

SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Rocaltrol 0.25 microgram Capsules.

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each capsule contains either 0.25 or 0.5 microgram of calcitriol.

Excipient(s) with known effect

Each 0.25 microgram capsule contains 2.87 – 4.37 mg sorbitol.

Each 0.5 microgram capsule contains 2.87 – 4.36 mg sorbitol.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Soft capsules.

Rocaltrol 0.25 microgram capsules: One length brown-orange to red-orange opaque and the other white to grey-yellow or grey-orange opaque.

Rocaltrol 0.5 microgram capsules: Both lengths brown-orange to red-orange opaque.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Rocaltrol is indicated for the correction of the abnormalities of calcium and phosphate metabolism in patients with renal osteodystrophy.

Rocaltrol is also indicated for the treatment of established post-menopausal osteoporosis.

4.2 Posology and method of administration

The dose of Rocaltrol should be carefully adjusted for each patient according to the biological response so as to avoid hypercalcaemia.

The effectiveness of treatment depends in part on an adequate daily intake of calcium, which should be augmented by dietary changes or supplements if necessary. The capsules should be swallowed with a little water.

Posology

Adults

Renal Osteodystrophy

The initial daily dose is 0.25 mcg of Rocaltrol. In patients with normal or only slightly reduced calcium levels, doses of 0.25 mcg every other day are sufficient. If no satisfactory response in the biochemical parameters and clinical manifestations of the disease is observed within 2 - 4 weeks, the daily dosage may be increased by 0.25 mcg at 2 - 4 week intervals. During this period, serum calcium levels should be determined at least twice weekly. Should the serum calcium levels rise to 1 mg/100ml (250 µmol/l) above normal (9 to 11 mg/100 ml or 2250 – 2750 µmol/l), or serum creatinine rises to > 120 µmol/l, treatment with Rocaltrol should be stopped immediately until normocalcaemia ensues. Most patients respond to between 0.5 mcg and 1.0 mcg daily. See section 4.5 for details of dose adjustments related to drug interactions.

An oral Rocaltrol pulse therapy with an initial dosage of 0.1 mcg/kg/week split into two or three equal doses given at the end of the dialysis has been shown to be effective in patients with osteodystrophy refractory to continuous therapy. A maximum total cumulative dosage of 12 mcg per week should not be exceeded.

Post-menopausal Osteoporosis

The recommended dose of Rocaltrol is 0.25 mcg twice daily.

Serum calcium and creatinine levels should be determined at 1, 3 and 6 months and at 6 monthly intervals thereafter.

Elderly

Clinical experience with Rocaltrol in elderly patients indicates that the dosage recommended for use in younger adults may be given without apparent ill-consequence.

Paediatric Population

The safety and efficacy of calcitriol capsules in children have not been sufficiently investigated to enable dosing recommendations. Limited data are available for the use of calcitriol capsules in paediatric patients.

Method of administration

Rocaltrol capsules are for oral administration only.

4.3 Contraindications

Rocaltrol is contraindicated:

- in patients with known hypersensitivity to calcitriol (or drugs of the same class) and any of the excipients listed in section 6.1
- in all diseases associated with hypercalcaemia
- in patients with evidence of metastatic calcification
- if there is evidence of vitamin D toxicity.

4.4 Special warnings and precautions for use

There is a close correlation between treatment with calcitriol and the development of hypercalcaemia.

All other vitamin D compounds and their derivatives, including proprietary compounds or foodstuffs which may be “fortified” with vitamin D, should be withheld during treatment with Rocaltrol.

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 µmol/l) above normal (9-11 mg/100 ml or 2250-2750 µmol/l), or serum creatinine rises to >120 µmol/l, treatment with Rocaltrol should be stopped immediately until normocalcaemia ensues (see section 4.2).

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.

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 a long acting vitamin D preparation (e.g. ergocalciferol (vitamin D₂) or colecalciferol) to calcitriol, it may take several months for the ergocalciferol level in the blood to return to the baseline value, thereby increasing the risk of hypercalcaemia (see section 4.9).

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

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

Rocaltrol capsules contain sorbitol

Rocaltrol contains 2.87 – 4.37 mg sorbitol in each 0.25 microgram capsule.

Rocaltrol contains 2.87 – 4.36 mg sorbitol in each 0.5 microgram capsule.

The additive effect of concomitantly administered products containing sorbitol (or fructose) and dietary intake of sorbitol (or fructose) should be considered.

The content of sorbitol in medicinal products for oral use may affect the bioavailability of other medicinal products for oral use administered concomitantly.

4.5 Interaction with other medicinal products and other forms of interaction

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 digitalis, as hypercalcaemia in such patients may precipitate cardiac arrhythmias (see section 4.4).

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 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.

Bile acid sequestrants including cholestyramine and sevelamer can reduce intestinal absorption of fat-soluble vitamins and therefore may impair intestinal absorption of calcitriol.

4.6 Fertility, pregnancy and lactation

Pregnancy

The safety of Rocaltrol during pregnancy has not been established.

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.

Breast-feeding

It should be assumed that exogenous calcitriol passes into 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.

4.7 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.

4.8 Undesirable effects

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

The most commonly reported adverse reaction was hypercalcaemia.

