PRODUCT MONOGRAPH

^{Pr}CALCIJEX®

calcitriol injection
1 mcg/mL and 2 mcg/mL

Vitamin D_3 metabolite

AbbVie Corporation
8401 Trans-Canada Highway
St-Laurent, Qc H4S 1Z1

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December 08, 1995

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CALCIJEX®

calcitriol injection

PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form/Strength	Clinically Relevant Non-medicinal Ingredients
Intravenous	Injectable / 1 mcg/mL and 2 mcg/mL	Anhydrous dibasic sodium phosphate, edetate disodium, monobasic sodium phosphate monohydrate, polysorbate 20, sodium ascorbate, sodium chloride.

INDICATIONS AND CLINICAL USE

CALCIJEX® (calcitriol injection) is indicated for:

- the management of hypocalcemia in patients undergoing chronic renal dialysis.

It has been also shown to significantly reduce elevated parathyroid hormone levels (PTH) in many of these patients. Reduction of PTH has been shown to result in an improvement in renal osteodystrophy.

Geriatrics (≥ 65 years of age):

Clinical studies of CALCIJEX® did not include sufficient numbers of subjects aged 65 years and over to determine whether they respond differently from younger subjects.

Pediatrics (< 18 years of age):

Safety and efficacy of CALCIJEX® have not been established in the pediatric population.

CONTRAINDICATIONS

- CALCIJEX® (calcitriol injection) is contraindicated in patients with previous hypersensitivity to vitamin D or its analogues and derivatives
- CALCIJEX® is contraindicated in patients with hypercalcemia or evidence of vitamin D toxicity
- CALCIJEX® is contraindicated in patients with previous hypersensitivity to calcitriol or to any ingredient in the formulation or component of the container. For a complete listing of components/excipients, see the **DOSAGE FORMS, COMPOSITION AND PACKAGING** section of the Product Monograph.

WARNINGS AND PRECAUTIONS

General

Since CALCIJEX® (calcitriol injection) is a potent cholecalciferol derivative with profound effects on intestinal absorption of dietary calcium and inorganic phosphate, vitamin D and its derivatives should be withheld during treatment to avoid possible additive effects and hypercalcemia.

Therapy with CALCIJEX® should only be considered when adequate laboratory facilities for monitoring of blood and urine chemistries are available. Overdosage of any form of vitamin D is dangerous. During treatment with CALCIJEX®, progressive hypercalcemia either due to hyper-responsiveness or overdosage may become so severe as to require emergency treatment (see **OVERDOSAGE**). Chronic hypercalcemia can lead to generalized vascular calcification, nephrocalcinosis, and calcifications of the cornea or other soft tissues. Radiographic evaluation of suspect anatomical regions may be useful in the early detection of this condition. **During treatment with calcitriol, the serum total calcium times serum inorganic phosphate product (Ca x P) should not exceed 70 mg^2/dL^2.**

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

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**).

Patient Selection and Follow-up: Patients with renal osteodystrophy and hypocalcemia, poorly managed by conventional vitamin D therapy, are likely to respond to CALCIJEX®. 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.

CALCIJEX® should be used with extreme caution in patients on digitalis. Hypercalcemia in such patients may precipitate cardiac arrhythmias (see **DRUG INTERACTIONS**).

Carcinogenesis and Mutagenesis

See **TOXICOLOGY, Mutagenicity and Carcinogenicity**.

Special Populations

Pregnant Women

Calcitriol has been reported to be teratogenic in rabbits when given orally 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 at doses up to 0.45 mcg/kg showed no evidence of teratogenic potential.

There are no adequate and well-controlled studies in pregnant women. CALCIJEX® should not be used during pregnancy unless the potential benefit to the mother justifies the potential risk to the fetus.

Nursing Women

It is not known whether calcitriol 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.

Pediatrics (< 18 years of age)

Safety and efficacy of CALCIJEX® in pediatric patients younger than eighteen years of age have not been established.

Geriatrics (≥ 65 years of age)

Clinical studies of CALCIJEX® did not include sufficient numbers of subjects aged 65 years and over to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients. 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.

