CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

NDA 21-027/S-015

Trade Name: Hectorol

Generic Name: Doxercalciferol

Sponsor: Genzyme Corporation

Approval Date: 12/8/2008

Indications: Hectorol is indicated for the treatment of secondary hyperparathyroidism in patients with chronic kidney disease on dialysis.

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 21-027/S-015

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 21-027/S-015

APPROVAL LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-027/S-015

Genzyme Corporation
Attention: Chandra Matthew, JD
Principal Associate Regulatory Affairs
500 Kendall Street
Cambridge, MA 02142

SUPPLEMENT APPROVAL

Dear Ms. Matthew:

Please refer to your supplemental new drug application dated April 18, 2008, received April 21, 2008, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Hectorol (doxercalciferol) Injection, 4 mcg/2mL (2 mcg/mL).

We acknowledge receipt of your submissions dated May 27, July 25, October 10, and November 18, 2008.

This supplemental new drug application provides for changes in the dosage formulation and packaging configuration from the currently approved Hectorol Injection and also the introduction of another manufacturer. The package insert is revised to include information on the vial presentation, which replaces the ampule, and excipients used in the new formulation. Also, the OVERDOSAGE section is revised.

We completed our review of this supplemental new drug application, as amended. It is approved, effective on the date of this letter, for use as recommended in the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format for the package insert (PI), final printed labeling (FPL) for the vial submitted November 18, 2008 and for carton labels submitted October 10, 2008.

PROMOTIONAL MATERIALS

In addition, submit three copies of the introductory promotional materials that you propose to use for this product. Submit all proposed materials in draft or mock-up form, not final print. Send one copy to the Division of Metabolism and Endocrinology Products and two copies of both the promotional materials and the package insert directly to:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Drug Marketing, Advertising, and Communications
5901-B Ammendale Road
Beltsville, MD 20705-1266

LETTERS TO HEALTH CARE PROFESSIONALS

If you issue a letter communicating important information about this drug product (i.e., a "Dear Health Care Professional" letter), we request that you submit a copy of the letter to this NDA and a copy to the following address:

MEDWATCH
Food and Drug Administration
5515 Security Lane
HFD-001, Suite 5100
Rockville, MD 20852

REPORTING REQUIREMENTS

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, call Haley Seymour, Regulatory Project Manager, at (301) 796-2443.

Sincerely,

{See appended electronic signature page}

Mary H. Parks, M.D.
Director
Division of Metabolism and Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

Enclosures:
Package Insert
Vial label
Carton label

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Mary Parks

12/8/2008 08:37:48 PM

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 21-027/S-015

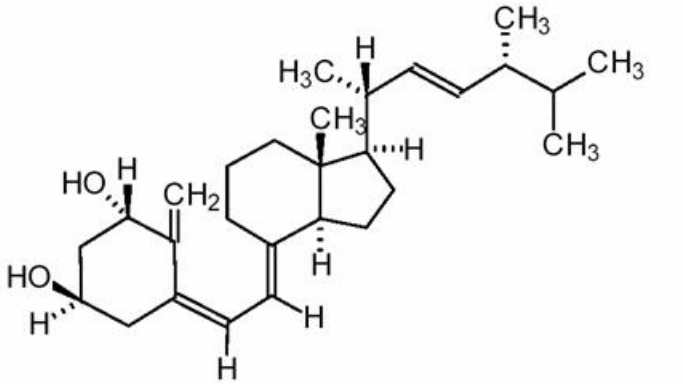
LABELING

HECTOROL - doxercalciferol injection, solution
Genzyme Corporation

DESCRIPTION

Doxercalciferol, the active ingredient in Hectorol®, is a synthetic vitamin D_2 analog that undergoes metabolic activation in vivo to form 1α,25-dihydroxyvitamin D_2 (1α,25-$(OH)_2D_2$), a naturally occurring, biologically active form of vitamin D_2. Hectorol is available as a sterile, clear, colorless aqueous solution for intravenous injection. Hectorol Injection is supplied in stoppered, single use 2 mL amber glass vials, with an aluminum seal and yellow flip-off cap. Each milliliter (mL) of solution contains doxercalciferol, 2 mcg; ethanol, 100%, 0.05 mL; Polysorbate 20, 10 mg; sodium chloride, 1.5 mg; butylated hydroxytoluene, 0.02 mg; sodium phosphate dibasic, heptahydrate, 14.4 mg; sodium phosphate monobasic, monohydrate, 1.8 mg; and disodium edetate, 1.1 mg. 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 structural formula presented in Figure 1.

Figure 1: Chemical Structure of Doxercalciferol



Other names frequently used for doxercalciferol are 1α-hydroxyvitamin D_2, 1α-OH-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 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 (due to lack of or insufficient 25-hydroxyvitamin D-1-alpha-hydroxylase activity) leads to secondary hyperparathyroidism, which contributes to the development of metabolic bone disease in patients with renal failure.

Pharmacokinetics and Metabolism

After intravenous administration, doxercalciferol is 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. Peak blood levels of 1α,25-$(OH)_2D_2$ are reached at 8 +/- 5.9 hours (mean +/- SD) after a single intravenous dose of 5 mcg of doxercalciferol. The mean elimination half-life of 1α,25-$(OH)_2D_2$ after an oral dose is approximately 32 to 37 hours with a range of up to 96 hours. The mean elimination half-life in patients with end stage renal disease (ESRD) and in healthy volunteers appears to be

similar following an oral dose. 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 Injection were evaluated in two open-label, single-arm, multi-centered clinical studies (Study C and Study D) in a total of 70 patients with chronic kidney disease on hemodialysis (Stage 5 CKD). Patients in Study C were an average age of 54 years (range: 23-73), were 50% male, and were 61% African-American, 25% Caucasian, and 14% Hispanic, and had been on hemodialysis for an average of 65 months. Patients in Study D were an average age of 51 years (range: 28-76), were 48% male, and 100% African-American and had been on hemodialysis for an average of 61 months. This group of 70 of the 138 patients who had been treated with Hectorol Capsules in prior clinical studies (Study A and Study B) received Hectorol Injection in an open-label fashion for 12 weeks following an 8-week washout (control) period. Dosing of Hectorol Injection was initiated at the rate of 4 mcg administered at the end of each dialysis session (3 times weekly) for a total of 12 mcg per week. The dosage of Hectorol was adjusted in an attempt to achieve iPTH levels within a targeted range of 150 to 300 pg/mL. The dosage was increased by 2 mcg per dialysis session after 8 weeks of treatment if the iPTH levels remained above 300 pg/mL and were greater than 50% of baseline levels. The maximum dosage was limited to 18 mcg per week. If at any time during the trial iPTH fell below 150 pg/mL, Hectorol Injection was immediately suspended and restarted at a lower dosage the following week.