The ADRs 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 ADRs 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, Weight decreased
Psychiatric Disorders				Apathy, Psychiatric disturbances
Nervous System Disorders		Headache		Muscular weakness, Sensory disturbance, Somnolence
Cardiac Disorders				Cardiac arrhythmias
Gastrointestinal Disorders		Abdominal pain, Nausea	Vomiting	Constipation, Abdominal pain upper, Paralytic

				ileus
Skin and subcutaneous tissue disorders		Rash		Erythema, Pruritus
Musculoskeletal and Connective Tissue Disorders				Growth retardation
Renal and Urinary Disorders		Urinary tract infection		Polyuria, Nocturia
General disorders and administration site conditions				Calcinosis, Pyrexia, Thirst
Investigations			Blood creatinine increased	

Since calcitriol exerts vitamin D activity, adverse effects may occur 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 sections 4.2 and 4.4). Occasional acute symptoms include decreased appetite, headache, nausea, vomiting, abdominal pain or abdominal pain upper and constipation.

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.

Chronic effects may include muscular weakness, weight decreased, sensory disturbances, pyrexia, thirst, polydipsia, polyuria, dehydration, apathy, growth retardation and urinary tract infections.

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, pruritus and urticaria may occur in susceptible individuals.

Laboratory Abnormalities

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

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.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any

suspected adverse reactions via the Yellow Card Scheme website: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

4.9 Overdose

Treatment of asymptomatic hypercalcaemia (see section 4.2).

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.

Hypercalcaemia at higher levels (>3.2 mmol/L) may lead to renal insufficiency particularly if blood phosphate levels are normal or elevated due to impaired renal function.

Should hypercalcaemia occur following prolonged treatment, Rocaltrol should be discontinued until plasma calcium levels have returned to normal. A low-calcium diet will speed this reversal. Rocaltrol can then be restarted at a lower dose or given in the same dose but at less frequent intervals than previously.

In patients treated by intermittent haemodialysis, a low concentration of calcium in the dialysate may also be used. However, a high concentration of calcium in the dialysate may contribute to the development of hypercalcaemia.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Vitamin D and analogues

ATC code: A11CC04

Calcitriol is the most active known form of vitamin D₃ in stimulating intestinal calcium transport. It is normally formed in the kidneys from its immediate precursor, 25-hydroxycholecalciferol. In physiological amounts it augments the intestinal absorption of calcium and phosphate and plays a significant part in the regulation of bone mineralisation. The defective production of calcitriol in chronic renal failure contributes to the abnormalities of mineral metabolism found in that disorder.

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

Rocaltrol is a synthetic preparation of calcitriol. Oral administration of Rocaltrol to patients with chronic renal failure compensates for impaired endogenous production of calcitriol which is decreased when the glomerular filtration rate falls below 30 ml/min. Consequently, intestinal malabsorption of calcium and phosphate and the resulting hypocalcaemia are improved, thereby reversing the signs and symptoms of bone disease.

In patients with established post-menopausal osteoporosis, Rocaltrol increases calcium absorption, elevates circulating levels of calcitriol and reduces vertebral fracture frequency.

The onset and reversal of the effects of Rocaltrol are more rapid than those of other compounds with vitamin D activity and adjustment of the dose can be achieved sooner and more precisely. The effects of inadvertent overdosage can also be reversed more readily.

5.2 Pharmacokinetic properties

Absorption

Calcitriol is rapidly absorbed from the intestine. Peak serum concentrations following a single oral dose of 0.25-1µg Rocaltrol in healthy subjects were found within 2-6 hours.

After a single oral dose of 0.5 mcg Rocaltrol in healthy subjects, the average serum concentrations of calcitriol rose from a baseline value of 40.0 ± 4.4 pg/ml to 60.0 ± 4.4 pg/ml after two hours, and then fell to 53.0 ± 6.9 after four hours, to 50.0 ± 7.0 after eight hours, to 44 ± 4.6 after twelve hours and to 41.5 ± 5.1 pg/ml after 24 hours.

Distribution

During transport in the blood at physiological concentrations, calcitriol is mostly bound to a specific vitamin D binding protein (DBP), but also, to a lesser degree, to lipoproteins and albumin. At higher blood calcitriol concentrations, DBP appears to become saturated, and increased binding to lipoproteins and albumin occurs.

Biotransformation

Calcitriol is hydroxylated and oxidised in the kidney and in the liver by a specific cytochrome P450 enzyme: CYP24A1.

Several metabolites with different degrees of vitamin D activity have been identified.

Elimination

The elimination half-life of calcitriol in plasma ranges between 5 to 8 hours. However, the pharmacological effect of a single dose of calcitriol lasts at least 4 days. The elimination and absorption kinetics of calcitriol remain linear in a very broad dose range and up to 165 µg single oral dose. Calcitriol is excreted in the bile and may undergo an enterohepatic circulation.

5.3 Preclinical safety data

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

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Content

Butylhydroxyanisole E320
Butylhydroxytoluene E321
Medium-chain triglycerides

Shell

Gelatin

Glycerol

Karion 83 (Sorbitol E420, Mannitol E421, Hydrogenated hydrolysed starch)

Titanium dioxide E171

Iron oxide red E172

Iron oxide yellow E172

6.2 Incompatibilities

None.

6.3 Shelf life

3 years.

6.4 Special precautions for storage

Do not store above 25°C. Store in the original package and keep the blisters in the outer carton in order to protect from light and moisture.

6.5 Nature and contents of container

PVC opaque blisters containing 100 capsules (5 strips of 20 capsules).

6.6 Special precautions for disposal

Not applicable.

7 MARKETING AUTHORISATION HOLDER

Bone Guardian Limited

55 Baker Street
London
W1U 7EU
United Kingdom

8 MARKETING AUTHORISATION NUMBER(S)

PL 60494/0001

**9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE
AUTHORISATION**

13 January 2003

10 DATE OF REVISION OF THE TEXT

09/05/2025