HECTOROL® (doxercalciferol) capsules, for oral use
HECTOROL® (doxercalciferol) injection, for intravenous use

Initial U.S. Approval: 1999

**INDICATIONS AND USAGE**

HECTOROL is a synthetic vitamin D₃ analog:
- HECTOROL capsules are indicated for the treatment of secondary hyperparathyroidism in adult patients with Stage 3 or Stage 4 chronic kidney disease (CKD) and adult patients with CKD on dialysis. (1)
- HECTOROL injection is indicated for the treatment of secondary hyperparathyroidism in adult patients with CKD on dialysis. (1)

**DOSAGE AND ADMINISTRATION**

- Before initiating treatment, ensure serum calcium is not above the upper limit of normal. (2.1)
- Dosage for HECTOROL capsules in patients with:
  - Stage 3 or 4 CKD: Initiate dosing at 1 mcg orally once daily. Maximum dose is 3.5 mcg once daily. (2.2)
  - CKD on dialysis: Initiate dosing at 10 mcg orally three times weekly at dialysis (no more frequently than every other day). Maximum dose is 20 mcg three times weekly for a total of 60 mcg weekly. (2.3)
- Dosage for HECTOROL injection in patients with CKD on dialysis: Initiate dosing at 4 mcg by bolus intravenous administration three times weekly at the end of dialysis (no more frequently than every other day). Maximum dose is 18 mcg weekly. (2.4)
- Target the maintenance dose of HECTOROL to intact parathyroid hormone (PTH) levels within the desired therapeutic range and serum calcium within normal limits. (2)
- See Full Prescribing Information for dose titration, laboratory monitoring, and important administration instructions. (2)

**DOSAGE FORMS AND STRENGTHS**

- Capsules: 0.5 mcg, 1 mcg, and 2.5 mcg (3)
- Injection: (3)
  - 2 mcg/mL single-dose vial
  - 4 mcg/2 mL (2 mcg/mL) single-dose vial
  - 4 mcg/2 mL (2 mcg/mL) multiple-dose vial

**CONTRAINdications**

- Hypercalcemia (4)
- Vitamin D toxicity (4)
- Known hypersensitivity to doxercalciferol or any of the inactive ingredients of HECTOROL capsules or HECTOROL injection (4)

**WARNINGS AND PRECAUTIONS**

- Hypercalcemia: Can occur during treatment with HECTOROL and can lead to cardiac arrhythmias and seizures. Severe hypercalcemia may require emergency attention. Risk may be increased when used concomitantly with high dose calcium preparations, thiazide diuretics, or vitamin D compounds. Monitor serum calcium prior to initiation and during treatment and adjust dose accordingly. (2, 5.1)
- Digitalis Toxicity: Hypercalcemia increases the risk of digitalis toxicity. In patients using digitalis compounds, monitor serum calcium and patients for signs and symptoms of digitalis toxicity. Increase frequency of monitoring when initiating or adjusting the dose of HECTOROL. (5.2)
- Serious Hypersensitivity Reactions: Anaphylaxis, with symptoms of angioedema, hypotension, unresponsiveness, chest discomfort, shortness of breath, and cardiovascular arrest, has been reported in hemodialysis patients after administration of HECTOROL. Monitor patients upon treatment initiation for hypersensitivity reactions. Should a reaction occur, discontinue and treat. (5.3)
- Adynamic Bone Disease: May develop and increase risk of fractures if intact PTH levels are suppressed to abnormally low levels. Monitor intact PTH levels to avoid oversuppression and adjust dose if needed. (5.4)

**ADVERSE REACTIONS**

The most common adverse reactions in patients with Stage 3 or 4 CKD (incidence >5%) were infection, urinary tract infection, chest pain, angina pectoris, constipation, dyspepsia, anemia, leucopenia, dehydration, edema, depression, hypotension, insomn, asthma, paresthesia, cough increased, dyspnea, pruritus, sinusitis, and rhinitis. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Genzyme Corporation at 1-800-745-4447 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

