AUSTRALIAN PRODUCT INFORMATION
Rocaltrol (calcitriol)

1. NAME OF THE MEDICINE
Calcitriol

2. QUALITATIVE AND QUANTITATIVE COMPOSITION
Rocaltrol 0.25 microgram capsules containing 0.25micrograms of calcitriol.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM
Soft capsules

Capsules are opaque, coloured half brown-orange to red-orange and half white to grey-yellow/grey-orange.

4. CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS
Rocaltrol is indicated for the treatment of established osteoporosis diagnosed by objective measuring techniques, such as densitometry, or by radiographic evidence of a traumatic fracture.

Rocaltrol is also indicated for the prevention of corticosteroid-induced osteoporosis in patients commencing oral steroid therapy in a dose and regimen expected to result in a significant bone loss.

Rocaltrol is indicated in the treatment of hypocalcaemia in patients with uraemic osteodystrophy, hypoparathyroidism and in hypophosphataemic rickets.

4.2 DOSE AND METHOD OF ADMINISTRATION

Dose
The optimal daily dose of Rocaltrol must be carefully determined for each patient and indication. Dosage optimisation should be accompanied by regular monitoring of serum calcium concentration.

When the optimal dosage of Rocaltrol has been determined, the serum calcium levels should be checked regularly. As soon as serum calcium nears hypercalcaemic levels (1 mg per 100 ml [0.25 mmol/L] above normal 9-11 mg per 100 ml [2.25-2.75 mmol/L] on average), the dosage of Rocaltrol should be substantially reduced or treatment stopped altogether until normocalcaemia ensues. If hypercalcaemia occurs, the drug should be immediately discontinued until normocalcaemia ensues. Withdrawal of additional doses of calcium can also be of benefit in bringing about rapid normalisation of serum calcium levels. Careful consideration should also be given to lowering the dietary calcium intake.

Should hypercalcaemia occur, Rocaltrol should be suspended immediately and 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 microgram lower than that previously used.

Adults

Osteoporosis

Established Osteoporosis

The recommended dose of Rocaltrol is 0.25 microgram twice daily. If a satisfactory response is not obtained with this dose, it may be increased, with regular serum calcium monitoring, to a maximum of 0.5 microgram twice daily. This increased dose should rarely be necessary.

Corticosteroid-Induced Osteoporosis

The recommended dose is 0.25 microgram twice daily for steroid doses equivalent to < 10 mg/day of oral prednisone increasing to 0.75 microgram/day for steroid doses > 10 mg/day oral prednisone.

Dietary calcium intake should not exceed 1000 mg/day (see section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE).

Other Indications

Uraemic osteodystrophy:

The recommended initial dose of Rocaltrol is 0.25 microgram/day. If a satisfactory response in the biochemical parameters and clinical manifestations of the disease state is not observed, dosage may be increased by 0.25 microgram/day at intervals of two to four weeks. Patients with normal or only slightly reduced serum calcium levels may respond to Rocaltrol doses of 0.25 microgram every other day. Most patients undergoing haemodialysis respond to dosages between 0.5 and 1 microgram daily.

Hypoparathyroidism and rickets:

The recommended initial dose of Rocaltrol is 0.25 microgram per day given in the morning. If a satisfactory response in the biochemical parameters and clinical manifestations of the disease are not observed, the dose may be increased at intervals of two to four weeks.

Malabsorption is occasionally noted in patients with hypoparathyroidism, therefore larger doses of Rocaltrol may be needed.

Laboratory Monitoring

For safety reasons, it is essential that regular monitoring of serum calcium concentration be performed during therapy with Rocaltrol. Blood samples should be taken without a tourniquet where possible to minimise local calcium effects.

Osteoporosis, including corticosteroid-induced osteoporosis

Patients should be monitored at the commencement of therapy, at 2 to 4 weeks, and thereafter at 2 to 3 monthly intervals.

