

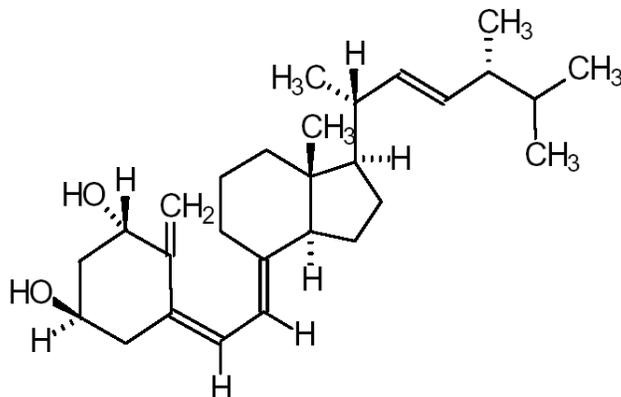
1 **HECTOROL[®] (doxercalciferol capsules)**

2 **DESCRIPTION**

3 Doxercalciferol, the active ingredient in Hectorol[®], is a synthetic vitamin D₂ analog that
4 undergoes metabolic activation *in vivo* to form 1 α ,25-dihydroxyvitamin D₂ (1 α ,25-
5 (OH)₂D₂), a naturally occurring, biologically active form of vitamin D₂. Hectorol is
6 available as soft gelatin capsules containing 0.5 mcg, 1 mcg or 2.5 mcg doxercalciferol.
7 Each capsule also contains fractionated triglyceride of coconut oil, ethanol, and butylated
8 hydroxyanisole (BHA). The capsule shells contain gelatin, glycerin and titanium
9 dioxide. In addition, the 0.5 mcg capsule shells contain yellow iron oxide and FD&C
10 Red No. 40, the 1 mcg capsule shells contain FD&C Yellow No. 6, and the 2.5 mcg
11 capsule shells contain yellow iron oxide.

12 Doxercalciferol is a colorless crystalline compound with a calculated molecular weight of
13 412.66 and a molecular formula of C₂₈H₄₄O₂. It is soluble in oils and organic solvents,
14 but is relatively insoluble in water. Chemically, doxercalciferol is (1 α ,3 β ,5Z,7E,22E)-
15 9,10-secoergosta-5,7,10(19),22-tetraene-1,3-diol. The structural formula is presented in
16 **Figure 1** below:

17 **Figure 1: Chemical Structure of Doxercalciferol**



18
19 Other names frequently used for doxercalciferol are 1 α -hydroxyvitamin D₂, 1 α -OH-D₂,
20 and 1 α -hydroxyergocalciferol.

21 **CLINICAL PHARMACOLOGY**

22 Vitamin D levels in humans depend on two sources: (1) exposure to the ultraviolet rays
23 of the sun for conversion of 7-dehydrocholesterol in the skin to vitamin D₃
24 (cholecalciferol) and (2) dietary intake of either vitamin D₂ (ergocalciferol) or vitamin
25 D₃. Vitamin D₂ and vitamin D₃ must be metabolically activated in the liver and the
26 kidney before becoming fully active on target tissues. The initial step in the activation
27 process is the introduction of a hydroxyl group in the side chain at C-25 by the hepatic

28 enzyme, CYP 27 (a vitamin D-25-hydroxylase). The products of this reaction are 25-
29 (OH)D₂ and 25-(OH)D₃, respectively. Further hydroxylation of these metabolites occurs
30 in the mitochondria of kidney tissue, catalyzed by renal 25-hydroxyvitamin D-1-α-
31 hydroxylase to produce 1α,25-(OH)₂D₂, the primary biologically active form of vitamin
32 D₂, and 1α,25-(OH)₂D₃ (calcitriol), the biologically active form of vitamin D₃.

