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Hectorol[®] (doxercalciferol injection)

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

2 **DESCRIPTION**

3 Doxercalciferol, the active ingredient in Hectorol[®], is a synthetic vitamin D₂ analog that undergoes
4 metabolic activation *in vivo* to form 1 α ,25-dihydroxyvitamin D₂ (1 α ,25-(OH)₂D₂), a naturally
5 occurring, biologically active form of vitamin D₂. Hectorol is available as a sterile, clear, colorless
6 aqueous solution for intravenous injection.

7 Hectorol single-use injection is supplied in a stoppered 2 mL amber glass vial containing either 4
8 mcg/2 mL or 2 mcg/mL. Each vial includes an aluminum seal and yellow (4 mcg/2 mL) or green
9 (2 mcg/mL) flip-off cap. Each milliliter (mL) of solution contains doxercalciferol, 2 mcg; ethanol,
10 100%, 0.05 mL; Polysorbate 20, 10 mg; sodium chloride, 1.5 mg; butylated hydroxytoluene, 0.02 mg;
11 sodium phosphate dibasic, heptahydrate, 14.4 mg; sodium phosphate monobasic, monohydrate, 1.8 mg;
12 and disodium edetate, 1.1 mg.

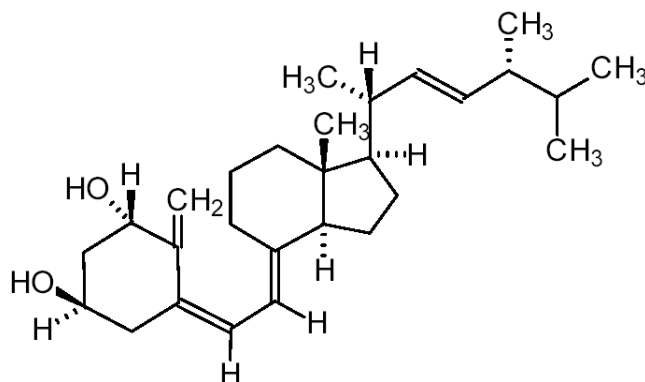
13 Hectorol is also supplied as a multi-dose injection contained within a stoppered 2 mL amber glass vial
14 containing 4 mcg/2 mL. Each vial includes an aluminum seal and an orange plastic flip-off cap. Each
15 milliliter (mL) of solution contains doxercalciferol, 2 mcg; ethanol, 100%, 0.075 mL; Polysorbate 20,
16 10 mg; sodium chloride, 1.5 mg; butylated hydroxytoluene, 0.02 mg; sodium phosphate dibasic,
17 heptahydrate, 14.4 mg; sodium phosphate monobasic, monohydrate, 1.8 mg; and disodium edetate, 1.1
18 mg.

19 Doxercalciferol is a colorless crystalline compound with a calculated molecular weight of 412.66 and a
20 molecular formula of C₂₈H₄₄O₂. It is soluble in oils and organic solvents, but is relatively insoluble in
21 water. Chemically, doxercalciferol is (1 α ,3 β ,5Z,7E,22E)-9,10-secoergosta-5,7,10(19),22-tetraene-1,3-
22 diol and has the structural formula presented in Figure 1.

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

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24
25 Other names frequently used for doxercalciferol are 1 α -hydroxyvitamin D₂, 1 α -OH-D₂, and 1 α -
26 hydroxyergocalciferol.

27 **CLINICAL PHARMACOLOGY**

28 Vitamin D levels in humans depend on two sources: (1) exposure to the ultraviolet rays of the sun for
29 conversion of 7-dehydrocholesterol in the skin to vitamin D₃ (cholecalciferol) and (2) dietary intake of
30 either vitamin D₂ (ergocalciferol) or vitamin D₃. Vitamin D₂ and vitamin D₃ must be metabolically
31 activated in the liver and kidney before becoming fully active on target tissues. The initial step in the
32 activation process is the introduction of a hydroxyl group in the side chain at C-25 by the hepatic
33 enzyme, CYP 27 (a vitamin D-25-hydroxylase). The products of this reaction are 25-(OH)D₂ and 25-
34 (OH)D₃, respectively. Further hydroxylation of these metabolites occurs in the mitochondria of kidney
35 tissue, catalyzed by renal 25-hydroxyvitamin D-1- α -hydroxylase to produce 1 α ,25-(OH)₂D₂, the
36 primary biologically active form of vitamin D₂, and 1 α ,25-(OH)₂D₃ (calcitriol), the biologically active
37 form of vitamin D₃.