Hypocalcaemia/Uraemic Osteodystrophy/Hypoparathyroidism/Hypophosphataemic Rickets

Serum calcium, phosphorus, magnesium and alkaline phosphatase and 24-hour urinary calcium and phosphorus should be determined periodically. During the initial phase of the medication, serum calcium should be determined at least twice weekly. Subsequently, monitoring should also be undertaken at 2 to 4 weeks and at 2 to 3 monthly intervals thereafter.

Special populations

Paediatric populations

The safety and efficacy of Rocaltrol capsules in children have not been sufficiently investigated to enable dosing recommendations (see section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE).

Geriatric populations

No dosage adjustment is necessary in elderly patients. (see section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE).

Information for the Patient

It is recommended that patients receive instruction in dietary management and that they be warned of the consequences and implications of not adhering strictly to the diet recommendations in relation to intake of calcium and vitamin D (see section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE). Patients should also be informed of the symptoms of hypercalcaemia, which include weakness, nausea and vomiting.

4.3 CONTRAINDICATIONS

Hypercalcaemia or Vitamin D toxicity.

Hypersensitivity to calcitriol or drugs of the same class, or any of the excipients in Rocaltrol.

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Concomitant therapy with other vitamin D compounds

Since Rocaltrol is the most potent metabolite of vitamin D available, other vitamin D compounds should be withheld during treatment in order to avoid the development of hypervitaminosis D.

If patients are "changed over" from ergocalciferol to calcitriol it may take many months for blood levels of ergocalciferol to return to pre-treatment values. Overdosage of any form of vitamin D is dangerous (see section 4.9 OVERDOSE). Chronic hypercalcaemia can lead to generalised vascular calcification, nephrocalcinosis and other soft-tissue calcification.

Hypercalcaemia

A strong relationship exists between calcitriol therapy and the development of hypercalcaemia. In some trials in uraemic osteodystrophy, up to 40% of patients receiving calcitriol treatment became hypercalcaemic.

Sudden increases in calcium consumption due to dietary change (e.g. dairy products) or injudicious calcium supplements may precipitate hypercalcaemia. Patients and relatives should receive instruction in dietary management, be informed about the symptoms of hypercalcaemia, and be warned of the consequences of not adhering to dietary recommendations. Although an adequate dietary intake of calcium is important in patients with postmenopausal osteoporosis, calcitriol does increase calcium absorption in these patients and calcium supplements may lead to hypercalcaemia and are not recommended unless the dietary intake is clearly inadequate (see section 4.2 DOSE AND METHOS OF ADMINISTRATION, and section 4.8 ADVERSE EFFECTS (UNDESRIABLE EFFECTS)).

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

Serum phosphate levels
Calcitriol raises serum inorganic phosphate levels. While this is a desirable effect in patients with hypophosphataemic states, caution must be taken in patients with renal failure. (see section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE).

Hypophosphataemic Rickets
Patients with hypophosphataemic rickets (familial hypophosphataemia) should pursue their oral phosphate therapy. However, the possible stimulation of intestinal phosphate absorption may modify the requirement for phosphate supplements. During the stabilisation phase of treatment with Rocaltrol, serum calcium levels should be checked at least twice weekly (see section 4.2 DOSE AND METHOD OF ADMINISTRATION).

Ectopic calcification
Calcitriol may increase plasma phosphate levels. While this effect is desirable in hypophosphataemic osteomalacia, it may cause ectopic calcification, especially in patients with renal failure. Plasma phosphate levels should be kept normal in such patients by the oral administration of phosphate binding agents.

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

Immobilisation
Patients immobilised after surgical procedures are more at risk of developing hypercalcaemia, therefore more frequent monitoring is recommended.

Use in renal impairment
Special care should be taken when administering Rocaltrol to patients with renal dysfunction. More frequent monitoring in these patients is appropriate (see section 4.2 DOSE AND METHOD OF ADMINISTRATION).