33 **Mechanism of Action**

34 Calcitriol (1α,25-(OH)₂D₃) and 1α,25-(OH)₂D₂ regulate blood calcium at levels required
35 for essential body functions. Specifically, the biologically active vitamin D metabolites
36 control the intestinal absorption of dietary calcium, the tubular reabsorption of calcium
37 by the kidney and, in conjunction with parathyroid hormone (PTH), the mobilization of
38 calcium from the skeleton. They act directly on bone cells (osteoblasts) to stimulate
39 skeletal growth, and on the parathyroid glands to suppress PTH synthesis and secretion.
40 These functions are mediated by the interaction of these biologically active metabolites
41 with specific receptor proteins in the various target tissues. In patients with chronic
42 kidney disease (CKD), deficient production of biologically active vitamin D metabolites
43 (due to lack of or insufficient 25-hydroxyvitamin D-1-alpha-hydroxylase activity) leads
44 to secondary hyperparathyroidism, which contributes to the development of metabolic
45 bone disease.

46 **Pharmacokinetics and Metabolism**

47 Doxercalciferol is absorbed from the gastrointestinal tract and activated by CYP 27 in the
48 liver to form 1α,25-(OH)₂D₂ (major metabolite) and 1α,24-dihydroxyvitamin D₂ (minor
49 metabolite). Activation of doxercalciferol does not require the involvement of the
50 kidneys.

51 In healthy volunteers, peak blood levels of 1α,25-(OH)₂D₂, the major metabolite of
52 doxercalciferol, are attained at 11-12 hours after repeated oral doses of 5 to 15 mcg of
53 Hectorol and the mean elimination half-life of 1α,25-(OH)₂D₂ is approximately 32 to 37
54 hours with a range of up to 96 hours. The mean elimination half-life in patients with end-
55 stage renal disease (ESRD) on dialysis appears to be similar. Hemodialysis causes a
56 temporary increase in 1α,25-(OH)₂D₂ mean concentrations, presumably due to volume
57 contraction. 1α,25-(OH)₂D₂ is not removed from blood during hemodialysis.

58 **Clinical Studies**

59 **Dialysis:**

60 The safety and effectiveness of Hectorol were evaluated in two double-blind, placebo-
61 controlled, multicentered clinical studies (Study A and Study B) in a total of 138 patients
62 with chronic kidney disease on hemodialysis (Stage 5 CKD). Patients in Study A were
63 an average age of 52 years (range: 22-75), were 55% male, and were 58% African-
64 American, 31% Caucasian, and 11% Hispanic, and had been on hemodialysis for an

65 average of 53 months. Patients in Study B were an average of 52 years (range: 27-75),
66 were 45% male, and 99% African-American, and 1% Caucasian, and had been on
67 hemodialysis for an average of 56 months. After randomization to two groups, eligible
68 patients underwent an 8-week washout period during which no vitamin D derivatives
69 were administered to either group. Subsequently, all patients received Hectorol in an
70 open-label fashion for 16 weeks followed by a double-blind period of 8 weeks during
71 which patients received either Hectorol or placebo. The initial dose of Hectorol during
72 the open-label phase was 10 micrograms after each dialysis session (3 times weekly) for
73 a total of 30 mcg per week. The dosage of Hectorol was adjusted as necessary by the
74 investigator in an attempt to achieve intact parathyroid hormone (iPTH) levels within a
75 targeted range of 150 to 300 pg/mL. The maximum dosage was limited to 20 mcg after
76 each dialysis session (60 mcg/week). If at any time during the trial iPTH fell below 150
77 pg/mL, Hectorol was immediately suspended and restarted at a lower dosage the
78 following week.

79 **Results:**

80 One hundred and six of the 138 patients who were treated with Hectorol during the 16-
81 week open-label phase achieved iPTH levels \leq 300 pg/mL. Ninety-four of these patients
82 exhibited plasma iPTH levels \leq 300 pg/mL on at least 3 occasions. Eighty-seven patients
83 had plasma iPTH levels $<$ 150 pg/mL on at least one occasion during the open-label
84 phase of study participation.

85 Mean weekly doses during the 16-week open-label period in Study A ranged from 14.8
86 mcg to 28.7 mcg. In Study B, the mean weekly doses during the 16-week open-label
87 period ranged from 19.2 mcg to 28 mcg.

