# PRODUCT MONOGRAPH

# HECTOROL®
# (Doxercalciferol)

## 2.5 µg Capsules

## VITAMIN D ANALOGUE

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## PRODUCT MONOGRAPH

## NAME OF PRODUCT

HECTOROL® (doxercalciferol) Capsules

## THERAPEUTIC CLASSIFICATION

Vitamin D Analogue

## ACTIONS AND CLINICAL PHARMACOLOGY

Human supply of vitamin D depends on two sources: (1) exposure to the ultraviolet rays of the sun for conversion of 7-dehydrocholesterol in the skin to vitamin $D_3$ (cholecalciferol) and (2) dietary supplementation with either vitamin $D_2$ (ergocalciferol) or vitamin $D_3$. Vitamin $D_2$ and vitamin $D_3$ must be metabolically activated in the liver and kidney before becoming fully active on target tissues. The initial step in this activation process is the introduction of an hydroxyl group in the side chain at C-25 by an hepatic enzyme, CYP 27 (a vitamin D-25-hydroxylase). The products of this reaction are 25-(OH)$D_2$ and 25-(OH)$D_3$, respectively. Further hydroxylation of these metabolites occurs in the mitochondria of kidney tissue, catalyzed by renal 25-hydroxyvitamin D-1-$\alpha$-hydroxylase to produce 1$\alpha$,25-$(OH)_2D_2$, the primary biologically active form of vitamin $D_2$, and 1$\alpha$,25-$(OH)_2D_3$ (calcitriol), the biologically active form of vitamin $D_3$.

Calcitriol (1$\alpha$,25-$(OH)_2D_3$) and 1$\alpha$,25-$(OH)_2D_2$ regulate blood calcium at levels required for essential body functions. Specifically, the biologically active vitamin D metabolites control the intestinal absorption of dietary calcium, the tubular reabsorption of calcium

by the kidney and, in conjunction with parathyroid hormone (PTH), the mobilization of calcium from the skeleton. They act directly on bone cells (osteoblasts) to stimulate skeletal growth, and on the parathyroid glands to suppress PTH synthesis and secretion. These functions are mediated by the interaction of these biologically active metabolites with specific receptor proteins in the various target tissues. In uremic patients, deficient production of active vitamin D metabolites leads to secondary hyperparathyroidism, which contributes to the development of metabolic bone disease in patients with renal failure.

Doxercalciferol is absorbed from the gastrointestinal tract, and activated by CYP 27 in the liver to form 1α,25-$(OH)_2D_2$ (major metabolite) and 1α,24-dihydroxyvitamin $D_2$ (minor metabolite). Activation of doxercalciferol does not require the involvement of the kidneys.

In healthy volunteers, peak blood levels of 1α,25-$(OH)_2D_2$, the major metabolite of doxercalciferol, are attained at 11-12 hours after repeated oral doses of 5 to 15 µg of HECTOROL (doxercalciferol) and the mean half-life of 1α,25-$(OH)_2D_2$ elimination is approximately 32 to 37 hours with a range of up to 96 hours. The half-life in patients with end-stage renal disease (ESRD) on dialysis appears to be similar. Hemodialysis causes a temporary increase in 1α,25-$(OH)_2D_2$ mean concentrations, presumably due to volume contraction. 1α,25-$(OH)_2D_2$ is not removed from blood during hemodialysis.

**Clinical Studies**

The safety and effectiveness of HECTOROL were evaluated in two clinical studies in patients with chronic renal disease on hemodialysis. After randomization to two groups, eligible patients underwent an 8-week washout period during which no vitamin D derivatives were administered to either group. Subsequently, all patients received HECTOROL in an open-label fashion for 16 weeks followed by a double-blind period of 8 weeks during which patients received either HECTOROL or placebo. The initial dose of HECTOROL during the open-label phase was 10 µg after each dialysis session (3 times weekly) for a total of 30 µg per week. The dosage of HECTOROL was adjusted as necessary by the investigator in order to achieve intact parathyroid hormone (iPTH) levels within a targeted range of 150 to 300 pg/mL [16.5 to 33 pmol/L]. The maximum dosage was limited to 20 µg after each dialysis (60 µg/week). If at any time during the trial iPTH fell below 150 pg/mL [16.5 pmol/L], HECTOROL was immediately suspended and restarted at a lower dosage the following week.

*Results:*

Decreases in plasma iPTH from baseline values were calculated, using, as baseline, the average of the last 3 values obtained during the 8-week washout phase and are displayed in the table below.

