been reported to reduce intestinal absorption of fat-soluble vitamins; as such it may impair intestinal absorption of Rocaltrol. (Also see WARNINGS and PRECAUTIONS [General] sections.)

Carcinogenesis, mutagenesis, impairment of fertility: Long-term studies in animals have not been conducted to evaluate the carcinogenic potential of Rocaltrol. There was no evidence of mutagenicity as studied by the Ames method. No significant effects of Rocaltrol on fertility and/or general reproductive performances were reported.

Pregnancy: Teratogenic effects: Pregnancy Category C. Rocaltrol has been found to be teratogenic in rabbits when given in doses 4 and 15 times the dose recommended for human use. All 15 fetuses in 3 litters at these doses showed external and skeletal abnormalities. However, none of the other 23 litters (156 fetuses) showed significant abnormalities compared with controls. Teratogenicity studies in rats showed no evidence of teratogenic potential. There are no adequate and well-controlled studies in pregnant women. Rocaltrol should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nonteratogenic effects: In the rabbit, dosages of 0.3 mcg/kg/day administered on days 7 to 18 of gestation resulted in 19% maternal mortality, a decrease in mean fetal body weight and a reduced number of newborn surviving to 24 hours. A study of peri- and postnatal development in rats resulted in hypercalcemia in the offspring of dams given Rocaltrol at doses of 0.08 or 0.3 mcg/kg/day, hypercalcemia and hypophosphatemia in dams at doses of 0.08 or 0.3 mcg/kg/day, and increased serum urea nitrogen in dams given Rocaltrol at a dose of 0.3 mcg/kg/day. In another study in rats, maternal weight gain was slightly reduced at a dose of 0.3 mcg/kg/day administered on days 7 to 15 of gestation.

The offspring of a woman administered 17 to 36 mcg/day of Rocaltrol (17 to 144 times the recommended dose) during pregnancy manifested mild hypercalcemia in the first two days of life which returned to normal at day 3.

Nursing mothers: 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 Rocaltrol in nursing infants, a mother should not nurse while taking this drug.

Pediatric use: Safety and efficacy of Rocaltrol in children undergoing dialysis have not been established.

ADVERSE REACTIONS: Since Rocaltrol is believed to be the active hormone which exerts vitamin D activity in the body, adverse effects are, in general, similar to those encountered with excessive vitamin D intake. The early and late signs and symptoms of vitamin D intoxication associated with hypercalcemia include:

Early: Weakness, headache, somnolence, nausea, vomiting, dry mouth, constipation, muscle pain, bone pain and metallic taste.

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

In clinical studies on hypoparathyroidism and pseudohypoparathyroidism, hypercalcemia was noted on at least one occasion in about 1 in 3 patients and hypercalciuria in about 1 in 7. Elevated serum creatinine levels were observed in about 1 in 6 patients (approximately one half of whom had normal levels at baseline).

One case of erythema multiforme was confirmed by rechallenge.

OVERDOSAGE: Administration of Rocaltrol to patients in excess of their daily requirements can cause hypercalcemia, hypercalciuria and hyperphosphatemia. High intake of calcium and phosphate concomitant with Rocaltrol may lead to similar abnormalities. High levels of calcium in the dialysate bath may contribute to the hypercalcemia.

Treatment of Hypercalcemia and Overdosage: General treatment of hypercalcemia (greater than 1 mg/dl above the upper limit of the normal range) consists of immediate discontinuation of Rocaltrol therapy, institution of a low calcium diet and withdrawal of calcium supplements. Serum calcium 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 mcg/day less than prior therapy. Serum calcium levels should be obtained at least twice weekly after all dosage changes and subsequent dosage titration. In dialysis

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 018044/S018/S019/S024

MEDICAL REVIEW(S)

ORIGINAL

AUG - 1 1996

NDA 18-044 (S-024) Rev. Competed : 8/1/96
Rocaltrol
Hoffmann-La Roche Inc.

Review and Evaluation of Clinical Data

1. **Name of drug:** Trade: Rocaltrol
   Generic: Calcitriol
   Chemical: 1,25(OH)2 D3

2. **Dosage form and route of administration:** 0.25 and 0.5 mcg capsules for p.o. use.