**DRUG INTERACTIONS**

- Cytochrome P450 inhibitors: Formation of the active doxercalciferol moiety may be hindered and may necessitate dosage adjustment. Monitor intact PTH and serum calcium concentrations closely. (7)
- Enzyme inducers: Formation of the active doxercalciferol moiety may be affected and may necessitate dosage adjustment. Monitor intact PTH and serum calcium concentrations closely. (7)
- Magnesium-containing products: Combined use may cause hypermagnesemia. Monitor serum magnesium concentrations more frequently and adjust dose as needed. (7)
- Cholestyramine: May impair absorption of HECTOROL capsules. Administer HECTOROL capsules at least 1 hour before or 4 to 6 hours after taking cholestyramine. (7)
- Mineral oil or other substances that may affect absorption of fat: May impair absorption of HECTOROL capsules. Administer HECTOROL capsules at least 1 hour before or 4 to 6 hours after taking substances that may affect absorption.

See 17 for PATIENT COUNSELING INFORMATION

Revised: 11/2018

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2.6 Drug Interactions that May Require Dosage Adjustments of HECTOROL

Increased monitoring of serum calcium and dose adjustment of HECTOROL may be necessary when given concurrently with drugs that may increase the risk of hypercalcemia [see Drug Interactions (7)]. Increased monitoring of both serum calcium and intact PTH levels as well as dose adjustment of HECTOROL may be necessary when given concurrently with cytochrome P450 inhibitors or enzyme inducers [see Drug Interactions (7)].

3 DOSAGE FORMS AND STRENGTHS

Capsules: soft gelatin, oval capsules with imprinted “g” available as:
- 0.5 mcg (salmon color)
- 1 mcg (peach color)
- 2.5 mcg (butter-yellow color)
Adverse reactions in patients with CKD on dialysis HECTOROL capsules have been evaluated in two placebo-controlled, double-blind studies in patients with CKD on hemodialysis. Patients were treated with HECTOROL capsules (n=61) or placebo (n=61) [see Clinical Studies (14.2)]. After randomization to two groups, eligible patients underwent an 8-week washout period during which no vitamin D derivatives were administered to either group. Subsequently, all patients received HECTOROL capsules in an open-label fashion for 16 weeks followed by a double-blind period of 8 weeks during which patients received either HECTOROL capsules or placebo. Adverse reactions occurring in the HECTOROL capsule groups at a frequency of 2% or greater, and more frequently than in the placebo group are presented in Table 2.

Table 2: Adverse Reactions Occurring in ≥2% HECTOROL Capsule-Treated Patients with CKD on Dialysis and Greater than Placebo in Two Double-Blind Clinical Studies

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>HECTOROL (n=61)</th>
<th>Placebo (n=61)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Edema</td>
<td>34%</td>
<td>21%</td>
</tr>
<tr>
<td>Malaise</td>
<td>28%</td>
<td>20%</td>
</tr>
<tr>
<td>Headache</td>
<td>28%</td>
<td>18%</td>
</tr>
<tr>
<td>Nausea/Vomiting</td>
<td>21%</td>
<td>20%</td>
</tr>
<tr>
<td>Dizziness</td>
<td>12%</td>
<td>10%</td>
</tr>
<tr>
<td>Dyspnea</td>
<td>12%</td>
<td>7%</td>
</tr>
<tr>
<td>Pruritus</td>
<td>8%</td>
<td>7%</td>
</tr>
<tr>
<td>Bradycardia</td>
<td>7%</td>
<td>5%</td>
</tr>
<tr>
<td>Anorexia</td>
<td>5%</td>
<td>3%</td>
</tr>
<tr>
<td>Dyspepsia</td>
<td>5%</td>
<td>2%</td>
</tr>
<tr>
<td>Arthralgia</td>
<td>5%</td>
<td>0%</td>
</tr>
<tr>
<td>Weight increase</td>
<td>5%</td>
<td>0%</td>
</tr>
<tr>
<td>Abscess</td>
<td>3%</td>
<td>0%</td>
</tr>
<tr>
<td>Sleep disorder</td>
<td>3%</td>
<td>0%</td>
</tr>
</tbody>
</table>