Results:

Fifty-two of the 70 patients who were treated with Hectorol Injection achieved iPTH levels ≤ 300 pg/mL. Forty-one of these patients exhibited plasma iPTH levels ≤ 300 pg/mL on at least 3 occasions. Thirty-six patients had plasma iPTH levels < 150 pg/mL on at least one occasion during study participation.

Mean weekly doses in Study C ranged from 8.9 mcg to 12.5 mcg. In Study D, the mean weekly doses ranged from 9.1 mcg to 11.6 mcg.

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 period and are displayed in the table below. Plasma iPTH levels were measured weekly during the 12-week study.

Table 1: iPTH Summary Data for Patients Receiving Hectorol® Injection:

iPTH Level	**Study C (n=28)**	**Study D (n=42)**	**Combined Protocols (n=70)**
Baseline (Mean of Weeks -2, -1, and 0)			
Mean (SE)	698 (60)	762 (65)	736 (46)
Median	562	648	634
On-treatment (Week 12*)			
Mean (SE)	406 (63)	426 (60)	418 (43)
Median	311	292	292
Change from Baseline**			
Mean (SE)	-292 (55)	-336 (41)	-318 (33)
Median	-274	-315	-304
P-value***	.004	.001	<.001

*Values were carried forward for the two patients on study for 10 weeks

**Treatment iPTH minus baseline iPTH

***Wilcoxon one-sample test

In both studies, iPTH levels increased progressively and significantly in 62.9% of patients during the 8-week washout (control) period during which no vitamin D derivatives were administered. In contrast, Hectorol Injection treatment resulted in a clinically significant reduction (at least 30%) from baseline in mean iPTH levels during the 12-week open-label treatment period in more than 92% of the 70 treated patients.

Table 2 shows the numbers of patients who achieved iPTH levels below 300 pg/mL on one, two, or three or more non-consecutive occasions during the 12-week treatment period. Thirty-seven of 70 patients (53%) had plasma iPTH levels within the targeted range (150-300 pg/mL) during Weeks 10-12.

Table 2: Number of times iPTH ≤ 300 pg/mL

	1	**2**	**≥3**
Study C	3/28	0/28	16/28
Study D	4/42	4/42	25/42

INDICATIONS AND USAGE

Hectorol is indicated for the treatment of secondary hyperparathyroidism in patients with chronic kidney disease on dialysis.

CONTRAINDICATIONS

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

WARNINGS

Overdosage of any form of vitamin D, including Hectorol 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 for cardiac arrhythmias and seizures and may potentiate 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 be maintained at $<55\ mg^2/dL^2$ in patients with chronic kidney disease. 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_2, pharmacologic doses of vitamin D and its derivatives should be withheld during Hectorol 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 Hectorol in reducing blood PTH levels. If hypercalcemia occurs after initiating Hectorol therapy, the dose of Hectorol and/or calcium-containing phosphate binders should be decreased. If hyperphosphatemia occurs after initiating Hectorol, the dose of Hectorol should be decreased and/or the dose of phosphate binders increased. (See dosing recommendations for Hectorol under **DOSAGE AND ADMINISTRATION** section.)

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 Injection are hypercalcemia, hyperphosphatemia, and oversuppression of PTH (iPTH less than 150 pg/mL). 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 maximize PTH suppression while maintaining serum calcium and phosphorus levels within prescribed ranges.

In two open-label, single-arm, multi-centered studies, the incidence of hypercalcemia and hyperphosphatemia increased during therapy with Hectorol Injection (see **Adverse Reactions** section). The observed increases during Hectorol treatment underscore the importance of regular safety monitoring of serum calcium and phosphorus levels throughout treatment. Patients with higher pre-treatment serum levels of calcium (> 10.5 mg/dL) or phosphorus (> 6.9 mg/dL) 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.

Table 3: Incidence Rates of Hypercalcemia and Hyperphosphatemia in Two Phase 3 Studies with Hectorol® Injection

Study	Hypercalcemia (per 100 patient weeks)		Hyperphosphatemia (per 100 patient weeks)	
	Washout (Off Treatment)	Open-Label (Treatment)	Washout (Off Treatment)	Open-Label (Treatment)
Study C	0.9	0.9	0.9	2.4
Study D	0.3	1.0	1.2	3.7

Information for the Patient
The patient, spouse, or guardian should be informed about adherence to instructions about diet, calcium supplementation, and avoidance of the use of nonprescription drugs without prior approval from the patient's physician. Patients should also be carefully informed about the symptoms of hypercalcemia (see **ADVERSE REACTIONS** section).

Laboratory Tests
Serum levels of iPTH, calcium, and phosphorus should be determined prior to initiation of Hectorol treatment. During the early phase of treatment (i.e., first 12 weeks), serum iPTH, calcium, and phosphorus levels should be determined weekly. For dialysis patients in general, serum or plasma iPTH and serum calcium, phosphorus, and alkaline phosphatase should be determined periodically.

Drug Interactions
Specific drug interaction studies have not been conducted. Magnesium-containing antacids and Hectorol should not be used concomitantly because such use may lead to the development of hypermagnesemia (see **WARNINGS**). Although not examined specifically, enzyme inducers (such as glutethimide and phenobarbital) may affect the 25-hydroxylation of Hectorol and may necessitate dosage adjustments. Cytochrome P450 inhibitors (such as ketoconazole and erythromycin) may inhibit the 25-hydroxylation of Hectorol. Hence, formation of the active Hectorol moiety may be hindered.

Carcinogenesis, Mutagenesis, Impairment of Fertility
Long-term studies in animals to evaluate the carcinogenic potential of doxercalciferol 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. Doxercalciferol caused structural chromatid and chromosome aberrations in an *in vitro* human lymphocyte clastogenicity assay with metabolic activation. However, doxercalciferol was negative in an *in vivo* mouse micronucleus clastogenicity assay. Doxercalciferol 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 oral dose of 60 mcg/wk based on mcg/m^2 body surface area).

Use in Pregnancy
Pregnancy Category B
Reproduction studies in rats 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 oral dose of 60 mcg/week based on mcg/m^2 body surface area, respectively) have revealed no teratogenic or fetotoxic effects due to doxercalciferol. 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 doxercalciferol 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.