88 Decreases in plasma iPTH from baseline values were calculated using as baseline the
89 average of the last 3 values obtained during the 8-week washout phase and are displayed
90 in **Table 1** below.

Table 1: iPTH Summary Data for Dialysis Patients Receiving Hectorol[®]

		iPTH (pg/mL) 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) < 0.001 0.72	526.5 ± 872.2 (29) < 0.001
	Week 24 (double-blind)	404.4 ± 262.9 (21) < 0.001 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) < 0.001 0.91	485.9 ± 443.4 (32) < 0.001
	Week 24 (double-blind)	459.8 ± 443.0 (35) < 0.001 < 0.001	871.9 ± 623.6 (30) < 0.065

* all subjects; last value carried to discontinuation

91

92 In both studies, iPTH levels increased progressively and significantly in 65.9% of the
 93 patients during the 8-week washout (control) period during which no vitamin D
 94 derivatives were administered. In contrast, Hectorol treatment resulted in a statistically
 95 significant reduction from baseline in mean iPTH levels during the 16-week open-label
 96 treatment period in more than 93.5% of the 138 treated patients. During the double-blind
 97 period (weeks 17 to 24), the reduction in mean iPTH levels was maintained in the
 98 Hectorol treatment group compared to a return to near baseline in the placebo group.

99 In the clinical trials, the values for iPTH varied widely from patient to patient and from
 100 week to week for individual patients. **Table 2** shows the numbers of patients within each
 101 group who achieved and maintained iPTH levels below 300 pg/mL during the open-label

102 and double-blind phases. Seventy-four of 138 patients (53.6%) had plasma iPTH levels
103 within the target range (150-300 pg/mL) during Weeks 14-16.

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

		1		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

104

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

107 **Pre-dialysis:**

108 The safety and effectiveness of Hectorol were evaluated in two clinical studies in 55
109 patients with Stage 3 or Stage 4 chronic kidney disease. Eighty-two percent of the
110 patients were male, the average age was 64.6 years, 51% were Caucasian, 40% African-
111 American, and the average serum iPTH level at baseline was 194.6 pg/mL. While levels
112 of 25-(OH) vitamin D were not evaluated at baseline, retrospective assessments of stored
113 serum revealed that the mean ± SD serum 25-(OH) vitamin D was 18.5 ± 8.1 ng/mL
114 (range: < 5 to 54 ng/mL) in the study population.

115 After randomization to two groups, eligible patients underwent an 8-week washout
116 period during which no vitamin D derivatives were administered to either group.
117 Subsequently, one group received Hectorol and the other placebo during a double-blind
118 period of 24 weeks. The initial dose of Hectorol was 1 mcg per day. The dosage of
119 Hectorol was adjusted as necessary by the investigator in order to reduce intact
120 parathyroid hormone (iPTH) levels to a target of ≥ 30% below post-washout baseline.
121 The maximum dosage was limited to 3.5 mcg per day. If at any time during the trial
122 iPTH fell below 15 pg/mL, Hectorol was immediately suspended and restarted at a lower
123 dosage the following week.

124 **Results:**

125 Decreases in the mean plasma iPTH from baseline values were calculated using as
126 baseline the average of the last 2 values obtained during the 8-week washout phase. In
127 analyses of pooled data from the two studies, iPTH levels decreased from baseline by an

128 average of 101.4 pg/mL in the Hectorol group and by 4.4 pg/mL in the placebo group
129 (p<0.001). Greater reductions of iPTH with Hectorol compared to placebo were
130 observed in each study. Twenty (74%) of 27 subjects in the Hectorol group achieved
131 mean plasma iPTH suppression of $\geq 30\%$ from baseline for the last four weeks of
132 treatment, whereas two (7%) of the 28 subjects treated with placebo achieved this level
133 of iPTH suppression. In the Hectorol-treated patients, the reductions in plasma iPTH
134 were associated with a reduction in serum bone-specific alkaline phosphatase.

135 **INDICATIONS AND USAGE**

136 **Dialysis Patients:** Hectorol is indicated for the treatment of secondary
137 hyperparathyroidism in patients with chronic kidney disease on dialysis.

