CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

Application Number: 020862

Trade Name: HECTOROL CAPSULES 2.5 mcg

Generic Name: DOXERCALCIFEROL

Sponsor: BONE CARE INTERNATIONAL

Approval Date: 6/9/99

INDICATION(s): TO REDUCE ELEVATED iPTH LEVELS IN THE MANAGEMENT OF SECONDARY HYPERPARATHYROIDISM IN PATIENTS UNDERGOING CHRONIC RENAL DIALYSIS

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION: 020862

CONTENTS

	Included	Pending Completion	Not Prepared	Not Required
Approval Letter	X			
Tenative Approval Letter				X
Approvable Letter				X
Final Printed Labeling	X			
Medical Review(s)	X			
Chemistry Review(s)	X			
EA/FONSI				X
Pharmacology Review(s)	X			
Statistical Review(s)	X			
Microbiology Review(s)				X
Clinical Pharmacology Biopharmaceutics Review(s)	X			
Bioequivalence Review(s)				X
Administrative/ Correspondence Document(s)	X			

CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number: 020862

APPROVAL LETTER

NDA 20-862

Bone Care International
Attention: Ms. Darlene Kyllo, RAC
Director, Compliance, Quality & Regulatory Affairs
One Science Court
Madison, WI 53711

Dear Ms. Kyllo:

Please refer to your new drug application (NDA) dated March 7, 1998, received March 9, 1998, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Hectorol (doxercalciferol) Capsules, 2.5 mcg.

We acknowledge receipt of your submissions dated March 16 and 25, April 8 and 27, May 22, June 10, July 16, October 8, November 4, 5, 16, and 24, and December 3, 7, 14, 17, 22, 25, and 30, 1998, and January 12, 14(2), and 28, February 1 and 12, April 2, 16, and 22, May 5, 21, and 27, and June 1, 3, 8, and 9 (3), 1999. Your December 17, 1998, submission was a major amendment.

This new drug application provides for the use of Hectorol (doxercalciferol) Capsules to reduce elevated iPTH levels in the management of secondary hyperparathyroidism in patients undergoing chronic renal dialysis.

We have completed the review of this application, as amended, and have concluded that adequate information has been presented to demonstrate that the drug product is safe and effective for use as recommended in the agreed upon labeling text. Accordingly, the application is approved effective on the date of this letter.

The final printed labeling (FPL) must be identical to the submitted labeling (package insert, immediate container, and carton labels, submitted June 9, 1999). Marketing the product with FPL that is not identical to the approved labeling text may render the product misbranded and an unapproved new drug.

Please submit 20 copies of the FPL as soon as it is available, in no case more than 30 days after it is printed. Please individually mount ten of the copies on heavy-weight paper or similar material. For administrative purposes, this submission should be designated "FPL for approved NDA 20-862." Approval of this submission by FDA is not required before the labeling is used.

We remind you of your Phase 4 commitments specified in your submission dated May 27, 1999. These commitments, which you agreed to complete and submit the revised regulatory tests and testing results by July 1, 2000, are listed below.

The Phase 4 Commitments are Chemistry /Manufacturing related.

Protocols, data, and final reports should be submitted to this NDA as correspondence. In addition, under 21 CFR 314.82(b)(2)(vii), we request that you include a status summary of each commitment in your annual report to this NDA. The status summary should include expected completion and submission dates and any changes in plans since the last annual report. For administrative purposes, all submissions, including supplements, relating to these Phase 4 commitments should be clearly designated "Phase 4 Commitments."

Be advised that, as of April 1, 1999, all applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred (63 *FR* 66632). We are waiving the pediatric study requirement for this application at this time.

Validation of the regulatory methods has not been completed. At the present time, it is the policy of the Center not to withhold approval because the methods are being validated. Nevertheless, we expect your continued cooperation to resolve any problems that may be identified.

In addition, please submit three copies of the introductory promotional materials that you propose to use for this product. All proposed materials should be submitted in draft or mock-up form, not final print. Please send one copy to the Division of Metabolic and Endocrine Drug Products and two copies of both the promotional materials and the package insert directly to:

Division of Drug Marketing, Advertising, and Communications, HFD-40
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857

Please submit one market package of the drug product when it is available.

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

If you have any questions, contact Randy Hedin, R.Ph., Senior Regulatory Management Officer, at (301) 827-6392.