Monitoring and Laboratory Tests

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

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

ADVERSE REACTIONS

Adverse Drug Reaction Overview

The following adverse reactions have been reported in association with CALCIJEX® (calcitriol injection) treatment.

The most frequently reported adverse effect is hypercalcemia (35% approximately 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 serum glutamic oxaloacetic transaminase (SGOT) and/or serum glutamic pyruvic transaminase (SGPT), elevated alkaline phosphatase, hypercalciuria, hypermagnesemia, hyperphosphatemia, elevated lymphocytes, elevated hematocrit, elevated neutrophils, and elevated hemoglobin.

The adverse effects of CALCIJEX® 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:

Early

Asthenia, headache, somnolence, nausea, cardiac arrhythmias, excessive thirst, vomiting, dry mouth, constipation, myalgia, bone pain, dysgeusia, decreased appetite, abdominal pain, and dyspepsia.

Late

Polyuria, polydipsia, decreased appetite, weight decreased, nocturia, conjunctival deposit, pancreatitis, photophobia, rhinorrhoea, pruritus, hyperthermia, libido decreased, blood urea increased, albuminuria, hypercholesterolemia, aspartate aminotransferase increased, alanine aminotransferase increased, calcinosis, hypertension, cardiac arrhythmias, muscular weakness, paresthesia, dehydration, apathy, urinary tract infections, and rarely, overt psychosis.

Clinical Trial Adverse Drug Reactions

> *Because clinical trials are conducted under very specific conditions the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse drug reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates.*

CALCIJEX® was studied in 20 patients undergoing maintenance hemodialysis for chronic renal disease (see **CLINICAL TRIALS**, Study CP5691). This open-label study had no comparator; each patient served as his/her own control. Patients received CALCIJEX® three times weekly, post-dialysis over a treatment period of 4 to 8 weeks. Doses were titrated for each patient based upon serum total calcium response.

Abnormal Hematologic and Clinical Chemistry Findings

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

Post-Market Adverse Drug Reactions

Hypersensitivity reactions have been commonly reported in Post-Market Clinical Trials at a frequency of 2.3%. Rare postmarketing reports of anaphylaxis have also been received. Occasional mild pain and localized redness at the injection site have been observed. The adverse drug reactions occurring in patients receiving CALCIJEX® in seven Post Market Clinical Studies are summarized for a total of 485 subjects randomized to CALCIJEX® (Table 1).

Table 1: Summary of ADRs Occurring in Patients Receiving Calcitriol in CALCIJEX® Post Market Clinical Trials

System Organ Class	Very Common	Common	Uncommon	Not Known
Infections and Infestations		Urinary tract infection		

System Organ Class	Very Common	Common	Uncommon	Not Known
Immune System Disorders		Hypersensitivity*		
Metabolism and Nutrition Disorders		Decreased appetite Dehydration		Polydipsia Hypercholesterolemia
Psychiatric Disorders				Libido decreased Apathy Psychosis
Nervous System Disorders	Headache	Somnolence Paresthesia	Dysgeusia	
Eye Disorders				Conjuctival deposit Photophobia
Cardiac Disorders				Cardiac arrhythmia
Vascular Disorders		Hypertension		
Respiratory, Thoracic and Mediastinal Disorders			Rhinorrhoea	
Gastrointestinal Disorders		Nausea Vomiting Constipation Abdominal pain Dyspepsia	Pancreatitis Dry mouth	
Skin and Subcutaneous Tissue Disorders		Pruritus		
Musculoskeletal and Connective Tissue Disorders		Myalgia	Bone pain Muscular weakness	
Renal and Urinary Disorders				Polyuria Nocturia Albuminuria
General Disorders and Administration Site Conditions	Pain	Injection site pain Asthenia	Injection site reaction Calcinosis	Hyperthermia
Investigations			Weight decreased Aspartate aminotransferase increased	Blood urea increased Alanine aminotransferase increased

*Anaphylaxis has not been observed in clinical trials.

DRUG INTERACTIONS

Drug-Drug Interactions

The drugs listed in **Table 1** are based on potential interactions due to the expected magnitude and seriousness of the interaction.