138 **Pre-Dialysis Patients:** Hectorol is indicated for the treatment of secondary
139 hyperparathyroidism in patients with Stage 3 or Stage 4 chronic kidney disease.

140 **CONTRAINDICATIONS**

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

143 **WARNINGS**

144 Overdosage of any form of vitamin D, including Hectorol, is dangerous (see
145 **OVERDOSAGE**). Progressive hypercalcemia due to overdosage of vitamin D and its
146 metabolites may be so severe as to require emergency attention. Acute hypercalcemia
147 may exacerbate tendencies for cardiac arrhythmias and seizures and may potentiate the
148 action of digitalis drugs. Chronic hypercalcemia can lead to generalized vascular
149 calcification and other soft-tissue calcification. The serum calcium times serum
150 phosphorus (Ca X P) product should be maintained at $< 55 \text{ mg}^2/\text{dL}^2$ in patients with
151 chronic kidney disease. Radiographic evaluation of suspect anatomical regions may be
152 useful in the early detection of this condition.

153 Since doxercalciferol is a precursor for $1\alpha,25\text{-(OH)}_2\text{D}_2$, a potent metabolite of vitamin
154 D_2 , pharmacologic doses of vitamin D and its derivatives should be withheld during
155 Hectorol treatment to avoid possible additive effects and hypercalcemia.

156 Oral calcium-based or other non-aluminum-containing phosphate binders and a low
157 phosphate diet should be used to control serum phosphorus levels in patients with chronic
158 kidney disease. Uncontrolled serum phosphorus exacerbates secondary
159 hyperparathyroidism and can lessen the effectiveness of Hectorol in reducing blood PTH
160 levels. If hypercalcemia occurs after initiating Hectorol therapy, the dose of Hectorol
161 and/or calcium-containing phosphate binders should be decreased. If hyperphosphatemia
162 occurs after initiating Hectorol, the dose of Hectorol should be decreased and/or the dose
163 of phosphate binders increased. (See dosing recommendations for Hectorol under

164 **DOSAGE AND ADMINISTRATION** section.)

165 Magnesium-containing antacids and Hectorol should not be used concomitantly in
166 patients on chronic renal dialysis because such use may lead to the development of
167 hypermagnesemia.

168 **PRECAUTIONS**

169 **General**

170 Active vitamin D sterols should not be used as initial treatment of nutritional vitamin D
171 deficiency (as defined by low 25-hydroxy vitamin D). Patients should be checked and
172 treated for nutritional vitamin D deficiency prior to initiating treatment with Hectorol.

173 The principal adverse effects of treatment with Hectorol are hypercalcemia,
174 hyperphosphatemia, hypercalciuria, and oversuppression of PTH (iPTH less than
175 150 pg/mL). Prolonged hypercalcemia can lead to calcification of soft tissues, including
176 the heart and arteries, and hyperphosphatemia can exacerbate hyperparathyroidism.
177 Hypercalciuria can accelerate the onset of renal failure through nephrocalcinosis.
178 Oversuppression of PTH may lead to adynamic bone syndrome. All of these potential
179 adverse effects should be managed by regular patient monitoring and appropriate dosage
180 adjustments. During treatment with Hectorol, patients usually require dose titration, as
181 well as adjustment in co-therapy (i.e., dietary phosphate binders) in order to maximize
182 PTH suppression while maintaining serum calcium and phosphorus within prescribed
183 ranges.

184 **Dialysis:** In four adequate and well-controlled studies, the incidence of hypercalcemia
185 and hyperphosphatemia increased during therapy with Hectorol. The observed increases
186 during Hectorol treatment, although occurring at a low rate, underscore the importance of
187 regular safety monitoring of serum calcium and phosphorus levels throughout treatment.
188 Patients with higher pre-treatment serum levels of calcium (> 10.5 mg/dL) or phosphorus
189 (> 6.9 mg/dL) were more likely to experience hypercalcemia or hyperphosphatemia.
190 Therefore, Hectorol should not be given to patients with a recent history of
191 hypercalcemia or hyperphosphatemia, or evidence of vitamin D toxicity.