Sincerely,

John K. Jenkins, M.D., F.C.C.P.
Director
Office of Drug Evaluation II
Center for Drug Evaluation and Research

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 020862

FINAL PRINTED LABELING

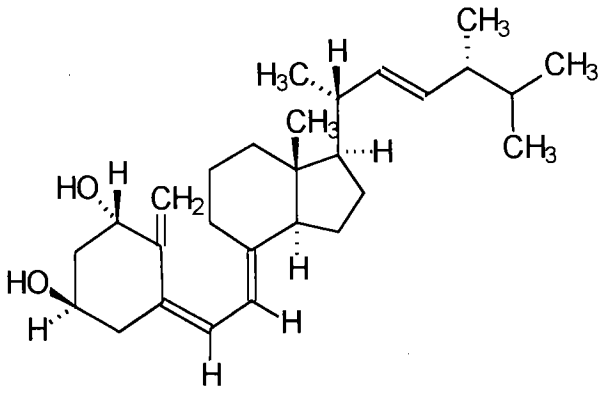
Submission date: June 9, 1999

HECTOROL™ CAPSULES
(Doxercalciferol)

DESCRIPTION

Doxercalciferol, the active ingredient in Hectorol, is a synthetic vitamin D analog that undergoes metabolic activation *in vivo* to form 1α,25-dihydoxyvitamin D_2 (1α,25-$(OH)_2D_2$), a naturally occurring, biologically active form of vitamin D_2. Hectorol is available as soft gelatin capsules containing 2.5 mcg doxercalciferol. Each capsule also contains butylated hydroxyanisole (BHA), ethanol, and fractionated triglyceride of coconut oil. Gelatin capsule shells contain glycerin, D&C Yellow No. 10, and titanium dioxide.

Doxercalciferol is a colorless crystalline compound with a calculated molecular weight of 412.66 and a molecular formula of $C_{28}H_{44}O_2$. It is soluble in oils and organic solvents, but is relatively insoluble in water. Chemically, doxercalciferol is (1α,3β,5Z,7E,22E)-9,10-secoergosta-5,7, 10(19)22-tetraene-1,3-diol and has the following structural formula:



Other names frequently used for doxercalciferol are 1α-OH-D_2, 1α-hydroxyvitamin D_2, and 1α-hydroxyergocalciferol.

CLINICAL PHARMACOLOGY

Vitamin D levels in humans depend 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 intake of either vitamin D_2 (ergocalciferol) or vitamin D_3. Vitamin D_2 and vitamin D_3 must be metabolically activated in the liver and the kidney before becoming fully active on target tissues. The initial step in the activation process is the introduction of a hydroxyl group in the side chain at C-25 by the 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-α-hydroxylase to produce 1α,25-$(OH)_2D_2$, the primary biologically active form of vitamin D_2, and 1α,25-$(OH)_2D_3$ (calcitriol), the biologically active form of vitamin D_3.

Mechanism of action

Calcitriol (1α,25-$(OH)_2D_3$) and 1α,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 biologically active vitamin D metabolites leads to secondary hyperparathyroidism, which contributes to the development of metabolic bone disease in patients with renal failure.

Pharmacokinetics and Metabolism

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 mcg of Hectorol 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 micrograms after each dialysis session (3 times weekly) for a total of 30 mcg 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. The maximum dosage was limited to 20 mcg after each dialysis (60 mcg/week). If at any time during the trial iPTH fell below 150 pg/mL, 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 means ± s.d. (n*) p Value *v.* Baseline p Value *v.* Placebo	
		Hectorol	Placebo
Study A	Baseline	797.2 ± 443.8 (30) n.a. 0.97	847.1 ± 765.5 (32)
	Week 16 (open-label)	384.3 ± 397.8 (24) < .001 0.72	526.5 ± 872.2 (29) < .001
	Week 24 (double-blind)	404.4 ± 262.9 (21) < .001 0.008	672.6 ± 356.9 (24) 0.70
Study B	Baseline	973.9 ± 567.0 (41) n.a. 0.81	990.4 ± 488.3 (35)
	Week 16 (open-label)	476.1 ± 444.5 (37) < .001 0.91	485.9 ± 443.4 (32) < .001
	Week 24 (double-blind)	459.8 ± 443.0 (35) < .001 < .001	871.9 ± 623.6 (30) < .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.

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 during the open-label and double-blind phases.

		Number of times iPTH ≤ 300 pg/mL.					
		Only 1		Only 2		≥ 3	
		Hectorol	Placebo	Hectorol	Placebo	Hectorol	Placebo
Study A	Weeks 1 – 16 (open-label)	2/30	2/32	0/30	0/32	22/30	23/32
	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 USAGE

Hectorol is indicated for the reduction of elevated iPTH levels in the management of secondary hyperparathyroidism in patients undergoing chronic renal dialysis.

CONTRAINDICATIONS

Hectorol should not be given to patients with a tendency towards hypercalcemia or evidence of vitamin D toxicity.

WARNINGS

Overdosage of any form of vitamin D is dangerous (see **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 70. 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 (10.6 to 11.2 mg/dL for 3 consecutive determinations) or increased to correct persistent mild hyperphosphatemia (7.0 to 8.0 mg/dL for 3 consecutive determinations).

Magnesium containing antacids and Hectorol 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 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, calcium supplementation, and avoidance of the use of nonprescription drugs without prior approval from their

physician. Patients should also be carefully informed about the symptoms of hypercalcemia (see **ADVERSE REACTIONS** section).