Table 1. Established or Potential Drug-Drug Interaction

Proper name	Ref	Effect	Clinical comment
Anticonvulsants (e.g. diphenylhydantoin and barbiturates)	T	↑ calcitriol elimination and ↓ calcitriol effect	Patients under concurrent treatment with such agents may require slightly higher doses of calcitriol.
Corticosteroids	T	May counteract the effects of vitamin D analogs	May worsen bone disease and demineralization.
Digitalis	T	Possible increase of digitalis toxicity	Hypercalcemia in patients on digitalis may precipitate cardiac arrhythmias.
Magnesium-containing preparations (e.g. antacids)	T	↑ intestinal absorption of magnesium	Magnesium-containing antacids and calcitriol should not be used concomitantly, since such use may lead to the development of hypermagnesemia.
Thiazide diuretics	T	↑ risk of hypercalcemia	Thiazide diuretics act on the distal tubule and inhibit reabsorption of sodium and potassium. This in turn stimulates the reabsorption of calcium, therefore, an increase in calcium level.

Legend: T = Theoretical

Drug-Food Interactions

Interactions with food have not been established.

Drug-Herb Interactions

Interactions with herbal products have not been established.

Drug-Laboratory Interactions

Interactions with laboratory tests have not been established.

DOSAGE AND ADMINISTRATION

Dosing Considerations

- **CALCIJEX® is for intravenous injection only.**
- **The optimal dose of CALCIJEX® (calcitriol injection) must be carefully determined for each patient.**
- The effectiveness of CALCIJEX® 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.

Recommended Dose and Dosage Adjustment

The recommended initial dose of CALCIJEX® is 0.5 mcg (0.01 mcg/kg) administered three times weekly, every other day. 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 mcg at two to four week intervals. During this titration period, serum calcium and phosphorous levels should be obtained at least twice weekly. If hypercalcemia or a serum calcium times phosphate product greater than 70 is noted, the drug should be immediately discontinued until these parameters normalize. The CALCIJEX® dose should then be reinitiated at a lower dose. Doses may need to be reduced as the PTH levels decrease and commensurate with PTH, serum calcium and phosphorous levels.

Most patients undergoing hemodialysis respond to doses between 0.5 and 3 mcg (0.01 to 0.05 mcg/kg) three times per week.

Administration

CALCIJEX® can be administered as a bolus dose intravenously through the catheter at the end of hemodialysis.

OVERDOSAGE

For management of a suspected drug overdose, contact your regional Poison Control Centre.

Administration of CALCIJEX® (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 CALCIJEX® may cause similar abnormalities (see **WARNINGS AND PRECAUTIONS** and **ADVERSE REACTIONS**). 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 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, CALCIJEX® therapy may be reinstituted at a dose of 0.5 mcg 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 CALCIJEX® 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.

ACTION AND CLINICAL PHARMACOLOGY

Mechanism of Action

There is evidence that calcitriol (1,25-$(OH)_2$ D_3) is the biologically active form of vitamin D responsible, in part, for maintaining calcium and phosphorous homeostasis.

Calcitriol stimulates the intestinal transport of calcium. The active transport of calcium occurs primarily in the duodenum. Although the exact mechanism by which this occurs is uncertain, most evidence suggests that calcitriol enhances calcium movement across the brush border into the intestinal cells. Evidence further suggests that a specific calcium-binding protein, which is stimulated by calcitriol, acts to augment the entry of calcium into the cell. In addition, calcitriol may exert a nuclear effect by directing the synthesis of messenger RNA which in turn stimulates the synthesis of new proteins which are thought to be involved in the calcium transport process.

Bone is the second tissue at which calcitriol acts to mobilize calcium for circulation. Whether calcitriol can directly stimulate bone mineralization or whether it leads to mineralization by increasing the levels of calcium and phosphate in the extracellular fluid surrounding bone remains unclear. Cytosolic receptor proteins for calcitriol in bone cells have been isolated.

In acutely uremic rats, calcitriol has been shown to stimulate intestinal calcium absorption. In bone, calcitriol, in conjunction with parathyroid hormone, stimulates resorption of calcium; and in the kidney, calcitriol increases the tubular reabsorption of calcium.