192 **Pre-dialysis:** In two clinical studies, the incidences of hypercalcemia and
193 hyperphosphatemia during therapy with Hectorol were similar to placebo therapy, and no
194 episodes of hypercalciuria were observed. The baseline median 25-(OH) vitamin D
195 levels of patients enrolled in these studies was 17.2 ng/mL. Ninety-three percent of
196 patients had 25-(OH) vitamin D levels less than 30 ng/mL; 26% had 25-(OH) vitamin D
197 levels \geq 20 to < 30 ng/mL; 58% had levels > 10 to < 20 ng/mL; 7% had levels > 5 to < 10
198 ng/mL; and 2% had levels < 5 ng/mL. The incidences of hypercalcemia,
199 hyperphosphatemia, and hypercalciuria in patients treated with Hectorol for
200 hyperparathyroidism related to pre-dialysis renal insufficiency has not been fully studied

201 when 25-(OH) vitamin D levels are greater than or equal to 30 ng/mL.

202 **Information for the Patient**

203 The patient, spouse, or guardian should be informed about compliance with dosage
204 instructions, adherence to instructions about diet, calcium supplementation, and
205 avoidance of the use of nonprescription drugs without prior approval from their
206 physician. Patients should also be carefully informed about the symptoms of
207 hypercalcemia (see **ADVERSE REACTIONS** section).

208 Patients' total combined elemental calcium intake (dietary and phosphate binder) should
209 not exceed 2 g daily.

210 **Laboratory Tests**

211 Serum or plasma iPTH and serum calcium, phosphorus, and alkaline phosphatase should
212 be determined periodically. In the early phase of treatment for dialysis patients, iPTH,
213 serum calcium, and serum phosphorus should be determined prior to initiation of
214 Hectorol treatment and weekly thereafter. For pre-dialysis patients, serum levels of
215 calcium and phosphorus and plasma levels of iPTH should be monitored at least every
216 two weeks for 3 months after initiation of Hectorol therapy or following dose-
217 adjustments in Hectorol therapy, then monthly for 3 months, and every 3 months
218 thereafter.

219 **Drug Interactions**

220 Specific drug interaction studies have not been conducted. Cholestyramine has been
221 reported to reduce intestinal absorption of fat-soluble vitamins; therefore, it may impair
222 intestinal absorption of doxercalciferol. Magnesium-containing antacids and Hectorol
223 should not be used concomitantly because such use may lead to the development of
224 hypermagnesemia (see **WARNINGS**). The use of mineral oil or other substances that
225 may affect absorption of fat may influence the absorption and availability of Hectorol.
226 Although not examined specifically, enzyme inducers (such as glutethimide and
227 phenobarbital) may affect the 25-hydroxylation of Hectorol and may necessitate dosage
228 adjustments. Cytochrome P450 inhibitors (such as ketoconazole and erythromycin) may
229 inhibit the 25-hydroxylation of Hectorol. Hence, formation of the active Hectorol moiety
230 may be hindered.

231 **Carcinogenesis, Mutagenesis, Impairment of Fertility**

232 In a 104-week carcinogenicity study in rats, there was an increased incidence of benign
233 and malignant adrenal pheochromocytomas in both males and females at oral doses of
234 0.04, 0.13 and 0.39 mcg/kg/day (≤ 1 times the human exposure in pre-dialysis patients
235 with a maximum recommended dose of 3.5 mcg/day or 24.5 mcg/week). This increased
236 incidence of pheochromocytomas in rats may be due to altered calcium homeostasis by

237 doxercalciferol. No evidence of genetic toxicity was observed in an *in vitro* bacterial
238 mutagenicity assay (Ames test) or a mouse lymphoma gene mutation assay.
239 Doxercalciferol caused structural chromatid and chromosome aberrations in an *in vitro*
240 human lymphocyte clastogenicity assay with metabolic activation. However,
241 doxercalciferol was negative in an *in vivo* mouse micronucleus clastogenicity assay.
242 Doxercalciferol had no effect on male or female fertility in rats at oral doses up to 2.5
243 mcg/kg/day (approximately 3 times the maximum recommended human dose of 60
244 mcg/week based on mcg/m² body surface area).