Laboratory Tests

For dialysis patients, serum or plasma iPTH and serum calcium, phosphorus, and alkaline phosphatase should be determined periodically. In the early phase of treatment, iPTH, serum calcium, and serum phosphorus should be determined prior to initiation of Hectorol treatment and weekly thereafter.

Drug Interactions

Cholestyramine has been reported to reduce intestinal absorption of fat-soluble vitamins; therefore, it may impair intestinal absorption of doxercalciferol. Magnesium-containing antacids and Hectorol should not be used concomitantly, because such use may lead to the development of hypermagnesemia. (see **WARNINGS**) The use of mineral oil or other substances that may affect absorption of fat may influence the absorption and availability of Hectorol. Although not examined specifically, both enzyme inducers (such as glutethimide and phenobarbital) and enzyme inhibitors (such as phenytoin) may affect the 25-hydroxylation of Hectorol and may necessitate dosage adjustments.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Long-term studies in animals to evaluate the carcinogenic potential of Hectorol have not been conducted. No evidence of genetic toxicity was observed in an *in vitro* bacterial mutagenicity assay (Ames test) or a mouse lymphoma gene mutation assay. Hectorol caused structural chromatid and chromosome aberrations in an *in vitro* human lymphocyte clastogenicity assay with metabolic activation. However, Hectorol was negative in an *in vivo* mouse micronucleus clastogenicity assay. Hectorol had no effect on male or female fertility in rats at oral doses up to 2.5 mcg/kg/day (approximately 3 times the maximum recommended human dose of 60 mcg/week based on mcg/m^2 body surface area).

Use in Pregnancy

Pregnancy Category B

Reproduction studies in rat and rabbits, at doses up to 20 mcg/kg/day and 0.1 mcg/kg/day (approximately 25 times and less than the maximum recommended human dose of 60 mcg/week based on mcg/m^2 body surface area, respectively) have revealed no teratogenic or fetotoxic effects due to Hectorol. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Nursing Mothers

It is not known whether this drug is excreted in human milk. Because other vitamin D derivatives 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 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 **CLINICAL PHARMACOLOGY/Clinical Studies**) 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		
Bradycardia	6.6	4.9
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	0.0
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.

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 blood urea nitrogen (BUN), albuminuria, hypercholesterolemia, elevated serum aspartate transaminase (AST) and alanine transaminase (ALT), ectopic calcification, hypertension, cardiac arrhythmias, and, rarely, overt psychosis.

OVERDOSAGE

Administration of Hectorol to patients in excess doses can cause hypercalcemia, hypercalciuria, hyperphosphatemia, and over-suppression of PTH secretion leading in certain cases to adynamic bone disease. 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 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 suspension 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 that is at least 2.5 mcg 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 (10 minutes), induction of emesis or gastric lavage may be of benefit in preventing further absorption. If drug ingestion is discovered later than 10 minutes post-ingestion, 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 institution of a low calcium diet are also indicated in accidental overdosage. If persistent and markedly elevated serum calcium levels occur, there are a variety of therapeutic alternatives which may be considered. These include the use of drugs such as

phosphates and corticosteroids as well as measures to induce diuresis. Also, one may consider dialysis against a calcium-free dialysate.

DOSAGE AND ADMINISTRATION

The optimal dose of Hectorol must be carefully determined for each patient.

The recommended initial dose of Hectorol is 10.0 mcg administered three times weekly at 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. The dose may be increased at 8-week intervals by 2.5 mcg if iPTH is not lowered by 50% and fails to reach the target range. The maximum recommended dose of Hectorol is 20 mcg administered three times a week at dialysis for a total of 60 mcg per week. Drug administration should be suspended if iPTH falls below 100 pg/mL and restarted one week later at a dose that is at least 2.5 mcg lower than the last administered dose. During titration, iPTH, serum calcium, and serum phosphorus levels should be obtained weekly. If hypercalcemia, hyperphosphatemia, or a serum calcium times serum phosphorus product greater than 70 is noted, the drug should be immediately suspended until these parameters are appropriately lowered. Then, the drug should be restarted at a dose that is at least 2.5 mcg lower.

Dosing must be individualized and based on iPTH levels with monitoring of serum calcium and serum phosphorus levels. The following is a suggested approach in dose titration:

Initial Dosing

iPTH Level	Hectorol Dose
> 400 pg/mL	10.0 mcg three times per week at dialysis.

Dose Titration

iPTH Level	Hectorol Dose
Decreased by < 50% and above 300 pg/mL	Increase by 2.5 mcg at eight-week intervals as necessary
150 - 300 pg/mL	Maintain
< 100 pg/mL	Suspend for one week, then resume at a dose that is at least 2.5 mcg lower

HOW SUPPLIED

NDC 64894-825-50

2.5 mcg doxercalciferol in soft gelatin, sunshine yellow, oval capsules, imprinted **BCI**; bottles of 50.

Store at controlled room temperature 20° to 25°C (68° to 77°F) [see USP].