Paediatric use
Paediatric patients on long-term treatment with calcitriol are at risk of development of nephrocalcinosis. The younger the age at the commencement of therapy, and the higher the dose of calcitriol needed, the greater the risk. The drug should be used only if the benefits clearly outweigh the risks.

Use in the elderly
It is advised that in elderly patients suffering from ischaemic heart disease, serum calcium levels should be carefully monitored. If hypercalcaemia is observed, calcitriol therapy should be suspended immediately. It should also be remembered that geriatric patients receive many other drugs and that their compliance may not be ideal.

Effects on laboratory tests
Rocaltrol affects serum calcium levels and serum phosphate levels (see section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE and section 4.2 DOSE AND METHOD OF ADMINISTRATION). It is essential that regular monitoring of serum calcium concentration be performed during therapy with Rocaltrol.

4.5 INTERACTION WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTION

In patients being treated for osteoporosis, calcium-containing preparations should be avoided unless required for specific dietary purposes.

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

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

Magnesium containing antacids and Rocaltrol should not be used concomitantly, because such use may lead to the development of hypermagnesaemia.

Rocaltrol should be given cautiously to patients on digitalis because hypercalcaemia in such patients may precipitate cardiac arrhythmias.

The concomitant use of thiazide diuretics may precipitate hypercalcaemia.

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 concentration (normal value: 0.6 - 1.6 mmol/L).

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.

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on Fertility

No data available.

Use in Pregnancy - Category B3.

There are no adequate and well-controlled studies in pregnant women. Calcitriol has been found to be teratogenic in rabbits when given at doses of 0.08 and 0.3 micrograms/kg (approximately 1 and 5 times the maximum recommended dose based on mg/m^2). All 15 fetuses in 3 litters at these doses showed external and skeletal abnormalities. However, none of the other 23 litters (156 fetuses) showed external and skeletal abnormalities compared to controls. Teratogenicity studies in rats up to 0.3 micrograms/kg (approximately twice the maximum recommended dose based on mg/m^2) showed no evidence of teratogenic potential.

Calcitriol should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Use in Lactation

It should be assumed that exogenous calcitriol passes into the breast milk. In view of the possible adverse effects on the infant, mothers should not breast-feed while taking Rocaltrol.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

The effects of this medicine on a person's ability to drive and use machines were not assessed as part of its registration.

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

Clinical Trials

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

The most commonly reported adverse reaction was hypercalcaemia. Patients may also experience hypercalciuria.

The adverse effects 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 Adverse Effects 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	Dehydration, Polydipsia
Psychiatric Disorders				Apathy
Nervous System Disorders		Headache		Muscular weakness, Sensory disturbance, Drowsiness
Gastrointestinal Disorders		Abdominal pain, Nausea	Vomiting	Constipation, Abdominal pain upper, Diarrhoea
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 Rocaltrol exerts vitamin D activity in the body, adverse effects are, in general, similar to those encountered with excessive vitamin D intake.

Hypercalcaemia related to mechanism of action is the most important side effect and is manageable by dose modification. Hypercalcaemia has been demonstrated not to be an issue for Rocaltrol in the treatment of postmenopausal osteoporosis at the recommended dosage of 0.25 microgram twice daily. However, some women may require dose reductions (see section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE and section 4.2 DOSE AND METHOD OF ADMINISTRATION).

Acute hypercalcaemia may give rise to cardiac arrhythmia and/or arrest.

Signs and symptoms of vitamin D intoxication associated with hypercalcaemia include -

Acute: decreased appetite, weakness, headache, somnolence, nausea, vomiting, dry mouth, constipation, abdominal pain or abdominal pain upper, muscle pain, bone pain and metallic taste.

Chronic: muscular weakness, weight decreased, sensory disturbances, pyrexia, thirst, polydypsia, polyuria, , dehydration, apathy, growth retardation, nocturia, conjunctivitis (calcific), pancreatitis, photophobia, rhinorrhoea, hyperthermia, decreased libido, elevated BUN, albuminuria, hypercholesterolaemia, elevated AST and ALT, ectopic calcification, hypertension, cardiac arrhythmias, urinary tract infections and, rarely, overt psychosis.