38 **Mechanism of Action**

39 Calcitriol (1 α ,25-(OH)₂D₃) and 1 α ,25-(OH)₂D₂ regulate blood calcium at levels required for essential
40 body functions. Specifically, the biologically active vitamin D metabolites control the intestinal
41 absorption of dietary calcium, the tubular reabsorption of calcium by the kidney and, in conjunction

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42 with parathyroid hormone (PTH), the mobilization of calcium from the skeleton. They act directly on
43 bone cells (osteoblasts) to stimulate skeletal growth, and on the parathyroid glands to suppress PTH
44 synthesis and secretion. These functions are mediated by the interaction of these biologically active
45 metabolites with specific receptor proteins in the various target tissues. In uremic patients, deficient
46 production of biologically active vitamin D metabolites (due to lack of or insufficient 25-
47 hydroxyvitamin D-1-alpha-hydroxylase activity) leads to secondary hyperparathyroidism, which
48 contributes to the development of metabolic bone disease in patients with renal failure.

49 **Pharmacokinetics and Metabolism**

50 After intravenous administration, doxercalciferol is activated by CYP 27 in the liver to form 1 α ,25-
51 (OH)₂D₂ (major metabolite) and 1 α ,24-dihydroxyvitamin D₂ (minor metabolite). Activation of
52 doxercalciferol does not require the involvement of the kidneys.

53 Peak blood levels of 1 α ,25-(OH)₂D₂ are reached at 8 +/- 5.9 hours (mean +/- SD) after a single
54 intravenous dose of 5 mcg of doxercalciferol. The mean elimination half-life of 1 α ,25-(OH)₂D₂ after
55 an oral dose is approximately 32 to 37 hours with a range of up to 96 hours. The mean elimination
56 half-life in patients with end stage renal disease (ESRD) and in healthy volunteers appears to be similar
57 following an oral dose. Hemodialysis causes a temporary increase in 1 α ,25-(OH)₂D₂ mean
58 concentrations presumably due to volume contraction. 1 α ,25-(OH)₂D₂ is not removed from blood
59 during hemodialysis.

60 **Clinical Studies**

61 The safety and effectiveness of Hectorol Injection were evaluated in two open-label, single-arm, multi-
62 centered clinical studies (Study C and Study D) in a total of 70 patients with chronic kidney disease on
63 hemodialysis (Stage 5 CKD). Patients in Study C were an average age of 54 years (range: 23-73), were
64 50% male, and were 61% African-American, 25% Caucasian, and 14% Hispanic, and had been on
65 hemodialysis for an average of 65 months. Patients in Study D were an average age of 51 years (range:
66 28-76), were 48% male, and 100% African-American and had been on hemodialysis for an average of
67 61 months. This group of 70 of the 138 patients who had been treated with Hectorol Capsules in prior
68 clinical studies (Study A and Study B) received Hectorol Injection in an open-label fashion for 12

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69 weeks following an 8-week washout (control) period. Dosing of Hectorol Injection was initiated at the
70 rate of 4 mcg administered at the end of each dialysis session (3 times weekly) for a total of 12 mcg per
71 week. The dosage of Hectorol was adjusted in an attempt to achieve iPTH levels within a targeted
72 range of 150 to 300 pg/mL. The dosage was increased by 2 mcg per dialysis session after 8 weeks of
73 treatment if the iPTH levels remained above 300 pg/mL and were greater than 50% of baseline levels.
74 The maximum dosage was limited to 18 mcg per week. If at any time during the trial iPTH fell below
75 150 pg/mL, Hectorol Injection was immediately suspended and restarted at a lower dosage the
76 following week.

