IRISH MEDICINES BOARD ACT 1995

MEDICINAL PRODUCTS(LICENSING AND SALE)REGULATIONS, 1998

(S.I. No.142 of 1998)

PA0050/047/002
Case No: 2033493

The Irish Medicines Board in exercise of the powers conferred on it by the above mentioned Regulations hereby grants to

Roche Products Ltd

6 Falcon Way, Shire Park, **Welwyn Garden City**, **AL7 1TW**, **United Kingdom**

an authorisation, subject to the provisions of the said Regulations, in respect of the product

Rocaltrol 0.5 microgram capsules

The particulars of which are set out in Part I and Part II of the attached Schedule. The authorisation is also subject to the general conditions as may be specified in the said Regulations as listed on the reverse of this document.

This authorisation, unless previously revoked, shall continue in force from **16/02/2007** until **17/02/2010**.

Signed on behalf of the Irish Medicines Board this

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A person authorised in that behalf by the said Board.

Part II

Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Rocaltrol 0.5 microgram capsules

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each capsule contains 0.5 micrograms of calcitriol.

For excipients, see 6.1.

3 PHARMACEUTICAL FORM

Capsule, soft
Both lengths brown-red to orange-grey 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.

Adults
Renal Osteodystrophy
The initial daily dose is 0.25mcg of Rocaltrol. In patients with normal or only slightly reduced calcium levels, doses of 0.25mcg 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 0.25mcg 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 1mg/100ml (250 micromol/l) above normal (9 to 11mg/100ml or 2250 – 2750 micromol/l), or serum creatinine rises to > 120 micromol/l, treatment with Rocaltrol should be stopped immediately until normocalcaemia ensues. Most patients respond to between 0.5mcg and 1.0mcg daily. See section 4.5 for details of dose adjustments.

An oral Rocaltrol pulse therapy with an initial dosage of 0.1mcg/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 12mcg per week should not be exceeded.

Post-menopausal Osteoporosis

The recommended dose of Rocaltrol is 0.25mcg twice daily.

Serum calcium and creatinine levels should be determined at 1, 3 and 6 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.

Children
Dosage in children has not been established.

Rocaltrol capsules are for oral administration only.

4.3 Contraindications

Rocaltrol should not be given to patients with hypercalcaemia or evidence of metastatic calcification. The use of Rocaltrol in patients with known hypersensitivity to calcitriol (or drugs of the same class) and any of the constituent excipients is contra-indicated.

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

4.4 Special warnings and precautions for use

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_2) to calcitriol, it may take several months for the ergocalciferol level in the blood to return to baseline value.

An abrupt increase in calcium intake as a result of changes in diet (e.g. increased consumption of diary products) or uncontrolled intake of calcium preparations may trigger hypercalcaemia. Patients and families should be advised that strict adherence to prescribed diets is mandatory and they should be instructed on how to recognise the symptoms of hypercalcaemia.

Treatment does not obviate the need to control plasma phosphate with phosphate-binding agents. Since Rocaltrol affects phosphate transport in the gut and bone, the dose of phosphate-binding agent may need to be modified. The value for serum calcium multiplied by phosphate (Ca x P) should not be allowed to exceed $70mg^2/dl^2$.

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

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

Owing to the presence of sorbitol, patients with rare hereditary problems of fructose intolerance should not take this medicine.

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

Concomitant treatment with a thiazide diuretic increased 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.

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.

Administration of enzyme inducers such as phenytoin or Phenobarbital may lead to increased metabolism and hence reduced serum concentrations of calcitrol. Therefore higher doses of calcitriol may be necessary if these drugs are administered simultaneously.

A relationship of functional antagonism exists between vitamin D analogues, which promote calcium absorption, and corticosteroids, which inhibit it.

Colestyramine can reduce intestinal absorption of fat-soluble vitamins and therefore may impair intestinal absorption of calcitriol.

4.6 Pregnancy and lactation

The safety of Rocaltrol during pregnancy has not been established and it should be given only when the potential benefit has been weighed against the possible hazard. The usual caution in prescribing any drug for women of childbearing age should be observed.

It should be assumed that exogenous calcitriol passes into breast milk. 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

Not relevant.

4.8 Undesirable effects

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 rarely (≤ 0.001%).

Hypercalcaemia and hypercalciuria are the major side effects of Rocaltrol and indicate excessive dosage. Patients with tertiary hyperparathyroidism, renal failure, or on regular haemodialysis are particularly prone to develop hypercalcaemia. The clinical features of hypercalcaemia include anorexia, constipation, nausea, vomiting, headache, weakness, apathy and somnolence. Chronic manifestations may include fever, thirst/polydipsia, dehydration, polyuria, nocturia, abdominal pain, paralytic ileus, cardiac arrhythmias dystrophy, arrested growth, sensory disturbances and urinary tract infections. Rarely, overt psychosis and metastatic calcification may occur. The relatively short biological half-life of Rocaltrol permits rapid elimination of the compound when treatment is stopped and hypercalcaemia will recede within 2 - 7 days. This rate of reversal of biological effects is more rapid than when other vitamin D derivatives are used.