3. **Category or use of drug:** A vitamin D metabolite (active). Approved for use in the treatment of hypocalcemia and the resultant metabolic bone disease in patients undergoing chronic renal dialysis.

4. **Reason for supplemental submission:** FPl (revised June 1996).

5. **Date of supplemental submission:** July 9, 1996.

6. **Summary evaluation:**

   The **Adverse Reactions** section has been revised to report allergic reactions to Rocaltrol. Sponsor was requested by us to incorporate these reactions with Rocaltrol rechallenge under Adverse Reactions section of the labeling. The sponsor has added the following sentence at the end of this section: "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." The FPL with changes being effected is acceptable. Our Chemist may have some comments on editorial change regarding "Corporate Logo."

7. **Conclusion and recommendation:** The FPL (bearing the date of June 1996) to provide for a labeling change under Adverse Reactions section is acceptable.

/S/

S.N.Dutta, M.D.

/S/
8-1-96

APPEARS THIS WAY
ON ORIGINAL

CC: Orig. NDA 18-044 (S-024)
HFD-340
HFD-510/SND/8.1.96

NDA 18-044 (s-018)
Rocaltrol (Calcitriol)
Hoffmann-La Roche

Rev. Completed: 12/1/88

DEC 2 1988

Review and Evaluation of Clinical Data

1. Name of Drug: Trade: Rocaltrol
   Generic: Calcitriol

2. Dosage form and route of administration: 0.25 and 0.5 mcg capsules for p.o. use.

3. Category or use of drug: For use in the management of hypocalcemia in dialysis patients, and in hypocalcemia associated with postsurgical hypoparathyroidism, idiopathic hypoparathyroidism and pseudohypoparathyroidism.

4. Reason for supplemental submission and date: Labeling revision dated 11/22/88.

5. Summary evaluation:

   The sponsor has proposed The following labeling revisions:

   (1) Under section ADVERSE REACTIONS, nephrocalcinosis has been added under subheading "Late" (signs and symptoms of vitamin D intoxication).

   Comments: The current labeling has a statement regarding nephrocalcinosis (under section WARNINGS) associated with vitamin D overdosage and the resultant hypercalcemia. The above-mentiond revision of ADVERSE REACTIONS section is acceptable.

   (2) The sponsor has provided reprints of two published articles in which human milk has been reported to contain vitamin D activity (Weisman et al. J. Pediatrics 100: 745, 1982; Reeve, Chesney, and DeLuca, Am. J. Clin. Nutr. 36: 12, 1982). Based on these reports the sponsor has incorporated the following statement "Calcitriol may be excreted in human milk" under sections CLINICAL PHARMACOLOGY, and PRECAUTIONS (under subheading "Nursing mothers").

   (3) Under section OVERDOSAGE, "single dose" has been added to the statement regarding Oral LD_{50} (in mice and rats).

   (4) The sponsor has added a section entitled ANIMAL PHARMACOLOGY after DOSAGE and ADMINISTRATION section. The Pharmacology reviewer may be requested to comment on the proposed statements regarding animal pharmacology.

6. Conclusion and recommendation:

The proposed clinically relevant revisions (items # 1, 2,and 3) are acceptable. The Pharmacology reviewer may be requested to comment on the proposed statements incorporated under a new section entitled "Animal Pharmacology. The sponsor may be requested to submit Final Printed Labeling.

/S/

S. N. Dutta, M.D.

/S/

12-2-88

APPEARS THIS WAY
ON ORIGINAL

APPEARS THIS WAY
ON ORIGINAL

cc: Orig. NDA 18-044
HFD-340
HFD-510
HFD-510/Pierce
HFD-510/SND/12/2/88/Wang # 0757m

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 018044/S018/S019/S024

CHEMISTRY REVIEW(S)

ORIGINAL

DEC 18 1989

December 14, 1989

REVIEW OF CHEMISTRY AND MANUFACTURING CONTROLS

CHEMIST'S REVIEW DIVISION METABOLISM AND ENDOCRINE DRUGS HFD-510
Martin K. Bennett P.D.,Chemist

NAME AND ADDRESS OF APPLICANT

HOFFMANN-LA ROCHE
NUTLEY,NJ

NAME OF DRUG	GENERIC NAME	NDA NUMBER	SUPPLEMENT NUMBER
ROCALTROL	calcitriol capsules	18-044	S-019 3/8/89

SUPLEMENTS PROVIDE FOR

Update contols:

Revised specifications and directions for testing Rocaltrol capsules as well as stability testing.