77 *Results:*

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

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

84 Decreases in plasma iPTH from baseline values were calculated using as baseline the average of the
85 last 3 values obtained during the 8-week washout period and are displayed in the table below. Plasma
86 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

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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

87

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

93 Table 2 shows the numbers of patients who achieved iPTH levels below 300 pg/mL on one, two, or
94 three or more non-consecutive occasions during the 12-week treatment period. Thirty-seven of 70
95 patients (53%) had plasma iPTH levels within the targeted range (150-300 pg/mL) during Weeks 10-
96 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

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98 INDICATIONS AND USAGE

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

101 CONTRAINDICATIONS

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

104 Hectorol Injection is contraindicated in patients with previous hypersensitivity to doxercalciferol or any
105 of its ingredients (see **WARNINGS** and **ADVERSE REACTIONS**).

106 **WARNINGS**

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

115 Since doxercalciferol is a precursor for $1\alpha,25\text{-(OH)}_2\text{D}_2$, a potent metabolite of vitamin D₂,
116 pharmacologic doses of vitamin D and its derivatives should be withheld during Hectorol treatment to
117 avoid possible additive effects and hypercalcemia.

118 Oral calcium-based or other non-aluminum-containing phosphate binders and a low phosphate diet
119 should be used to control serum phosphorus levels in patients undergoing dialysis. Uncontrolled serum
120 phosphorus exacerbates secondary hyperparathyroidism and can lessen the effectiveness of Hectorol in
121 reducing blood PTH levels. If hypercalcemia occurs after initiating Hectorol therapy, the dose of
122 Hectorol and/or calcium-containing phosphate binders should be decreased. If hyperphosphatemia
123 occurs after initiating Hectorol, the dose of Hectorol should be decreased and/or the dose of phosphate
124 binders increased. (See dosing recommendations for Hectorol under **DOSAGE AND**
125 **ADMINISTRATION**).

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

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128 Serious hypersensitivity reactions, including fatal outcome, have been reported post marketing in
129 patients on hemodialysis following administration of Hectorol Injection. Hypersensitivity reactions
130 include anaphylaxis with symptoms of angioedema (involving face, lips, tongue and airways),
131 hypotension, unresponsiveness, chest discomfort, shortness of breath, and cardiopulmonary arrest.
132 These reactions may occur separately or together.

133
134 Monitor patients receiving Hectorol Injection upon initiation of treatment for hypersensitivity
135 reactions. Should a hypersensitivity reaction occur, discontinue Hectorol, monitor and treat if indicated
136 (see **CONTRAINDICATIONS**).

137 **PRECAUTIONS**

138 **General**

139 The principal adverse effects of treatment with Hectorol Injection are hypercalcemia,
140 hyperphosphatemia, and oversuppression of PTH (iPTH less than 150 pg/mL). Prolonged
141 hypercalcemia can lead to calcification of soft tissues, including the heart and arteries, and
142 hyperphosphatemia can exacerbate hyperparathyroidism. Oversuppression of PTH may lead to
143 adynamic bone syndrome. All of these potential adverse effects should be managed by regular patient
144 monitoring and appropriate dosage adjustments. During treatment with Hectorol, patients usually
145 require dose titration, as well as adjustment in co-therapy (i.e., dietary phosphate binders) in order to
146 maximize PTH suppression while maintaining serum calcium and phosphorus levels within prescribed
147 ranges.

148 In two open-label, single-arm, multi-centered studies, the incidence of hypercalcemia and
149 hyperphosphatemia increased during therapy with Hectorol Injection (see **ADVERSE REACTIONS**).
150 The observed increases during Hectorol treatment underscore the importance of regular safety
151 monitoring of serum calcium and phosphorus levels throughout treatment. Patients with higher pre-
152 treatment serum levels of calcium (> 10.5 mg/dL) or phosphorus (> 6.9 mg/dL) were more likely to
153 experience hypercalcemia or hyperphosphatemia. Therefore, Hectorol should not be given to patients
154 with a recent history of hypercalcemia or hyperphosphatemia, or evidence of vitamin D toxicity.