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

Mild, non-progressive and reversible elevations in levels of liver enzymes (SGOT, SGPT) have been noted in a few patients treated with Rocaltrol, but no pathological changes in the liver have been reported.

Hypersensitivity reactions (pruritus, rash, urticaria and, very rarely, severe erythematous skin disorders) may occur in susceptible individuals.

4.9 Overdose

In acute overdosage gastric lavage or induction of vomiting should be considered as soon after ingestion as possible provided that the drug was taken within the previous 6-8 hours. Liquid paraffin may be administered to promote faecal excretion.

The value for serum calcium multiplied by phosphate (Ca ×P) should not be allowed to exceed 70 mg^2/dl^2. Repeated serum calcium determinations are advisable.

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. Severe or persistent hypercalcaemia may be treated by administering phosphates and corticosteroids, ensuring adequate hydration, inducing a diuresis where practicable and by general supportive measures. Calcitonin may increase the rate of fall of serum calcium when bone resorption is increased.

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

Calcitriol has the greatest biological activity of the known vitamin D metabolites and 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.

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 30ml/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 0.25-1.0 mcg Rocaltrol were found within 3-6 hours.

Following multiple administration, serum calcitriol levels reached a steady state within 7 days, with a relationship to the dose of calcitriol administration.

Distribution

After a single oral dose of 0.5mcg Rocaltrol, the average serum concentrations of calcitriol rose from

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. 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 the foetal bloodstream and breast milk.

Metabolism

Several metabolites of calcitriol, each exerting different vitamin D activities have been identified: 1α, 25-dihydroxy-24-oxo-cholecalciferol, 1α, 23, 25-trihydroxy-24-oxo-cholecalciferol, 1α,24R,25-trihydroxycholecalciferol, 1α,25R-dihydroxycholecalciferol-26,23S-lactone, 1α,25S,26-trihydroxycholecalciferol, 1α,25-dihydroxy-23-oxo-cholecalciferol, and 1α-hydroxy-23-carboxy-24,25,26,27-tetranorcholecalciferol.

Elimination

The elimination half-life of calcitriol in serum is 9-10 hours. However, the pharmacological effect of a single dose of calcitriol lasts at least 4 days. Calcitriol is excreted in the bile and is subject to enterohepatic circulation.

After i.v. administration of radioactive calcitriol in healthy subjects, about 27% of the radioactivity is found in the faeces and about 7% in the urine within 24 hours.

After oral administration of 1 mcg radioactive calcitriol in healthy subjects, about 10% of the entire radioactivity was found in the urine with 24 hours. On the sixth day after i.v. administration of radioactive calcitriol, urine and faeces accounted for an average of 16% and 49% respectively of the cumulative excretion of radioactivity.

5.3 Preclinical safety data

Acute toxicity studies in mice and rats indicated that the oral approximate median lethal dose of calcitriol ranged from 1.35 to 3.9mg/kg. These values are several orders of magnitude higher than the proposed clinical dose of 0.25mcg twice daily (approximately 8 - 10ng/kg/day).

Subchronic toxicity studies in rats and dogs indicated that calcitriol at an oral dose of 20ng/kg/day (twice the usual human dosage) for up to 6 months produced no or minimal adverse effects. A dose of 80ng/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 300ng/kg/day (30 times the usual human dose) did not adversely affect reproduction. In rabbits, calcitriol produced some maternal and fetotoxic effects at an oral dose of 300ng/kg/day, but did not show any adverse effect at 20 or 80ng/kg/day (8 times the usual human dose).

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Capsule Contents
Butylated hydroxyanisole (E320)
Butylated hydroxytoluene (E321)
Triglycerides, medium chain

Capsule Shell

Gelatin
Glycerol
Karion 83 (Sorbitol, Mannitol, Hydrogenated hydrolysed starch)
Titanium dioxide (E171)
Canthaxanthin (E161)

6.2 Incompatibilities

Not applicable.

6.3 Shelf Life

3 years.

6.4 Special precautions for storage

Glass bottles:	Do not store above 30ºC.
Blisters:	Do not store above 25ºC. Store in the original package.

6.5 Nature and contents of container

Amber glass bottles with plastic screw caps containing 100 capsules and PVC opaque blister containing 100 capsules (5 strips of capsules).

Due to the use of a natural colouring agent, discolouration of the capsule may occur. This does not affect the quality of the medicine.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal of a used medicinal product or waste materials derived from such medicinal product and other handling of the product

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

PA 50/47/2

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 18 February 1980

Date of last renewal: 18 February 2005

10 DATE OF REVISION OF THE TEXT

February 2007