Calcitriol stimulates bone resorption which serves to mobilize calcium for the circulation, when an intestinal source of calcium is absent. This effect is related to the role of vitamin D in maintaining the homeostasis of calcium and phosphorous in plasma. In addition, calcitriol may interact directly with osteoblasts.

The mechanism whereby calcitriol acts on the kidney and parathyroid gland remains unclear. Evidence suggests that calcitriol may enhance renal tubular calcium reabsorption. Recent studies in parathyroidectomized animals suggest that calcitriol has a direct proximal tubular action in regulating the secretion of PTH by the parathyroid gland. Evidence suggests that calcitriol may affect the secretion of PTH through a direct action on the parathyroid gland and may be involved in the regulation of PTH synthesis and/or its secretion.

Pharmacodynamics

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.

Pharmacokinetics

Absorption

Not applicable as CALCIJEX® is an injectable drug.

Distribution

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 $alpha_2$ globulins. The pharmacologic activity of an administered dose of calcitriol is about 3 to 5 days.

Metabolism

Two metabolic pathways for calcitriol have been identified: conversion to 1,24,25-$(OH)_3D_3$ and to calcitroic acid.

STORAGE AND STABILITY

Store between 15 and 25°C; however, brief exposure up to 40°C does not adversely affect the product. Protect from light.

SPECIAL HANDLING INSTRUCTIONS

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

Discard unused portion.

DOSAGE FORMS, COMPOSITION AND PACKAGING

CALCIJEX® (calcitriol injection) is a sterile, isotonic, clear, aqueous solution for intravenous injection and is supplied in 1 mL ampoules available in 2 strengths: 1 mcg or 2 mcg of calcitriol.

Listing of Non-Medicinal Ingredients

Each 1 mL ampoule contains 1 or 2 mcg calcitriol, anhydrous dibasic sodium phosphate (buffer), edetate disodium, monobasic sodium phosphate monohydrate (buffer), polysorbate 20, sodium ascorbate and sodium chloride. The pH of the solution is approximately 7. It does not contain a preservative.

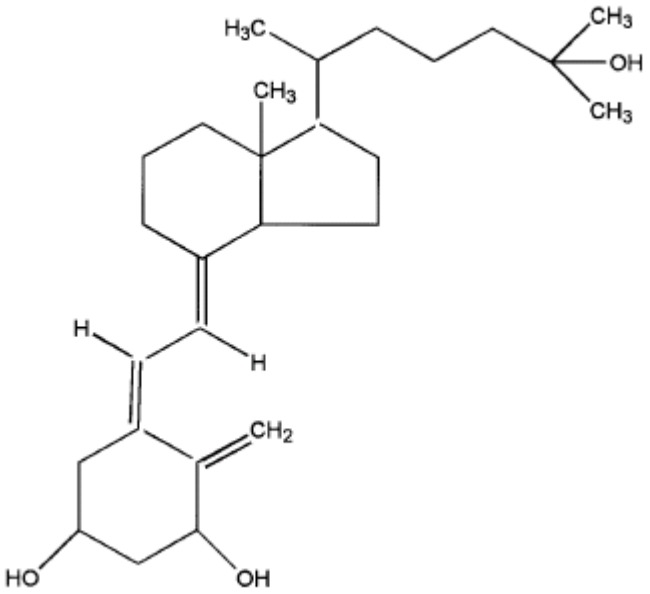
PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

Drug Substance

Proper name:	calcitriol	
Chemical name:	(5Z,7E)-9,10-secocholesta-5,7,10(19)-triene-1α,3β,25-triol	
Molecular formula and molecular mass:	$C_{27}H_{44}O_3$	416.64

Structural formula:



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

CLINICAL TRIALS

Study Demographics and Trial Design

Table 2. Summary of Patient Demographics for Clinical Trials in Management of Hypocalcemia in Patients Undergoing Chronic Renal Dialysis

Study #	Trial Design	Dosage, Route of Administration and Duration	Study Subjects (N=Number)	Mean Age (Range)	Gender (%M/F) Race (%B/C)
CP5691	Unblinded, multi-dose, three-period study	Initial dose: 0.25-1.0 mcg 3 times weekly post-dialysis Dose increases: weekly increments of 0.25 to 0.50 mcg Maximum dose: 1.75-4.0 mcg 3 times weekly post-dialysis No comparator: each patient served as his/her own control Intravenous Period 1: pre-treatment (3 weeks)[1] Period 2: treatment (4-8 weeks)[2] Period 3: post-treatment (3 weeks)[1]	20	48.3 years (21-67)	Gender: 55/45 Race: 75/25

1: No vitamin D therapy.

