

# Summary of Product Characteristics

## 1 NAME OF THE MEDICINAL PRODUCT

Rocaltrol 0.25 microgram Soft Capsules

## 2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each capsule contains 0.25 microgram of calcitriol.

Excipient(s) with known effect: 4.37 mg sorbitol

For a full list of excipients, see section 6.1.

## 3 PHARMACEUTICAL FORM

Capsule, soft

One length brown-orange to red-orange opaque and the other white to grey-yellow or grey-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

#### 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/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. Most patients respond to between 0.5 mcg and 1.0 mcg daily. See section 4.5 for details of dose adjustments.

An oral Rocaltrol pulse therapy with an initial dosage of 0.1 mcg/kg/week split into two or three equal doses given at night 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.

##### *Older people*

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 Rocaltrol in children have not yet been established. No data are available.

**Method of administration**

Rocaltrol capsules are for oral administration only.

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.

**4.3 Contraindications**

Rocaltrol is contraindicated:

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

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/100ml, 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).

Immobolised 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/100ml 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<sup>2</sup>/dl<sup>2</sup>.

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. 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.

If the patient is switched from ergocalciferol (vitamin D<sub>2</sub>) to calcitriol, it may take several months for the ergocalciferol level in the blood to return to the baseline value (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. Patients with rare hereditary problems of fructose intolerance should not take Rocaltrol capsules.

Patients being treated with Rocaltrol should be under regular surveillance and those being treated for renal osteodystrophy should be under the supervision of a specialist having at their disposal facilities to monitor the appropriate biochemical parameter.

#### **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

Animal studies are insufficient with respect to reproductive toxicity (see section 5.3). Rocaltrol should not be used during pregnancy unless the clinical condition of the woman requires treatment with calcitriol.

##### 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**

Rocaltrol has no or negligible influence on the ability to drive and use machines.

## 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.

Tabulated list of adverse reactions:

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<sup>®</sup> (calcitriol)**

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

Description of selected adverse reactions:

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

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<sub>3</sub> 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 via HPRA Pharmacovigilance, Earlsfort Terrace, IRL - Dublin 2; Tel: +353 1 6764971; Fax: +353 1 6762517.

Website: [www.hpra.ie](http://www.hpra.ie); E-mail: [medsafety@hpra.ie](mailto:medsafety@hpra.ie).

## **4.9 Overdose**

### **Symptoms**

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<sup>2</sup>/dl<sup>2</sup>. 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.

### **Management**

Treatment of asymptomatic hypercalcaemia (see section 4.2.)

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, 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

#### Mechanism of action

Calcitriol is the most active form of vitamin D<sub>3</sub> in stimulating intestinal calcium transport. It is normally formed in the kidneys from its immediate precursor, 25-hydroxycholecalciferol.

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.

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 uraemic rats calcitriol has been shown to stimulate intestinal calcium absorption.

In physiological amounts, calcitriol augments the intestinal absorption of calcium and phosphate and plays a significant part in the regulation of bone mineralisation.

The kidneys of uraemic patients cannot adequately produce 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.

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*

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

#### *Distribution*

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

*Biotransformation* 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.

***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.

***Renal impairment***

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

**5.3 Preclinical safety data**

Adverse reactions not observed in clinical studies, but seen in animals at exposure levels similar to clinical exposure levels and with possible relevance to clinical use were as follows: 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.

Effects in non-clinical studies were observed only at exposures considered sufficiently in excess of the maximum human exposure indicating little relevance to clinical use. 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**Capsule Contents

Butylhydroxyanisole (E320)  
Butyl hydroxytoluene (E321)  
Medium-chain triglycerides

Capsule Shell

Gelatin  
Glycerol  
Karion 83 (Sorbitol, Mannitol, Hydrogenated hydrolysed starch)  
Titanium dioxide (E171)  
Iron oxide red (E172)  
Iron oxide yellow (E172)

**6.2 Incompatibilities**

Not applicable.

### **6.3 Shelf life**

3 years.

### **6.4 Special precautions for storage**

Do not store above 25°C. Store in the original package 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 and other handling**

No special requirements.

## **7 MARKETING AUTHORISATION HOLDER**

Roche Products Limited  
6 Falcon Way  
Shire Park  
Welwyn Garden City  
AL7 1TW  
United Kingdom

## **8 MARKETING AUTHORISATION NUMBER**

PA0050/047/001

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

Date of first authorisation: 18 February 1980

Date of last renewal: 17 February 2010

## **10 DATE OF REVISION OF THE TEXT**

July 2015