

Calcitriol Injection **Vitamin D₃ metabolite**

CLINICAL PHARMACOLOGY

Calcitriol is the active form of vitamin D₃ (cholecalciferol). The natural or endogenous supply of vitamin D in man mainly depends on ultraviolet light for conversion of 7-dehydrocholesterol to vitamin D₃ in the skin. Vitamin D₃ must be metabolically activated in the liver and the kidney before it is fully active on its target tissues. The initial transformation is catalyzed by a vitamin D₃-25-hydroxylase enzyme present in the liver, and the product of this reaction is 25-hydroxyvitamin D₃ (calcifediol).

The latter undergoes hydroxylation in the mitochondria of kidney tissue, and this reaction is activated by the renal 25-hydroxyvitamin D₃-1-alpha-hydroxylase to produce 1,25-dihydroxyvitamin D₃ (calcitriol), the active form of vitamin D₃.

The known sites of action of calcitriol are intestine and bone, but additional evidence suggests that it also acts on the kidney and the parathyroid gland. Calcitriol is the most active known form of vitamin D₃ in stimulating intestinal calcium transport.

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 alpha₂ globulins. 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)₂D₃ and to calcitroic acid.

INDICATIONS AND CLINICAL USE

Calcitriol Injection is indicated in the management of hypocalcemia in patients undergoing chronic renal dialysis. It has been also shown to significantly reduce elevated parathyroid hormone levels in many of these patients. Reduction of PTH has been shown to result in an improvement in renal osteodystrophy.

CONTRAINDICATIONS

Calcitriol Injection should not be given to patients with previous hypersensitivity to calcitriol or any of its excipients, Vitamin D or its analogues and derivatives, hypercalcemia or evidence of vitamin D toxicity.

WARNINGS

Since Calcitriol Injection is a potent cholecalciferol derivative with profound effects on intestinal absorption of dietary calcium and inorganic phosphate, it should not be used concomitantly with other vitamin D products or its derivatives.

Therapy with Calcitriol Injection should only be considered when adequate laboratory facilities for monitoring of blood and urine chemistries are available. During treatment progressive hypercalcemia either due to hyper-responsiveness or overdosage may become so severe as to require emergency treatment (see **SYMPTOMS AND TREATMENT OF OVERDOSAGE**).

Chronic hypercalcemia can lead to generalized vascular calcification, nephrocalcinosis, calcifications of the cornea or other soft tissues. During treatment with calcitriol **THE SERUM TOTAL CALCIUM (mg/dL) TIMES SERUM INORGANIC PHOSPHATE PRODUCT (Ca x P) SHOULD NOT EXCEED 70.**

Dialysate calcium level of 7 mg % or above in addition to excessive dietary calcium supplements may lead to frequent episodes of hypercalcemia.

In patients on digitalis, hypercalcemia may precipitate cardiac arrhythmias; in such patients calcitriol should be used with extreme caution.

To control serum phosphorus levels and dietary phosphate absorption in patients undergoing dialysis, a non-aluminum phosphate-binding compound should be used. Magnesium-containing antacids may contribute towards hypermagnesemia in patients on chronic renal dialysis and should be avoided during therapy with calcitriol (see **Drug Interactions**).

Use in Pregnancy

Calcitriol, given orally, has been reported to be teratogenic in rabbits when given in doses 4 and 15 times the dose recommended for human use.

All 15 fetuses in 3 litters at these doses showed external and skeletal abnormalities.

However, none of the other 23 litters (156 fetuses) showed significant abnormalities compared with controls.

Teratology studies in rats showed no evidence of teratogenic potential. There are no adequate and well controlled studies in pregnant women. Calcitriol Injection should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

PRECAUTIONS

General

Patient Selection and Follow-up: Patients with renal osteodystrophy and hypocalcemia, poorly managed by conventional vitamin D therapy, are likely to respond to Calcitriol Injection. The desired therapeutic margin of calcitriol is narrow, therefore, the optimal daily dose must be carefully determined for each patient by dose titration to obtain satisfactory response in the biochemical parameters and clinical manifestations (see **DOSAGE AND ADMINISTRATION**).

Excessive dosage of calcitriol induces hypercalcemia and hypercalciuria; therefore, early in treatment during dosage adjustment, serum calcium and phosphorus should be determined at least twice weekly. A fall in serum alkaline phosphatase values may indicate impending hypercalcemia. Should hypercalcemia develop, the drug should be discontinued immediately until the serum calcium level has normalized. This may take several days to a week.

