PACKAGE INSERT TEMPLATE FOR CALCITRIOL- CAPSULE

Brand or Product Name

[Product name] Dosage form, Strength

Name and Strength of Active Substance(s)

Calcitriol……0.25 µg or 0.5 µg

Product Description

[Visual description of the appearance of the product (eg colour, viscosity etc)
eg

Pharmacodynamics

Calcitriol is one of the most important active metabolites of vitamin D3. 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 to 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, administration of Calcitriol 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 Calcitriol therapy.

In patients with vitamin D-dependent rickets the serum levels of calcitriol are low or absent. As the endogenous production of calcitriol in the kidney is insufficient, Calcitriol is considered as a replacement therapy.

In patients with vitamin D-resistant rickets and hypophosphatemia in whom plasma calcitriol levels are reduced, treatment with Calcitriol 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 Calcitriol therapy.

Pharmacokinetics

Absorption
Calcitriol is rapidly absorbed from the intestine. Peak serum concentrations following a single oral dose of 0.25-1.0 µg Calcitriol 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 administered.

Distribution
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 fetal bloodstream and the breast milk.

Metabolism
Calcitriol is hydroxylated and oxidized in the kidney and in the liver by a specific cytochrome P450 isoenzyme, 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, 1α,25-dihydroxy-23-oxo-cholecalciferol, 1α,25R,26-trihydroxy-23-oxo-cholecalciferol and 1α-hydroxy-23-carboxy-24,25,26,27-tetranorcholecalciferol.

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Elimination
Calcitriol goes through enterohepatic circulation and is excreted in the bile. The metabolites of calcitriol are excreted primarily in feaces and to a lesser amount in the urine. The elimination half-life of calcitriol in serum after single oral doses is about 5 to 8 hours in normal subjects.

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.

Indication

Established postmenopausal osteoporosis;
Renal osteodystrophy in patients with chronic renal failure, particularly those undergoing hemodialysis;
Postsurgical hypoparathyroidism; pseudohypoparathyroidism;
Vitamin D-dependent rickets; hypophosphatemic vitamin D-resistant rickets.
Predialysis patient: for the treatment of secondary hyperparathyroidism and resultant metabolic bone disease in patients with moderate to severe chronic renal failure (Creatinine Clearance 15 to 55ml/min);

In children, the Creatine Clearance value must be corrected for a surface area of 1.73 square metres. A serum intact parathyroid hormone (iPTH) level of more than or equals to 100 pg/ml is strongly suggestive of secondary hyperparathyroidism.

Recommended Dosage

The optimal daily dose of Calcitriol must be carefully determined for each patient on the basis of the serum calcium level. Calcitriol 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 Calcitriol is adequate but not excessive calcium intake (in adults: approximately 800 mg daily) at the beginning of therapy. Calcium supplements may be necessary.

Because of improved calcium absorption from the gastrointestinal tract, some patients on Calcitriol therapy 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.

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The total daily calcium intake (i.e. from food, and, where applicable, from drugs) should average approximately 800 mg and should not exceed 1000 mg.

Patient monitoring

During the stabilization phase of treatment with Calcitriol capsules, serum calcium levels should be checked at least twice weekly. When the optimal dosage of Calcitriol 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 Calcitriol 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 Calcitriol 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.

Special Dosage Instructions

- Postmenopausal osteoporosis*:*

The recommended dosage is 0.25 µg twice daily.
Serum calcium and creatinine levels should be determined at 1, 3 and 6 months and at 6 monthly 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/day at two to four-week intervals. During this period, serum calcium levels should be determined at least twice weekly. Most patients respond to between 0.5 µg and 1.0 µg daily.

An oral Calcitriol pulse therapy with an initial dosage of 0.1µg/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 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 hypercalcaemia is noted, Calcitriol therapy 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 the medication may be needed.

If the physician decides to prescribe Calcitriol 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

- Predialysis patients:

For the treatment of secondary hyperparathyroidism and resultant metabolic bone disease in patients with moderate to severe renal failure (Creatinine Clearance 15 to 55 ml/min; in children corrected for a surface area of 1.73 square meters), the recommended initial dose of Calcitriol is 0.25 µg/ml in adults and paediatric patients 3 years of age and older. The dosage may be increased if necessary to 0.5µg/day. For paediatric patients less than 3 years of age, the recommended initial dosage of Calcitriol is 10 to 15 ng/kg/day.

- Elderly patients:

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

- Infants and children:

During the first 2 years of life, a daily dosage of 0.01 - 0.1 µg/kg bodyweight is recommended as a guideline.

Mode of Administration

Oral

Contraindications

Calcitriol should not be given to patients with hypercalcaemia or evidence of vitamin D toxicity.

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This drug is contraindicated in patients with previous hypersensitivity to calcitriol or any of its excipients.

Warnings and Precautions

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 Calcitriol should be stopped immediately until normocalcaaemia ensues.
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 Calcitriol must continue their oral phosphate therapy. However, possible stimulation of intestinal absorption of phosphate by Calcitriol therapy 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 the medication, thereby ensuring that the development of hypervitaminosis D is avoided.

If the patient is switched from ergocalciferol (vitamin D2) to calcitriol, it may take several months for the ergocalciferol level in the blood to return to the baseline values (*see Overdosage*).

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

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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.

Interactions with Other Medicaments

General
Since Calcitriol is one of the most important active metabolites of vitamin D_3, pharmacological doses of vitamin D and its derivatives should be withheld during treatment with Calcitriol to avoid possible additive effects and hypercalcaemia.

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.

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 Calcitriol by patients on chronic renal dialysis.

Since Calcitriol 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.

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

Statement on Usage During Pregnancy and Lactation

Pregnancy
There are no adequate and well-controlled studies in pregnant women. Calcitriol should be used during pregnancy only if the potential benefit justifies the potential risk to the foetus.

Lactation
Available evidence and/or expert consensus is inconclusive or is inadequate for determining infant risk when used during breastfeeding. Weigh the potential benefits of drug treatment against potential risks before prescribing this drug during breastfeeding.

Adverse Effects / Undesirable Effects

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).

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

Overdose and Treatment

Treatment of asymptomatic hypercalcaemia:

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 Calcitriol 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 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.

Storage Conditions
[eg Store below….°C]
Protect from light and moisture.

Dosage Forms and Packaging Available
[Packaging type & pack size]

Name and Address of Manufacturer
[Name & full address of manufacturer]

Name and Address of Marketing Authorization Holder
[Name & full address of marketing authorization holder]

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Date of Revision of Package Insert
[day/month/year]

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