SCHEDULING STATUS

S4

PROPRIETARY NAME AND DOSAGE FORM

ROCALTROL® 0,25 µg (capsules)

ROCALTROL® 0,50 µg (capsules)

COMPOSITION

Each ROCALTROL® 0,25 µg capsule contains 0,25 µg calcitriol.

Each ROCALTROL® 0,50 µg capsule contains 0,50 µg calcitriol.

Excipients of capsule contents: butylhydroxyanisole, butylhydroxytoluene, medium-chain triglycerides.

Composition of capsule shell: gelatin, glycerol, sorbitol, mannitol, starch, titanium dioxide E171, red and yellow iron oxide E172.

PHARMACOLOGICAL CLASSIFICATION

A 22.1.4 Vitamin.

PHARMACOLOGICAL ACTION

Pharmacodynamic properties

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

The biological effects of calcitriol are mediated via the vitamin D receptor.

The two known sites of action of calcitriol are the intestine and bone, but additional evidence suggests that it also acts on the kidney and the parathyroid gland.

Pharmacokinetic properties

Absorption:

Peak plasma concentrations following a single oral dose of 0,25 to 1,0 µg of calcitriol were reached within 2 to 6 hours.

Metabolism:

Calcitriol is hydroxylated and oxidised in the kidney and in the liver by specific cytochrome P450 isoenzyme, 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. The elimination and absorption kinetics of calcitriol remain linear. Calcitriol is excreted in the bile and may undergo an enterohepatic circulation.

Pharmacokinetics in special clinical situations:

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

INDICATIONS

- As an adjunct treatment of established post-menopausal osteoporosis where hormones or bisphosphonates cannot be used.
- Renal bone disease (renal osteodystrophy) such as in chronic renal failure, especially on intermittent haemodialysis.
- Hypophosphataemic vitamin D resistant and pseudo vitamin D deficiency rickets and osteomalacia.
- Nutritional and malabsorptive rickets and osteomalacia.
- Hypoparathyroidism (idiopathic and post-surgical); pseudo-hypoparathyroidism

CONTRAINDICATIONS

Patients with hypercalcaemia or evidence of vitamin D intoxication.

Patients with known hypersensitivity to calcitriol (or medicines of the same class) or any of the excipients of ROCALTROL.

WARNINGS AND SPECIAL PRECAUTIONS

- The serum calcium times phosphate (Ca x P) product should not be allowed to exceed 5,6 $mmol^2/\ell^2$.
- Since ROCALTROL is the most potent metabolite of vitamin D available, vitamin D and its derivatives should be withheld during treatment, 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.
- Patients with normal renal function who are taking ROCALTROL should avoid dehydration. Adequate fluid intake should be maintained.
- Immobilised patients, e.g. those who have undergone surgery, are particularly exposed to the risk of hypercalcaemia.
- 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 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 (see SIDE EFFECTS). ROCALTROL should be stopped immediately when the serum calcium level exceeds the accepted normal upper limit or the serum creatinine exceeds the accepted normal upper limit for age. Treatment with ROCALTROL can be resumed as soon as normocalcaemia ensues.
- 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 soft tissue 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/litre) by the oral administration of appropriate phosphate-binding agents and a diet low in phosphate.The serum calcium times phosphate (Ca x P) product should not be allowed to exceed 5,6 $mmol^2/ℓ^2$.
- 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 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 DIRECTIONS FOR USE.

Effects on ability to drive and use machines

On the basis of the pharmacodynamics profile of reported adverse events, this product is presumed to be safe or unlikely to adversely affect such activities. Patients to determine effects before driving or using machines.

Contains sorbitol and may have a laxative effect.

Patients with a rare hereditary condition of sorbitol intolerance should not take ROCALTROL.

INTERACTIONS

- Diet: Dietary instructions, especially those concerning calcium supplements, should be strictly observed and uncontrolled intake of additional calcium containing preparations avoided.
- Thiazides: Concomitant treatment with a thiazide diuretic increases the risk of hypercalcaemia.
- Digitalis: Calcitriol dosage must be determined with care in patients undergoing treatment with digoxin, as hypercalcaemia in such patients may precipitate cardiac dysrhythmias.
- Other Vitamin D supplements: A relationship of functional antagonism exists between vitamin D analogues, which promote calcium absorption, and corticosteroids, which inhibit it.
- Antacids: 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 0,6 - 1,6 mmol/litre).
- 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 such as cholestyramine and sevelamer can reduce intestinal absorption of fat-soluble vitamins and may impair intestinal absorption of calcitriol.

PREGNANCY AND LACTATION

Pregnancy:

Vitamin D is teratogenic in animals. In a very limited number of pregnancies exposed to this formulation, there was no evidence of foetal abnormalities in humans. See DOSAGE AND DIRECTIONS FOR USE.

ROCALTROL should only be used in pregnant women with hypoparathyroidism when the expected therapeutic benefit clearly outweighs the possible adverse events and serum calcium levels can be carefully monitored. See DOSAGE AND DIRECTIONS FOR USE.

Lactation:

ROCALTROL may be excreted in human milk. A mother should not breastfeed whilst taking ROCALTROL.