| | | iPTH (pg/mL) [pmol/L]<br>means ± s.d. (n*)<br>p Value v. Baseline<br>p Value v. Placebo | |
|---|---|---|---|
| | | **Weeks 1-16 - HECTOROL<br>Weeks 17-24 - HECTOROL** | **Weeks 1-16 - HECTOROL<br>Weeks 17-24 - Placebo** |
| **Study A** | Baseline | 797.2 ± 443.8 (30) [87.69 ± 48.82]<br>n.a.<br>0.97 | 847.1 ± 765.5 (32) [93.18 ± 84.21] |
| | Week 16 (open-label)<br>(mean dose = 14.2 µg/week) | 384.3 ± 397.8 (24) [42.27 ± 43.76]<br><0.001<br>0.72 | 526.5 ± 872.2 (29) [57.91 ± 95.94]<br><0.001 |
| | Week 24 (double-blind)<br>(mean dose = 15.3 µg/week) | 404.4 ± 262.9 (21) [44.48 ± 28.92]<br><0.001<br>0.008 | 672.6 ± 356.9 (24) [73.99 ± 39.26]<br>0.70 |
| **Study B** | Baseline | 973.9 ± 567.0 (41) [107.13 ± 62.37]<br>n.a.<br>0.81 | 990.4 ± 488.3 (35) [108.94 ± 53.71] |
| | Week 16 (open-label)<br>(mean dose = 19.5 µg/week) | 476.1 ± 444.5 (37) [52.37 ± 48.89]<br><0.001<br>0.91 | 485.9 ± 443.4 (32) [53.45 ± 48.77]<br><0.001 |
| | Week 24 (double-blind)<br>(mean dose = 16.4 µg/week) | 459.8 ± 443.0 (35) [50.58 ±48.73]<br><0.001<br><0.001 | 871.9 ± 623.6 (30) [95.91 ± 68.60]<br><0.065 |

* all subjects; last value carried to discontinuation.

In both studies, HECTOROL treatment resulted in a statistically significant reduction from baseline in mean iPTH levels during the open-label period. During the double-blind period (weeks 17 to 24), the reduction in mean iPTH levels was maintained in the HECTOROL treatment group compared to a return to near baseline in the placebo group. Results of these studies showed that mean plasma iPTH stabilized at 300-400 pg/mL [33-44 pmol/L], with a long term maintenance dose of 15-20 µg/week of HECTOROL. This decrease in the administered dose (from an initial dose of 30 µg/week) reflected continued dose titration to maintain the iPTH level within the targeted range and to manage any incidences of hypercalcemia or hyperphosphatemia. Only 2.2% (3/138) of patients required the maximum dose of 60 µg/week.

In the clinical trials, the values for iPTH varied widely from patient to patient and from week to week for individual patients. The following table shows the numbers of patients

within each group who achieved and maintained iPTH levels below 300 pg/mL [33pmol/L] during the open-label and double-blind phases.

| | | Number of times iPTH ≤ 300 pg/mL [33 pmol/L] | | | | | |
|---|---|---|---|---|---|---|---|
| | | Only 1 | | Only 2 | | Only 3 | |
| | | HECTOROL | Placebo | HECTOROL | Placebo | HECTOROL | Placebo |
| Study A | Weeks 1-16 (open-label) | 2/30 | 2/32 | 0/30 | 0/32 | 22/30 | 21/32 |
| | Weeks 17-24 (double-blind) | 0/24 | 9/29 | 3/24 | 1/29 | 17/24 | 5/29 |
| Study B | Weeks 1-16 (open-label) | 2/41 | 4/35 | 1/41 | 0/35 | 29/41 | 21/35 |
| | Weeks 17-24 (double-blind) | 2/37 | 6/32 | 1/37 | 4/32 | 26/37 | 4/32 |

During the 8-week double-blind phase, more patients achieved and maintained the target range of values for iPTH with HECTOROL than with placebo.

## INDICATIONS AND CLINICAL USE

HECTOROL (doxercalciferol) is indicated for the reduction of elevated iPTH levels in the management of secondary hyperparathyroidism in patients undergoing chronic renal dialysis.

## CONTRAINDICATIONS

HECTOROL (doxercalciferol) should not be given to patients with hypercalcemia or current evidence of vitamin D toxicity.

## WARNINGS

Overdosage of any form of vitamin D is dangerous (see also **SYMPTOMS AND TREATMENT OF OVERDOSAGE**). Progressive hypercalcemia due to overdosage of vitamin D and its metabolites may be so severe as to require emergency attention. Acute hypercalcemia may exacerbate tendencies to cardiac arrhythmias and seizures and will affect the action of digitalis drugs. Chronic hypercalcemia can lead to generalized vascular calcification and other soft-tissue calcification. The serum calcium times serum phosphorus (Ca X P) product should not be allowed to exceed 5.7 (using mmol/L units). Radiographic evaluation of suspect anatomical regions may be useful in the early detection of this condition.

Since doxercalciferol is a precursor for $1\alpha,25\text{-}(OH)_2D_2$, a potent metabolite of vitamin D, pharmacologic doses of vitamin D and its derivatives should be withheld during doxercalciferol treatment to avoid possible additive effects and hypercalcemia.

Oral calcium-based or other non-aluminum containing phosphate binders and a low phosphate diet should be used to control serum phosphorus levels in patients undergoing dialysis. Uncontrolled serum phosphorus exacerbates secondary hyperparathyroidism and can lessen the effectiveness of doxercalciferol in reducing blood PTH levels. After initiating doxercalciferol therapy, the dose of phosphate binders should be decreased to correct persistent mild hypercalcemia (2.65 - 2.75 mmol/L for 3 consecutive determinations), or increased to correct persistent mild hyperphosphatemia (2.26 - 2.58 mmol/L for 3 consecutive determinations).

Magnesium containing antacids and HECTOROL (doxercalciferol) should not be used concomitantly in patients on chronic renal dialysis because such use may lead to the development of hypermagnesemia.

