Welcome to Hectorol®
Answers about vitamin D in stage 5 chronic kidney disease (CKD) patients on dialysis

Indication
Hectorol Injection is indicated for the treatment of secondary hyperparathyroidism in patients with CKD on dialysis.

Important Safety Information
You should not take Hectorol if you have a history of abnormally high calcium blood levels (hypercalcemia) or if you have very high vitamin D levels.

Please see full Important Safety Information on page 12.
Please see accompanying full Prescribing Information or click here.
Why is vitamin D important?

Vitamin D is a hormone that is important for strong bones. You get vitamin D from some of the foods you eat, from sunlight being absorbed into your skin, and by taking vitamin supplements.

Vitamin D has to be made “active” by passing through the liver and kidneys. Once it is active, it is turned into the hormone that helps balance calcium within your body, which is important for bone health.

Let’s get started!

Your doctor prescribed Hectorol®, a form of vitamin D. This booklet explains why vitamin D is important, why Hectorol has been prescribed for you, and how it can help you.

Important Safety Information

Overdosage of any form of vitamin D is dangerous and may require emergency attention.

Please see full Important Safety Information on page 12. Please see accompanying full Prescribing Information or click here.
How can Hectorol help me?

Your doctor has prescribed Hectorol to help treat your SHPT. Hectorol does not need the kidneys to help increase vitamin D in your body and lower your parathyroid hormone (PTH) levels. When you have CKD, vitamin supplements and natural sources of vitamin D may not lower your PTH level because they need your kidneys to work.

Ask your doctor what a healthy PTH range is for your body and what your PTH levels are. By taking Hectorol, you are helping to lower your PTH levels.

An introduction to Hectorol®

Hectorol is a prescription vitamin D hormone that treats secondary hyperparathyroidism (SHPT) in patients with CKD on dialysis.

Hectorol is different from natural vitamin D. You get natural vitamin D from some of the foods you eat, from sunlight being absorbed into your skin, or from vitamin supplements.

Important Safety Information

Before taking Hectorol, tell your doctor if you have ever had an irregular heartbeat or seizure, or if you are taking any digitalis drugs.

Please see full Important Safety Information on page 12. Please see accompanying full Prescribing Information or click here.
How to take Hectorol®

Hectorol is an injection that can be administered by a nurse or an infusion specialist. Once your doctor has prescribed Hectorol for you, it will be injected along with your dialysis solution during your hemodialysis treatments.

More resources for patients with CKD

American Association of Kidney Patients
1-800-749-2257
www.aakp.org

American Kidney Fund
1-800-638-8299
www.kidneyfund.org

National Kidney Foundation
1-800-622-9010
www.kidney.org

Talk to your team about your treatment

Remember, Hectorol can be an important part of your treatment plan. Be sure to follow your doctor’s instructions for each part of your treatment. Also, be sure to talk over any questions or concerns with your healthcare team.

Important Safety Information

Do not take other vitamin D related drugs if you are currently taking Hectorol.

It is important for anyone taking Hectorol to talk to their doctor before taking any non-prescription drugs or magnesium-containing antacids, supplements and herbal preparations and to adhere to instructions about following a low phosphorus diet and calcium supplementation.

Please see full Important Safety Information on page 12. Please see accompanying full Prescribing Information or click here.

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YOU are important to your success

Follow these tips to stay on track.

Take your medicine
- If you have any questions or concerns about how Hectorol® will be administered to you during your hemodialysis, talk to your doctor or nurse
- Be sure to take all of the medicines your doctor has prescribed, including any phosphate binders and supplements
  - Talk to your doctor about all of your current medicines before you start taking any new medicines

Nutrition
- Follow the food choices your dietitian has recommended

Stay involved
- Go to all of your scheduled healthcare appointments
- If you have any questions, ask your healthcare team for answers because YOU are in charge of taking care of your health

Know your health goal
- It is important to maintain the right levels of calcium, phosphorus, and PTH
- Talk to your doctor, nurse, or dietitian to find out what goals are right for you

Your goal:

<table>
<thead>
<tr>
<th>Date</th>
<th>Current PTH level</th>
<th>Goal PTH level</th>
</tr>
</thead>
</table>

Follow the steps your doctor recommends to help you reach your goals.

Important Safety Information

Your doctor should monitor your calcium, phosphorus and PTH levels.

Please see full Important Safety Information on page 12. Please see accompanying full Prescribing Information or click here.
**Indication**

Hectorol® Injection is indicated for the treatment of secondary hyperparathyroidism in patients with CKD on dialysis.

