Rocaltrol®

ATNAHS

Calcitriol

1. DESCRIPTION

1.1 Therapeutic / Pharmacologic Class of Drug

Biologically active form of vitamin D_3.

ATC code: A11CC04.

1.2 Type of Dosage Form

Capsules containing 0.25 µg and 0.5 µg calcitriol.

1.3 Route of Administration

Orally.

1.4 Qualitative and Quantitative Composition

Active ingredient: synthetic calcitriol (biologically active form of vitamin D_3).

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

Capsules 0.25 µg and 0.5 µg.

Excipients:
Capsules: Butylhydroxyanisol, butylhydroxytoluene, medium-chain triglycerides, gelatin, glycerol 85%, hydrogenated products of partially hydrolyzed starch, titanium dioxide (E 171), red and yellow iron oxide (E 172).

2. CLINICAL PARTICULARS

2.1 Therapeutic Indication(s)

Established postmenopausal osteoporosis.

Renal osteodystrophy in patients with chronic renal failure, particularly those undergoing hemodialysis.

Postsurgical hypoparathyroidism.

Idiopathic hypoparathyroidism.

Pseudohypoparathyroidism.

Vitamin D-dependent rickets.

Hypophosphatemic vitamin D-resistant rickets.

2.2 Dosage and Administration

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 at the beginning of therapy. Calcium supplements may be necessary and should be administered according to local guidelines.

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.

Patient monitoring
During the stabilization 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 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.

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 µg lower than that previously used. An estimate of daily dietary calcium intake should be made and the intake adjusted when indicated.

2.2.1 Special Dosage Instructions

- **Postmenopausal osteoporosis:**

The recommended dosage for Rocaltrol is 0.25 µg twice daily.

Serum calcium and creatinine levels should be determined at 1, 3, and 6 months and at 6- month 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 2-4 weeks, the daily dosage may be increased by 0.25 µg at two to four-week intervals. During this period, serum calcium levels should be determined at least twice weekly. Most patients respond to dosages between 0.5 µg and 1.0 µg daily.

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

- **Hypoparathyroidism, 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. If hypercalcemia 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.

- **Elderly patients:**

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

- **Pediatric patients:**

The safety and efficacy of calcitriol capsules in children have not been sufficiently investigated to enable dosing recommendations.

2.3 Contraindications

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

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

2.4 Warnings and Precautions

2.4.1 General

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 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 Dosage and Administration* [2.2]).

Immobilized 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 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 and low phosphate diet.

The serum calcium times phosphate (Ca x P) product should not be allowed to exceed 70 mg^2 / dl^2.

Patients with vitamin D-resistant rickets (familial hypophosphatemia) 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 ergocalciferol (vitamin D_2) to calcitriol, it may take several months for the ergocalciferol level in the blood to return to the baseline value (*see Overdose* [2.7]).

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

2.4.2 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.

2.4.3 Laboratory Tests

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 twice weekly (*see Dosage and Administration* [2.2]).

2.4.4 Interactions 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 Warnings and Precautions* [2.4]).

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 hypermagnesemia 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 hypophosphatemia) 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 drugs are administered simultaneously.

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

2.5 Use in Special Populations

2.5.1 Pregnancy

Supravalvular aortic stenosis has been produced in fetuses 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 fetus.

2.5.2 Nursing Mothers

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.

2.5.3 Pediatric Use

See Special Dosage Instructions [2.2.1]

2.5.4 Geriatric Use

See Special Dosage Instructions [2.2.1]

2.5.5 Renal Impairment

See Special Dosage Instructions [2.2.1]

2.6 Undesirable Effects

2.6.1 Clinical Trials

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 (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥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
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 Administration* [2.2], and *Warnings and Precautions* [2.4]). Occasional acute symptoms include decreased appetite, anorexia, headache, nausea, vomiting, abdominal pain or abdominal pain upper and constipation.

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, i.e. much faster than in treatment with vitamin D_3 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 hypercalcemia and hyperphosphatemia of > 6 mg/100 ml or > 1.9 mmol/l, calcinosis may occur; this can be seen radiographically.

Hypersensitivity reactions (rash, erythema, pruritus and urticaria, may occur in susceptible individuals.

2.6.1.1 Laboratory Abnormalities

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

2.6.2 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.

2.7 Overdose

Treatment of asymptomatic hypercalcaemia: (*See Dosage and Administration* [2.2]) .

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 mg^2 / dl^2. 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 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.

3. PHARMACOLOGICAL PROPERTIES AND EFFECTS

3.1 Pharmacodynamic Properties

3.1.1 Mechanism of Action

Calcitriol is the most active known form of vitamin D_3 in stimulating intestinal calcium transport.

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. 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 hypocalcaemia 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. 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.

3.1.2 Clinical / Efficacy Studies

Calcitriol is one of the most important active metabolites of vitamin D_3. It is normally formed in the kidney from its precursor, 25-hydroxycholecalciferol (25-HCC). Physiological daily production is normally 0.5-1.0 µg and is somewhat higher during periods of increased bone synthesis (e.g. growth or pregnancy). Calcitriol promotes intestinal absorption of calcium and regulates bone mineralization. The pharmacological effect of a single dose of calcitriol lasts about 3-5 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 normalizes 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 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, e.g. in association with neonatal hepatitis, biliary atresia, cystinosis and dietary calcium and vitamin D deficiency, have also benefited from Rocaltrol therapy.

3.2 Pharmacokinetic Properties

3.2.1 Absorption

Peak plasma concentrations following a single oral dose of 0.25 – 1.0 µg Rocaltrol were reached within 2 – 6 hours.

3.2.2 Distribution

During transport in the blood, calcitriol and other vitamin D metabolites are bound to specific plasma proteins.

3.2.3 Metabolism

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

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

3.2.4 Elimination

The elimination half-life of calcitriol in plasma ranges between 5 to 8 hours.

The elimination and absorption kinetics of calcitriol remain linear in a very broad dose range up to 165 µg single oral dose.

The pharmacological effect of a single dose of calcitriol lasts at least 4 days. Calcitriol is excreted in the bile and may undergo an enterohepatic circulation.

3.2.5 Pharmacokinetics in Special Populations

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

3.3 Preclinical Safety

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.

3.3.1 Impairment of Fertility

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 fetuses showing abnormalities, the possibilities that these findings were due to calcitriol administration could not be discounted.

4. PHARMACEUTICAL PARTICULARS

4.1 Storage

Capsules in Blister: Do not store above 25 °C, store in the original package and keep blister in the outer carton, in order to protect from light and moisture.

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

4.2 Special Instructions for Use, Handling and Disposal

Keep out of reach and sight of children.

Disposal of unused/expired medicines
The release of pharmaceuticals in the environment should be minimized. 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.

4.3 Packs

Capsules (red and white) 0.25 µg	100
Capsules (red) 0.5 µg	100

Medicine: keep out of reach of children

Current at Mar2021

Capsules

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Made for Atnahs Pharma UK Limited, Basildon, United Kingdom
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