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

6.2 Postmarketing Experience

The following adverse reactions have been identified during postapproval use of HECTOROL. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to estimate their frequency or to establish a causal relationship to drug exposure. Hypersensitivity reactions, including fatal outcome, have been reported in patients on hemodialysis following administration of HECTOROL injection. Hypersensitivity reactions include anaphylaxis with symptoms of angioedema (involving face, lips, tongue and airways), hypotension, unresponsiveness, chest discomfort, shortness of breath, cardiovascular arrest, pruritus, and skin burning sensation.

7 DRUG INTERACTIONS

Tables 3 and 4 include clinically significant drug interactions with HECTOROL.

Table 3: Clinically Significant Drug Interactions with HECTOROL Injection and HECTOROL Capsules

<table>
<thead>
<tr>
<th>Drugs that May Increase the Risk of Hypercalcemia</th>
<th>Clinical Impact</th>
<th>Clinical Impact</th>
</tr>
</thead>
<tbody>
<tr>
<td>Concomitant administration of high doses of calcium-containing preparations or other vitamin D compounds may increase the risk of hypercalcemia. Thiazide diuretics are known to induce hypercalcemia by reducing excretion of calcium in the urine.</td>
<td>Monitor serum calcium concentrations more frequently and adjust HECTOROL dose as needed [see Warnings and Precautions (5.1)].</td>
<td>Monitor patients for signs and symptoms of digitalis toxicity and increase frequency of serum calcium monitoring when initiating or adjusting the dose of HECTOROL in patients receiving digitalis compounds [see Warnings and Precautions (5.2)].</td>
</tr>
<tr>
<td>Digitalis Compounds</td>
<td>Doxercalferol can cause hypercalcemia which can potentiate the risk of digitalis toxicity.</td>
<td>Monitor patients for signs and symptoms of digitalis toxicity and increase frequency of serum calcium monitoring when initiating or adjusting the dose of HECTOROL in patients receiving digitalis compounds [see Warnings and Precautions (5.2)].</td>
</tr>
<tr>
<td>Enzyme Inducers</td>
<td>Doxercalferol is activated by CYP 27 in the liver. Cytochrome P450 inhibitors may inhibit the 25-hydroxylation of doxercalferol and thus reduce the formation of active doxercalferol moiety [see Clinical Pharmacology (12.3)].</td>
<td>Monitor patients for signs and symptoms of digitalis toxicity and increase frequency of serum calcium monitoring when initiating or adjusting the dose of HECTOROL in patients receiving digitalis compounds [see Warnings and Precautions (5.2)].</td>
</tr>
<tr>
<td>Examples</td>
<td>Ketoconazole and erythromycin</td>
<td>Monitor patients for signs and symptoms of digitalis toxicity and increase frequency of serum calcium monitoring when initiating or adjusting the dose of HECTOROL in patients receiving digitalis compounds [see Warnings and Precautions (5.2)].</td>
</tr>
</tbody>
</table>

Table 4: Clinically Significant Drug Interactions with HECTOROL Capsules

<table>
<thead>
<tr>
<th>Cholestyramine</th>
<th>Clinical Impact</th>
<th>Clinical Impact</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cholestyramine has been reported to reduce intestinal absorption of fat-soluble vitamins. Therefore, it may impair intestinal absorption of HECTOROL capsules.</td>
<td>Monitor intact PTH and serum calcium concentrations closely.</td>
<td>Monitor patients for signs and symptoms of digitalis toxicity and increase frequency of serum calcium monitoring when initiating or adjusting the dose of HECTOROL in patients receiving digitalis compounds [see Warnings and Precautions (5.2)].</td>
</tr>
<tr>
<td>Intervention</td>
<td>Administer HECTOROL capsules at least 1 hour before or 4 to 6 hours after taking cholestyramine.</td>
<td>Monitor patients for signs and symptoms of digitalis toxicity and increase frequency of serum calcium monitoring when initiating or adjusting the dose of HECTOROL in patients receiving digitalis compounds [see Warnings and Precautions (5.2)].</td>
</tr>
<tr>
<td>Mineral Oil or other Substances that May Affect Absorption of Fat</td>
<td>The use of mineral oil or other substances that may affect absorption of fat may influence the absorption and availability of HECTOROL.</td>
<td>Monitor patients for signs and symptoms of digitalis toxicity and increase frequency of serum calcium monitoring when initiating or adjusting the dose of HECTOROL in patients receiving digitalis compounds [see Warnings and Precautions (5.2)].</td>
</tr>
</tbody>
</table>