Prolonged chronic hypercalcaemia or concurrent hypercalcaemia and hyperphosphataemia of > 1.9 mmol/L, calcinosis may occur; this can be seen radiographically.

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

Laboratory Abnormalities

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

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after registration 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 at www.tga.gov.au/reporting-problems.

4.9 OVERDOSE

Since calcitriol is a derivative of vitamin D, the symptoms of overdose are the same as for an overdose of vitamin D. Administration of Rocaltrol to patients in excess of their daily requirements can cause hypercalcaemia, hypercalciuria and hyperphosphataemia. High intake of calcium and phosphate concomitant with Rocaltrol may lead to similar symptoms. The serum calcium times phosphate (Ca x P) product should not be allowed to exceed 70 mg^2/dL^2. In patients with uraemic osteodystrophy, high levels of calcium in the dialysate may contribute to the development of hypercalcaemia.

Symptoms

Acute symptoms of vitamin D intoxication include anorexia, headache, vomiting and constipation.

Chronic symptoms include 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.

Treatment

Accidental Overdosage

The treatment of acute accidental overdosage of Rocaltrol should consist of general supportive measures. Serial serum electrolyte determinations (especially calcium), rate of urinary calcium excretion and assessment of electrocardiographic abnormalities due to hypercalcaemia should be obtained. Such monitoring is critical in patients receiving digitalis.

Discontinuation of supplemental calcium and a low calcium diet are also indicated in accidental overdosage.

Due to the relatively short duration of the pharmacological action of calcitriol, further measures are probably unnecessary. However, should persistent and markedly elevated serum levels occur, there are a variety of therapeutic alternatives that may be considered, depending on the patient's underlying condition. These include the use of drugs such as phosphates and corticosteroids as well as measures to induce an appropriate forced diuresis. The use of peritoneal dialysis against a calcium-free dialysate has also been reported.

Hypercalcaemia and Overdosage

General treatment of hypercalcaemia (greater than 1 mg/100 mL [0.25 mmol/L] above the upper limit of the normal range) consists of immediate discontinuation of Rocaltrol therapy, institution of a low calcium diet and withdrawal of calcium supplements. Serum calcium levels should be determined daily until normocalcaemia ensues. Hypercalcaemia frequently resolves in two to seven days. When serum calcium levels have returned to within normal limits, Rocaltrol therapy may be reinstituted at a dose of 0.25 microgram/day less than prior therapy. Serum calcium levels should be obtained at least twice weekly after all dosage changes and subsequent dosage titration. Persistent or markedly elevated serum calcium levels in dialysis patients may be corrected by dialysis against a calcium-free dialysate.

For information on the management of overdose, contact the Poisons Information Centre on 13 11 26 (Australia).

5. PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Pharmacotherapeutic group: Vitamin D and analogues, ATC code: A11CC04

Mechanism of Action

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.

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 - 1.0μg and is somewhat higher during periods of increased bone synthesis (e.g. growth or pregnancy).

The natural supply of vitamin D in humans depends mainly on exposure to ultraviolet rays of the sun for conversion of 7-dehydrocholesterol in the skin to vitamin D_3 (cholecalciferol). Vitamin

D_3 must be metabolically activated in the liver and the kidney before it is fully active as a regulator of calcium and phosphorus metabolism at target tissues. The initial transformation of vitamin D_3 is catalysed by a vitamin D_3-25-hydroxylase enzyme (25-OHase) present in the liver, and the product of this reaction is 25-hydroxyvitamin D_3 [25-(OH) D_3]. Hydroxylation of 25-(OH) D_3 occurs in the mitochondria of kidney tissue, activated by the renal 25-hydroxyvitamin D_3-1 alpha-hydroxylase (alpha-OHase), to produce 1,25-(OH)2 D_3 (calcitriol), the active form of vitamin D_3.