Geriatric Use
Of the 70 patients treated with Hectorol Injection in the two Phase 3 clinical studies, 12 patients were 65 years or over. In these studies, no overall differences in efficacy or safety were observed between patients 65 years or older and younger patients.

Hepatic Insufficiency
Studies examining the influence of hepatic insufficiency on the metabolism of Hectorol were inconclusive. Since patients with hepatic insufficiency may not metabolize doxercalciferol 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 Injection has been evaluated for safety in 70 patients with chronic renal disease on hemodialysis (who had been previously treated with oral Hectorol) from two 12-week, open-label, single-arm, multi-centered studies. (Dosage titrated to achieve target plasma iPTH levels, see **CLINICAL PHARMACOLOGY/Clinical Studies**.)
Because there was no placebo group included in the studies of Hectorol Injection, Table 4 provides the adverse event incidence rates from placebo-controlled studies of oral Hectorol.

Table 4: 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		
Pruritus	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, metallic taste, and anorexia.

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, sensory disturbances, dehydration, apathy, arrested growth, urinary tract infections, 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 1 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 Hectorol®

The treatment of acute accidental overdosage of Hectorol should consist of general supportive measures. 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, treatment with standard medical care should be followed, as needed. Based on similarities between Hectorol and its active metabolite, $1\alpha,25\text{-}(OH)_2D_2$, it is expected that Hectorol is not removed from the blood by dialysis.

DOSAGE AND ADMINISTRATION

Adult Administration:

For intravenous use only. The optimal dose of Hectorol must be carefully determined for each patient.

The recommended initial dose of Hectorol is 4 mcg administered intravenously as a bolus dose three times weekly at the end of 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 1 to 2 mcg if iPTH is not lowered by 50% and fails to reach the target range. Dosages higher than 18 mcg weekly have not been studied. Drug administration should be suspended if iPTH falls below 100 pg/mL and restarted one week later at a dose that is at least 1 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 phosphorus product greater than 55 mg^2/dL^2 is noted, the dose of Hectorol should be decreased or suspended and/or the dose of phosphate binders should be appropriately adjusted. If suspended, the drug should be restarted at a dose that is 1 mcg lower. Dosing must be individualized and based on iPTH levels with monitoring of serum calcium and serum phosphorus levels. Table 5 presents a suggested approach in dose titration.

Table 5: Initial Dosing

iPTH Level	Hectorol® Dose
>400 pg/mL	4 mcg three times per week at the end of dialysis, or approximately every other day
Dose Titration	
iPTH Level	Hectorol® Dose
Decrease by <50% and above 300 pg/mL	Increase by 1 to 2 mcg at eight-week intervals as necessary
Decrease by >50% and above 300 pg/mL	Maintain
150 - 300 pg/mL	Maintain
<100 pg/mL	Suspend for one week, then resume at a dose that is at least 1 mcg lower

Discard unused portion.

HOW SUPPLIED

Hectorol (doxercalciferol injection) is supplied in single-use amber glass vials containing 4 mcg doxercalciferol in 2 mL of solution; the closure consists of a fluorocarbon-coated chlorobutyl stopper, with an aluminum seal and a yellow plastic flip–off cap.

NDC 58468-0123-1 4 mcg/2 mL vial

Store at 25°C (77°F): excursions permitted to 15-30°C (59-86°F)

[see USP controlled room temperature]

Protect from light.

Rx only

Manufactured by: Genzyme Biosurgery

For: Genzyme Corporation

500 Kendall Street

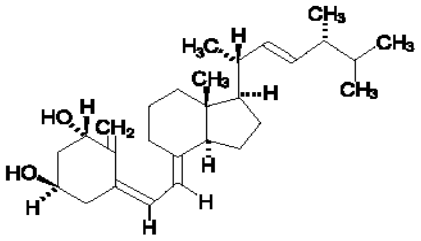
Cambridge, MA 02142

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 21-027/S-015

CHEMISTRY REVIEW(S)

CHEMIST'S REVIEW # 1	1. ORGANIZATION: PME	2. NDA Number: 21-027
3. Name and Address of Applicant (City & State) Genzyme Corporation 500 Kendall Street Cambridge, MA 02142		**4. Supplement(s)** **Number(s)** **Date(s)** SCF-015 4/18/08
5. Drug Name Hectorol®	**6. Nonproprietary Name** Doxercalciferol injection	**7. Amendments - Dates**
8. Supplement Provides For: a change in formulation, and packaging configuration from currently approved Hectorol Injection, as well as to introduce an additional manufacturer.		
9. Pharmacological Category Treatment of secondary hyperparathyroidism in patients with chronic kidney disease (CKD) on dialysis.	**10. How Dispensed** Rx	**11. Related NDAs**
12. Dosage Form(s) Vial 2 mL	**13. Potency** 4 mcg/2 mL (2 mcg/mL)	
14. Chemical Name and Structure: (1a,3b,5Z,7E,22E)-9,10-secoergosta-5,7,10(19),22-tetraene-1,3-diol  Molecular Formula: $C_{28}H_{44}O_2$ Molecular Weight: 412.66 CAS registry No.: 5457-75-0		**15. Records/Reports** **Current** **Yes X No** **Reviewed** **Yes No X**
16. Comments: This PA supplement to propose a change in formulation, and packaging configuration from the currently approved Hectorol Injection (2mcg/mL), as well as to introduce an additional manufacturer. The applicant has provided adequate data to support the proposed changes. A microbiological consult was requested on 5/21/08 for microbiology product quality assurance. The microbiology has recommended approval from microbiology product quality standpoint.		
17. Conclusions and Recommendations: The supplement is "**approved**" from the CMC standpoint, pending inspection.		
18. Reviewer:		
Name Kris Raman, Ph.D.	**Signature**	**Date Completed** 8/1/08, revised 8/21/08

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/s/

Kris Raman
8/21/2008 03:43:29 PM
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Jim Vidra
8/21/2008 03:47:24 PM
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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 21-027/S-015

MICROBIOLOGY REVIEW(S)

Product Quality Microbiology Review

21 AUGUST 2008

NDA: 21-027/SCF-015

Drug Product Name
Proprietary: Hectoral® Injection,
Non-proprietary: doxicalciferol
Drug Product Priority Classification: N/A

Review Number:

Dates of Submission(s) Covered by this Review

Letter	Stamp	Review Request	Assigned to Reviewer
April 18, 2008	April 21, 2008	May 21, 2008	May 22, 2008

Submission History (for amendments only) – N/A

Applicant/Sponsor
Name: Genzyme Corporation
Address: 15 Pleasant Street Connector
Representative: Framington, MA 01701
Telephone:

Name of Reviewer: Vinayak B. Pawar, Ph.D.