Calcitriol should be given cautiously to patients on digitalis, because hypercalcemia in such patients may precipitate cardiac arrhythmias (see **Drug Interactions**).

Use in Children

Safety and efficacy of Calcitriol Injection in children have not been established.

Nursing Mothers

It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from calcitriol, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Drug Interactions

Hypercalcemia in patients on digitalis may precipitate cardiac arrhythmias. Although the precise mechanism involved is unknown, there is evidence that long term anti-convulsant treatment, particularly with diphenylhydantoin and barbiturates, may interfere with the actions of vitamin D. Patients under concurrent treatment with such agents may require slightly higher doses of calcitriol.

Magnesium-containing antacids and calcitriol should not be used concomitantly, since such use may lead to the development of hypermagnesemia.

Corticosteroids may counteract the effects of vitamin D analogs.

Laboratory Tests

Serum calcium, inorganic phosphorus, magnesium, alkaline phosphatase as well as 24-hour urinary calcium and phosphorus should be determined periodically during maintenance therapy with calcitriol. During the initial phase of the medication, serum calcium and phosphorus should be determined more frequently (at least twice weekly). Periodic ophthalmological examinations and radiological evaluation of suspected anatomical regions for early detection of ectopic calcifications are advisable.

Carcinogenesis

Long-term studies in animals have not been performed to evaluate the carcinogenic potential of Calcitriol Injection.

Transplantation

The rate of bone loss can be excessive and may exceed 5% per year in the immediate post-transplant period. Recommendations for treating post-transplant bone loss with Calcitriol Injection have not been established.

Menopausal Osteoporosis Secondary to Decrease Estrogens

Efficacy has not been established for this patient population.

Information to be provided to the Patient

The patient and his or her immediate relatives should be informed about the need for compliance with dosage instructions, strict adherence to prescribed calcium intake, dietary and supplementary, and avoidance of unapproved non-prescription drugs or medications. Patients should also be made aware of the symptoms of hypercalcemia and should seek medical attention if such symptoms are noted (see **ADVERSE REACTIONS**).

ADVERSE REACTIONS

The following adverse reactions have been reported in association with Calcitriol Injection treatment:

The most frequently reported adverse effect is hypercalcemia (35% approx. after the 4th week of treatment).

The less frequently reported adverse effects were headache, nausea, vomiting, constipation, abdominal cramp, pruritis, conjunctivitis, agitation, extremity pain, apprehension, polyuria, insomnia, elevated SGOT and/or SGPT, elevated alkaline phosphatase, hypercalciuria, hypermagnesemia, hyperphosphatemia, elevated lymphocytes, elevated hematocrit, elevated neutrophils, elevated hemoglobin.

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

The adverse effects of Calcitriol Injection are, in general, similar to those encountered with excessive vitamin D intake. The early and late signs and symptoms associated with vitamin D intoxication and hypercalcemia are:

- a. **Early:** weakness, headache, somnolence, nausea, cardiac arrhythmias, excessive thirst, vomiting, dry mouth, constipation, muscle pain, bone pain, and metallic taste.
- b. **Late:** polyuria, polydipsia, anorexia, weight loss, nocturia, conjunctivitis (calcific), pancreatitis, photophobia, rhinorrhea, pruritus, hyperthermia, decreased libido, elevated BUN, albuminuria, hypercholesterolemia, elevated SGOT and SGPT, ectopic calcification, hypertension, cardiac arrhythmias, and rarely, overt psychosis.

SYMPTOMS AND TREATMENT OF OVERDOSAGE

Administration of Calcitriol Injection to patients in excess of their daily requirements can cause hypercalcemia, hypercalciuria and hyperphosphatemia. Conversely, high intake of calcium and phosphate concomitantly with therapeutic doses of Calcitriol Injection may cause similar abnormalities. In dialysis patients, high levels of calcium in the dialysis bath may contribute to hypercalcemia.

Treatment of Hypercalcemia in Patients Undergoing Hemodialysis

General treatment of hypercalcemia (more than 1 mg/dL or 0.25 mmol/L above the upper limit of the normal range) consists of immediate discontinuation of Calcitriol Injection 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 normocalcemia ensues. Hypercalcemia frequently resolves in two to seven days. When serum calcium levels have returned to within normal limits, Calcitriol Injection therapy may be reinstated at a dose of 0.5 µg less than prior therapy. Serum calcium levels should be carefully monitored (at least twice weekly) during this period of dosage adjustment and subsequent dosage titration.

Persistent or markedly elevated serum calcium levels may be corrected by dialysis against a calcium-free dialysate.