155

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

156

157 **Information for the Patient**

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

162 **Laboratory Tests**

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

167 **Drug Interactions**

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

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174 **Carcinogenesis, Mutagenesis, Impairment of Fertility**

175 Long-term studies in animals to evaluate the carcinogenic potential of doxercalciferol have not been
176 conducted. No evidence of genetic toxicity was observed in an *in vitro* bacterial mutagenicity assay
177 (Ames test) or a mouse lymphoma gene mutation assay. Doxercalciferol caused structural chromatid
178 and chromosome aberrations in an *in vitro* human lymphocyte clastogenicity assay with metabolic
179 activation. However, doxercalciferol was negative in an *in vivo* mouse micronucleus clastogenicity
180 assay. Doxercalciferol had no effect on male or female fertility in rats at oral doses up to 2.5
181 mcg/kg/day (approximately 3 times the maximum recommended human oral dose of 60 mcg/wk based
182 on mcg/m² body surface area).

183 **Use in Pregnancy**
184 **Pregnancy Category B**

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

191 **Nursing Mothers**

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

196 **Pediatric Use**

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

198 **Geriatric Use**

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199 Of the 70 patients treated with Hectorol Injection in the two Phase 3 clinical studies, 12 patients were
200 65 years or over. In these studies, no overall differences in efficacy or safety were observed between
201 patients 65 years or older and younger patients.

202 **Hepatic Insufficiency**

203 Studies examining the influence of hepatic insufficiency on the metabolism of Hectorol were
204 inconclusive. Since patients with hepatic insufficiency may not metabolize doxercalciferol
205 appropriately, the drug should be used with caution in patients with impaired hepatic function. More
206 frequent monitoring of iPTH, calcium, and phosphorus levels should be done in such individuals.

207 **ADVERSE REACTIONS**

208 Hectorol Injection has been evaluated for safety in 70 patients with chronic renal disease on
209 hemodialysis (who had been previously treated with oral Hectorol) from two 12-week, open-label,
210 single-arm, multi-centered studies. (Dosage titrated to achieve target plasma iPTH levels, see
211 **CLINICAL PHARMACOLOGY/Clinical Studies.**)

212 Because there was no placebo group included in the studies of Hectorol Injection, Table 4 provides the
213 adverse event incidence rates from placebo-controlled studies of oral Hectorol.

214

Table 4: 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

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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
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Skin

Pruritus	8.2	6.6
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A patient who reported the same medical term more than once was counted only once for that medical term.

215

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

219 *Early*

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

222 *Late*

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

228 **Postmarketing Experience**

229 Because these reactions are reported voluntarily from a population of uncertain size, it is not always
230 possible to estimate their frequency or to establish a causal relationship to drug exposure.

231 Hypersensitivity reactions, including fatal outcome, have been reported in patients on hemodialysis
232 following administration of Hectorol Injection. Hypersensitivity reactions include anaphylaxis with
233 symptoms of angioedema (involving face, lips, tongue and airways), hypotension, unresponsiveness,
234 chest discomfort, shortness of breath, cardiopulmonary arrest, pruritus and skin burning sensation (see
235 **WARNINGS**). These reactions may occur separately or together.

236 **OVERDOSAGE**

237 Administration of Hectorol to patients in excess doses can cause hypercalcemia, hypercalciuria,
238 hyperphosphatemia, and over-suppression of PTH secretion leading in certain cases to adynamic bone
239 disease. High intake of calcium and phosphate concomitant with Hectorol may lead to similar
240 abnormalities. High levels of calcium in the dialysate bath may contribute to hypercalcemia.

241 **Treatment of Hypercalcemia and Overdosage**

242 General treatment of hypercalcemia (greater than 1 mg/dL above the upper limit of the normal range)
243 consists of immediate suspension of Hectorol therapy, institution of a low calcium diet, and withdrawal
244 of calcium supplements. Serum calcium levels should be determined at least weekly until
245 normocalcemia ensues. Hypercalcemia usually resolves in 2 to 7 days. When serum calcium levels
246 have returned to within normal limits, Hectorol therapy may be reinstated at a dose that is at least 1
247 mcg lower than prior therapy. Serum calcium levels should be obtained weekly after all dosage

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248 changes and during subsequent dosage titration. Persistent or markedly elevated serum calcium levels
249 may be corrected by dialysis against a reduced calcium or calcium-free dialysate.