2: CALCIJEX® administered 3 times weekly, post-hemodialysis; 2 to 6 weeks of dose adjustment followed by 2 weeks at optimal dose.

Definitions: B/C = Black / Caucasion; M/F = Male / Female.

Study Results

The safety and efficacy of CALCIJEX® (calcitriol injection) in the management of hypocalcemia in patients undergoing maintenance hemodialysis for chronic renal disease were investigated in Study 1. Twenty patients received calcitriol; doses were titrated for each patient based upon serum total calcium response.

The primary parameter for determining efficacy was serum total calcium. Serum levels of ionized calcium, phosphorus, magnesium, and alkaline phosphatase were also measured to determine the effect, if any, of calcitriol on these parameters. A significant increase ($p < 0.001$) in serum total calcium (CaT) of 1.7 ± 0.2 mcg/dL was observed during the last two weeks of treatment compared with the last week of the pre-treatment period, where CaT decreased by 1.2 ± 0.2 mcg/dL ($p < 0.001$). Mean serum C-terminal parathyroid hormone (PTH) levels decreased to 50% of pre-treatment values during Period 2 and returned to pre-treatment levels by the end of Period 3.

DETAILED PHARMACOLOGY

In human studies, calcitriol is rapidly absorbed from the intestine. Vitamin D metabolites are known to be transported in blood, bound to a specific $alpha_2$ globulin.

A vitamin D-resistant state may exist in uremic patients because of the failure of the kidney to adequately convert precursors to the active compound, calcitriol.

Recent reports have indicated that vitamin D analogues may cause a deterioration of renal function in chronic renal failure patients who are not on renal dialysis.

Calcitriol administered intravenously or intraperitonealy was found to be a simple and effective means to suppress secondary hyperparathyroidism in patients undergoing hemodialysis or ambulatory peritoneal dialysis.

TOXICOLOGY

Acute Toxicity

The acute toxicity of calcitriol administered by a variety of routes was studied in mice and rats. The lethal dosages are shown in **Table 3**.

Table 3. Acute Toxicity of CALCIJEX® in Mice and Rats Median Lethal Dosages

Species	Route	LD_{50} mcg/kg
Mice	intraperitoneal	1900
	oral	1350
	subcutaneous	145
Rat	subcutaneous	66

Definition: LD_{50} = Lethal dose that killed 50% of the animals.

The primary signs of toxicity included decreased lacrimation, ataxia, body temperature decrease and somnolence.

Subacute Toxicity

Rat

Neonatal rats (15/sex/dose) were administered calcitriol once daily for 14 to 16 days at oral doses of 0, 0.06, 0.19 and 0.64 mcg/kg/day. Five controls, four low-dose, two mid-dose, and fifteen high-dose pups died during the two-week treatment period. Some of the deaths were attributed to dosing accidents, but more than half of the deaths in the high-dose group were drug-related. An additional 6 high-dose pups died during a 7-week "recovery" period. Drug-related deaths resulted from metastatic calcification alone or in combination with the stress imposed by weaning.

Many high-dose pups were considerably smaller than pups in the other groups, exhibited subcutaneous white patches on head and lower jaw and developed splayed limbs, and had higher serum calcium levels than controls. Gross and histologic changes reflective of metastatic calcification were seen in a number of organs including kidney and heart. Nephrocalcinosis was the most consistent histologic lesion noted.

No significant signs of toxicity were noted in low-dose pups examined soon after final treatment, but 3 of 8 low-dose animals examined after the 7-week "recovery" period exhibited a minimal degree of renal calcification. The observed effects, were deemed to be entirely attributable to the induction of hypercalcemia in previously normocalcemic animals.

Neonatal rats (15/sex/dose) were treated intramuscularly once daily for 14 to 16 consecutive days with calcitriol at doses of 0, 0.13, 0.38 and 1.28 mcg/kg/day. The majority of the animals were killed following the last treatment, but a number of pups were maintained on a 7-week "recovery" period.