## PRECAUTIONS

### *General*

The principal adverse effects of treatment with HECTOROL (doxercalciferol) are hypercalcemia, hyperphosphatemia, and oversuppression of PTH. Prolonged hypercalcemia can lead to calcification of soft tissues, including the heart and arteries, and hyperphosphatemia can exacerbate hyperparathyroidism. Oversuppression of PTH may lead to adynamic bone syndrome. All of these potential adverse effects should be managed by regular patient monitoring and appropriate dosage adjustments. During treatment with HECTOROL, patients usually require dose titration, as well as adjustment in co-therapy (i.e., dietary phosphate binders) in order to effect and sustain PTH suppression while maintaining serum calcium and phosphorus within prescribed ranges.

In four adequate and well-controlled studies, the incidence of hypercalcemia and hyperphosphatemia increased during therapy with HECTOROL. The observed increases during HECTOROL treatment, although occurring at a low rate, underscore the importance of regular safety monitoring of serum calcium and phosphorus levels throughout treatment. Patients with higher pre-treatment serum levels of calcium or phosphorus were more likely to experience hypercalcemia or hyperphosphatemia. Therefore, HECTOROL should not be given to patients with a recent history of hypercalcemia or hyperphosphatemia, or evidence of vitamin D toxicity.

***Information for the Patient***

The patient, spouse, or guardian should be informed about compliance with dosage instructions, adherence to instructions about diet and calcium supplementation and the use of nonprescription drugs that have not been approved by the treating physician. Patients should also be carefully informed about the symptoms of hypercalcemia (see **ADVERSE REACTIONS** section).

***Laboratory Tests***

For dialysis patients, serum or plasma PTH and serum calcium, phosphorus, and alkaline phosphatase should be determined periodically. In the early phase of treatment, serum calcium and phosphorus should be determined weekly.

***Drug Interactions***

No formal drug-drug interaction studies have been completed with doxercalciferol. All vitamin D compounds, when administered with digitalis, may increase the potential for hypercalcemia and cardiac arrythmias. Cholestyramine has been reported to reduce intestinal absorption of fat-soluble vitamins; e.g., it may impair intestinal absorption of doxercalciferol. Magnesium-containing antacid and doxercalciferol should not be used concomitantly, because such use may lead to the development of hypermagnesemia. The use of mineral oil or other substances that may affect absorption of fat may influence the absorption and availability of HECTOROL. Due to possible increased risk for hypercalcemia, pharmacologic doses of Vitamin D and its derivatives should be withheld during doxercalciferol treatment. Calcium supplementation and calcium-based phosphate binders may need to be adjusted when co-administered with doxercalciferol, based on regular analysis of serum calcium and phosphorus levels. Although not examined specifically, hepatic enzyme inducers (e.g., phenobarbitol) and cytochrome P450 inhibitors (e.g., ketoconazole) may potentially interfere with Vitamin D metabolism

affecting the 25-hydroxylation of vitamin D. Patients under concurrent treatment with such agents may require dosage adjustments

Analysis of 48 concomitant medications used by subjects participating in the two pivotal trials suggested that nifedipine may accelerate the onset of PTH suppression. Also, 10 (see Table below) medications were identified that may have influence on plasma levels of $1\alpha,25(OH)_2D_2$. Further studies are required to confirm and expand these preliminary observations.

Concomitant use of diphenhydramine, guaifensisen, and erythropoietin were found to increase the chance that a subject would experience hypercalcemia. Conversely, enalapril decreased this chance.

Guaifensisen, hepatitis B vaccine and diphenhydramine were found to increase the chance that a subject would experience hyperphosphatemia, while nitroglycerin and acetylsalicylic acid decreased this chance.

Use of amoxicillin and ferrous sulfate with doxercalciferol were found to increase the likelihood of a subject experiencing an adverse event having a possible, probable, known, or unknown relationship to the drug test. Hypertonic saline, however, was found to decrease this chance.

**Concomitant medications observed to have a statistically significant effect on plasma levels of $1\alpha,25(OH)_2D_2$.**

| Influence on $1\alpha,25(OH)_2D_2$ | Concomitant medications | P-value |
|---|---|---|
| Increases | Acetaminophen/Codeine | 0.004 |
| Decreases | Amoxicillin | 0.048 |
| Decreases | Acetylsalicylic Acid | 0.009 |
| Increases | Cimetidine | 0.030 |
| Decreases | Dipyridamole | 0.015 |
| Decreases | Erythromycin | 0.036 |
| Increases | Hydrocodone | 0.034 |
| Increases | Influenza Vaccine | 0.033 |
| Decreases | Promethazine | 0.007 |
| Decreases | Sodium Bicarbonate | 0.023 |

***Drug-Demographic and Drug-Disease Interactions***

No formal pharmacokinetic and pharmacodynamic studies have been undertaken.

An analysis has been completed which compared treatment-related adverse events (including hypercalcemia and hyperphosphatemia) observed during the two pivotal trials to the primary cause of End-Stage Renal Disease (ESRD), identified from subject medical histories. Since there was a wide variation in the descriptive terms used between the investigators, a standardized listing of the diagnoses was compiled.

The primary causes for ESRD in subjects in the two pivotal trials are as follows:

| | | |
|---|---|---|
| Congenital Dysplasia | Obstructive Disease | Nephrosclerosis |
| Nephrotoxicity | Alport's Syndrome | Diabetes Mellitus |
| Reflux Nephropathy | Cystic Disease | Hypertension |
| Glomerulosclerosis | Glomerulonephritis | Lupus Erythematosus |

The influence of these primary diagnosis on the likelihood that a subject would experience hypercalcemia, hyperphosphatemia, or an adverse event during treatment with doxercalciferol was evaluated by comparing the percentage of subjects experiencing each type of adverse event having a given diagnosis with the percentage of subjects not experiencing the same event having that same diagnosis. Differences between corresponding percentages were analyzed by the Chi-squared test.