245 **Use in Pregnancy**

246 **Pregnancy Category B**

247 Reproduction studies in rats and rabbits, at doses up to 20 mcg/kg/day and 0.1
248 mcg/kg/day (approximately 25 times and less than the maximum recommended human
249 dose of 60 mcg/week based on mcg/m² body surface area, respectively) have revealed no
250 teratogenic or fetotoxic effects due to doxercalciferol. There are, however, no adequate
251 and well-controlled studies in pregnant women. Because animal reproduction studies are
252 not always predictive of human response, this drug should be used during pregnancy only
253 if clearly needed.

254 **Nursing Mothers**

255 It is not known whether doxercalciferol is excreted in human milk. Because other
256 vitamin D derivatives are excreted in human milk and because of the potential for serious
257 adverse reactions in nursing infants from doxercalciferol, a decision should be made
258 whether to discontinue nursing or to discontinue the drug, taking into account the
259 importance of the drug to the mother.

260 **Pediatric Use**

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

262 **Geriatric Use**

263 Of the 138 patients treated with Hectorol Capsules in two Phase 3 clinical studies, 30
264 patients were 65 years or over. In these studies, no overall differences in efficacy or
265 safety were observed between patients 65 years or older and younger patients.

266 **Hepatic Insufficiency**

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

271 **ADVERSE REACTIONS**

272 **Dialysis:** Hectorol has been evaluated for safety in clinical studies in 165 patients with
 273 chronic kidney disease on hemodialysis. In two placebo-controlled, double-blind,
 274 multicenter studies, discontinuation of therapy due to any adverse event occurred in 2.9%
 275 of 138 patients treated with Hectorol for four to six months (dosage titrated to achieve
 276 target iPTH levels, see **CLINICAL PHARMACOLOGY/Clinical Studies**) and in 3.3%
 277 of 61 patients treated with placebo for two months. Adverse events occurring in the
 278 Hectorol group at a frequency of 2% or greater and more frequently than in the placebo
 279 group are presented in **Table 3** below:

Table 3: Adverse Events Reported by $\geq 2\%$ 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
Musculoskeletal 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.

280

281 **Pre-dialysis:** Hectorol has been evaluated for safety in clinical studies in 55 patients
282 (27 active and 28 placebo) with chronic kidney disease, Stages 3 or 4. In two placebo-
283 controlled, double-blind, multicenter studies, discontinuation of therapy due to any
284 adverse event occurred in one (3.7%) of 27 patients treated with Hectorol for 24 weeks
285 (dosage titrated to achieve target iPTH levels, see **CLINICAL**
286 **PHARMACOLOGY/Clinical Studies**) and in three (10.7%) of 28 patients treated with
287 placebo for 24 weeks. Adverse events occurring in the Hectorol group at a frequency of
288 5% or greater and more frequently than in the placebo group are as follows: **Body as a**
289 **Whole** – Infection, Chest Pain; **Digestive System** – Constipation, Dyspepsia;
290 **Hematologic and Lymphatic** – Anemia; **Metabolic and Nutritional** – Dehydration;
291 **Nervous System** – Depression, Hypertonia, Insomnia, Paresthesia; **Respiratory System**
292 – Cough increased, Dyspnea, Rhinitis.

293 Potential adverse effects of Hectorol are, in general, similar to those encountered with
294 excessive vitamin D intake. The early and late signs and symptoms of vitamin D
295 intoxication associated with hypercalcemia include:

296 **Early**

297 Weakness, headache, somnolence, nausea, vomiting, dry mouth, constipation, muscle
298 pain, bone pain, metallic taste, and anorexia.

299 **Late**

300 Polyuria, polydipsia, anorexia, weight loss, nocturia, conjunctivitis (calcific),
301 pancreatitis, photophobia, rhinorrhea, pruritus, hyperthermia, decreased libido, elevated
302 blood urea nitrogen (BUN), albuminuria, hypercholesterolemia, elevated serum aspartate
303 transaminase (AST) and alanine transaminase (ALT), ectopic calcification, hypertension,
304 cardiac arrhythmias, sensory disturbances, dehydration, apathy, arrested growth, urinary
305 tract infections, and, rarely, overt psychosis.

