

Data Sheet

Rocaltrol[®]

Calcitriol 1 microgram per millilitre oral solution

Biologically active form of vitamin D₃

Pharmaceutical Form

Oral solution containing 1 mcg/mL calcitriol.

Qualitative and Quantitative Composition

Active ingredient

Synthetic calcitriol (biologically active form of vitamin D₃) 1 mcg/mL.

Excipients

Butylated hydroxyanisole, butylated hydroxytoluene and medium chain triglycerides.

Appearance

Rocaltrol solution is a clear, oily liquid almost colourless to slightly yellowish.

Clinical Particulars

Therapeutic Indications

- Established postmenopausal osteoporosis.
- Renal osteodystrophy in patients with chronic renal failure, particularly those undergoing haemodialysis.
- Secondary hyperparathyroidism in patients with moderate to severe chronic renal failure (pre-dialysis).
- Postsurgical hypoparathyroidism.
- Idiopathic hypoparathyroidism.
- Pseudohypoparathyroidism.
- Vitamin D-dependent rickets.
- Hypophosphataemic vitamin D-resistant rickets.
- Prevention of corticosteroid induced osteoporosis.

Dosage and Method of Administration

Standard dosage

The optimal daily dose of Rocaltrol must be carefully determined for each patient on the basis of the serum calcium level. Rocaltrol therapy should always be started at the lowest possible dose and should not be increased without careful monitoring of serum calcium (see Patient monitoring).

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

Because of improved calcium absorption from the gastrointestinal tract, some patients on Rocaltrol may be maintained on a lower calcium intake. Patients who tend to develop hypercalcaemia may require only low doses of calcium or no supplementation at all.

The total daily calcium intake (i.e. from food, and, where applicable, from medicines) should average approximately 800 mg and should not exceed 1,000 mg.

Every package of Rocaltrol solution contains a graduated dropper for administration of individual doses. The administered volume of Rocaltrol solution can be calculated either in mL or drops: 0.1 mL of the solution corresponds to 0.1 mcg of the active ingredient (calcitriol) or 1 drop of solution contains 0.02 mcg calcitriol.

After opening, the original screw cap can be replaced by the cap that is attached to the dropper. The cap should be closed tightly after use. Discard any remaining solution six weeks after opening.

Patient monitoring

During the stabilisation phase of treatment with Rocaltrol, serum calcium levels should be checked at least twice weekly. When the optimal dosage of Rocaltrol has been determined, serum calcium levels should be checked every month (or as given below for individual indications). Samples for serum calcium estimation should be taken without a tourniquet.

As soon as the serum calcium levels rise to 1 mg/100 mL (250 micromol/L) above normal (9-11 mg/100 mL, or 2,250-2,750 micromol/L), or serum creatinine rises to > 120 micromol/L, treatment with Rocaltrol should be stopped immediately until normocalcaemia ensues.

During the periods of hypercalcaemia, serum calcium and phosphate levels must be determined daily. When normal levels have been attained, the treatment with Rocaltrol can be continued, at a daily dose 0.25 mcg lower than that previously used. An estimate of daily dietary calcium intake should be made and the intake adjusted when indicated.

Special dosage instructions

Postmenopausal osteoporosis

The recommended dosage for Rocaltrol is 0.25 mcg twice daily.

Serum calcium and creatinine levels should be determined at one, three and six months and at six-monthly intervals thereafter.

Renal osteodystrophy (dialysis patients)

The initial daily dose is 0.25 mcg. In patients with normal or only slightly reduced serum calcium levels, doses of 0.25 mcg every other day are sufficient. If no satisfactory response in the biochemical parameters and clinical manifestations of the disease is observed within two to four weeks, the daily

dosage may be increased by 0.25 mcg at two to four-week intervals. During this period, serum calcium levels should be determined at least twice weekly. Most patients respond to between 0.5 mcg and 1.0 mcg daily.

An oral Rocaltrol pulse therapy with an initial dosage of 0.1 mcg/kg/week split into two or three equal dosages given at night was found to be effective even in patients refractory to continuous therapy. A maximum total cumulative dosage of 12 mcg per week should not be exceeded.

Secondary hyperparathyroidism (pre-dialysis patients)

The recommended initial dosage of Rocaltrol for the treatment of secondary hyperparathyroidism and resultant metabolic bone disease in patients with moderate to severe renal failure i.e. creatinine clearance (C_{cr}) 15 to 55 mL/min, is 0.25 mcg/day in adults and in paediatric patients three years of age or older (corrected for a surface area of 1.73m²). This dosage may be increased if necessary to 0.5 mcg/day.