Subjects with lupus erythematosus (4 subjects) were observed to have a higher chance of expereincing hyperphosphatemia than those that did not have the diagnosis. Similarly, a higher rate of hypercalcemia was detected for subjects with glomerulosclerosis. There was an increase in adverse event rate in subjects with cystic disease, based on five subjects. Due to the small numbers of subjects included in these comparisons, further analyses in larger study populations are needed to confirm these preliminary observations.

***Use in Pregnancy***

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

***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 doxercalciferol, 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.

***Pediatric Use***

Safety and efficacy of HECTOROL in pediatric patients have not been established.

***Hepatic Insufficiency***

Since patients with hepatic insufficiency may not metabolize HECTOROL appropriately, the drug should be used with caution in patients with impaired hepatic function. More frequent monitoring of iPTH, calcium, and phosphorus levels should be done in such individuals.

## ADVERSE REACTIONS

HECTOROL (doxercalciferol) has been evaluated for safety in clinical studies in 165 patients with chronic renal disease on hemodialysis. In two placebo-controlled, double-blind, multicenter studies, discontinuation of therapy due to any adverse event occurred in 2.9% of 138 patients treated with HECTOROL for four to six months (dosage titrated to achieve target iPTH levels, (See ACTIONS and CLINICAL PHARMACOLOGY) and in 3.3% of 61 patients treated with placebo for two months. Adverse events occurring in the HECTOROL group at a frequency of 2% or greater and more frequently than in the placebo group are presented in the following table.

| Adverse Events Reported by ≥2% of HECTOROL treated patients and more frequently than placebo during the double-blind phase of two Clinical Studies | | |
|---|---|---|
| **Adverse Event** | **HECTOROL (n=61) %** | **Placebo (n=61) %** |
| **Body as a Whole** | | |
| Abscess | 3.3 | 0.0 |
| Headache | 27.9 | 18.0 |
| Malaise | 27.9 | 19.7 |
| **Cardiovascular System** | | 4.9 |
| Bradycardia | 6.6 | |
| **Digestive System** | | |
| Anorexia | 4.9 | 3.3 |
| Constipation | 3.3 | 3.3 |
| Dyspepsia | 4.9 | 1.6 |
| Nausea/Vomiting | 21.3 | 19.7 |
| **Musculo-Skeletal System** | | |
| Arthralgia | 4.9 | 0 |
| **Metabolic and Nutritional** | | |
| Edema | 34.4 | 21.3 |
| Weight increase | 4.9 | 0.0 |
| **Nervous System** | | |
| Dizziness | 11.5 | 9.8 |
| Sleep disorder | 3.3 | 0.0 |
| **Respiratory System** | | |
| Dyspnea | 11.5 | 6.6 |
| **Skin** | | |
| Pruritis | 8.2 | 6.6 |
| A patient who reported the same medical term more than once was counted only once for that medical term. | | |

In four adequate and well-controlled studies, the incidence of hypercalcemia and hyperphosphatemia increased during therapy with HECTOROL. The observed increases during HECTOROL treatment, although occurring at a low rate, underscore the importance of regular safety monitoring of serum calcium and phosphorus levels throughout treatment. Patients with higher pre-treatment serum levels of calcium or phosphorus were more likely to experience hypercalcemia or hyperphosphatemia. Therefore, HECTOROL should not be given to patients with a recent history of hypercalcemia or hyperphosphatemia, or evidence of vitamin D toxicity.

Potential adverse effects of HECTOROL 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, and metallic taste.

***Late***

Polyuria, polydipsia, anorexia, weight loss, nocturia, conjunctivitis (calcific), pancreatitis, photophobia, rhinorrhea, pruritus, hyperthermia, decreased libido, elevated BUN, albuminuria, hypercholesterolemia, elevated serum AST and ALT, ectopic calcification, hypertension, cardiac arrhythmias, and, rarely, overt psychosis.

## SYMPTOMS AND TREATMENT OF OVERDOSAGE

Administration of HECTOROL (doxercalciferol) to patients in excess of their daily requirements can cause hypercalcemia, hypercalciuria, hyperphosphatemia, and over-suppression of parathyroid hormone secretion leading in certain cases to adynamic bone. High intake of calcium and phosphate concomitant with HECTOROL may lead to similar abnormalities. High levels of calcium in the dialysate bath may contribute to the hypercalcemia.

***Treatment of Hypercalcemia and Overdosage***

General treatment of hypercalcemia (greater than 1 mg/dL above the upper limit of the normal range) consists of immediate discontinuation of HECTOROL therapy, institution

of a low calcium diet, and withdrawal of calcium supplements. Serum calcium levels should be determined at least weekly until normocalcemia ensues. Hypercalcemia usually resolves in 2 to 7 days. When serum calcium levels have returned to within normal limits, HECTOROL therapy may be reinstituted at a dose which is 2.5 µg lower than prior therapy. Serum calcium levels should be obtained weekly after all dosage changes and during subsequent dosage titration. Persistent or markedly elevated serum calcium levels may be corrected by dialysis against a reduced calcium or calcium-free dialysate.