8 PRECAUTIONS

In patients receiving HECTOROL in conjunction with parenteral nutrition therapy, the risk of hypercalcaemia is expected to be similar to those reported in placebo-controlled studies of HECTOROL capsules presented in Table 2.
Doxercalciferol undergoes metabolic activation. Doxercalciferol is a colorless crystalline compound with a calculated molecular weight of 460.5. Serum calcium levels should be measured until normal.

**Clinical Considerations**

Disease-associated maternal and/or embryofetal risk

Chronic kidney disease in pregnancy increases the risk for maternal hypertension and preeclampsia, miscarriage, preterm delivery polyhydramnios, stillbirth, and low-birth-weight infants.

Data

Animal data

There were no adverse effects on fetal development when doxercalciferol was administered at doses up to 20 mcg/kg/day in pregnant rats or doses up to 0.1 mcg/kg/day in pregnant rabbits during the period of organogenesis.

**Data**

**8.2 Lactation**

**Risk Summary**

There is no information available on the presence of doxercalciferol in human milk, the effects of the drug on the breastfed infant, or the effects of the drug on milk production. Infants exposed to HECTOROL through breast milk should be monitored for signs and symptoms of hypercalcemia (see Clinical Considerations).

The developmental and health benefits of breastfeeding should be considered along with the mother’s clinical need for HECTOROL and any potential adverse effects on the infant.

Infants exposed to doxercalciferol injection through breast milk should be monitored for signs and symptoms of hypercalcemia, including seizures, vomiting, constipation, and weight loss. Monitoring of serum calcium in the infant should be considered.

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

**8.5 Geriatric Use**

Clinical studies of HECTOROL did not include sufficient numbers of patients 65 years or over to determine whether they respond differently from younger subjects. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic or cardiac function, and of concomitant disease or other drug therapy.

**8.6 Hepatic Impairment**

Patients with hepatic impairment may not metabolize HECTOROL appropriately. More frequent monitoring of intact PTH, calcium, and phosphorus levels should be done in patients with hepatic impairment.

**10 OVERDOSAGE**

Overdosage of HECTOROL may lead to hypercalcemia, hypercalciuria, and hyperphosphatemia (see Warnings and Precautions (5.1)). The treatment of acute overdosage should consist of supportive measures and discontinuation of HECTOROL administration. Serum calcium levels should be measured until normal.

Based on similarities between doxercalciferol and its active metabolite, 1α,25-(OH)2D3, it is expected that doxercalciferol is not removed from the blood by dialysis.

**11 DESCRIPTION**

HECTOROL contains doxercalciferol, which is a synthetic vitamin D2 analog. Doxercalciferol undergoes metabolic activation in vivo to form 1α,25-dihydroxyvitamin D2 (1α,25-(OH)2D2), a naturally occurring, biologically active form of vitamin D2.