PHARMACOLOGICAL CATEGORY	HOW DISPENSED	DOSAGE FORM	POTENCY
Vitamin D analog	Rx	capsule	0.25&0.5ug

COMMENTS

1.

2.

3.

CONCLUSIONS AND RECOMMENDATIONS

SUPPLEMENT MAY BE APPROVED

REVIEWING CHEMIST SIGNATURE DATE COMPLETED
MARTIN K. BENNETT /S/ 12-14-89
DISTRIBUTION ORIGINAL REVIEWER DIVISION
INITIALED BY /S/ 12/18/89

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 018044/S018/S019/S024

PHARMACOLOGY REVIEW(S)

S-018

ORIGINAL

MAY 2 5 1989

NDA 18-044 5/12/89
Hoffmann-La Roche
Nutley, N.J.
11/28/88

Review and Evaluation of Pharmacology abd Toxicology Dat
Amendment of 11/22/88

Drug: Rocaltrol

Category: Vitamin D metabolite

This submission contains the response of the sponsor to Agency's letter of July 21, 1988.

In the letter of July 21, 1988 the Agency suggested that a statement be incorporated into the package insert for Rocaltrol capsules regarding the occurrence of kidney lesions in dogs at about two times the maximum allowable human dose of 2 ug/day. In response to Agency's request the sponsor indicated that in order to reflect the fact that lesions occur in other tissues as well and not only in at the doses cited in the letter the sponsor recommended that an Animal Pharmacology section be added to the insert. The sponsor also made the following labeling revision.

I. Nephrocalcinosis has been added to the Adverse Reactions section.

II. The sponsor enclosed two reprints of recent findings. These two reprints revealed that vitamin D and its metabolits have been identified in human milk. The sponsor has revised the labeling to state that calcitriol may be excreted in human milk.

III. Finally the statement regarding oral LD_{50} values has been clarified by adding "single dose."

Comments: Rocaltrol is an approved drug.

The sponsor's response is adequate.

The submitted information does not change the safety evaluation of the drug.

Recommendation: None

/S/

I. Huang, Ph. D.

CC: Orig NDA, HFD-345, HFD-510, HFD-510AJordan,. HFD-510/IHuang, HFD-502/JWeissinger

/S/

5/25/89

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 018044/S018/S019/S024

CORRESPONDENCE

NDA NO. 18044 REF. NO. 044

NDA SUPPL FOR 012

ORIGINAL
NDA SUPPLEMENT

Roche Pharmaceuticals
A Member of the Roche Group

Hoffmann-La Roche Inc.
340 Kingsland Street
Nutley, New Jersey 07110-1199

Direct Dial (201) 812-3683
Fax (201) 812-3554

July 9, 1996

Food and Drug Administration
Division of Anti-Infective Drug Products, HFD-520
Office of Drug Evaluation II
Center for Drug Evaluation and Research
ATTN: DOCUMENT CONTROL ROOM
5600 Fishers Lane
Rockville, MD 20857-1706

Ladies and Gentlemen:

Re: NDA 18-044 / Rocaltrol® (calcitriol) Capsules
Special Supplement -- Changes Being Effected
Final Printed Labeling

In accord with 21 CRF 314.70(c)(2)(i), provided herein is a revision to the Rocaltrol package insert in response to a December 18, 1995 telephone conversation between Mr. Randy Hedin, Project Manager, Division of Metabolism and Endocrine Drug Products, and the undersigned. During this conversation, a labeling change was requested in reference to the September 18, 1995 Periodic Adverse Drug Experience Report. In response to this request, submitted herewith are fifteen copies of final printed labeling, ten of which are individually mounted (date code 0696).

The change to the package insert is found under ADVERSE REACTIONS to report an allergic reaction observed with Rocaltrol rechallenge. The sentence now reads as follows: "One case of erythema multiforme and one case of allergic reaction (swelling of lips and hives all over the body) were confirmed by rechallenge." Additionally, an editorial change was made to the corporate logo.

During the above-mentioned telephone call, it was agreed that this information be provided as a Special Supplement -- Changes Being Effected. If you have any questions, please do not hesitate to contact the undersigned.