One control, one mid-dose and two high-dose pups died during the two-week treatment period; six additional mid-dose and seven additional high-dose pups died during the "recovery" period. Drug-related deaths resulted from metastatic calcification or renal tubular necrosis.

Subcutaneous white patches on the head and splayed limbs were observed at the high-dose, 1.28 mcg/kg/day. Mean body weights of males in all groups were significantly less than the control mean. Serum calcium levels were elevated in all animals receiving calcitriol.

Gross pathologic changes included white streaks of spots on the liver, heart and diaphragm. Metastatic calcification was the principal treatment-related histologic lesion found in all treatment groups. Nephrocalcinosis, gastric mineralization and calcium deposition in heart, aorta and respiratory system were consistently seen. Residual calcium deposits tended to be less severe in the tissues of the recovery animals.

Rats (10/sex/dose) were injected intramuscularly with calcitriol at dosage levels of 0, 0.03, 0.13 and 0.64 mcg/kg/day for 14 days. Dosage groups consisted of 10 males and 10 females. There were six deaths at 0.64 mcg/kg/day during the study. Apparent signs of toxicity observed at 0.13 and 0.64 mcg/kg/day included labored breathing, reduced motor activity, corneal opacities, decreased defecation and elevated serum calcium levels.

Elevation in blood urea nitrogen (BUN) and decreases in total serum protein and potassium, body weight and food consumption were noted at 0.64 mcg/kg/day. Microscopic lesions found included calcification of the myocardial fibers, arteriosclerosis of the coronary and aortic arteries, nephrolithiasis, calcification of the stomach and the large intestine and thymus hypoplasia. The only histopathological change observed at 0.03 and 0.13 mcg/kg/day was an increase in phagocytosis by the large cortical cells of the thymus. The thymus hypoplasia was considered to be attributable to a high degree of stress consequent upon debilitation and possibly severe electrolyte changes. Corneal opacities observed were not considered by the authors to be drug-related. The maximum tolerated dosage was 0.03 mcg/kg/day in this study.

Immature rats (10/sex/dose) were administered calcitriol once daily for a minimum of six weeks beginning on postnatal Day 15. At doses of 0, 0.02, 0.06 and 0.20 mcg/kg/day, no evidence of toxicity attributable to calcitriol administration was noted. The "no-effect" level was determined to be 0.20 mcg/kg/day in these animals.

Dog

Dogs (3/sex/dose) were injected intramuscularly with calcitriol at dosage levels of 0, 0.02, 0.06 and 0.21 mcg/kg/day for 14 days. There were no deaths in the study. Thinness, dehydration, decreased activity, ocular discharge, decreased body weight and food consumption were observed at 0.06 and 0.21 mcg/kg/day. Significantly elevated serum calcium levels were noted at the two higher dosage levels (0.06 and 0.21 mcg/kg/day). Calcium deposition was not evident in the tissues at any dosage level. Therefore, a dosage of 0.02 mcg/kg/day was considered to be the maximum-tolerated dose in this study.

Mutagenicity and Carcinogenicity

There was no evidence of mutagenicity as studied by the Ames Method. Concentrations as high as 1000 mcg were found to be non mutagenic to Salmonella strain.

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

Reproduction and Teratology

Fertility and General Reproductive Performance

Calcitriol was administered orally to male rats for 60 days prior to mating and to female rats (24/dosage) from 14 days prior to mating until sacrifice of the females either on gestation Day 13 or on lactation day 21. Dosages tested were 0, 0.002, 0.08 and 0.30 mcg/kg/day. No adverse effects on either fertility or neonatal development were noted. All F_0 generation animals survived. It was concluded that under the conditions of this study there were no adverse effects observed on either reproductive parameters or the pups themselves at dosages as great as 0.30 mcg/kg/day of calcitriol.

Teratology

Calcitriol was orally administered to pregnant rats (20/dosage) from gestation Day 7 to gestation Day 15. Dosages tested were 0 (control), 0.02, 0.08 and 0.30 mcg/kg/day. Numbers of fetuses, implantation sites and resorption sites were counted. Fetuses were weighed and examined for external abnormalities. One-third of the fetuses in each litter were examined for visceral abnormalities, two-thirds of the fetuses in each litter were prepared for skeletal evaluation.