Conclusion: Recommended for approval from microbiology product quality standpoint.

Product Quality Microbiology Data Sheet

A. **1.** **TYPE OF SUBMISSION:** Prior Approval Supplement

2. **SUBMISSION PROVIDES FOR:** A change in formulation, packaging configuration and adding Genzyme Biosurgery as a manufacturing site.

3. **MANUFACTURING SITE:** Genzyme Biosurgery Ridgefield, NJ

4. **DOSAGE FORM, ROUTE OF ADMINISTRATION AND STRENGTH/POTENCY:** 4mcg/2mL intravenous solution.

5. **METHOD(S) OF STERILIZATION:** (b) (4).

6. **PHARMACOLOGICAL CATEGORY:** Treatment of Hyperthyroidism.

B. **SUPPORTING/RELATED DOCUMENTS:** None.

C. **REMARKS:** The purpose of this Prior Approval Supplement is to propose a change in formulation which will enable the product to be (b) (4) rather than the previously approved (b) (4). As part of the (b) (4) formulation, the packaging configuration was changed from pre-scored amber glass ampoule to a stoppered amber glass vial. The manufacturing process was developed at Genzyme Biosurgery based on the approved process developed at Draxis with improvements. Genzyme Biosurgery is therefore added as an additional manufacturing site. Five volumes of the application were submitted for review.

filename: **C:\my documents\review\Supplements\NO21027S015R1**

Executive Summary

I. Recommendations

A. Recommendation on Approvability - Recommended for approval from microbiology product quality standpoint.

B. Recommendations on Phase 4 Commitments and/or Agreements, if Approvable – N/A

II. Summary of Microbiology Assessments

A. Brief Description of the Manufacturing Processes that relate to Product Quality Microbiology – An alternate formulation is created by Genzyme in pursuit of a more desirable formulation of the drug product that is able to be (b) (4). The packaging is therefore changed from ampoule to a vial.

B. Brief Description of Microbiology Deficiencies - None

C. Assessment of Risk Due to Microbiology Deficiencies – N/A

III. Administrative

A. Reviewer's Signature _____

Vinayak. B. Pawar, Ph.D.
CDER/OPS/NDMS

B. Endorsement Block _____

James McVey, Team Leader
CDER/OPS/NDMS

C. CC Block

N/A

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/s/

Vinayak Pawar
8/21/2008 01:49:39 PM
MICROBIOLOGIST

Recommended for approval

James McVey
8/21/2008 02:07:49 PM
MICROBIOLOGIST
I concur.

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 21-027/S-015

OTHER REVIEW(S)

REGULATORY PROJECT MANAGER LABELING REVIEW

Division of Metabolism and Endocrinology Products

Application Number: 21-027/S-015

Name of Drug: Hectorol (doxercalciferol injection) 4 mcg/ 2mL (2 mcg/mL)

Applicant: Genzyme Corporation

Material Reviewed:

Supplement Letter/Receipt Dates: April 18, 2008, received April 21, 2008

Amendment Dates: October 10 and November 18, 2008

Project Manager: Haley Seymour

Background

Hectorol Injection is indicated for the treatment of secondary hyperparathyroidism in patients with chronic kidney disease (CKD) on dialysis. Hectorol Injection is indicated for the treatment of secondary hyperparathyroidism in patients with chronic kidney disease, on dialysis.

This supplemental application also provides for a change from ampule to vial, change in the formulation, change in the packaging configuration, and the addition of another manufacturing site. In addition, this supplemental application provides for changes to the *OVERDOSAGE* section of the package insert regarding language stating that Hectorol is not dialyzable.

The November 18, 2008, submission was compared to the most recently approved labeling S-013, approved, July 20, 2006, for the package insert. The carton and vial labels were compared to the final printed carton and container labels submitted January 16, 2001, for the original NDA approved April 6, 2000.

This labeling format conforms with 21 CFR201.80.

DMEP Review

The changes to the November 18, 2008, package insert with respect to the last approved package insert (S-013) are described below.

- Header, HECTOROL INJECTION (doxercalciferol)

  changed to:

  HECTOROL-doxercalciferol injection, solution
  Genzyme Corporation

Comment:
This is a format/content change for SPL.

Description:

- "Hectorol is available as a sterile, clear, essentially colorless to faint yellow, aqueous solution for intravenous injection. (b) (4) [redacted]

  changed to:

- **Hectorol Injection is supplied in stoppered, single-use 2 mL amber glass vials, with an aluminum seal and yellow flip-off cap. Each milliliter (mL) of solution contains doxercalciferol, 2 mcg; ethanol, 100%, 0.05 mL; Polysorbate 20, 10 mg; sodium chloride, 1.5 mg; butylated hydroxytoluene, 0.02 mg; sodium phosphate dibasic, heptahydrate, 14.4 mg; sodium phosphate monobasic, monohydrate, 1.8 mg; and disodium edetate, 1.1mg."**

Comment:
These changes were found acceptable by the chemist, Dr. Raman.

Precautions:
General

- The principal adverse effects of treatment with Hectorol Injection are hypercalcemia, hyperphosphatemia, and oversuppression of iPTH (less than 150 pg/ml). Prolonged hypercalcemia can lead to calcification of soft tissues, including the heart and arteries, and hyperphosphatemia can exacerbate hyperparathyroidism. Oversuppression of iPTH 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 adjustments in co-therapy (i.e., dietary phosphate binders) in order to maximize iPTH suppression while maintaining serum calcium and phosphorus levels within prescribed ranges.

changed to:

The principal adverse effects of treatment with Hectorol Injection are hypercalcemia, hyperphosphatemia, and oversuppression of PTH (iPTH less than 150 pg/mL). 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 adjustments in co-therapy (i.e., dietary phosphate binders) in order to maximize PTH suppression while maintaining serum calcium and phosphorus levels within prescribed ranges.

Comment:
This change was found acceptable by the Medical Officer, Theresa Kehoe.

OVERDOSAGE:

Treatment of Accidental Overdosage of Hectorol

- The treatment of acute accidental overdosage of Hectorol should consist of general supportive measures. 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 digitals. 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 that 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.

changed to:

Treatment of Accidental Overdosage of Hectorol

The treatment of acute accidental overdosage of Hectorol should consist of general supportive measures. 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, treatment with standard medical care should be followed, as needed. Based on similarities between Hectorol and its active metabolite, $1\alpha,25\text{-}(OH)_2D_2$, it is expected that Hectorol is not removed from the blood by dialysis

Comment:
The Medical Officer, Theresa Kehoe finds the following language acceptable:

DOSAGE AND ADMINISTRATION:

- The addition of "For intravenous use only".