REVIEWS COMPLETED

CSO ACTION:
☒ LETTER ☐ N.A.I. ☐ MEMO

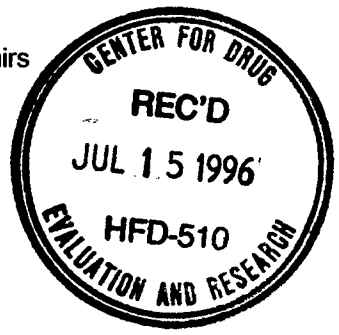
/S/ 10/24/96
CSO INITIALS DATE

Sincerely,

HOFFMANN-LA ROCHE INC.

Betty C. Holland

Betty C. Holland
Program Director
Drug Regulatory Affairs



BCH:esm/pb
Enclosure
HLR No. 1996-797

NDA No. 18-044 REF. NO. S-019

NDA SUPPLEMENT FOR SCS

/S/

Hoffmann-La Roche

Hoffmann-La Roche Inc.
340 Kingsland Street
Nutley, New Jersey 07110-1199

Direct Dial (201) 235-3694

March 8, 1989

REVIEWS COMPLETED

CSO ACTION:

☒ LETTER ☐ N.A.I.

/S/ 3/13/89

CSO INITIALS DATE

Division of Metabolism and Endocrine Drug Products
Center for Drug Evaluation and Research, HFD-510
Attn: DOCUMENT CONTROL ROOM 14B-03
5600 Fishers Lane
Rockville, MD 20857

Gentlemen:

Re: ROCALTROL (calcitriol) CAPSULES - NDA 18-044

In accord with the provisions of 21 CFR 314.70(b)(2), we submit herewith revised specifications and directions for testing Rocaltrol Capsules as well as revised stability testing methodology for these capsules.

For the convenience of the reviewer, the principal revisions are tabulated below. Other revisions are editorial in nature.

I. Rocaltrol Capsules 0.25 µg and 0.5 µg

A.

B.

C.

1.

2.

3.

4.

II. -

A.

B.

In the attached submission certain pages are marked CONFIDENTIAL because the materials on the pages constitute trade secrets or commercial or financial information which is privileged or confidential within the meaning of the Freedom of Information Act (5 USC 552). If for any reason Food and Drug Administration officials should feel that disclosure of any of the materials marked CONFIDENTIAL should be made to any member of the public we expect that because of the importance of maintaining secrecy of these materials to Hoffmann-La Roche Inc. you will first consult with us on the issue of disclosure.

Your early review and approval of these revised specifications and directions for testing are respectfully requested.

Sincerely,

HOFFMANN-LA ROCHE INC.

APPEARS THIS WAY
ON ORIGINAL

Mary E. Reilly

Mary E. Reilly
Senior Manager
Drug Regulatory Affairs

MER:jk

Attachment

HLR No. 89167

APPEARS THIS WAY
ON ORIGINAL

/S/ 3/9/90 Verbal /S/ 11/29/88

Hoffmann-La Roche

Hoffmann-La Roche Inc.
340 Kingsland Street
Nutley, New Jersey 07110-1199

Direct Dial 201-235-3694

November 22, 1988

Clinical Tech aspects OK /S/ 1/24

NDA NO. 18-044 REF. NO. S-018

NDA SUPPL FOR SLR

REVIEWS COMPLETED

CSO ACTION:

☒ LETTER ☐ N.A.I.

/S/ 3/13/90

CSO INITIALS DATE

Division of Metabolism and Endocrine
Drug Products
Center for Drug Evaluation and Research, HFD-510
Attn: DOCUMENT CONTROL ROOM 14B-03
5600 Fishers Lane
Rockville, Maryland 20857

Gentlemen:

Re: ROCALTROL CAPSULES - NDA 18-044
ROCALTROL CAPSULES -

Reference is made to the Agency letter of July 21, 1988, suggesting that a statement be incorporated into the package insert for Rocaltrol Capsules regarding the occurrence of kidney lesions in dogs at about two times the maximum allowable human dose of 2 mcg/day.

We have reviewed your request and the animal data. In order to reflect the fact that lesions occur in other tissues as well, and not only at the doses cited in your letter, we recommend that an ANIMAL PHARMACOLOGY section be added to the insert, as indicated on the attached draft.

