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.

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

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

Pharmacokinetics

Absorption
Calcitriol is rapidly absorbed from the intestine. Peak serum concentrations following a single dose of 0.25-1.0 µg Rocaltrol were found within 3-6 hours. Following multiple administration, serum calcitriol levels reached a steady state within 7 days.

Distribution
After a single oral dose of 0.5 µg Rocaltrol, the average serum concentrations of calcitriol rose from a baseline value of 40.0±4.4 µg/ml to 60.0±4.4 µg/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 after twelve hours and to 41.5±5.1 µg/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 fetal bloodstream and the breast milk.

Elimination
The elimination half-life of calcitriol is 3-6 hours. However, the pharmacological effect of a single dose of calcitriol lasts about 3-5 days. Calcitriol is
Precautions
There is a close correlation between treatment with calcitriol and the development of hypercalcemia. In studies of patients with uremic osteodystrophy, hypercalcemia was found to occur in up to 40% of calcitriol-treated patients. An abrupt increase in calcium intake as a result of changes in diet (e.g., increased consumption of dairy products) or uncontrolled intake of calcium preparations may trigger hypercalcemia. Patients and their families should be advised that strict adherence to the prescribed diet is mandatory and they should be instructed on how to recognize the symptoms of hypercalcemia.

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

In patients with normal renal function, chronic hypercalcemia may be associated with an increase in serum creatinine.

Caution is required in patients with a history of renal calculi and patients with coronary heart disease.

Calcitriol increases organic phosphate levels in serum. While this is desirable in patients with hypophosphatemia, caution is called for in patients with renal failure because of the danger of ectopic calcification. In such cases, the plasma phosphate level should be maintained at the normal level (2-5 mg/100 ml or 0.65-1.62 mmol/l) by the oral administration of appropriate phosphate-binding agents such as aluminium hydroxide or aluminium carbonate. Patients with vitamin D-resistant rickets (familial hypophosphatemia) which 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 stabilization phase of treatment with Rocaltrol, serum calcium levels should be checked at least

Indications
Postmenopausal osteoporosis; renal osteodystrophy in patients with chronic renal failure, particularly those undergoing hemodialysis; postsurgical hypo-parathyroidism; idiopathic hypo-parathyroidism; pseudohypopara-thyroidism; vitamin D-dependent rickets; hypophosphatemic vitamin D-resistant rickets.

Contraindications
Rocaltrol (or drugs of the same class) is contraindicated in all diseases associated with hypercalcemia. Use of Rocaltrol in patients with known hypersensitivity to its constituents is also contraindicated,

Side Effects
Rocaltrol does not produce Side Effects as long as the dosage does not exceed the individual patient’s needs. 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. hypercalcemia syndrome or calcium intoxication (depending on the severity and duration of hypercalcemia).

In concurrent hypercalcemia and hyperphosphatemia of >6mg/100 ml or >1.9 mmol per l, soft-tissue calcification may occur; this can be seen radiographically. Because of the short biological half-life of calcitriol, pharmacokinetic investigations have shown normalization of elevated serum calcium within a few days of treatment withdrawal or of a dosage reduction, i.e. much faster than in treatment with vitamin D$_3$ preparations.
twice weekly (see also Dosage and 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 values (see Overdosage). Patients with normal renal function who are taking ROCALTROL should avoid dehydration. Adequate fluid intake should be maintained.

Pregnancy and Nursing Mothers
Studies of reproductive toxicology in animals have not yielded unequivocal findings, and no controlled studies on the effect of exogenous calcitriol on pregnancy and fetal development have been performed in human subjects. Consequently, ROCALTROL should be administered only if the benefits outweigh the potential risk to the fetus.

It should be assumed that exogenous calcitriol passes into the breast milk. In view of the possible Side Effects on the infant, mothers should not breastfeed while taking ROCALTROL.

Overdosage
Treatment of asymptomatic hypercalcemia: see Special dosage instructions.

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. A high calcium level in the dialysate may contribute to the development of hypercalcemia.

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

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

The following measures should be considered in treatment of accidental overdosage: immediate gastric lavage or induction of vomiting to prevent further absorption. Administration of liquid paraffin to promote fecal excretion. Repeated serum calcium determinations are advisable. If elevated calcium levels persist in the serum, phosphates and corticosteroids may be administered and measures instituted to bring about adequate diuresis.

Stability
Store below 30°C and protect from light. This medicine should not be used after the expiry date (EXP) shown on the pack.

Drug Interactions
Since calcitriol is one of most important active metabolites of vitamin D₃, vitamin D and its derivatives should be withheld during treatment with calcitriol to avoid possible additive effects and hypercalcemia.

Dietary instructions, especially concerning calcium supplements, should be strictly observed, and uncontrolled intake of additional calcium-containing preparations avoided.

Concomitant treatment with a thiazide diuretic increases the risk of hypercalcemia in patients with hypoparathyroidism. Calcitriol dosage must be determined with care in patients undergoing treatment with digitalis, as hypercalcemia in such patients may precipitate cardiac arrhythmias.

A relationship of functional antagonism exists between vitamin D analogues, which promote calcium absorption, and corticosteroids, which inhibit it. Magnesium-containing drugs (e.g., antacids) may cause hypermagnesemia and should therefore not be taken during therapy with ROCALTROL by patients on chronic renal dialysis. Since calcitriol also has an effect on phosphate transport in the intestine, kidneys and bones, the dosage of phosphate-binding agents must be adjusted in accordance with the serum phosphate concentration (normal values:
In adults, the total daily calcium intake (from dietary and medicinal sources) should be approximately 800 mg and must not exceed 1000 mg. 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 hypercalcemia may require only low doses of calcium or no supplementation at all.

**Special Dosage Instructions**

**Postmenopausal Osteoporosis**
The recommended dosage is 0.25 µg twice daily. The capsules should be swallowed unchewed. Calcium supplements should be prescribed for patients whose dietary calcium intake is less than 500 mg. Daily calcium must not exceed 1000 mg. Serum calcium and creatinine levels should be determined at 4 weeks, 3 and 6 months and 6 monthly intervals thereafter.

**Renal Osteodystrophy (Dialysis Patients)**
The initial daily dose is 0.25 µg. In patients with normal or only slightly reduced serum calcium levels, doses of 0.25 µg 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 dosage may be increased by 0.25 µg/day 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 µg and 1.0 µg daily. Higher doses may be necessary in patients receiving concomitant barbiturates or anticonvulsants.

**Hypoparathyroidism and Rickets**
The recommended initial dose of Rocaltrol is 0.25 µg/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. Malabsorption is occasionally noted in patients with hypoparathyroidism hence, larger doses of Rocaltrol may be needed.