HOW SUPPLIED:

- Hectorol (doxercalciferol) Injection is supplied in pre-scored amber glass ampules.

  changed to:

  Hectorol (doxercalciferol injection) is supplied in single-use 2 mL amber glass vials; the closure consists of a fluorocarbon-coated chlorobutyl stopper, with an aluminum seal and a yellow plastic flip-off cap.

Comment:
These changes were found acceptable by Microbiologist, Dr. Pawar, and Chemist, Dr. Ramon.

NDC Number	Volume	mcg/ampule
64894-840-50	2 mL	4

  changed to:

  (b) (4)

- **Store at 15° to 25° C (59° to 77° F). Protect from light**

  changed to:

  Store at 25° C (77° F): excursions permitted to 15-30° C (59-86° F)
  [see USP controlled room temperature]

  Protect from light.

  Rx only

- Manufactured by Draxis Pharma, Inc. for
  Bone Care International, Inc., Middleton, WI 53652 888-389-4242
  2000, Bone Care International, Inc.

PI-002A-03 09/04

changed to:

Manufactured by: Genzyme Biosurgery
For: Genzyme Corporation
500 Kendall Street
Cambridge, MA 02142

HECTOROL and GENZYME are registered trademarks of Genzyme Corporation

Comment:
These changes were found acceptable by chemist, Dr. Raman.

DMEP Review

The changes to the April 18, 2008, carton and vial labels with respect to the last approved carton and vial labels from the original NDA from January 16, 2001, are described below.

(b) (4)

[redacted]

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Comment:
These changes were found acceptable by chemist, Dr. Raman.

Additional minor editorial changes were made such as the addition of table and figure titles, minor text revisions in cross-reference to tables and figures, and reformatting of table footnotes, which were found acceptable by the project manager.

DMEPA review requested the following changes:

Vial Label

1. Add the statement “Discard after use” after the statement “Single-use vial”.
2. Relocate the single-use vial-discard after use and “For intravenous use only” statements to where the “Rx only” statement and company logo are currently located. This will allow all important information (i.e. proprietary name, established name, product strength, single-use only, and route of administration statements) to be read without having to turn the vial, thereby reducing the potential that of any of this important

information will be overlooked.

3. Decrease the size of the company logo in comparison to the proprietary name.

Comment:
The company has made these changes.

Package Insert-How Supplied Section

1. Revise the first paragraph to read:

   "Hectorol (doxercalciferol injection) is supplied in a single use amber glass vial containing 4 mcg/2mL…"

2. [redacted] (b) (4) (b) (4)

   Revise to read as follows:
   NDA 54868-0123-1 4 mcg/2 mL vial

Comment:
The company has made these changes.

Recommendations

This proposed labeling has been reviewed by the Chemist, Kris Ramon (ONDQA, Division IV, Branch VII) , Microbiologist, Vinayak Pawar, (OPS/NDMS), Medical Officer, Theresa Kehoe (DMEP, ODE II), and the project manager who agree to the changes. The changes recommended by DMEPA have been made by the company in their November 18, 2008, submission. The labeling is acceptable, and the supplement may be approved.

_____

Haley Seymour
Regulatory Project Manager

CPMS Concurrence: Enid Galliers/11/25/08 and 12/1/08

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/s/

Haley Seymour
12/4/2008 02:29:45 PM
CSO

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology

Date:	October 20, 2008
To:	Mary Parks, MD., Director Division of Metabolism and Endocrinology Products
Through:	Kristina C. Arnwine, Pharm.D., Acting Team Leader Carol Holquist, R.Ph., Director Division of Medication Error Prevention and Analysis
From:	Robin E. Duer, R.N., M.B.A., Safety Evaluator Division of Medication Error Prevention and Analysis
Subject:	Label and Labeling Review
Drug Name:	HECTOROL® (doxercalciferol injection), 4 mcg/2 mL
Application Type/Number:	NDA 21-027
Submission Number:	SCF-015
Applicant:	Genzyme Corporation
OSE RCM #:	2008-1336

CONTENTS

EXECUTIVE SUMMARY

The results of the Label and Labeling Risk Assessment determined that the presentation of information in the How Supplied section of the package insert is confusing. The product strength should be revised to read "4 mcg/2 mL". Additionally, we noted the company name on the container label appears in a large font size in comparison to the proprietary name. The proposed name and strength need to be the most prominent information on the label. Additionally, there is no instruction to discard the vial after use.

The Division of Medication Error Prevention and Analysis (DMEPA) provides recommendations in Section 6 that aim at reducing the risk of medication errors due to these needed areas of improvement.

1 BACKGROUND

1.1 INTRODUCTION

This review was written in response to a request from the Division of Metabolism and Endocrinology Products (DMEP) to evaluate the proposed HECTOROL® Injection labeling. The Division is concerned that there is a discrepancy in the expression of drug strength in one sentence in the "How Supplied" section of the package insert.

1.2 REGULATORY HISTORY

HECTOROL® Injection was originally approved by the FDA on April 6, 2000 under NDA 21-027. The Applicant filed a prior approval supplement for this NDA on April 21, 2008 (S-015) which proposed a change in formulation from (b) (4) formulation. Additionally, the packaging configuration was changed from a pre-scored, amber glass ampule to a stoppered, amber glass vial, and an additional manufacturer was introduced. On October 10, 2008 the Applicant submitted revised, final labeling including the package insert, vial label and carton labeling. The revised labeling incorporated changes to the "Overdosage-Treatment of Accidental Overdosage of HECTOROL®" section of the package insert as negotiated and requested by DMEP.

On May 25, 2008 DMEPA conducted a Medication Error Post-Marketing Safety Review (OSE #05-0060) of Hectorol Injection and Hectorol Capsules since through routine post-marketing surveillance medication errors had been identified. Seven cases had been found containing errors related to the use of trailing zeros, dangerous abbreviations, and confusion over the total drug with both products. None of the cases resulted in patient harm or patients receiving the wrong dose of Hectorol. Label and labeling revision recommendations were made by DMEPA at the time address the medication errors noted above, and those revisions were incorporated by the Applicant in an October 21, 2005 labeling submission. At that time DMEP requested that DMEPA conduct another review of the Hectorol Injection and Hectorol Capsules labeling, and that review was completed on November 8, 2005 (OSE #05-0321). At that time additional label and labeling revision recommendations were made by DMEPA concerning enhancement of the readability of the container label, and more specific language regarding route of administration information for the carton and package insert labeling for Hectorol Injection.