Doxercalciferol is a colorless crystalline compound with a calculated molecular weight of 412.66 and a molecular formula of C28H40O2. It is soluble in oils and organic solvents, but is relatively insoluble in water. Doxercalciferol is (1α,5α,6α,7β,8β,9α,10α,11β,12α,12′α,13β,14β,16α,17β,19α,20β,22α,23α,24α,25α,26α,27α,28α,29α,30α,31α,32α,32′α,33α,34α,35α,36α,37α,38α,39α,40α,41α,42α)-dihydroxy-3β,7α,10(19),22-tetraene-1,3-diol. The structural formula is:

**Capsules**

HECTOROL capsules are soft gelatin capsules containing 0.5 mcg, 1 mcg, or 2.5 mcg doxercalciferol for oral use. Each capsule also contains butylated hydroxyanisole (BHA), ethanol, and fractionated triglyceride of coconut oil. The capsule shells contain gelatin, gelatin, and titanium dioxide. In addition, the 0.5 mcg capsule shells contain yellow iron oxide and FD&C Red No. 40, the 1 mcg capsule shells contain FD&C Yellow No. 6, and the 2.5 mcg capsule shells contain yellow iron oxide.

**Injection**

HECTOROL injection 1 mL single-dose vials contain 2 mcg/mL of doxercalciferol. HECTOROL injection 2 mL single-dose vials contain 4 mcg/mL of doxercalciferol. Each milliliter (mL) of solution contains 2 mcg doxercalciferol and the following inactive ingredients: butylated hydroxytoluene (0.02 mg); disodium edetate (1.1 mg); ethanol, 100% (0.05 mL); polysorbate 20 (10 mg); sodium chloride (1.5 mg); sodium phosphate dibasic, heptahydrate (14.4 mg); and sodium phosphate monobasic, monohydrate (1.8 mg).

**12 CLINICAL PHARMACOLOGY**

**12.1 Mechanism of Action**

Doxercalciferol is a synthetic vitamin D2 analog that requires metabolic activation to form the active 1α,25-(OH)2D2 metabolite, which binds to the vitamin D receptor (VDR) to result in the selective activation of vitamin D responsive pathways. Vitamin D and doxercalciferol have been shown to reduce PTH levels by inhibiting PTH synthesis and secretion.

**12.2 Pharmacokinetics**

Absorption

In healthy volunteers, peak blood levels of 1α,25-(OH)2D2, the major metabolite of doxercalciferol, are attained at 8 hours after a single intravenous dose of HECTOROL and at 11 to 12 hours following capsule dose.

Elimination

The mean elimination half-life of 1α,25-(OH)2D2 after an oral dose is approximately 32 to 37 hours with a range of up to 96 hours.

Metabolism

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

**13 NONCLINICAL TOXICOLOGY**

**13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility**

In a 104-week carcinogenicity study in rats, there was an increased incidence of benign adrenal cortical tumors in rats given doxercalciferol in both males and females at oral doses of 0.04, 0.13, and 0.39 mcg/kg/day (less than the maximum recommended human oral dose of 60 mcg/kg/day based on mg/m2 body surface area). This increased incidence of pheochromocytomas in rats may be due to altered calcium homeostasis by doxercalciferol.

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 chromatin and chromosome aberrations in an in vivo 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/kg/day based on mg/m2 body surface area).

**14 CLINICAL STUDIES**

**14.1 Clinical Studies of HECTOROL Capsules in Patients with Stage 3 or 4 CKD**

The safety and effectiveness of HECTOROL capsules were evaluated in two clinical studies in 55 patients with Stage 3 or 4 CKD. Eighty-two percent of the patients were male, the average age was 65 years, 51% were Caucasian, 39% African-American, and the average serum intact PTH level at baseline was 195 pg/mL. While levels of 25-(OH) vitamin D were not evaluated at baseline, retrospective assessments of stored serum revealed that the mean ± SD serum 25-(OH) vitamin D was 19 ± 8 ng/mL (range: <3 to 54 ng/mL) in the study population.

After randomization to two groups, eligible patients underwent an 8-week washout period during which no vitamin D derivatives were administered to either group. Subsequently, one group received HECTOROL capsules and the other placebo during the double-blind period of 24 weeks. The initial dose of HECTOROL capsules was 1 mcg per day. The average dose of HECTOROL capsules required as necessary by the investigator to reduce intact PTH levels to a target of ≤30% below postwashout baseline. The maximum dosage was limited to 3.5 mcg per day. If at any time during the trial the intact PTH fell below 15 µg/mL, HECTOROL capsules were immediately suspended and restarted at a lower dosage the following week.