306 **OVERDOSAGE**

307 Administration of Hectorol to patients in excess doses can cause hypercalcemia,
308 hypercalciuria, hyperphosphatemia, and oversuppression of PTH secretion leading in
309 certain cases to adynamic bone disease. High intake of calcium and phosphate
310 concomitant with Hectorol may lead to similar abnormalities. High levels of calcium in
311 the dialysate bath may contribute to hypercalcemia.

312 **Treatment of Hypercalcemia and Overdosage**

313 General treatment of hypercalcemia (greater than 1 mg/dL above the upper limit of the
314 normal range in dialysis patients; > 10.7 mg/dL in pre-dialysis patients) consists of

315 immediate suspension of Hectorol therapy, institution of a low calcium diet, and
 316 withdrawal of calcium supplements. Serum calcium levels should be determined at least
 317 weekly until normocalcemia ensues. Hypercalcemia usually resolves in 2 to 7 days.
 318 When serum calcium levels have returned to within normal limits, Hectorol therapy may
 319 be reinstated at a dose that is lower (at least 2.5 mcg in dialysis patients and 0.5 mcg in
 320 pre-dialysis patients) than prior therapy. In dialysis patients, serum calcium levels should
 321 be obtained weekly after all dosage changes and during subsequent dosage titration.
 322 Persistent or markedly elevated serum calcium levels may be corrected by dialysis
 323 against a reduced calcium or calcium-free dialysate.

324 **Treatment of Accidental Overdosage of Doxercalciferol**

325 The treatment of acute accidental overdosage of Hectorol should consist of general
 326 supportive measures. If drug ingestion is discovered within a relatively short time (10
 327 minutes), induction of emesis or gastric lavage may be of benefit in preventing further
 328 absorption. If drug ingestion is discovered later than 10 minutes post-ingestion, the
 329 administration of mineral oil may promote its fecal elimination. Serial serum electrolyte
 330 determinations (especially calcium), rate of urinary calcium excretion, and assessment of
 331 electrocardiographic abnormalities due to hypercalcemia should be obtained. Such
 332 monitoring is critical in patients receiving digitalis. Discontinuation of supplemental
 333 calcium and institution of a low calcium diet are also indicated in accidental overdosage.
 334 If persistent and markedly elevated serum calcium levels occur, treatment with standard
 335 medical care should be followed, as needed. Based on similarities between Hectorol and
 336 its active metabolite, $1\alpha,25\text{-(OH)}_2\text{D}_2$, it is expected that Hectorol is not removed from the
 337 blood by dialysis.

338 **DOSAGE AND ADMINISTRATION**

339 *Adult Administration:*

340 The optimal dose of Hectorol must be carefully determined for each patient. **Table 4**
 341 provides the current recommended therapeutic target levels for iPTH in patients with
 342 chronic kidney disease:

Table 4: Target Range of Intact Plasma PTH by Stage of CKD

CKD Stage	GFR (mL/min/1.73m ²)	Target "intact" PTH (pg/mL)
3	30 - 59	35 - 70
4	15 - 29	70 - 110
5	< 15 (or dialysis)	150 - 300

From Table 15 of National Kidney Foundation, *K/DOQI Clinical Practice Guidelines for Bone Metabolism and Disease in Chronic Kidney Disease*. Am J Kidney Dis 42:S1-S202, 2003 (suppl 3)