**Important Safety Information for Hectorol (doxercalciferol) Injection**

- You should not take Hectorol if you have a history of abnormally high calcium blood levels (hypercalcemia) or if you have very high vitamin D levels.
- Overdosage of any form of vitamin D is dangerous and may require emergency attention.
- Before taking Hectorol, tell your doctor if you have ever had an irregular heartbeat or seizure, or if you are taking any digitalis drugs.
- Do not take other vitamin D related drugs if you are currently taking Hectorol.
- It is important for anyone taking Hectorol to talk to their doctor before taking any non-prescription drugs or magnesium-containing antacids, supplements and herbal preparations and to adhere to instructions about following a low phosphorus diet and calcium supplementation.
- Your doctor should monitor your calcium, phosphorus and PTH levels.
- Tell your doctor if you experience symptoms of hypercalcemia such as weakness, headache, drowsiness, nausea, vomiting, dry mouth, constipation, muscle pain, bone pain, metallic taste and loss of appetite.
- The main side effects of treatment with Hectorol are hypercalcemia, hyperphosphatemia, and oversuppression of PTH. Your doctor may ask you questions to see if you are experiencing any symptoms related to these conditions.
- During treatment, your doctor may change your dose of Hectorol as well as the dose of your phosphate binder.
- Common side effects seen in Hectorol-treated patients on dialysis were swelling, headache, ill feeling, nausea/vomiting, dizziness, shortness of breath, itching and slow heartbeat.
- Tell your doctor if you are pregnant or nursing.
- This drug should be used with caution if you have impaired liver function.

Please see accompanying full Prescribing Information or click here.

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Doxercalciferol is a vitamin D metabo
tes that are mediated by the interaction of these biologically active metabolites with

\[ \text{Vitamin D} \rightarrow \text{25-OH-D} \rightarrow \text{1,25-(OH)}_2\text{D} \]

The safety and effectiveness of Hectorol Injection were evaluated in two open-label, single-arm, multi-centered clinical studies (Study A 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, tive. Further hydroxylation of these metabolites occurs in the mitochondria of kidney

\[ \text{1,25-(OH)}_2\text{D} \rightarrow \text{1,25-(OH)}_3\text{D} \]

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. 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 3 or more 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.

Other names frequently used for doxercalciferol are 1α-hydroxyvitamin D₃, 1α-OH-D₃, and 1α-hydroxycholecalciferol.

**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 D₃ (cholecalciferol) and (2) dietary intake of either vitamin D₂ (ergocalciferol) or vitamin D₃. Vitamin D₂ and vitamin D₃ 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 D₂-hydroxylase). The products of this reaction are 25-(OH)D₃ and 25-(OH)D₂, respectively. Further hydroxylation of these metabolites occurs in the mitochondria of kidney tissue, catalyzed by renal 25-hydroxyvitamin D-1α-hydroxylase to produce 1α,25-(OH)₂D₃, the primary biologically active form of vitamin D₂ and 1α,25-(OH)₂D₃ (calcitriol), the biologically active form of vitamin D₃.

**Mechanism of Action**

Calcitriol (1α,25-(OH)₂D₃) and 1α,25-(OH)₂D₂ 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 insuffici
tion of 25-hydroxyvitamin D-1α-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)₂D₂ (major metabolite) and 1α,24,25-trihydroxyvitamin D₃ (minor metabolite). Activation of doxercalciferol does not require the involvement of the kidneys. Peak blood concentrations of 1α,25-(OH)₂D₂ 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)₂D₂ 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)₂D₃ mean concentrations presumably due to volume contraction. 1α,25-(OH)₂D₃ is not removed from blood during hemodialysis.

**Clinical Studies**

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

<table>
<thead>
<tr>
<th>iPTH 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 (SE)</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>Mean (SE)</td>
<td>406 (63)</td>
<td>426 (60)</td>
</tr>
<tr>
<td>Median</td>
<td>311</td>
<td>292</td>
<td>292</td>
</tr>
<tr>
<td>Change from Baseline</td>
<td>Mean (SE)</td>
<td>-292 (55)</td>
<td>-336 (41)</td>
</tr>
<tr>
<td>Median</td>
<td>-274</td>
<td>-315</td>
<td>-304</td>
</tr>
<tr>
<td>P-value‡</td>
<td>&lt;.004</td>
<td>.001</td>
<td>&lt;.001</td>
</tr>
</tbody>
</table>

† 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>
<thead>
<tr>
<th>iPTH Level</th>
<th>Study C</th>
<th>Study D</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>3/28</td>
<td>0/28</td>
</tr>
<tr>
<td>2</td>
<td>0/28</td>
<td>4/42</td>
</tr>
<tr>
<td>≥3</td>
<td>12/28</td>
<td>25/42</td>
</tr>
</tbody>
</table>

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 OVERDOSE). 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 × P) product should be maintained at <55 mg2/dL2 in patients with chronic kidney disease. Radiographic evaluation of suspect anatomical regions may be useful in the early detection of this condition.