Calcitriol binds to an intracellular receptor, a member of the steroid receptor superfamily. The calcitriol-receptor complex interacts with specific DNA sequences that regulate transcription and protein synthesis in a variety of cells including osteoblasts, mucosal cells of the intestine, renal tubular cells and parathyroid cells. The changes in protein synthesis induced in these cells by calcitriol are responsible for its profound physiological effects. A vitamin D-resistant state exists in uraemic patients because of the failure of the kidney to convert precursors to the active compound. The uraemic state may also inhibit the binding of the calcitriol receptor to its specific DNA responsive elements.

The key role of calcitriol in the regulation of bone and calcium homeostasis, which includes stimulating effects on osteoblastic activity in the skeleton, provides a sound pharmacological basis for its therapeutic effects in osteoporosis. Treatment of established osteoporosis with calcitriol is associated with an increase in bone density and a reduction in new vertebral fractures. Established osteoporosis is defined as the finding of: bone mineral density measurements of 2 or more standard deviations below the gender specific peak bone mass; or the presence or history of osteoporotic fracture. Calcitriol also reduces bone loss associated with corticosteroid therapy.

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, administration of calcitriol normalises reduced intestinal absorption of calcium, hypocalcaemia, increased serum alkaline phosphatase and serum parathyroid hormone concentration.

In patients with hypophosphataemic rickets and hypophosphataemia, treatment with calcitriol reduces tubular elimination of phosphates and, in conjunction with concurrent phosphate treatment, corrects some skeletal abnormalities.

Clinical trials

Females with osteoporosis

The pathophysiology of osteoporosis is essentially the same in females and males. There are few data on the safety and efficacy of Rocaltrol on fracture rates and bone mineral density in premenopausal women.

Post-menopausal osteoporosis

Calcitriol versus calcium

The pivotal evidence for the efficacy of Rocaltrol in post-menopausal osteoporosis is provided by a three year, open label multicentre randomised comparison of calcitriol versus calcium in 432 patients (calcitriol n = 213, calcium n = 219). Vertebral fracture rate was assessed by X-ray evidence. Treatment with calcitriol 0.25 microgram twice daily for three years resulted in a three-fold reduction in the rate of new vertebral fractures in women with post-menopausal osteoporosis compared with calcium supplementation of 1000 mg daily. There was a reduction in the number of patients with new fractures, the number of new

fractures per se and the fracture rate expressed as fractures per 100 patient years in the calcitriol group when compared to the calcium group. The differences between calcitriol and calcium groups increased over the three-year study period, reaching significance by the second year. Serum calcium and creatinine were monitored regularly and dosage was halved if levels became elevated. Hypercalcaemia was reported in two patients.

Calcitriol versus placebo
A randomised, double blind, placebo-controlled trial was conducted in 40 patients (calcitriol n = 18, placebo n = 22). Rocaltrol was increased from an initial dose of 0.25 microgram twice daily until hypercalcaemia developed, at which point the dosage was adjusted and calcium intake reduced to maintain stable serum and urinary calcium. Dietary calcium was maintained at 1000 mg per day and 400 IU vitamin D was administered to each patient. After two years, Rocaltrol treated patients had an increase in spine bone density of 1.94% measured by dual photon absorptiometry compared to a decrease of 3.92% in patients on placebo (p = 0.001). The sample size was too small to show positive data on fracture rate after two years.