***Treatment of Accidental Overdosage of Doxercalciferol***

The treatment of acute accidental overdosage of HECTOROL should consist of general supportive measures. If drug ingestion is discovered within a relatively short time, induction of emesis or gastric lavage may be of benefit in preventing further absorption. If the drug has passed through the stomach, the administration of mineral oil may promote its fecal elimination. Serial serum electrolyte determinations (especially calcium), 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 a low calcium diet are also indicated in accidental overdosage. Due to the relatively short duration of the pharmacological action of HECTOROL, further measures are probably unnecessary. However, should 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 and corticosteroids as well as measures to induce an appropriate forced diuresis. Dialysis against a calcium-free dialysate has also been reported.

## DOSAGE AND ADMINISTRATION

**Adult Administration:**

The optimal dose of HECTOROL (doxercalciferol) must be carefully determined for each patient.

The recommended initial dose of HECTOROL is 10.0 µg administered three times weekly after dialysis (approximately every other day). The initial dose should be adjusted, as needed, in order to lower blood iPTH into the range of 150 to 300 pg/mL [16.5 to 33 pmol/L]. The dose may be increased at 8-week intervals by 2.5 µg if PTH is not lowered by 50% and fails to reach the target range.

The maximum recommended dose of HECTOROL is 20 µg administered three times a week at dialysis for a total of 60 µg per week. **Results of clinical studies with HECTOROL showed that mean plasma iPTH stabilized at 300-400 pg/mL [33-44 pmol/L], with a long term maintenance dose of 15-20 µg/week.**

Drug administration should be suspended if iPTH falls below 100 pg/mL [11 pmol/L] and restarted one week later at a dose which is 2.5 µg lower than the last administered dose. During titration, iPTH, serum calcium, and phosphorus levels should be obtained weekly. If hypercalcemia, hyperphosphatemia, or a serum calcium times phosphorus product greater than 5.7 (using mmol/L units) is noted, the drug should be immediately discontinued until these parameters are appropriately lowered. Then, the drug should be restarted at a dose which is 2.5 µg lower.

Incremental dosing must be individualized and based on iPTH, levels. The following is a suggested approach in dose titration:

| PTH Level | HECTOROL (doxercalciferol) Dose |
|---|---|
| > 400 pg/mL | 10.0 µg three times per week after dialysis |
| Decreased by < 50% and above 300 pg/mL | Increase by 2.5 µg at eight-week intervals as necessary |
| 150 - 300 pg/mL | Maintain. In maintenance studies most patients were maintained on a dose of 15-20 µg/week. This decrease in the administered dose (from an initial dose of 30 µg/week) reflected continued dose titration to maintain the PTH level within the targeted range and to manage any incidences of hypercalcemia or hyperphosphatemia. Only 2.2% (3/138) of patients required the maximum dose of 60 µg/week. |
| ≥100 pg/mL but below 150 pg/mL | Reduce dose by 2.5 µg. |
| < 100 pg/mL | Suspend for one week, then resume at a dose which is 2.5 µg lower |

## PHARMACEUTICAL INFORMATION

Drug Substance

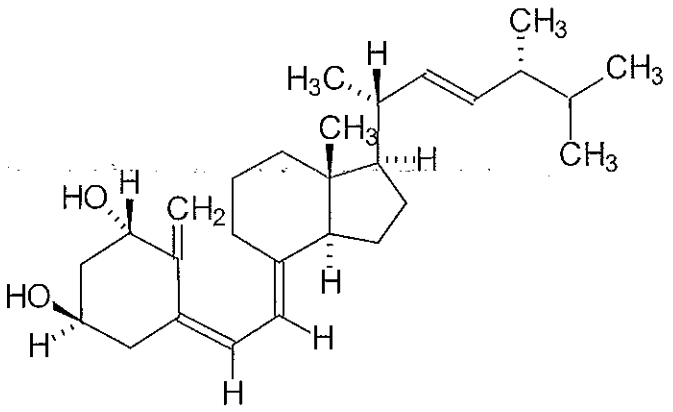
Common name: Doxercalciferol

Chemical name: 9,10-secoergosta-5,7,10(19)22-tetraen-1,3,diol-(1a,3B,5Z,7E,22E)

Other names: 1α-OH-$D_2$, 1α-hydroxyvitamin $D_2$, and 1α-hydroxyergocalciferol

Empirical formula: $C_{28}H_{44}O_2$

Structural formula:




Molecular weight: 412.66

Description:
Doxercalciferol, is a colorless crystalline compound, soluble in oils and organic solvents, but relatively insoluble in water.

Composition

Each capsule contains:

Medicinal ingredient: Doxercalciferol, 2.5 µg

Non-medicinal ingredients: butylated hydroxyanisole (BHA), ethanol and fractionated triglyceride of coconut oil. Gelatin capsule shells contain glycerin, D&C Yellow No. 10 and titanium dioxide.

Stability And Storage Recommendations

Store at controlled room temperature 15° - 25°C (59° to 77°F).

Availability Of Dosage Form

HECTOROL Capsules contain 2.5 µg doxercalciferol. They are soft gelatin, sunshine yellow, oval capsules, imprinted with "BCI" in black ink. Available in bottles of 50.

## PHARMACOLOGY

**The primary activity of doxercalciferol as a therapy for secondary hyperparthyroidism in renal disease is to reduce elevated levels of PTH in blood.** This activity of doxercalciferol has been clearly demonstrated in controlled clinical trials, but not in nonclinical studies. The only animal studies of PTH suppression have been performed with calcitriol. Based on the functional equivalence of calcitriol and $1\alpha,25(OH)_2D_2$, the primary active metabolite of doxercalciferol, studies conducted with calcitriol accurately reflect the pharmacology of $1\alpha,25(OH)_2D_2$.