Doxercalciferol is a precursor for 1α,25-(OH)₂D₃, a potent metabolite of vitamin D₂. Pharmacologic doses of vitamin D₂ 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 phosphorus 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 treatment, the dose of Hectorol should be decreased.
Hectorol, the dose of Hctercol 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 phosphorous 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 phosphorous 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

<table>
<thead>
<tr>
<th>Study</th>
<th>Hypercalcemia (per 100 patient weeks)</th>
<th>Hyperphosphatemia (per 100 patient weeks)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Washout (Off Treatment)</td>
<td>Open-Label (Treatment)</td>
</tr>
<tr>
<td>Study C</td>
<td>0.9</td>
<td>0.9</td>
</tr>
<tr>
<td>Study D</td>
<td>0.3</td>
<td>1.0</td>
</tr>
</tbody>
</table>

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 gluthemide 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. Henc, 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 genec 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 in vivo 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 based on mcg/m² 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/kg based on mcg/m² 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 mothers 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

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>Hectorol® (n=61)</th>
<th>Placebo (n=61)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Body as a Whole</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Abscess</td>
<td>3.3</td>
<td>0.0</td>
</tr>
<tr>
<td>Headache</td>
<td>27.9</td>
<td>18.0</td>
</tr>
<tr>
<td>Malaise</td>
<td>27.9</td>
<td>19.7</td>
</tr>
<tr>
<td>Cardiovascular System</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bradycardia</td>
<td>6.6</td>
<td>4.9</td>
</tr>
<tr>
<td>Digestive System</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anorexia</td>
<td>4.9</td>
<td>3.3</td>
</tr>
<tr>
<td>Constipation</td>
<td>3.3</td>
<td>3.3</td>
</tr>
<tr>
<td>Dyspepsia</td>
<td>4.9</td>
<td>1.6</td>
</tr>
<tr>
<td>Nausea/Vomiting</td>
<td>21.3</td>
<td>19.7</td>
</tr>
<tr>
<td>Musculo-Skeletal System</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Arthralgia</td>
<td>4.9</td>
<td>0.0</td>
</tr>
<tr>
<td>Metabolic and Nutritional System</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Edema</td>
<td>34.4</td>
<td>21.3</td>
</tr>
<tr>
<td>Weight increase</td>
<td>4.9</td>
<td>0.0</td>
</tr>
<tr>
<td>Nervous System</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dizziness</td>
<td>11.5</td>
<td>9.8</td>
</tr>
<tr>
<td>Sleep disorder</td>
<td>3.3</td>
<td>0.0</td>
</tr>
<tr>
<td>Respiratory System</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dyspnea</td>
<td>11.5</td>
<td>6.6</td>
</tr>
<tr>
<td>Skin</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pruritus</td>
<td>8.2</td>
<td>6.6</td>
</tr>
<tr>
<td>A patient who reported the same medical term more than once was counted only once for that medical term.</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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 Hectol 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, Hectol therapy may be re instituted 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 Hectol®

The treatment of acute accidental overdosage of Hectol 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, treatment with standard medical care should be followed, as needed. Based on similarities between Hectol and its active metabolite, 1α,25-(OH)2D3, it is expected that Hectol is not removed from the blood by dialysis.

DOSAGE AND ADMINISTRATION

Adult Administration:

For intravenous use only. The optimal dose of Hectol must be carefully determined for each patient. The recommended initial dose of Hectol 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 not 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/mL is noted, the dose of Hectol 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

<table>
<thead>
<tr>
<th>iPTH Level</th>
<th>Hectol® Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;400 pg/mL</td>
<td>4 mcg three times per week at the end of dialysis, or approximately every other day</td>
</tr>
</tbody>
</table>

### Dose Titration

<table>
<thead>
<tr>
<th>iPTH Level</th>
<th>Hectol® Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Decrease by &lt;50% and above 300 pg/mL</td>
<td>Increase by 1 to 2 mcg at eight-week intervals as necessary</td>
</tr>
<tr>
<td>Decrease by &gt;50% and above 300 pg/mL</td>
<td>Maintain</td>
</tr>
<tr>
<td>150 - 300 pg/mL</td>
<td>Maintain</td>
</tr>
<tr>
<td>&lt;100 pg/mL</td>
<td>Suspend for one week, then resume at a dose that is at least 1 mcg lower</td>
</tr>
</tbody>
</table>

Multi-Dose Vial

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

HOW SUPPLIED

Single-Use Vial

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

NDC 58468-0123-1  4 mcg/2 mL single-use vial
NDC 58468-0126-1  2 mcg/1 mL single-use vial

Multi-Dose Vial

Hectol is also supplied in multi-dose 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 an orange plastic flip-off cap.

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

STORAGE

Single-Use Vial

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

Multi-Dose Vial

Store unopened multi-dose vials at 25°C (77°F): excursions permitted to 15-30°C (59-86°F) [see USP controlled room temperature] Store opened multi-dose vials at 2-8°C (36-46°F) Protect from light. Rx only

Manufactured by: Genzyme Biosurgery
For: Genzyme Corporation
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Cambridge, MA 02142

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