Phase II studies of Rocaltrol in post-menopausal osteoporosis were undertaken in the USA and involved a total of 93 patients. The primary endpoint was effect on vertebral fracture rates. Dose titration resulted in a mean dose of 0.5 to 0.6 microgram/day. Two studies were very similar, with an initial two-month placebo treatment for all patients, followed by a ten-month double-blind comparison of Rocaltrol and placebo, with a subsequent extension of 12 to 30 months during which all patients received Rocaltrol. The third study compared Rocaltrol with placebo in an initial six-month single-blind evaluation, with a subsequent open phase of up to 24 months Rocaltrol treatment. Dietary calcium was supplemented to 600 mg per day in the two double-blind trials. A highly significant reduction was noted in the fracture rate in patients treated with Rocaltrol in comparison with placebo in the three double blind studies. Overall, there was a statistically significant association between Rocaltrol treatment and the suppression of fractures. Calcium absorption was significantly increased in the Rocaltrol groups in all three studies.

<u>Males with osteoporosis</u>
There are few data on the safety and efficacy of Rocaltrol on fracture rates and bone mineral density in osteoporotic men.

Calcitriol versus calcium
A randomised double-blind, placebo-controlled pilot trial assessed the efficacy of calcitriol 0.25 micrograms twice daily versus calcium 500 mg twice daily for 24 months in men with osteoporosis. Twenty-one men were randomised to receive calcitriol and 20 to receive calcium. Due to the size of the study no valid conclusions were drawn regarding the efficacy in terms of bone mineral density (BMD) and vertebral fracture rates.

<u>Corticosteroid-induced osteoporosis</u>
A randomised, double blind, placebo and comparator-controlled trial was conducted in 103 enrolled male and female patients with rheumatic, immunological or respiratory disease. The subjects enrolled within four weeks of starting long-term corticosteroid therapy. The three treatment groups were the placebo group (n = 29, calcium 1000 mg/day), calcitriol group (n = 34, oral calcium 1000 mg/day, calcitriol 0.5 - 1 microgram/day) and the calcitriol plus calcitonin group (n = 29, oral calcium 1000 mg/day, calcitriol 0.5 - 1 microgram/day, intranasal calcitonin 400 IU/day). Each treatment group received active treatment for 12 months and was followed up for a further 12 months.

The primary efficacy end-point was bone mineral density measured at the lumbar spine, femoral neck and distal radius by photon absorptiometry. Serum levels of parathyroid hormone, 25-hydroxyvitamin D, 1,25-dihydroxyvitamin D and osteocalcin and urinary levels of calcium, hydroxyproline and creatinine were also measured. The bone density measurements and biochemical analyses were made at baseline and then every four months for two years. Serum calcium was measured at one, three and five weeks and every two months thereafter.

After the first year both treatment groups showed a similar and statistically significant reduction in bone loss at the lumbar spine but not at the femoral neck or distal radius compared to the placebo group. In the second year, this reduction in bone loss was no longer apparent in the calcitriol group. However, this group did receive a higher cumulative dose of corticosteroids during the second year.

The study medications were generally well tolerated with few adverse effects. The most frequent events were hypercalcaemia and rhinorrhoea. Hypercalcaemia was seen in one placebo group patient, one calcitriol group patients and eight calcitriol plus calcitonin group patients. Other less frequently reported adverse events included rash, headache and gastrointestinal symptoms.

5.2 PHARMACOKINETIC PROPERTIES

Absorption

Calcitriol is rapidly absorbed from the intestine. Peak serum concentrations (above basal values) were reached within 3 to 6 hours following oral administration of single doses of 0.25 to 1.0 microgram of ROCALTROL.

Distribution

Following a single oral dose of 0.5 microgram mean serum concentrations of calcitriol rose from a baseline value of 40.0 $\pm$ 4.4 (S.D.) pg/ml to 60.0 $\pm$ 4.4 pg/ml at 2 hours and declined to 53.0 $\pm$ 6.9 at 4 hours, 50 $\pm$ 7.0 at 8 hours, 44 $\pm$ 4.6 at 12 hours and 41.5 $\pm$ 5.1 at 24 hours.

Calcitriol and other vitamin D metabolites are transported approximately 99.9% bound to specific plasma proteins in the blood.

Metabolism

Calcitriol is hydroxylated and oxidized by CYP24A1.

