PACKAGE INSERT TEMPLATE FOR CALCITRIOL - INJECTION

Brand or Product Name

[Product name] Dosage form, Strength

Name and Strength of Active Substance(s)

Calcitriol ….. 1µg/ml or 2µg/ml

Product Description

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

Pharmacodynamics

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 0.5-1.0 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.

Pharmacokinetics

Calcitriol when administered by bolus injection is rapidly available in the blood stream. Vitamin D metabolites are known to be transported in blood, bound to specific plasma proteins. The pharmacologic activity of an administered dose of calcitriol is about 3 to 5 days. Two metabolic pathways for calcitriol have been identified, conversion to 1,24,25-(OH)3D3 and to calcitroic acid.

Indication

Calcitriol injection is indicated in the management of hypocalcaemia in patients undergoing chronic renal dialysis. It has been shown to significantly reduce elevated parathyroid hormone (PTH) levels.
Reduction of PTH has been shown to result in an improvement in renal osteodystrophy.

Recommended Dosage

The optimal dose of calcitriol injection must be carefully determined for each patient.
The effectiveness of calcitriol therapy is predicated on the assumption each patient is receiving an adequate and appropriate daily intake of calcium. The Recommended Daily Allowance (RDA) for calcium in adults is 800 mg. To ensure each patient receives an adequate daily intake of calcium, the physician should either prescribe a calcium supplement or instruct the patient in proper dietary measures.

The usual recommended initial dose of calcitriol, depending on the severity of the hypocalcaemia and/or secondary hyperparathyroidism, is 1.0 µg (0.02 µg /kg) to 2.0 µg administered three times weekly, approximately every other day.

Doses as small as 0.5 µg and as large as 4.0 µg thrice weekly have been used as an initial dose. Calcitriol can be administered as a bolus dose intravenously. If a satisfactory response in the biochemical parameters and clinical manifestations of the disease state is not observed, the dose may be increased by 0.5 to 1.0 µg at two to four week intervals.

Incremental dosing from 0.25 µg to 2.0 µg has been used and maximal doses up to 8 µg three times per week have been reported.

During this titration period, serum calcium and phosphorus levels should be obtained at least twice weekly, and if hypercalcaemia is noted, the drug should be immediately discontinued until these parameters are normal.

Then, the calcitriol dose should be reinitiated at a lower dose. Doses may need to be reduced as the PTH levels decrease in response to the therapy. Thus, incremental dosing must be individualized and commensurate with PTH, serum calcium and phosphorus levels.

Mode of Administration

Intravenous

Contraindications

Calcitriol should not be given to patients with hypercalcaemia or evidence of vitamin D toxicity. This drug is contraindicated in patients with previous hypersensitivity to calcitriol or any of its excipients.

Warnings and Precautions

Since calcitriol is the most potent metabolite of vitamin D available, prescription based doses of vitamin D and its derivatives should be withheld during treatment to avoid possible additive effects and hypocalcaemia.

A non-aluminium phosphate-binding compound should be used to control serum phosphorus levels in patients undergoing dialysis.

Overdosage of any form of vitamin D is dangerous. Progressive hypercalcaemia due to overdosage of vitamin D and its metabolites may be so severe as to require emergency attention. Chronic hypercalcaemia can lead to generalized vascular calcification, nephrocalcinosis and other soft-tissue calcification. The serum calcium times phosphate (Ca x P) product should not be allowed to exceed 70 mg^2/dL^2. Radiographic evaluation of suspect anatomical regions may be useful in early detection of this condition.

General

Excessive dosage of calcitriol injection induces hypercalcaemia and in some instances hypercalcinuria; therefore, early in treatment during dosage adjustment, serum calcium and phosphorus should be determined at least twice weekly. Should hypercalcaemia develop, the drug should be discontinued immediately.

Adynamic bone disease may develop if PTH levels are suppressed to abnormal levels. If biopsy is not being done for other (diagnostic) reasons, PTH levels may be used to indicate the rate of bone turnover. If PTH levels fall below recommended target range (1.5 to 3 times the upper limit of normal), in patients treated with calcitriol, the calcitriol dose should be reduced or therapy discontinued. Discontinuation of calcitriol therapy may result in rebound effect, therefore, appropriate titration downward to a maintenance dose is recommended.

Updated December 2012

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

Information for the Patient
The patient should be informed about adherence to instructions about diet and calcium supplementation and avoidance of the use of unapproved non-prescription drugs, including magnesium-containing antacids. Patients should also be carefully informed about the symptoms of hypercalcaemia.

Laboratory Tests
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 and phosphorus should be determined more frequently (twice weekly).

Paediatric Use
There is limited data on the use of calcitriol in paediatric patients. Safety and efficacy of calcitriol in children have not been established.

Geriatric Use
In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosage range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

Interactions with Other Medicaments

General
Since calcitriol is one of the most important active metabolites of vitamin D3, 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

Updated December 2012

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 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 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.

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.

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 fetus.

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

Rare cases of hypersensitivity reactions have been reported including anaphylaxis and localized redness at the injection site. Occasional mild pain on injection has been observed.

Adverse effects of calcitriol injection are, in general, similar to those encountered with excessive vitamin D intake. The early and late signs and symptoms of vitamin D intoxication associated with hypercalcemia include:

Early
Weakness, headache, somnolence, nausea, vomiting, dry mouth, constipation, muscle pain, bone pain, metallic taste, anorexia, abdominal pain, and epigastric discomfort.

Late
Polyuria, polydipsia, anorexia, weight loss, nocturia, conjunctivitis (calcific), pancreatitis, photophobia, rhinorrhea, pruritus, hyperthermia, decreased libido, elevated Blood Urea Nitrogen (BUN), albuminuria, hypercholesterolemia, elevated liver transaminases, ectopic calcification, nephrocalcinosis, hypertension, cardiac arrhythmias, dystrophy, sensory disturbance, dehydration, apathy, urinary tract infections, and, rarely, overt psychosis.

Overdose and Treatment

Administration of calcitriol injection to patients in excess of their requirements can cause hypercalcaemia, hypercalciuria and hyperphosphatemia. High intake of calcium and phosphate concomitant with calcitriol may lead to similar abnormalities.

Treatment of Hypercalcaemia and Overdosage in Patients on Hemodialysis
General treatment of hypercalcaemia (greater than 1 mg/dL above the upper limit of normal range) consists of immediate discontinuation of calcitriol therapy, institution of a low calcium diet and withdrawal of calcium supplements. Decreasing calcium concentration in the dialysate solution may be considered. Serum calcium levels should be determined daily until normocalcaemia ensues.

Hypercalcaemia usually resolves in 2 to 7 days. When serum calcium levels have returned to within normal limits, calcitriol therapy may be reinstituted at a dose 0.5 µg less than prior therapy. Serum calcium levels should be obtained at least twice weekly during dose titration.

Treatment of Accidental Overdosage of calcitriol Injection
The treatment of acute accidental overdosage of calcitriol 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 initiation of a low calcium diet are also indicated in accidental overdosage. Should elevated serum calcium levels persist, there are a variety of therapeutic alternatives which may be considered, depending on the patients' underlying condition. Temporizing management approaches reported in the literature include: forced saline diuresis,

haemodialysis against a calcium-free dialysate and the use of drugs such as bisphosphonates, mithramycin, calcitonin, glucocorticoids and gallium nitrate.

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]

Date of Revision of Package Insert

[day/month/year]