1.3 PRODUCT INFORMATION

HECTOROL® Injection is indicated for the treatment of secondary hyperparathyroidism in patients with chronic kidney disease on dialysis. The recommended initial dose is 4 mcg administered intravenously as a bolus three times weekly at the end of 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 1 mcg to 2 mcg if iPTH is not lowered by 50% and fails to reach the target range. HECTOROL® Injection is currently available in a 4 mcg/2 mL pre-scored, amber glass ampules.

2 METHODS AND MATERIALS

This section describes the methods and materials used by medication error prevention staff to conduct a label, labeling, and/or packaging risk assessment. The primary focus of the assessments is to identify and remedy potential sources of medication error prior to drug approval. The Division of Medication Error Prevention and Analysis (DMEPA) defines a medication error as any preventable event that may cause or lead to inappropriate medication use or patient harm while the medication is in the control of the health care professional, patient, or consumer. [1]

2.1 LABEL AND LABELING RISK ASSESSMENT

The label and labeling of a drug product are the primary means by which practitioners and patients (depending on configuration) interact with the pharmaceutical product. The container labels and carton labeling communicate critical information including proprietary and established name, strength, form, container quantity, expiration, and so on. The package insert and patient package insert labeling is intended to communicate to practitioners and patients, all information relevant to the approved uses of the drug, including the correct dosing and administration.

Given the critical role that the label and labeling has in the safe use of drug products, it is not surprising that 33 percent of medication errors reported to the USP-ISMP Medication Error Reporting Program may be attributed to the packaging and labeling of drug products, including 30 percent of fatal errors.[2]

Because medication error prevention staff analyze reported misuse of drugs, our staff are able to use this experience to identify potential errors with all medication similarly packaged, labeled or prescribed. We use FMEA and the principles of human factors to identify potential sources of error with the proposed product labels and insert labeling, and provided recommendations that aim at reducing the risk of medication errors.

Genzyme submitted the following HECTOROL® Injection labeling for the Agency's review on October 10, 2008 (see Appendices):

- Vial label (see Appendix A)
- Carton labeling (see Appendix B)
- Package Insert (PI) (Appendix C)

Additionally, DMEPA reviewed the currently marketed ampule label, carton labeling and package insert for HECTOROL® Injection for the purpose of comparing them with the proposed vial label, carton labeling and package insert.

2.2 ADVERSE EVENT REPORTING SYSTEM (AERS)

On October 7, 2008, DMEPA conducted a search of the FDA Adverse Event Reporting System (AERS) database to determine if any medication errors involving HECTOROL® Injection have been reported since the last DMEPA search was conducted on May 25, 2005. The following criteria were used: MedDRA High Level Group Term (HLGT) 'Medication Errors' and the Preferred term (PT) 'Pharmaceutical Product Complaint' with the active ingredients (doxercalciferol), trade name (Hectorol), and the verbatim term 'Hect%'.

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[1] National Coordinating Council for Medication Error Reporting and Prevention. http://www.nccmerp.org/aboutMedErrors html. Last accessed 10/11/2007.

[2] Institute of Medicine. Preventing Medication Errors. The National Academies Press: Washington DC. 2006. p275.

The cases were manually reviewed to determine if medication errors occurred involving the label/labeling and/or nomenclature. Those cases that did not describe a medication error were excluded from further analysis. The cases that did describe a medication error were categorized by type of error. We reviewed the cases within each category to identify contributing factors.

3 RESULTS

3.1 LABEL AND LABELING RISK ASSESSMENT

3.1.1 Container label

The logo for the company name is too large and is located too high on the label.

The statement "Discard after use" is missing.

The "Rx only" statement is too prominent.

3.1.2 Package Insert

The information in the "How Supplied" section is confusing.

3.2 ADVERSE EVENT REPORTING SYSTEM (AERS)

The search retrieved four cases involving HECTOROL® Injection. Three cases involved adverse events reported by patients who received Hectorol Injection along with other concomitant medications. The adverse events were not associated with medication errors involving Hectorol Injection. The remaining case dated June 6, 2005, was submitted by a pharmacist who reported a potentially hazardous medication label error for Hectorol Injection because of trailing zeros used for whole number doses in the labeling. This problem was subsequently corrected by the company in the October 2005 version of the Hectorol Injection labeling.

4 DISCUSSION

Our Label and Labeling Risk Assessment of S-015 noted several areas of needed improvement for the proposed Hectorol Injection vial label. We noted the statement "Discard after use" is not present on the container label. "Discard after use" should be included since the vial should not be re-used. We have had cases of Hepatitis B and Hepatitis C reported from the re-use of single-use vials that have not carried this statement.

We also note the "Rx only" statement and company logo are presented more prominently than the "Single-use vial" and route of administration statements. Relocating the "Single-use vial" and route of administration statements to where the "Rx only" and company logo are located will allow practitioners to read all of the important information (i.e. proprietary name, established name, product strength, single-use only, and route of administration statements) at once without having to turn the vial, thereby potentially preventing the information from being overlooked.

The review division specifically asked us to evaluate how the strength was expressed in the How Supplied section. We agree with their concerns that the applicant's proposed presentation is confusing. We recommend that the strength be expressed in terms [redacted] (b) (4)

5 CONCLUSIONS

We concur with the Division that the expression of strength in the How Supplied section is confusing. We also noted other areas of needed improvement. Full recommendations appear below in section 6.

6 RECOMMENDATIONS

6.1 COMMENTS TO THE DIVISION

Based upon our assessment of the labeling DMEPA has identified areas of needed improvement.

We would appreciate feedback on the final outcome of this review. We would be willing to meet with the Division for further discussion, if needed. Please copy us on any communication to the applicant with regard to this review. If you have further questions or need clarifications, please contact Cheryl Campbell, Project Manager, at 301-796-0723.

6.2 COMMENTS TO THE APPLICANT

A. Vial Label

1. Add the statement "Discard after use" after the statement "Single-use vial".
2. Relocate the Single-use vial-Discard after use" and "For intravenous use only" statements to where the "Rx only" statement and company logo are currently located. This will allow all important information (i.e. proprietary name, established name, product strength, single-use only, and route of administration statements) to be read without having to turn the vial, thereby reducing the potential that of any of this important information will be overlooked.
3. Decrease the size of the company logo in comparison to the proprietary name.