Decreases in the mean plasma intact PTH from baseline values were calculated using as baseline the average of the last 2 values obtained during the 8-week washout phase. In analyses of pooled data from the two studies, intact PTH levels decreased from baseline by an average of 101 µg/mL in the HECTOROL capsules group and by 4.5 µg/mL in the placebo group (p < 0.001). Twenty (74%) of 27 subjects in the HECTOROL capsules group achieved mean plasma intact PTH suppression of ≤30% from baseline for the last four weeks of treatment, whereas 2 (7%) of the 28 subjects treated with placebo achieved this level of intact PTH suppression.

**14.2 Clinical Studies of HECTOROL Capsules in Patients with CKD on Dialysis**

The safety and effectiveness of HECTOROL capsules were evaluated in two double-blind, placebo-controlled, multicenter clinical studies (Study A and Study B) in a total of 1138 patients with CKD on hemodialysis. Patients in Study A were an average of 52 years (range: 22 to 75), were 55% male, and were 58% African-American, 31% Caucasian, and 11% Hispanic, and had been on hemodialysis for an average of 53 months. Patients in Study B were an average of 52 years (range: 27 to 75), were 45% male, and 99%
African-American, and 1% Caucasian, and had been on hemodialysis for an average of 56 months. After randomization to two groups, eligible patients underwent an 8-week washout period during which no vitamin D derivatives were administered to either group. Subsequently, all patients received HECTOROL capsules in an open-label fashion for 16 weeks followed by a double-blind period of 8 weeks during which patients received either HECTOROL capsules or placebo. The initial dose of HECTOROL capsules during the open-label phase was 10 mcg after each dialysis session (3 times weekly) for a total of 30 mcg per week. The dosage of HECTOROL was adjusted as necessary by the investigator to achieve intact PTH levels within 150 pg/mL to 300 pg/mL. The maximum dosage was limited to 20 mcg after each dialysis session (60 mcg/week). If at any time during the trial intact PTH fell below 150 pg/mL, HECTOROL was immediately suspended and restarted at a lower dosage the following week. Mean weekly doses during the 16-week open-label period ranged from 15 mcg to 29 mcg in Study A and from 19 mcg to 28 mcg in Study B.

One hundred and six (77%) of the 138 patients who were treated with HECTOROL capsules during the 16-week open-label phase achieved intact PTH levels ≤300 pg/mL. Ninety-four (68%) of these patients exhibited plasma intact PTH levels ≤300 pg/mL on at least one occasion during the open-label phase of study participation. Decreases in plasma intact PTH from baseline values were calculated using as baseline the average of the last 3 values obtained during the 8-week washout phase and are displayed in Table 5.

### Table 5: Intact PTH Summary Data for Patients with CKD on Dialysis Receiving HECTOROL Capsules in Studies A and B

<table>
<thead>
<tr>
<th>Study</th>
<th>Intact PTH (pg/mL)</th>
<th>HECTOROL Capsules</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>p-value vs Baseline</td>
<td>p-value vs Placebo</td>
<td></td>
</tr>
<tr>
<td>Study A</td>
<td>Baseline</td>
<td>797.2 ± 443.8 (30)</td>
<td>847.1 ± 765.5 (32)</td>
</tr>
<tr>
<td></td>
<td>Week 16 (open-label)</td>
<td>384.3 ± 397.8 (24)</td>
<td>526.5 ± 872.2 (29)</td>
</tr>
<tr>
<td></td>
<td>Week 24 (double-blind)</td>
<td>404.4 ± 262.9 (21)</td>
<td>672.6 ± 356.9 (24)</td>
</tr>
<tr>
<td>Study B</td>
<td>Baseline</td>
<td>973.9 ± 567.0 (41)</td>
<td>990.4 ± 488.3 (35)</td>
</tr>
<tr>
<td></td>
<td>Week 16 (open-label)</td>
<td>476.1 ± 444.5 (37)</td>
<td>485.9 ± 443.4 (32)</td>
</tr>
<tr>
<td></td>
<td>Week 24 (double-blind)</td>
<td>459.8 ± 443.0 (35)</td>
<td>871.9 ± 623.6 (30)</td>
</tr>
</tbody>
</table>

NA = not applicable
*All subjects; last value carried to discontinuation.