Calcitriol decreases PTH levels both directly, by inhibiting the transcription of the parathyroid hormone gene, and indirectly, by increasing serum calcium which in turn decreases secretion of PTH by the parathyroid glands.

Chertow *et al.* (1975) were the first to report that administration of calcitriol to rats *in vivo* decreased immunoreactive PTH in serum without an increase in serum calcium. An intraperitoneal injection of 130 pmol calcitriol produced a statistically significant 43% decrease in serum PTH after four hours.

A number of studies with parathyroid cells or tissue *in vitro* have demonstrated the suppression of PTH secretion by calcitriol. Chertow *et al.* (1975) found a statistically significant decrease in PTH secreted from bovine parathyroid tissue incubated for four hours with calcitriol (1 and 100 nM). These findings were confirmed by Cantley *et al.* (1985) and Chan *et al.* (1986) with bovine parathyroid cells. Cantley *et al.* found that calcitriol suppressed PTH secretion from bovine parathyroid cells in a dose dependent manner from $10^{-11}$ - $10^{-7}$ M. Chan *et al.* reported that calcitriol at a concentration of

0.1 ng/mL suppressed PTH secretion from cultured bovine parathyroid cells by 32% after a 48 hour incubation.

A direct effect of calcitriol on mRNA production was reported by Silver *et al.* (1985) using cultured bovine parathyroid cells. Incubation of these cells with calcitriol at concentrations varying from 10 pM to 0.1 µM caused a direct decrease in mRNA down to 50% of control values at 48 hours. Russell *et al.* (1986) demonstrated that this decrease in mRNA was the result of direct suppression of transcription of the parathyroid hormone gene by calcitriol.

The direct effect of calcitriol on inhibition of PTH gene transcription *in vivo* was shown by Silver *et al.* (1986). Intraperitoneal injection of calcitriol to rats decreased the levels of preproparathyroid hormone mRNA, the mRNA to the hormone precursor in the parathyroid glands, as measured by blot hybridization. Preproparathyroid hormone mRNA levels were <4% of basal level at 48 hr after injection of 100 pmol calcitriol, with no increase in serum calcium. Similarly, the *in vitro* nuclear transcription from parathyroid glands from rats previously treated with calcitriol was about 10% that of glands from control rats.

**The secondary activities of doxercalciferol as a therapy for secondary hyperparathyroidism in renal disease are to normalize serum calcium, to augment bone mass, and to suppress endogenous production of calcitriol.**

*Normalization of serum calcium*

Effects on calcium metabolism were the first reported biological activities of doxercalciferol (Lam *et al.*, 1974). Vitamin D-deficient male rats fed a low calcium diet were injected intrajugularly with 0.25 µg of doxercalciferol. Intestinal calcium transport was increased within 3 hours, and reached a maximum of approximately 2.5 times the control value within about 12 hours. Mobilization of calcium from bone, as measured by an increase in serum calcium in these same animals, followed a similar pattern. Similar results have been reported by Sjöden *et al.* (1984) from the same model.

*Augmentation of bone mass*

In the first report of the biological activity of doxercalciferol by Lam *et al.* (1974), the authors indicated that doxercalciferol had an antirachitic potency three times that of vitamin $D_2$ in the stimulation of bone calcification. In these rachitic animals, the drug increased the supply of calcium to the bone.

In the ovariectomized rat, estrogen depletion induces bone loss in the cancellous bone of the vertebrae. Erben and coworkers (Erben *et al.*, 1997) demonstrated that this osteopenia can be prevented by treatment with vitamin D metabolites, probably by diminishing bone turnover through inhibition of PTH secretion. Ovariectomized rats were administered calcitriol, 1α,25$(OH)_2D_2$, doxercalciferol, or 1α-OH-$D_3$ for 16 weeks, beginning 2 weeks after surgery. Calcitriol and 1α,25$(OH)_2D_2$ slightly inhibited vertebral cancellous bone loss relative to the control, sham-operated rats; however, 1α-OH-$D_3$ and doxercalciferol markedly inhibited bone loss in these animals, by 64% and 84%, respectively. The effects of these two compounds on calcium homeostasis differed: 1α-OH-$D_3$ produced a 5-fold increase in urinary calcium excretion, whereas doxercalciferol produced only a 2-fold increase. The authors concluded, "compared to 1α-OH-$D_3$, doxercalciferol combined at least equal or higher bone-protective activity in ovariectomized rats with distinctly less pronounced effects on calcium homeostasis".

*Suppression of endogenous calcitriol*

In rats orally administered doxercalciferol at 0.39 or 2.5 µg/kg/day for 7 days, the serum concentration of calcitriol decreased to one-half to one-third of the level observed in control rats, respectively. Similarly, cynomolgus monkeys administered 0.39, 2.5, or 25 µg/kg/day doxercalciferol for 8 days showed dose-dependent decreases in calcitriol from 175 pg/ml in control animals to 15 pg/ml in the highest dosed animals. The authors proposed that the lowering of endogenous calcitriol resulted from feedback inhibition of the renal 25-dihydroxyvitamin D-1α-hydroxylase (Knutson *et al.* 1995).