Maternal weight gain was significantly reduced in dams receiving 0.3 mcg/kg/day. No biologically significant adverse effects on rat embryonic or fetal development were observed at any of the tested dosages. There was no evidence that calcitriol was teratogenic in rats.

Calcitriol was orally administered to pregnant rabbits from gestation Day 7 to gestation Day 18. Dosages tested were 0, 0.02, 0.08 and 0.30 mcg/kg/day for 31, 16, 15 and 16 rabbits respectively. Numbers of live or dead pups, resorption sites, corpora lutea and implantation sites were recorded. Fetuses were examined for external abnormalities, dissected to check for visceral abnormalities and prepared for skeletal evaluation.

Marked weight loss occurred among high-dose dams; 3 high-dose animals died (2 clearly as a result of hypervitaminosis D). The mean litter size was reduced and the resorption frequency was increased among high-dose dams. Although not statistically significant, these changes were considered to be biologically significant by the authors. The percentage of viable pups that survived 24 hours of incubation was significantly decreased at the highest dose. The average fetal body weight was slightly reduced at this dosage as well. While the overall incidence of external, visceral and skeletal anomalies was comparable among all groups, one entire litter in each of the 0.08 and 0.30 mcg/kg groups exhibited multiple external malformations. These malformations included open eyelids, microphthalmia, cleft palate, reduced long bones, gnarled paws, pes caves, shortened ribs and sternebral defects in 9 mid-dose fetuses and open eyelids, reduced long bones and shortened ribs in 6 high-dose fetuses. The authors concluded that while

the low incidence of litters involved, the lack of clear dose-response and the lack of statistical significance made it uncertain that these abnormalities were related to calcitriol administration, this possibility could not be discounted.

Perinatal and Postnatal Studies

Calcitriol was orally administered to pregnant rats (20/dosage) from gestation Day 15 through Day 21 of lactation. Dosages tested were 0, 0.02, 0.08 and 0.30 mcg/kg/day. Hypercalcemia and hypophosphatemia were noted in dams receiving 0.08 and 0.30 mcg/kg/day. Serum sampled from pups on postnatal Day 21 was hypercalcemic in both the mid- and high-dose groups. Aside from this no adverse effects on reproduction or pup growth and survival were observed at the tested dosages.

Special Studies

Vein-irritation Study

Calcitriol was given intravenously into an ear vein in rabbits at doses of 5 mcg/kg which is ten times the proposed maximum dosage. Calcitriol was found not to be irritating to veins.

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PART III: CONSUMER INFORMATION

PrCALCIJEX®
calcitriol injection

This leaflet is PART III of a three-part "Product Monograph" published when CALCIJEX® was approved for sale in Canada and is designed specifically for consumers. This leaflet is a summary and will not tell you everything about CALCIJEX®. Contact your doctor or pharmacist if you have any questions about the drug.

ABOUT THIS MEDICATION

What the medication is used for:

- The management of hypocalcemia (low calcium levels) in patients undergoing chronic renal dialysis.

What it does:

CALCIJEX® helps to regulate calcium levels in the blood.

When it should not be used:

You should not use CALCIJEX® if you:

- are allergic to calcitriol, or vitamin D or its analogues and derivatives, or any of the non-medicinal ingredients in CALCIJEX®
- have high calcium levels (hypercalcemia)
- have high vitamin D levels (vitamin D toxicity).

What the medicinal ingredient is:

calcitriol

What the important non-medicinal ingredients are:

Anhydrous dibasic sodium phosphate, edentate disodium, monobasic sodium phosphate monohydrate, polysorbate 20, sodium ascorbate, sodium chloride.

What dosage forms it comes in:

CALCIJEX® is supplied in 1 mL ampoules containing 1 mcg or 2 mcg of calcitriol.

WARNINGS AND PRECAUTIONS

BEFORE you use CALCIJEX® talk to your doctor or pharmacist if:

- you are allergic to vitamin D or to any ingredient of CALCIJEX®
- you are on digitalis
- you are pregnant or nursing
- you are taking other vitamin D product or its derivatives.