B. Package Insert-How Supplied Section

1. Revise the first paragraph to read:

   "Hectorol (doxercalciferol injection) is supplied in a single use amber glass vial containing 4 mcg/2 mL…"

2. [redacted] (b) (4) is confusing. Revise to read as follows:

   NDC 58468-0123-1 4 mcg/2 mL vial

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/s/

Robin E Duer
10/20/2008 04:46:30 PM
DRUG SAFETY OFFICE REVIEWER

Kristina Arnwine
10/20/2008 04:52:50 PM
DRUG SAFETY OFFICE REVIEWER

Carol Holquist
10/20/2008 04:55:25 PM
DRUG SAFETY OFFICE REVIEWER

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 21-027/S-015

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

From: Seymour, Haley
Sent: Friday, November 07, 2008 11:38 AM
To: 'Mathew, Chandra'
Subject: FW: Information Request - NDA 21-027/ S-015 Hectorol Injection

Hi Chandra,

Enid had difficulty forwarding this email to you. Please let us know if you agree to our changes as we requested below.

Thanks.

Haley

From: Galliers, Enid M
Sent: Thursday, November 06, 2008 4:24 PM
To: 'chaandra.matthew@genzyme.com'
Cc: Seymour, Haley
Subject: Information Request - NDA 21-027/ S-015 Hectorol Injection

Hello Chandra,

Haley is on leave today but will be in the office tomorrow, abut I wanted you to get this quickly. We just received a request for some labeling changes from the safety folks and would like to ask if you agree to incorporate the changes in your pending supplement. Please let us know if you agree to them and when you can submit revised labeling. It would be helpful if you could provide a mock-up of the revised vial label.

A. Vial Label:

1. Add the statement "Discard after use" following the statement "Single-use vial."
2. Relocate the Single-use vial-Discard after use" and "For intravenous use only" statements to where the "Rx only" statement and company logo are currently located. This will allow all important information (i.e., proprietary name, established name, product strength, single-use only, and route of administration statements) to be read without having to turn the vial, thereby reducing the potential that any of this important information will be overlooked.
3. Decrease the size of the company log in comparison to the proprietary name.

B. Package Insert - HOW SUPPLIED section:

1. Revise the first paragraph to read:
"Hectorol (doxercalciferol injection) is supplied in a single use amber glass vial containing 4 mcg/2 mL . . . "

2. [redacted] (b) (4)

Revise to read as follows: NDC 58468-0123-1 4 mcg/2 mL vial

Thank you,

Enid

Enid Galliers
Chief, Project Management Staff
Division of Metabolism and Endocrinology Products
Center for Drug Evaluation and Research
Food and Drug Administration
Phone: 301-796-1211
Fax: 301-796-9712
email: enid.galliers@fda hhs.gov

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/s/

Haley Seymour
11/18/2008 10:41:10 AM
CSO

From: Seymour, Haley
Sent: Tuesday, August 26, 2008 12:06 PM
To: 'Nicole.Oliynyk@genyme.com'
Cc: 'Maria.Iacovelli@genzyme.com'
Subject: NDA 21-027 S-015

NDA 21-027 Hectoral (doxercalciferol injection) 4 mcg/2ml (2mcg/ml) S-015

Reference is made to your April 18, 2008, submission which containing changes in the label.

In the product label, under Treatment of Accidental Overdosage of Hectorol, line 261, you propose to remove the term (b) (4) These two chemical entities are not interchangeable. Please provide your rationale for making this change as well as the supporting clinical studies that evaluate the use of bisphosphonates for treatment of vitamin D overdose.

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/s/

Haley Seymour
8/26/2008 12:10:18 PM
CSO

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

REQUEST FOR CONSULTATION

TO *(Office/Division)*: OSE Consults: Cheryl Campbell
Attention: Medication Errors

FROM (*Name, Office/Division, and Phone Number of Requestor)*: DMEP
(HFD-510) Haley Seymour/ W O B.22 Rm3373/x6 2443

DATE	IND NO.	NDA NO.	TYPE OF DOCUMENT	DATE OF DOCUMENT
August 14, 2008		21-027	S-015	April 18, 2008

NAME OF DRUG	PRIORITY CONSIDERATION	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE
Hectoral Injection			ASAP

NAME OF FIRM: Genzyme

REASON FOR REQUEST

I. GENERAL

- ☐ NEW PROTOCOL
- ☐ PROGRESS REPORT
- ☐ NEW CORRESPONDENCE
- ☐ DRUG ADVERTISING
- ☐ ADVERSE REACTION REPORT
- ☐ MANUFACTURING CHANGE / ADDITION
- ☐ MEETING PLANNED BY
- ☐ PRE-NDA MEETING
- ☐ END-OF-PHASE 2a MEETING
- ☐ END-OF-PHASE 2 MEETING
- ☐ RESUBMISSION
- ☐ SAFETY / EFFICACY
- ☐ PAPER NDA
- ☐ CONTROL SUPPLEMENT
- ☐ RESPONSE TO DEFICIENCY LETTER
- ☐ FINAL PRINTED LABELING
- ☐ LABELING REVISION
- ☐ ORIGINAL NEW CORRESPONDENCE
- ☐ FORMULATIVE REVIEW
- ☐ OTHER *(SPECIFY BELOW)*:

II. BIOMETRICS

- ☐ PRIORITY P NDA REVIEW
- ☐ END-OF-PHASE 2 MEETING
- ☐ CONTROLLED STUDIES
- ☐ PROTOCOL REVIEW
- ☐ OTHER (SPECIFY BELOW):
- ☐ CHEMISTRY REVIEW
- ☐ PHARMACOLOGY
- ☐ BIOPHARMACEUTICS
- ☐ OTHER (SPECIFY BELOW):

III. BIOPHARMACEUTICS

- ☐ DISSOLUTION
- ☐ BIOAVAILABILTY STUDIES
- ☐ PHASE 4 STUDIES
- ☐ DEFICIENCY LETTER RESPONSE
- ☐ PROTOCOL - BIOPHARMACEUTICS
- ☐ IN-VIVO WAIVER REQUEST

IV. DRUG SAFETY

- ☐ PHASE 4 SURVEILLANCE/EPIDEMIOLOGY PROTOCOL
- ☐ DRUG USE, e.g., POPULATION EXPOSURE, ASSOCIATED DIAGNOSES
- ☐ CASE REPORTS OF SPECIFIC REACTIONS (List below)
- ☐ COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP
- ☐ REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY
- ☐ SUMMARY OF ADVERSE EXPERIENCE
- ☐ POISON RISK ANALYSIS

V. SCIENTIFIC INVESTIGATIONS

- ☐ CLINICAL
- ☐ NONCLINICAL

COMMENTS / SPECIAL INSTRUCTIONS: In the "How supplied" section the expression of strengths is 2 ml and the contents on carton and vial are expressed as 4 mcg/2 ml should it be the same in both places, or is it acceptable as is. Thanks!