DOSAGE AND DIRECTIONS FOR USE

Standard dosage

The optimal daily dosage of ROCALTROL must be carefully determined for each patient (adults as well as children) on the basis of 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.

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

Treatment with ROCALTROL should be stopped immediately as soon as the serum calcium level exceeds the accepted normal upper limit or the serum creatinine exceeds the accepted normal upper limit for age. Treatment should be stopped 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 of 0,25 µg lower than that previously used. An estimate of daily dietary calcium intake should be made and the intake adjusted when indicated. 24 hour urine calcium should be monitored (initially every month, then 6 monthly) since it will increase long before the serum calcium or renal function deteriorates.

Special dosage instructions

Post-menopausal osteoporosis

The recommended ROCALTROL dosage is 0,25 µg twice daily. The response should be monitored with annual bone mineral densitometry measurements. Guard against hypercalciuria.

Serum calcium and creatinine levels and 24 hour urine calcium should be determined at 4 weeks, 3 and 6 months and at 6 monthly intervals thereafter. Discontinuation of supplemental calcium may be useful in rapidly re-establishing normocalcaemia.

Renal osteodystrophy (dialysis patients)

The initial daily dose is 0,25 µg. Patients with normal or slightly reduced serum calcium levels may respond to ROCALTROL in doses of 0,25 µg every other day. If satisfactory response in the biochemical parameters and clinical manifestations of the disease state is not observed within 2 - 4 weeks, the daily dosage may be increased by 0,25 µg at two to four week intervals. During this titration period, serum calcium levels should be determined at least twice weekly and if hypercalcaemia is noted, ROCALTROL should be immediately discontinued or the dosage substantially reduced until normocalcaemia ensues. Most patients respond to dosages between 0,5 µg and 1,0 µg daily.

Indices of response for renal osteodystrophy and hyperparathyroidism include levels of plasma calcium, alkaline phosphatase, parathyroid hormone, urinary calcium excretion as well as radiographic and histological investigations.

Intermittent (pulse) therapy

Oral intermittent (pulse) therapy with ROCALTROL two or three times weekly has been shown to be effective, even in patients refractory to continuous therapy. Serum calcium levels should be monitored to prevent hypercalcaemia. A maximum cumulative dosage of 12 µg per week should not be exceeded.

Hypoparathyroidism, rickets

The recommended initial dose of ROCALTROL is 0,25 µg per 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 necessary.

If the medical practitioner decides to prescribe ROCALTROL to a pregnant woman with hypoparathyroidism, an increased dose may be required during the latter half of the gestation, with dose reduction post-partum or during lactation.

Patients with marked bone disease (other than those with renal failure) may tolerate a higher dose without developing hypercalcaemia. However, failure of the plasma calcium to rise promptly in osteomalacic patients does not necessarily mean that a higher dose is required, since calcium from increased intestinal calcium absorption may be incorporated into demineralised bone. The dose requirements generally decrease in bone disorders at a time when there is biochemical or radiographic evidence of bone healing.

Elderly patients

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

Paediatric patients

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

SIDE-EFFECTS

Clinical Trials

The adverse reactions (ADR) listed below reflect the experience from investigational studies of ROCALTROL. 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®

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				Soft tissue calcification, Pyrexia, Thirst
Investigations			Increased blood creatinine	Decreased weight

Adverse effects may occur which are similar to those due to excessive dose of vitamin D, i.e. hypercalcaemia syndrome or calcium intoxication (depending on the severity and duration of hypercalcaemia). See DOSAGE AND DIRECTIONS FOR USE and WARNINGS AND SPECIAL PRECAUTIONS. 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 D_3 preparations.

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

In concurrent hypercalcaemia and hyperphosphatemia of > 6 mg/100 mℓ or > 1,9 mmol/ℓ, soft tissue calcification may occur; this can be seen radiographically.

Hypersensitivity reactions including rash, erythema, pruritus, and urticarial may occur in susceptible individuals.

Laboratory Abnormalities

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

KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENT

The initial signs and symptoms of vitamin D intoxication associated with hypercalcaemia include weakness, fatigue, somnolence, headache, anorexia, nausea, vomiting, diarrhoea and pruritus.

Appropriate symptomatic and supportive treatment includes fluids to prevent renal stone damage.

IDENTIFICATION

ROCALTROL® 0,25 µg: Soft gelatin capsules: One half brown-orange to red-orange, opaque and the other half white to grey-yellow or grey-orange, opaque.

ROCALTROL® 0,50 µg: Soft gelatin capsules: Brown-orange to red-orange, opaque.

PRESENTATION

ROCALTROL® 0,25 µg: Blister packs or amber glass bottles containing 30 or 60 capsules

ROCALTROL® 0,50 µg: Blister packs or amber glass bottles containing 30 or 60 capsules

STORAGE INSTRUCTIONS

Store at or below 25 °C. Protect from light and moisture.

Medicine: Keep out of reach of children.

Do not use this medicine after the expiry date printed on the packaging.

REGISTRATION NUMBER

ROCALTROL® 0,25 µg: M/22.1.4/84

ROCALTROL® 0,50 µg: M/22.1.4/85

NAME AND BUSINESS ADDRESS OF THE HOLDER OF THE CERTIFICATE OF REGISTRATION

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