Hypoparathyroidism, rickets

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 this period, serum calcium levels should be determined at least twice weekly. If hypercalcaemia is noted, Rocaltrol should be immediately discontinued until normocalcaemia ensues. Careful consideration should also be given to lowering the dietary calcium intake.

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

If the physician decides to prescribe Rocaltrol to a pregnant woman with hypoparathyroidism, an increased dose may be required during the latter half of gestation, with dose reduction postpartum or during lactation.

Prevention of corticosteroid induced osteoporosis

The recommended dosage range for the prevention of corticosteroid induced osteoporosis is 0.5-0.75 mcg per day. Serum calcium and creatinine levels should be obtained at two to four weeks after initiating treatment then at three and six months and every six months thereafter. If hypercalcaemia is noted, the medicine should be immediately discontinued until normocalcaemia ensues. While an adequate dietary calcium intake is important, ordinarily it is more convenient to titrate medicine dosage around the customary calcium intake of the patient.

Elderly patients

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

Infants and children

For the treatment of infants and young children Rocaltrol is available as a solution. As for adults, the optimal daily dosage for children must be determined on the basis of the serum calcium level.

The solution should be put first into a spoon and then mixed into the child's drink (e.g. orange juice).

During the first two years of life, a daily dosage of 0.01-0.1 mcg/kg bodyweight is recommended as a guideline.

Contraindications

Rocaltrol is contraindicated in all diseases associated with hypercalcaemia. Use of Rocaltrol in patients with known hypersensitivity to Rocaltrol (or medicines of the same class) and any of the constituent excipients is contraindicated.

Rocaltrol is contraindicated if there is evidence of vitamin D toxicity.

Special Warnings and Special Precautions for Use

There is a close correlation between treatment with calcitriol and the development of hypercalcaemia. 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 hypercalcaemia. Patients and their families should be advised that strict adherence to the prescribed diet is mandatory and they should be instructed on how to recognise the symptoms of hypercalcaemia. As soon as the serum calcium levels rise to 1 mg/100 mL (250 micromol/L) above normal (9-11 mg/100 mL, or 2,250-2,750 micromol/L), or serum creatinine rises to > 120 micromol/L, treatment with Rocaltrol should be stopped immediately until normocalcaemia ensues (see Dosage and Method of Administration).

Immobilised patients, e.g. those who have undergone surgery, are particularly exposed to the risk of hypercalcaemia.

Calcitriol increases inorganic phosphate levels in serum. While this is desirable in patients with hypophosphataemia, 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 hypophosphataemia) who are being treated with Rocaltrol must continue their oral phosphate therapy. However, possible stimulation of intestinal absorption of phosphate by Rocaltrol should be taken into account since this effect may modify the need for phosphate supplementation. The regular laboratory investigations that are required include serum determinations of calcium, phosphorus, magnesium and alkaline phosphatase and of the calcium and phosphate content in 24-hour urine. During the stabilisation phase of treatment with Rocaltrol, serum calcium levels should be checked at least twice weekly (see Dosage and Method of Administration).

Since calcitriol is the most effective vitamin D metabolite available, no other vitamin D preparation should be prescribed during treatment with Rocaltrol, thereby ensuring that the development of hypervitaminosis D is avoided.

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

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

Interactions with other Medicinal Products and other Forms of Interaction

Since calcitriol is one of the most important active metabolites of vitamin D₃, pharmacological doses of vitamin D and its derivatives should be withheld during treatment with Rocaltrol to avoid possible additive effects and hypercalcaemia.

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 hypercalcaemia. Calcitriol dosage must be determined with care in patients undergoing treatment with digoxin, as hypercalcaemia in such patients may precipitate cardiac arrhythmias (see Special Warnings and Special Precautions for Use).

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

Magnesium-containing medicines (e.g. antacids) may cause hypermagnesaemia and should therefore not be taken during therapy with Rocaltrol by patients on chronic renal dialysis.

Since Rocaltrol 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 hypophosphataemia) should continue their oral phosphate therapy. However, possible stimulation of intestinal phosphate absorption by calcitriol should be taken into account since this effect may modify the requirement for phosphate supplements.

Administration of enzyme inducers such as phenytoin or phenobarbital may lead to increased metabolism and hence reduced serum concentrations of calcitriol. Therefore higher doses of calcitriol may be necessary if these medicines are administered simultaneously.

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

Pregnancy and Lactation

Supravalvular aortic stenosis has been produced in foetuses 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. Rocaltrol should be used during pregnancy only if the benefits outweigh the potential risk to the foetus.