We have also made the following labeling revisions:

1) In light of the current WARNING statement regarding overdosage of Vitamin D and the resultant hypercalcemia which can lead to nephrocalcinosis, and information previously reported to the Agency, nephrocalcinosis has been added to the ADVERSE REACTIONS section.

2) Upon review of the two attached reprints regarding identification of Vitamin D and its metabolites in human milk, we have revised the labeling to state that calcitriol may be excreted in human milk.

3) Finally, the statement regarding oral LD_{50} values has been clarified by adding "single dose."

All proposed revisions are annotated on a copy of the current approved labeling for Rocaltrol Capsules. Four sets are submitted herewith to NDA 18-044

Your early review and approval of this revised labeling are respectfully requested.

Sincerely,

HOFFMANN-LA ROCHE INC.

APPEARS THIS WAY
ON ORIGINAL

Mary E. Reilly
Senior Manager
Drug Regulatory Affairs

MER/cs

HLR No. 88869

APPEARS THIS WAY
ON ORIGINAL

ORIGINAL

Roche Pharmaceuticals
a division of Hoffmann-La Roche Inc.

/S/

340 Kingsland Street
Nutley, New Jersey 07110-1199

Direct Dial (201) 235-5005

LR/BF
S-018

**SPECIAL SUPPLEMENT
CHANGES BEING
EFFECTED**

August 28, 1990

Division of Metabolism and Endocrine Drug Products
Center for Drug Evaluation and Research, HFD-510
Attn: Document Control Room 14B-03
5600 Fishers Lane
Rockville, Maryland 20857

/S/

Gentlemen:

S-018

Re: ROCALTROL (calcitriol) CAPSULES - NDA 18-044, (S-[redacted])

Reference is made to your letter dated March 13, 1990, which requested that final printed labeling for Rocaltrol should be identical to the draft labeling submitted November 22, 1988 except for the following revisions:

1. In the **OVERDOSAGE** section, the following text has been deleted; "The single dose oral toxicity of calcitriol is as follows:

SPECIES	**LD_{50} (mg/Kg)**
mouse	2.0
rat	>5.0"

2. The following statement has been added to the last sentence of the **WARNINGS** section; "Studies in dogs and rats given calcitriol for up to 26 weeks have shown that small increases of calcitriol above endogenous levels can lead to abnormalities of calcium metabolism with the potential for calcification of many tissues in the body."

As requested in your March 13, 1990 letter, (12 copies) of final printed labeling (dated June 1990) are enclosed.

CSO ACTION:

☒ LETTER ☐ N.A.I.

/S/ 4/2/91

Your early review and approval of this final printed labeling are respectfully requested.

APPEARS THIS WAY
ON ORIGINAL

APPEARS THIS WAY
ON ORIGINAL

Sincerely,

HOFFMANN-LA ROCHE INC.

Anthony J. Corrado
Senior Regulatory Specialist
Drug Regulatory Affairs

AJC/cr
Attachments
HLR No. 90868

APPEARS THIS WAY
ON ORIGINAL

Roche Pharmaceuticals
a division of Hoffmann-La Roche Inc.

340 Kingsland Street
Nutley, New Jersey 07110-1199

Direct Dial 201-235-5005

NDA SUPPL AMENDMENT
LR/AF
S-018

February 12, 1991

Division of Metabolism and Endocrine Drug Products
Center for Drug Evaluation and Research, HFD-511
Attn: Ms. Nancy N. Clagett, Room 14B-04
5600 Fishers Lane
Rockville, Maryland 20857

Dear Ms. Clagett:

Re: ROCALTROL (calcitriol) CAPSULES - NDA 18-044 (S-018)

As requested in our February 11, 1991 telephone conversation, 11 copies of final printed labeling for Rocaltrol Capsules (dated June 1990) are enclosed.

Please contact me if you have any question regarding this information.

Sincerely,

HOFFMANN-LA ROCHE INC.

APPEARS THIS WAY
ON ORIGINAL

Anthony J. Corrado
Senior Regulatory Specialist
Drug Regulatory Affairs

AJC:kt
Attachments
HLR No. 91-177

APPEARS THIS WAY
ON ORIGINAL

REVIEWS COMPLETED

CSO ACTION:

☒ LETTER ☐ N.A.I.

CSO INITIALS 4/2/91 DATE