Submission located in EDR

SIGNATURE OF REQUESTOR	METHOD OF DELIVERY (Check one)
Haley Seymour	☒ DFS ☐ EMAIL ☐ MAIL ☐ HAND
PRINTED NAME AND SIGNATURE OF RECEIVER	PRINTED NAME AND SIGNATURE OF DELIVERER

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/s/

Haley Seymour

8/14/2008 01:53:37 PM

Date: August 21, 2008

Ref: NDA 21-027/SCF-015 (A Prior Approval Supplement)

Subject: Establishment Inspection

The Office of Compliance has given an overall recommendation for the facilities related to the above NDA. A copy of EER report is attached.

Kris Raman, Ph.D.

Quality Reviewer
DPME

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/s/

Kris Raman
8/21/2008 04:40:47 PM
CHEMIST

Ramesh Raghavachari
8/21/2008 04:48:21 PM
CHEMIST
Signed for Dr. James D. Vidra

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-027/S-015 **PRIOR APPROVAL SUPPLEMENT**

Genzyme Corporation
Attention: Maria Iacovelli
Manager, Regulatory Affairs
500 Kendall Street
Cambridge, MA 02142

Dear Ms. Iacovelli:

We have received your supplemental new drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for the following:

Name of Drug Product: Hectorol (doxercalciferol injection) 4 mcg/2 mL, 2 mcg/1 mL

NDA Number: 21-027

Supplement number: 015

Date of supplement: April 18, 2008

Date of receipt: April 21, 2008

This supplemental application proposes the following changes in the formulation, and packaging configuration from the currently approved Hectorol Injection, as well as to introduce an additional manufacturer.

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on June 20, 2008, in accordance with 21 CFR 314.101(a). If the application is filed, the user fee goal date will be **October 21, 2008.**

Please cite the application number listed above at the top of the first page of all submissions to this application. Send all submissions, electronic or paper, including those sent by overnight mail or courier, to the following address:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Metabolism and Endocrinology Products
5901-B Ammendale Road
Beltsville, MD 20705-1266

If you have any questions, call me at (301) 796-2443.

Sincerely,

{See appended electronic signature page}

Haley Seymour
Regulatory Project Manager
Division of Metabolism and Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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/s/

Haley Seymour

5/6/2008 01:36:44 PM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

REQUEST FOR CONSULTATION

TO *(Office/Division)*: Jim McVey, HFD-805, 301-796-1572

FROM (*Name, Office/Division, and Phone Number of Requestor)*: Teshara G. Bouie, ONDQA, Division of Post-Marketing Assessment, 301-796-1649

DATE	IND NO.	NDA NO.	TYPE OF DOCUMENT	DATE OF DOCUMENT
May 21, 2008		21-027	SCF-015	April 18, 2008

NAME OF DRUG	PRIORITY CONSIDERATION	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE
Hectoral Injection			August 1, 2008

NAME OF FIRM: Genzyme

REASON FOR REQUEST

I. GENERAL

- ☐ NEW PROTOCOL
- ☐ PROGRESS REPORT
- ☐ NEW CORRESPONDENCE
- ☐ DRUG ADVERTISING
- ☐ ADVERSE REACTION REPORT
- ☒ MANUFACTURING CHANGE / ADDITION
- ☐ MEETING PLANNED BY
- ☐ PRE-NDA MEETING
- ☐ END-OF-PHASE 2a MEETING
- ☐ END-OF-PHASE 2 MEETING
- ☐ RESUBMISSION
- ☐ SAFETY / EFFICACY
- ☐ PAPER NDA
- ☐ CONTROL SUPPLEMENT
- ☐ RESPONSE TO DEFICIENCY LETTER
- ☐ FINAL PRINTED LABELING
- ☐ LABELING REVISION
- ☐ ORIGINAL NEW CORRESPONDENCE
- ☐ FORMULATIVE REVIEW
- ☐ OTHER *(SPECIFY BELOW)*:

II. BIOMETRICS

- ☐ PRIORITY P NDA REVIEW
- ☐ END-OF-PHASE 2 MEETING
- ☐ CONTROLLED STUDIES
- ☐ PROTOCOL REVIEW
- ☐ OTHER (SPECIFY BELOW):
- ☐ CHEMISTRY REVIEW
- ☐ PHARMACOLOGY
- ☐ BIOPHARMACEUTICS
- ☐ OTHER (SPECIFY BELOW):

III. BIOPHARMACEUTICS

- ☐ DISSOLUTION
- ☐ BIOAVAILABILTY STUDIES
- ☐ PHASE 4 STUDIES
- ☐ DEFICIENCY LETTER RESPONSE
- ☐ PROTOCOL - BIOPHARMACEUTICS
- ☐ IN-VIVO WAIVER REQUEST

IV. DRUG SAFETY

- ☐ PHASE 4 SURVEILLANCE/EPIDEMIOLOGY PROTOCOL
- ☐ DRUG USE, e.g., POPULATION EXPOSURE, ASSOCIATED DIAGNOSES
- ☐ CASE REPORTS OF SPECIFIC REACTIONS (List below)
- ☐ COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP
- ☐ REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY
- ☐ SUMMARY OF ADVERSE EXPERIENCE
- ☐ POISON RISK ANALYSIS

V. SCIENTIFIC INVESTIGATIONS

- ☐ CLINICAL
- ☐ NONCLINICAL

COMMENTS / SPECIAL INSTRUCTIONS: This supplement provides for a change in formulation and packaging configuration from the currently approved drug product as well as to introduce an additional manufacturer. Please review.

This supplement is located in the EDR.

PDUFA Goal Date: August 21, 2008

SIGNATURE OF REQUESTOR	METHOD OF DELIVERY (Check one)
Teshara G. Bouie	☒ DFS ☐ EMAIL ☐ MAIL ☐ HAND
PRINTED NAME AND SIGNATURE OF RECEIVER	PRINTED NAME AND SIGNATURE OF DELIVERER

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/s/

Teshara Bouie
5/21/2008 09:41:00 AM