It should be assumed that exogenous calcitriol passes into the breast milk. In view of the potential for hypercalcaemia 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.

Effects on 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.

Undesirable Effects

Clinical Trials

The adverse effects listed below reflect the experience from investigational studies of Rocaltrol, and the post-marketing experience.

The most commonly reported adverse reaction was hypercalcaemia.

The adverse effects listed in Table 1 are presented by system organ class and frequency categories, defined using the following convention: Very common ($\geq 1/10$); common ($\geq 1/100$ to $< 1/10$); uncommon ($\geq 1/1,000$ to $< 1/100$); rare ($\geq 1/10,000$ 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 Adverse Effects Occurring in Patients Receiving Rocaltrol®(calcitriol)

System Organ Class	Very common	Common	Uncommon	Not known
Immune System Disorders				Hypersensitivity, Urticaria
Metabolism and Nutrition Disorders	Hypercalcaemia		Decreased appetite	Polydipsia, Dehydration
Psychiatric Disorders				Apathy
Nervous System Disorders		Headache		Muscular weakness, Sensory disturbance
Gastrointestinal Disorders		Abdominal pain, Nausea	Vomiting	Constipation, Abdominal pain upper
Skin and subcutaneous tissue disorders		Rash		Erythema, Pruritus
Musculoskeletal and Connective Tissue Disorders				Growth retardation
Renal and Urinary Disorders		Urinary tract infection		Polyuria
General disorders and administration site conditions				Calcinosis, Pyrexia, Thirst
Investigations			Blood creatinine increased	Weight decreased

Since calcitriol exerts vitamin D activity, adverse effects may occur which are similar to those found when an excessive dose of vitamin D is taken, i.e. hypercalcaemia syndrome or calcium intoxication

(depending on the severity and duration of hypercalcaemia) (see Dosage and Method of Administration, Special Warnings and Special Precautions for Use).

Signs and symptoms of vitamin D intoxication associated with hypercalcaemia include:

Acute: decreased appetite, weakness, headache, somnolence, nausea, vomiting, dry mouth, constipation, abdominal pain or abdominal pain upper, muscle pain, bone pain, and metallic taste.

Chronic: muscular weakness, sensory disturbances, pyrexia, thirst, polydipsia, polyuria, dehydration, apathy, growth retardation, weight decreased, nocturia, conjunctivitis (calcific), pancreatitis, photophobia, rhinorrhoea, hyperthermia, decreased libido, elevated BUN, albuminuria, hypercholesterolaemia, elevated AST and ALT, ectopic calcification, hypertension, cardiac arrhythmias, and urinary tract infections and, rarely, overt psychosis.

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

In concurrent hypercalcaemia 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, pruritis, and urticaria may occur in susceptible individuals.

Laboratory Abnormalities

In patients with normal renal function, chronic hypercalcaemia may be associated with a blood creatinine increased.

Post Marketing

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 hypercalcaemia, occurring at a rate of 0.001 % or less.

Overdose

Treatment of asymptomatic hypercalcaemia: see Dosage and Method of Administration.

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 Rocaltrol 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 hypercalcaemia.

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 treatment of accidental overdosage: immediate gastric lavage or induction of vomiting to prevent further absorption. Administration of liquid paraffin to promote faecal 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.

Pharmacological Properties and Effects

Calcitriol is one of the most important active metabolites of vitamin D₃. It is normally formed in the kidney from its precursor, 25-hydroxycholecalciferol (25-HCC). Physiological daily production is normally 0.5-1.0 mcg and is somewhat higher during periods of increased bone synthesis (e.g. growth or pregnancy). Calcitriol promotes intestinal absorption of calcium and regulates bone mineralisation. The pharmacological effect of a single dose of calcitriol lasts about three to five days.

The key role of calcitriol in the regulation of calcium homeostasis, which includes stimulating effects on osteoblastic activity in the skeleton, provides a sound pharmacological basis for its therapeutic effects in osteoporosis.

In patients with marked renal impairment, synthesis of endogenous calcitriol is correspondingly limited or may even cease altogether. This deficiency plays a key role in the development of renal osteodystrophy.

In patients with renal osteodystrophy, oral administration of Rocaltrol normalises reduced intestinal absorption of calcium, hypocalcaemia, increased serum alkaline phosphatase and serum parathyroid hormone concentration. It alleviates bone and muscle pain and corrects the histological alterations that occur in osteitis fibrosa and other mineralisation defects.

In patients with postsurgical hypoparathyroidism, idiopathic hypoparathyroidism, and pseudohypoparathyroidism, hypocalcaemia and its clinical manifestations are alleviated by Rocaltrol therapy.