HECTOROL capsules treatment resulted in a statistically significant reduction from baseline in mean intact PTH levels in the 16-week open-label treatment period in more than 94% of the 138 treated patients. During the double-blind period (weeks 17 to 24), the reduction in mean intact PTH levels was maintained in the HECTOROL capsules treatment group compared to a return to baseline in the placebo group.

### Table 6: Intact PTH Summary Data for Patients with CKD on Dialysis Receiving HECTOROL Injection in Studies C and D

<table>
<thead>
<tr>
<th>Intact PTH Level</th>
<th>Study C (n=28)</th>
<th>Study D (n=42)</th>
<th>Combined Protocols (n=70)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean (±SD)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline (Mean of Weeks -2, -1, and 0)</td>
<td>698 (60)</td>
<td>762 (65)</td>
<td>736 (46)</td>
</tr>
<tr>
<td>Median</td>
<td>562</td>
<td>648</td>
<td>634</td>
</tr>
<tr>
<td>On-treatment (Week 12)</td>
<td>406 (63)</td>
<td>426 (60)</td>
<td>418 (43)</td>
</tr>
<tr>
<td>Median</td>
<td>311</td>
<td>292</td>
<td>292</td>
</tr>
<tr>
<td>Change from Baseline</td>
<td>-292 (55)</td>
<td>-336 (41)</td>
<td>-318 (33)</td>
</tr>
<tr>
<td>Median</td>
<td>-274</td>
<td>-315</td>
<td>-304</td>
</tr>
<tr>
<td>P-value</td>
<td>0.004</td>
<td>0.001</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

*All subjects; last value carried to discontinuation.
†Treatment intact PTH minus baseline intact PTH
‡Wilcoxon one-sample test

HECTOROL treatment resulted in at least 30% reduction from baseline in mean intact PTH levels during the 12-week open-label treatment period in more than 92% of the 70 treated patients.

### HOW SUPPLIED/STORAGE AND HANDLING

**How Supplied:**
HECTOROL capsules are oval, soft gelatin capsules supplied as follows.

- 0.5 mcg: salmon g bottle of 50 capsules
- 1 mcg: peach g bottle of 50 capsules
- 2.5 mcg: butter-yellow g bottle of 50 capsules

**Storage and Handling:**
HECTOROL injection is a clear, colorless solution supplied in 2 mL amber glass vials as follows.

- 2 mcg/mL: 50 × 2 mL single-dose vials
- 4 mcg/mL: 50 × 2 mL multiple-dose vials
- 4 mcg/mL: 50 × 2 mL multiple-dose vials

For more detailed information, please refer to the package insert.
17 PATIENT COUNSELING INFORMATION

Hypercalcemia
Advise patients to contact a health care provider if they develop symptoms of elevated calcium (e.g. feeling tired, difficulty thinking clearly, loss of appetite, nausea, vomiting, constipation, increased thirst, increased urination and weight loss) [see Warnings and Precautions (5.1)].

Hypersensitivity
Inform patients that hypersensitivity reactions can occur with HECTOROL [see Warnings and Precautions (5.3)].

Monitoring
Inform patients that they will need routine monitoring of laboratory parameters such as calcium and intact PTH while receiving HECTOROL. Inform patients that more frequent monitoring is necessary during the initiation of therapy, following dose changes or when potentially interacting medications are started or discontinued [see Dosage and Administration (2), Drug Interactions (7)].

Drug Interactions
Advise patients to inform their physician of all medications, including prescription and nonprescription drugs, and supplements they are taking. Advise patients to also inform their physician that they are receiving HECTOROL if a new medication is prescribed [see Drug Interactions (7)].