250 **Treatment of Accidental Overdosage of Hectorol[®]**

251 The treatment of acute accidental overdosage of Hectorol should consist of general supportive
252 measures. Serial serum electrolyte determinations (especially calcium), rate of urinary calcium
253 excretion, and assessment of electrocardiographic abnormalities due to hypercalcemia should be
254 obtained. Such monitoring is critical in patients receiving digitalis. Discontinuation of supplemental
255 calcium and institution of a low calcium diet are also indicated in accidental overdosage. If persistent
256 and markedly elevated serum calcium levels occur, treatment with standard medical care should be
257 followed, as needed. Based on similarities between Hectorol and its active metabolite, $1\alpha,25\text{-(OH)}_2\text{D}_2$,
258 it is expected that Hectorol is not removed from the blood by dialysis.

259 **DOSAGE AND ADMINISTRATION**

260 **Adult Administration:**

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

262 The recommended initial dose of Hectorol is 4 mcg administered intravenously as a bolus dose three
263 times weekly at the end of dialysis (approximately every other day). The initial dose should be
264 adjusted, as needed, in order to lower blood iPTH into the range of 150 to 300 pg/mL. The dose may
265 be increased at 8-week intervals by 1 to 2 mcg if iPTH is not lowered by 50% and fails to reach the
266 target range. Dosages higher than 18 mcg weekly have not been studied. Drug administration should
267 be suspended if iPTH falls below 100 pg/mL and restarted one week later at a dose that is at least 1
268 mcg lower than the last administered dose. During titration, iPTH, serum calcium, and serum
269 phosphorus levels should be obtained weekly. If hypercalcemia, hyperphosphatemia, or a serum
270 calcium times phosphorus product greater than $55 \text{ mg}^2/\text{dL}^2$ is noted, the dose of Hectorol should be
271 decreased or suspended and/or the dose of phosphate binders should be appropriately adjusted. If
272 suspended, the drug should be restarted at a dose that is 1 mcg lower.

273 Dosing must be individualized and based on iPTH levels with monitoring of serum calcium and serum

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274 phosphorus levels. Table 5 presents a suggested approach in dose titration.

Table 5: Initial Dosing

<u>iPTH Level</u>	<u>Hectorol[®] Dose</u>
>400 pg/mL	4 mcg three times per week at the end of dialysis, or approximately every other day

Dose Titration

<u>iPTH Level</u>	<u>Hectorol[®] Dose</u>
Decreased by <50% and above 300 pg/mL	Increase by 1 to 2 mcg at eight-week intervals as necessary
Decreased 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

275

276 **Multi-Dose Vial**

277 After initial vial use, the contents of the multi-dose vial remain stable up to 3 days when stored at 2-
278 8°C (36-46°F). Discard unused portion of multi-dose vial after 3 days. (See **HOW SUPPLIED** and
279 **STORAGE**).

280 **HOW SUPPLIED**

281 **Single-Use Vial**

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282 Hectorol (doxercalciferol injection) is supplied in single-use amber glass vials containing 4 mcg
283 doxercalciferol in 2 mL of solution or 2 mcg in 1 mL of solution. The closure consists of a
284 fluorocarbon-coated chlorobutyl stopper, with an aluminum seal and either a yellow (4 mcg/2 mL) or
285 green (2 mcg/mL) plastic flip-off cap. Discard unused portion of single-use vial.

286 NDC 58468-0123-1 4 mcg/2 mL single-use vial

287 NDC 58468-0126-1 2 mcg/mL single-use vial

288 **Multi-Dose Vial**

289 Hectorol is also supplied in multi-dose amber glass vials containing 4 mcg doxercalciferol in 2 mL of
290 solution. The closure consists of a fluorocarbon-coated chlorobutyl stopper, with an aluminum seal
291 and an orange plastic flip-off cap.

292 NDC 58468-0127-1 4 mcg/2 mL multi-dose vial

293 **STORAGE**

294 **Single-Use Vial**

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

297 **Protect from light.**

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298 **Multi-Dose Vial**

299 **Store unopened multi-dose vials at 25°C (77°F): excursions permitted to 15-30°C (59-86°F)**
300 **[see USP controlled room temperature]**

301 **Store opened multi-dose vials at 2-8°C (36-46°F)**

302 **Protect from light.**

303 **Rx only**

304 Manufactured by: Genzyme Biosurgery

305 For: Genzyme Corporation

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