343

344 *Dialysis:*

345 The recommended initial dose of Hectorol is 10 mcg administered three times weekly at
 346 dialysis (approximately every other day). The initial dose should be adjusted, as needed,
 347 in order to lower blood iPTH into the range of 150 to 300 pg/mL. The dose may be
 348 increased at 8-week intervals by 2.5 mcg if iPTH is not lowered by 50% and fails to
 349 reach the target range. The maximum recommended dose of Hectorol is 20 mcg
 350 administered three times a week at dialysis for a total of 60 mcg per week. Drug
 351 administration should be suspended if iPTH falls below 100 pg/mL and restarted one
 352 week later at a dose that is at least 2.5 mcg lower than the last administered dose. During
 353 titration, iPTH, serum calcium, and serum phosphorus levels should be obtained weekly.
 354 If hypercalcemia, hyperphosphatemia, or a serum calcium times serum phosphorus
 355 product greater than $55 \text{ mg}^2/\text{dL}^2$ is noted, the dose of Hectorol should be decreased or
 356 suspended and/or the dose of phosphate binders should be appropriately adjusted. If
 357 suspended, the drug should be restarted at a dose that is at least 2.5 mcg lower.

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

Table 5: Dialysis Dosing Recommendations

Initial Dosing	
<u>iPTH Level</u>	<u>Hectorol® Dose</u>
> 400 pg/mL	10 mcg three times per week at dialysis
Dose Titration	
<u>iPTH Level</u>	<u>Hectorol® Dose</u>
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

361

362 *Pre-dialysis:*

363 The recommended initial dose of Hectorol is 1 mcg administered once daily. The initial
 364 dose should be adjusted, as needed, in order to lower blood iPTH to within target ranges
 365 (see table below). The dose may be increased at 2-week intervals by 0.5 mcg to achieve

366 the target range of iPTH. The maximum recommended dose of Hectorol is 3.5 mcg
367 administered once per day.

368 Serum levels of calcium and phosphorus and plasma levels of iPTH should be monitored
369 at least every two weeks for 3 months after initiation of Hectorol therapy or following
370 dose adjustments in Hectorol therapy, then monthly for 3 months, and every 3 months
371 thereafter. If hypercalcemia, hyperphosphatemia, or a serum calcium times phosphorus
372 product greater than 55 mg²/dL² is noted, the dose of Hectorol should be decreased or
373 suspended and/or the dose of phosphate binders should be appropriately adjusted. If
374 suspended, the drug should be restarted at a dose that is at least 0.5 mcg lower.

375 Dosing must be individualized and based on iPTH levels with monitoring of serum
376 calcium and serum phosphorus levels. **Table 6** presents a suggested approach in dose
377 titration:

Table 6: Pre-dialysis Dosing Recommendations

Initial Dosing	
<u>iPTH Level</u>	<u>Hectorol[®] Dose</u>
> 70 pg/mL (Stage 3)	1 mcg once per day
> 110 pg/mL (Stage 4)	
Dose Titration	
<u>iPTH Level</u>	<u>Hectorol[®] Dose</u>
Above 70 pg/mL (Stage 3)	Increase by 0.5 mcg at two-week intervals as necessary
110 pg/mL (Stage 4)	
35 - 70 pg/mL (Stage 3)	Maintain
70 - 110 pg/mL (Stage 4)	
< 35 pg/mL (Stage 3)	Suspend for one week, then resume at a dose that is at least 0.5 mcg lower
< 70 pg/mL (Stage 4)	

378

379 **HOW SUPPLIED**

380 NDC 58468-0120-1

381 0.5 mcg doxercalciferol in soft gelatin, salmon, oval capsules, imprinted **g**; foil induction

- 382 sealed bottles of 50.
- 383 NDC 58468-0124-1
- 384 1 mcg doxercalciferol in soft gelatin, peach, oval capsules, imprinted **g**; foil induction
385 sealed bottles of 50.
- 386 NDC 58468-0121-1
- 387 2.5 mcg doxercalciferol in soft gelatin, butter yellow, oval capsules, imprinted **g**; foil
388 induction sealed bottles of 50.
- 389 **Store at 25°C (77°F): excursions permitted to 15-30°C (59-86°F)**
390 **[see USP controlled room temperature]**
- 391 Manufactured by Catalent Pharma Solutions for
392 Genzyme Corporation, 500 Kendall Street, Cambridge, MA 02142 800-847-0069
- 393 HECTOROL and GENZYME are registered trademarks of Genzyme Corporation.
- 394 6800 (12/10)