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, 1α25-dihydroxy-23-oxo-cholecalciferol, 1α25R,26-trihydroxy-23-oxo-cholecalciferol and 1α-hydroxy-23-carboxy-24,25,26,27-tetranorcholecalciferol. 1α,25R-dihydroxycholecalciferol-26,23S-lactone is the major metabolite in humans.

Excretion

The elimination half-life of calcitriol from serum was found to range from 3 to 6 hours. However, the pharmacological effect of a single dose of calcitriol lasts about three to five days. Enterohepatic recycling and biliary excretion occur. Following intravenous administration of radiolabelled calcitriol in normal subjects, approximately 27% and 7% of the radioactivity

appeared in the faeces and urine respectively, within 24 hours. When a 1 microgram oral dose of radiolabelled calcitriol was administered to normals, approximately 10% of the total radioactivity appeared in urine within 24 hours. Cumulative excretion of radioactivity on the sixth day following intravenous administration of radiolabelled calcitriol averaged 16% in urine and 49% in faeces.

There is evidence that maternal calcitriol may enter the fetal circulation.

5.3 PRECLINICAL SAFETY DATA

Genotoxity
No data available.

Carcinogenicity
Long term animal studies have not been conducted to evaluate the carcinogenic potential of calcitriol. Calcitriol is not mutagenic *in vitro* in the Ames test. No significant effects of calcitriol on fertility and/or general reproductive performances were observed in a study in rats at oral doses of up to 0.3 micrograms/kg (approximately 3 times the maximum recommended dose based on body surface area).

6. PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS
Content
Butylated hydroxyanisole
Butylated hydroxytoluene
Medium chain triglycerides

Capsule shell
Gelatin, glycerol
Karion 83
Titanium dioxide
Iron oxide red
Iron oxide yellow.

6.2 INCOMPATIBILITIES
Incompatibilities were either not assessed or not identified as part of the registration of this medicine.

6.3 SHELF LIFE
In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

6.4 SPECIAL PRECAUTIONS FOR STORAGE
Store below 25° C
Store in the original package and blister in the outer carton to protect from light and moisture.

6.5 NATURE AND CONTENTS OF CONTAINER
PVC opaque blisters containing 100 capsules (5 strips of 20 capsules)

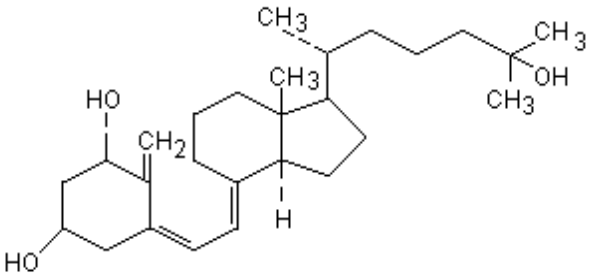
6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

The release of medicines into the environment should be minimised. 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.

6.7 PHYSIOCHEMICAL PROPERTIES

Chemical structure



The chemical name for calcitriol is (5*Z*,7*E*)-9,10-secocholesta-5,7,10(19)-triene-1α,3β,25-triol (calcitriol), the molecular formula is $C_{27}H_{44}O_3$. Calcitriol has a molecular weight of 416.65.

CAS number

32222-06-3

Calcitriol is a white, crystalline compound, which occurs naturally in humans. It is soluble in organic solvents but practically insoluble in water.

7. MEDICINE SCHEDULE (POISONS STANDARD)

Schedule 4 – Prescription Only Medicine

8. SPONSOR

Roche Products Pty Limited
ABN 70 000 132 865
Level 8, 30 – 34 Hickson Road
Sydney NSW 2000
AUSTRALIA

Medical enquiries: 1800 233 950

9. DATE OF FIRST APPROVAL

18 March 2003

10. DATE OF REVISION OF THE TEXT

21 June 2018

Summary table of changes

Section Changed	Summary of new information
All sections	New PI format
8	Sponsor address updated