A similar lowering of endogenous calcitriol has been observed in multidose toxicity studies. With rats and monkeys, decreases in endogenous calcitriol during administration of doxercalciferol occurred concurrently with increases in the active metabolite, $1\alpha,25(OH)_2D_2$. Thus, no sign of vitamin D deficiency was observed in any of the studies.

## TOXICOLOGY

Acute toxicity studies have been performed in two species, namely mouse and rat. These studies are listed in Table 1.

Doxercalciferol was moderately toxic by the oral route and toxic by the intraperitoneal (IP) route. Mice appeared more sensitive to the drug than rats, and males of both species somewhat more sensitive than the respective females.

Clinical findings included reduced activity, dyspnea, ataxia as well as reduced defecation. Deaths occurred 3 to 5 days after dosing by the oral route in rats and 4 to 8 days after dosing in mice. Tan foci on the heart and pale kidneys were seen at necropsy at termination of the study with congestive changes in animals that died during the study.

**Tabular List of Acute Toxicity Studies (Table 1)**

| Species | Initial Group/ Age at Study Initiation | Mode of Administration/ Formulation | Doses (µg/kg) | Duration (days) | $LD_{50}$ (µg/kg) | |
|---|---|---|---|---|---|---|
| | | | | | M | F |
| Mouse | 5M + 5F/ 4 weeks | Gavage/ Coconut oil | 0, 160, 320, 630, 1250 | 21 | 449 | 495 |
| | 5M + 5F/ 4 weeks | Injection - Intraperitoneal/ Coconut oil | 0, 3.8, 7.5, 15, 30, 60 | 21 | 35.1 | 30-60 |
| Rat | 5M + 5F/ 8-10 weeks | Gavage/ Coconut oil | 1250, 2500, 5000, 10000 | 15 | 1700 | 1800 |
| | 5M +5F/ 8 weeks | Injection - Intraperitoneal/ Coconut oil | 0, 17, 33, 65, 130, 250 | 21 | 17-33 | 64.9 |

Multidose toxicity studies have been performed in three species, namely mouse, rat and cynomolgus monkey, with durations of up to 52 weeks. These studies are listed in the Table 2.

The toxicity observed in all the multidose studies is that expected from a vitamin D compound; no unexpected toxic responses were noted. Toxicity arose when increased serum calcium overwhelmed the animal's compensatory mechanisms to control the calcium concentration in the blood and mineralization occurred in many tissues, principally kidney, heart, and blood vessels.

**Tabular List of Multidose Toxicity Studies (Table 2)**

| Species | Strain | Initial Group/ Age at Study Initiation | Mode of Administration/ Formulation | Doses µg/kg/day | Duration (wks) | NOEL* (µg/kg) |
|---|---|---|---|---|---|---|
| Mouse | CD-1 (IRC) | 5M +5F/ 5 wks | Gavage/ Coconut oil | 0, 0.1, 0.5, 2.5, 12.5 | 4 | 0.5 |
| Rat | Crj:SD(CD®) | 10M/ 5 wks | Gavage/ Coconut oil | 0, 0.1, 0.5, 2.5, 12.5 | 4 | 0.1 |
| | Charles River CD® | 15M + 15F/ 6-8 wks | Gavage/ Coconut oil | 0, 0.06, 0.39, 2.5 | 13 | 0.06 |
| | Charles River Crl CD® VAF PLUS | 35M + 35F/ 6 wks | Gavage/ Coconut oil | 0, 0.02, 0.06, 0.55, 5.0 | 52 | 0.06 |
| Monkey | Cynomolgus | 1M + 1F/ unknown | Gavage/ Coconut oil | 0, 6, 20, 60 | 2 | NA |
| | Cynomolgus | 4M + 4F/ young adult | Gavage/ Coconut oil | 0, 0.06, 0.39, 2.5 | 13 | 0.39 |
| | Cynomolgus | 5M + 5F/ young adult | Gavage/ Coconut oil | 0, 0.06, 0.6, 6.0, 20.0 | 52 | 0.6 |

*Non-Observable Effect Level

Four special toxicity studies were also conducted, two of which were with rats and two with monkeys. The rat studies were performed to evaluate the effects of doxercalciferol on serum biochemistry and determine metabolite levels with high doses of doxercalciferol and to evaluate the potential toxicity of doxercalciferol when administered by intravenous injection. The two monkey studies were performed to examine effects of doxercalciferol on urine chemistry and examine variability in urinalysis of this species and to evaluate consistency of control urinalysis values in this species. These studies are listed in Table 3.

**Tabular List of Special Toxicity Studies (Table 3)**

| Species | Purpose | Initial Group/ Age at Study Initiation | Mode of Administration / Formulation | Doses (µg/kg/day) | Duration (days) | Findings |
|---|---|---|---|---|---|---|
| Rat | To evaluate the effects of Doxercalciferol on serum biochemistry & determine metabolite levels with high doses of Doxercalciferol | 6M + 6F/ 6-7 wks | Gavage/ Coconut oil | 0, 6, 20, 100 | 14 | All findings consistent with the effects of high levels of a vitamin D compound.<br><br>Dose dependent increase in the active metabolite, 1α,25(OH)2D2 and another active metabolite, 1α,24(OH)2D2 noted. |
| | To evaluate the potential toxicity of Doxercalciferol when administered by intravenous injection | 10M + 10F/ 6-7 wks | Intravenous injection/ Aqueous solution | 0, 0.025, 0.25, 2.5 | 28 | No treatment-related local irritation at site of injection observed. Lesions did not differ from those of oral formulation. |
| Monkey | To examine effects of Doxercalciferol on urine chemistry & examine variability in urinalysis of this species | 12F/ Unknown | Oral/ orange section | 2.5, 25 | 8 - 9 | Urinalysis values variable in this species |
| | To evaluate consistency of control urinalysis values in this species | 4M/ Unknown | Not applicable | Not applicable | 14 | Urinalysis values variable in this species |