In patients with vitamin D-dependent rickets, serum levels of calcitriol are low or absent. As the endogenous production of calcitriol in the kidney is insufficient, Rocaltrol is considered as a replacement therapy.

In patients with vitamin D-resistant rickets and hypophosphataemia in whom plasma calcitriol levels are reduced, treatment with Rocaltrol reduces tubular elimination of phosphates and, in conjunction with concurrent phosphate treatment, normalises bone development.

Patients with various other forms of rickets, e.g. in association with neonatal hepatitis, biliary atresia, cystinosis and dietary calcium and vitamin D deficiency, have also benefited from Rocaltrol therapy.

Pharmacodynamic Properties

Mechanism of action

The biological effects of calcitriol are mediated by the vitamin D receptor, a nuclear hormone receptor expressed in most cell types and functioning as a ligand-activated transcription factor that binds to specific DNA sites to modify the expression of target genes.

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 D₃ in stimulating intestinal calcium transport. In acutely uraemic rats calcitriol has been shown to stimulate intestinal calcium absorption.

The kidneys of uraemic patients cannot adequately synthesise calcitriol, the active hormone formed from precursor Vitamin D. Resultant hypocalcaemia and secondary hyperparathyroidism are a major cause of the metabolic bone disease of renal failure. However, other bone-toxic substances which accumulate in uraemia (e.g., aluminium) may also contribute.

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

Pharmacokinetic Properties

Absorption

Calcitriol is rapidly absorbed from the intestine. Peak serum concentrations following a single oral dose of 0.25-1.0 mcg Rocaltrol were found within three to six hours.

Following multiple administration, serum calcitriol levels reached a steady state within seven days, with a relationship to the dose of calcitriol administered.

Distribution

After a single oral dose of 0.5 mcg Rocaltrol, 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. During transport in the blood, calcitriol and other vitamin D metabolites are bound to specific plasma proteins.

It can be assumed that exogenous calcitriol passes from the maternal blood into the foetal bloodstream and breast milk.

Metabolism

Calcitriol is hydroxylated and oxidized in the kidney and in the liver by a specific cytochrome P450 isoenzyme; CYP24A1.

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

Elimination

The elimination half-life of calcitriol in serum is nine to ten hours.

The elimination kinetics of calcitriol remain linear up to a 96 mcg dose, corresponding to a very broad dose range.

However, the pharmacological effect of a single dose of calcitriol lasts at least seven days. Calcitriol is excreted in the bile and is subject to enterohepatic circulation.

After IV administration of radioactive calcitriol in healthy subjects, about 27 % of the radioactivity is found in the faeces and about 7 % in the urine within 24 hours.

After oral administration of 1 mcg radioactive calcitriol in healthy subjects, about 10 % of the entire radioactivity was found in the urine within 24 hours. On the sixth day after IV administration of radioactive calcitriol, urine and faeces accounted for an average of 16 % and 49 % respectively of the cumulative excretion of radioactivity.

Pharmacokinetics in special populations

In patients with nephrotic syndrome or in those undergoing haemodialysis, serum levels of calcitriol were reduced and time to peak levels was prolonged.

Preclinical safety

Acute toxicity studies in mice and rats indicated that the oral approximate 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 mcg twice daily (approximately 8 – 10 ng/kg/day).

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 six months produced no or minimal adverse effects. A dose of 80 ng/kg/day (8 times the usual human dosage) for up to six months produced moderate adverse effects; changes seen appeared to be primarily the result of prolonged hypercalcaemia.

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, calcitriol produced some maternal and foetotoxic effects at an oral dose of 300 ng/kg/day, but did not show any adverse effect at 20 or 80 ng/kg/day (eight times the usual human dose).

Pharmaceutical Particulars

Stability

This medicine should not be used after the expiry date shown on the pack.

Rocaltrol solution is stable for six weeks after being opened.

Special Precautions for Storage

Store Rocaltrol solution at or below 30°C, protect from light.

Disposal of Medicines

The release of medicines into the environment should be minimised. Medicines should not be disposed of via wastewater and disposal through household waste should be avoided. Unused or expired medicine should be returned to a pharmacy for disposal.

Packs

Rocaltrol oral solution 1 mcg/mL is supplied in a single 10 mL glass bottle with a glass graduated pipette.

Medicine Classification

Prescription medicine

Name and Address

Distributed in New Zealand by:
Roche Products (New Zealand) Ltd
PO Box 12492 Penrose
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NEW ZEALAND

Customer enquiries: 0800 656 464

Date of Preparation

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