The safety and effectiveness of CALCIJEX® in children under 18 years of age have not been established.

INTERACTIONS WITH THIS MEDICATION

Drugs that may interact with CALCIJEX® include:

- digitalis
- anti-seizure medications (e.g., diphenylhydantoin and barbiturates)
- antacids containing magnesium
- corticosteroids
- thiazide diuretics (e.g., hydrochlorothiazide)

PROPER USE OF THIS MEDICATION

The effectiveness of CALCIJEX® therapy is based on the assumption that each patient is receiving an adequate daily intake of calcium.

To ensure that each patient receives an adequate daily intake of calcium, the physician may either prescribe a calcium supplement or instruct the patient in appropriate dietary measures.

Usual dose:

The dose will be decided by your doctor and be given through a catheter three times per week at the end of hemodialysis. You should also take your prescribed daily dose of calcium and follow the instructions on diet and supplement intake.

Overdose:

If you think you have been given more CALCIJEX® than you should have, talk to your doctor or nurse or contact a poison control center.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

The most common side effect of CALCIJEX® is hypercalcemia (high calcium levels).

Early symptoms (within first few months of use of drug) of hypercalcemia and vitamin D toxicity include: weakness, headache, feeling sleepy, nausea, irregular heart beat, excessive thirst, vomiting, dry mouth, constipation, abdominal pain, loss of appetite, discomfort or unpleasant sensation in the upper abdomen, muscle pain, bone pain, and metallic taste.

Late symptoms (with continued [chronic] use of drug): too much protein in your urine, loss of appetite, feeling indifferent or lack of emotion, abnormal heart beat, swelling or infection near your eyelid, decreased sex drive, loss of water/not enough water in your body, abnormal changes in bone and muscle development, deposit of calcium salt in tissues, excessive nitrogen in your urine,

elevated liver function tests, high cholesterol, high blood pressure, feeling too hot, too much calcium in your kidneys, needing to urinate at night, inflammation of the pancreas, sensitivity to light, excessive thirst, increased need to urinate, itching, loss of contact with reality, runny nose, changes in sensation such as pain, touch, pressure and temperature sensation, urinary tract infections, and weight loss.

If these side effects do not go away or if you experience other side effects which are not listed above, talk to your doctor right away.

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM

Symptom/effect		Talk with your doctor or pharmacist		Stop taking drug and call your doctor or pharmacist
		Only if severe	In all cases	
Common	elevated blood calcium		√	
	allergic reactions such as:			√
	- hives			√
	- difficulty breathing			√
	- rapid drop in blood pressure			√
	dehydration such as:		√	
	- light-headedness		√	
	- dizziness		√	
	- weakness		√	
	- dry mouth		√	
	- increased thirst		√	
	- decreased production of urine		√	

This is not a complete list of side effects. For any unexpected effects while taking CALCIJEX®, contact your doctor or pharmacist.

HOW TO STORE IT

Store between 15 and 25°C. Protect from light.

REPORTING SUSPECTED SIDE EFFECTS

You can report any suspected adverse reactions associated with the use of health products to the Canada Vigilance Program by one of the following 3 ways:

- **Report on line at:** www.healthcanada.gc.ca/medeffect
- **Call toll-free at 1-866-234-2345**
- **Complete a Canada Vigilance Reporting Form and:**
  - **Fax toll-free to 1-866-678-6789**
  - **Mail to: Canada Vigilance Program**
    Health Canada
    Postal Locator 0701D
    Ottawa, ON K1A 0K9

Postage paid labels, Canada Vigilance Reporting Form and the adverse reaction reporting guidelines are available on the MedEffect™ Canada Web site at http://www.healthcanada.gc.ca/medeffect

NOTE: Should you require information related to the management of side effects, contact your health professional. The Canada Vigilance Program does not provide medical advice.

MORE INFORMATION

This document plus the full product monograph, prepared for health professionals can be found at:

www.abbvie.ca
or by contacting the sponsor, AbbVie Corporation, St-Laurent, QC, H4S 1Z1 at 1-888-704-8271.

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