Treatment of Accidental Overdosage

The treatment of acute accidental overdosage with Calcitriol Injection should consist of general supportive measures. Serial serum electrolyte determinations (especially calcium ion), rate of urinary calcium excretion, and assessment of electrocardiographic abnormalities due to hypercalcemia should be obtained. Such monitoring is critical in patients receiving digitalis. Discontinuation of supplemental calcium and low calcium diet are also indicated in accidental overdosage. Due to the relatively short pharmacological action of calcitriol, further measures are probably unnecessary. Should, however, persistent and markedly elevated serum calcium levels occur, there are a variety of therapeutic alternatives which may be considered, depending on the patient's underlying condition. These include the use of drugs such as phosphates, corticosteroids, bisphosphonates, mithramycin, calcitonin, glucocorticoids, and galium nitrate as well as measures to induce an appropriate forced saline diuresis. The use of peritoneal dialysis against a calcium-free dialysate has also been reported.

DOSE AND ADMINISTRATION

THE OPTIMAL DOSE OF CALCITRIOL INJECTION MUST BE CAREFULLY DETERMINED FOR EACH PATIENT.

The effectiveness of Calcitriol Injection therapy is predicated on the assumption that each patient is receiving an adequate daily intake of calcium. The recommended daily allowance for calcium in adults is in the order of 1 g.

To ensure that each patient receives an adequate daily intake of calcium, the physician should either prescribe a calcium supplement or instruct the patient in appropriate dietary measures. However, because of improved calcium absorption from the gastrointestinal tract, some patients may be maintained on a lower calcium intake or no supplementation at all.

The recommended initial dose of Calcitriol Injection is 0.5 µg (0.01 µg/kg) administered three times weekly, every other day. Calcitriol Injection can be administered as a bolus dose intravenously through the catheter at the end of hemodialysis. If a satisfactory response in the biochemical parameters and clinical manifestations of the disease state is not observed, the dose may be increased by 0.25 to 0.50 µg at two to four week intervals. During this titration period, serum calcium and phosphorus levels should be obtained at least twice weekly, and if hypercalcemia is noted, the drug should be immediately discontinued until normocalcemia ensues. Most patients undergoing hemodialysis respond to doses between 0.5 and 3.0 µg (0.01 to 0.05 µg/kg) three times per week.

FURTHER INFORMATION: Higher dosing regimens have been studied in the literature. These academic trials are limited with respect to sample size but suggest evidence of healing of secondary hyperparathyroidism. Clinical studies are currently in progress to further evaluate this dosing regimen.

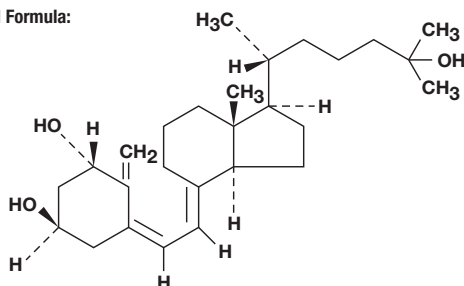
PHARMACEUTICAL INFORMATION

Drug Substance

Proper Name: Calcitriol

Chemical Name: 9,10-secocholesta-5,7,10(19)-triene-1,3,25-triol, (1 α ,3 β ,5Z,-7E)-;

Structural Formula:



Molecular Formula: C₂₇H₄₄O₃

Molecular Weight: 416.64

Description

Calcitriol is a white crystalline powder, slightly soluble in methanol, ethanol, ethyl acetate and relatively insoluble in water. The melting point is 111 - 115°C.

COMPOSITION

Calcitriol is available as a sterile, isotonic, clear, aqueous solution for intravenous injection.

Each 1 mL Calcitriol Injection ampoule contains:

Calcitriol	1 µg
Edetate Disodium (stabilizer)	1.1 mg
Polysorbate 20	4 mg
Sodium Chloride (tonicity)	1.5 mg
Sodium ascorbate (stabilizer)	10 mg

Dibasic sodium phosphate, anhydrous and monobasic sodium phosphate, monohydrate as buffers and water for injection q.s. The pH of the solution is approximately 7. It does not contain a preservative.

STABILITY AND STORAGE RECOMMENDATIONS

Store at room temperature, between 15 and 30°C. Protect from light, freezing or excessive heat.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit. Discard unused portion.

AVAILABILITY OF DOSAGE FORMS

Calcitriol Injection is supplied in 1 mL amber ampoules containing 1 µg of calcitriol. C730101 1 µg/mL, 1 mL amber ampoule in boxes of 10 ampoules.

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