***Reproduction Studies***

Studies were performed to assess the effect of oral doxercalciferol on the fertility and reproductive performance (formerly Segment I) in rats, on development during organogenesis (formerly Segment II) in rats and rabbits, and perinatal and postnatal development (formerly Segment III) in rats. These studies are listed in the Table 4.

The rat was used as the model for studying the potential effects of oral doxercalciferol on all three phases of reproduction, including fertility and reproductive performance, development during the period of organogenesis, and perinatal and postnatal development of offspring. In this species, none of the reproductive parameters investigated differed between the groups treated with doxercalciferol and the study controls and/or historical controls, despite pronounced evidence of maternal toxicity in the high level dosage groups.

Rabbits were studied as a second model for effects of oral doxercalciferol on development during the period of organogenesis. Although fetal weight and incidence of fetal malformations in rabbits in the mid and/or high dose groups were different from the control group, statistical significance was not reached for any parameter.

## Tabular List of Reproduction Studies (Table 4)

| Species | Strain | Initial Group/ Age at Study Initiation | Mode of Administration/ Formulation | Doses µg/kg/day | Time Dosed | Findings |
|---|---|---|---|---|---|---|
| Segment I - Fertility and Reproductive Performance | | | | | | |
| Rat | Jcl:Wistar | 27M + 27F/<br><br>6 wk M + 11 wk F | Gavage/ Coconut oil | 0, 0.06, 0.39, 2.5 | M - from 9 weeks before mating to day when F mates reached lactation day 22<br>F - from 2 weeks before mating to gestation day 19 or lactation day 21 | No observed effect level for parent animals = 0.39 µg/kg<br><br>No effect on fertility or reproductive performance up to 2.5 µg/kg |
| Segment II - Teratology (Developmental Toxicity) | | | | | | |
| Rat | Sprague-Dawley Crl:CD®BR VAF/Plus® | 150F/ 80-120 days | Gavage/ Coconut oil | 0, 1, 10, 20, 100 | Gestation days 6-17 | No observed effect level for developmental toxicity = 20 µg/kg/day<br><br>No observed effect level for maternal toxicity = 1 µg/kg/day |
| Rabbit | New Zealand White | 30F/ 5-7 months | Gavage/ Coconut oil | 0, 0.003, 0.01, 0.03, 0.1, 0.3 | Gestation days 6-18 | No observed effect level for developmental toxicity = 0.03 µg/kg/day |
| | New Zealand White | 80F/ 5-7 months | Gavage/ Coconut oil | 0, 0.03, 0.10, 0.30 | Gestation days 6-18 | No observed adverse effect level for maternal toxicity = 0.03 µg/kg/day |
| Segment III - Perinatal-Postnatal | | | | | | |
| Rat | Sprague-Dawley Crl:CD®BR VAF/Plus® | 125F/ 80-120 days | Gavage/ Coconut oil | 0, 0.25, 2.5, 15, 25 | Gestation day 6 - lactation day 20 | No observed effect level for developmental and reproductive effects = 15 µg/kg/day |

***Mutagenicity Studies***

The capacity of doxercalciferol to induce mutations has been investigated in four experimental models. No evidence of genetic toxicity was observed in an *in vitro* bacterial mutagenicity assay (Ames test) or a mouse lymphoma gene mutation assay. Doxercalciferol caused structural chromatid and chromosome aberrations in an *in vitro* human lymphocyte clastogenicity assay with metabolic activation. However, doxercalciferol was considered to be non-clastogenic in this assay since part of these findings was within historical control values. Furthermore, doxercalciferol was negative in an *in vivo* mouse micronucleus clastogenicity assay.

These studies are listed in the Table 5.

***Carcinogenicity***

No carcinogenicity studies were conducted.

Vitamins in general, and more specifically Vitamin D and its natural metabolites are not considered to be carcinogens.

HECTOROL (doxercalciferol), a synthetic compound, is also considered to be not a carcinogen, as it is converted *in vivo* to 1α,25-dihydroxyvitamin $D_2$, the natural active metabolite of vitamin $D_2$.

## Tabular List of Mutagenicity Studies (Table 5)

| Type | Species | Assay | Dose range | Findings |
|---|---|---|---|---|
| *In vitro* | *S.* typhimurium | "Ames assay"<br><br>Point mutation reversion to histidine independence | 31.3 - 2000 µg/plate | Non-mutagenic |
| | *E.* coli | | 31.3 - 2000 µg/plate | Non-mutagenic |
| | Mouse | Lymphoma forward mutation (thymidine kinase locus) | 0.667 - 100 µg/mL | Non-mutagenic |
| | Man | Lymphocyte chromosome aberration | 1.00 - 100 µg/mL | Non-clastogenic |
| *In vivo* | Mouse | Micronucleus induction (screen for clastogenic [chromosome breaking] effects) | 0.25 - 1 mg/kg p.o. | Non-clastogenic |

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