HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use HECTOROL safely and effectively. See full prescribing information for HECTOROL.

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 D_2 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)
- Know 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 cardiopulmonary 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, leukopenia, dehydration, edema, depression, hypertonia, insomnia, asthenia, paresthesia, cough increased, dyspnea, pruritus, sinusitis, and rhinitis. (6.1)
The most common adverse reactions in patients with CKD on dialysis (incidence >5%) were headache, malaise, edema, nausea/vomiting, dyspnea, dizziness, pruritus, and bradycardia. (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: 6/2025

FULL PRESCRIBING INFORMATION: CONTENTS*

1 INDICATIONS AND USAGE
2 DOSAGE AND ADMINISTRATION
2.1 Prior to Initiation of HECTOROL Capsules or Injection
2.2 Dosage Recommendations for HECTOROL Capsules in Patients with Stage 3 or 4 CKD
2.3 Dosage Recommendations for HECTOROL Capsules in Patients with CKD on Dialysis
2.4 Important Administration Instructions for HECTOROL Injection
2.5 Dosage Recommendations for HECTOROL Injection in Patients with CKD on Dialysis
2.6 Drug Interactions that May Require Dosage Adjustments of HECTOROL
3 DOSAGE FORMS AND STRENGTHS
4 CONTRAINDICATIONS
5 WARNINGS AND PRECAUTIONS
5.1 Hypercalcemia
5.2 Digitalis Toxicity
5.3 Serious Hypersensitivity Reactions
5.4 Adynamic Bone Disease
6 ADVERSE REACTIONS
6.1 Clinical Trials Experience
6.2 Postmarketing Experience
7 DRUG INTERACTIONS
8 USE IN SPECIFIC POPULATIONS
8.1 Pregnancy
8.2 Lactation
8.4 Pediatric Use
8.5 Geriatric Use
8.6 Hepatic Impairment
10 OVERDOSAGE
11 DESCRIPTION
12 CLINICAL PHARMACOLOGY
12.1 Mechanism of Action
12.3 Pharmacokinetics
13 NONCLINICAL TOXICOLOGY
13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
14 CLINICAL STUDIES
14.1 Clinical Studies of HECTOROL Capsules in Patients with Stage 3 or 4 CKD
14.2 Clinical Studies of HECTOROL Capsules in Patients with CKD on Dialysis
14.3 Clinical Studies of HECTOROL Injection in Patients with CKD on Dialysis
16 HOW SUPPLIED/STORAGE AND HANDLING
17 PATIENT COUNSELING INFORMATION

*Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

- 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.
- HECTOROL injection is indicated for the treatment of secondary hyperparathyroidism in adult patients with CKD on dialysis.

2 DOSAGE AND ADMINISTRATION

2.1 Prior to Initiation of HECTOROL Capsules or Injection

- Ensure serum calcium is not above the upper limit of normal before initiating treatment with HECTOROL capsules or injection [see Warnings and Precautions (5.1)].

2.2 Dosage Recommendations for HECTOROL Capsules in Patients with Stage 3 or 4 CKD

- Initiate HECTOROL capsules at a dose of 1 mcg orally once daily.
- Target the maintenance dose of HECTOROL to intact parathyroid hormone (PTH) levels within the desired therapeutic range and serum calcium within normal limits.
- Monitor serum calcium, phosphorus, and intact PTH levels at least every two weeks for 3 months after initiation of therapy or dose adjustment, then monthly for 3 months, and every 3 months thereafter.
- Titrate the dose of HECTOROL capsules based on intact PTH. The dose may be increased at 2-week intervals by 0.5 mcg to achieve the desired therapeutic range of intact PTH. The maximum recommended dose of HECTOROL capsules is 3.5 mcg administered once daily. Prior to raising the dose, ensure serum calcium is within normal limits.
- Suspend or decrease the dose if intact PTH is persistently and abnormally low to reduce the risk of adynamic bone disease [see Warnings and Precautions (5.4)] or if serum calcium is consistently above the normal range to reduce the risk of hypercalcemia [see Warnings and Precautions (5.1)]. If suspended, the drug should be restarted after one week at a dose that is at least 0.5 mcg lower.

2.3 Dosage Recommendations for HECTOROL Capsules in Patients with CKD on Dialysis

- Initiate HECTOROL capsules at a dose of 10 mcg orally administered three times weekly at dialysis (no more frequently than every other day).
- Target the maintenance dose of HECTOROL to intact parathyroid hormone (PTH) levels within the desired therapeutic range and serum calcium within normal limits.
- Monitor serum calcium, phosphorus, and intact PTH levels frequently (e.g., weekly) after initiation of therapy or dose adjustment.

- Titrate the dose of HECTOROL capsules based on intact PTH. The dose may be increased at 8-week intervals by 2.5 mcg to achieve the desired therapeutic range of intact PTH. The maximum recommended dose of HECTOROL is 20 mcg administered three times weekly at dialysis for a total dose of 60 mcg weekly. Prior to raising the dose, ensure serum calcium is within normal limits.
- Suspend or decrease the dose if intact PTH is persistently and abnormally low to reduce the risk of adynamic bone disease [see Warnings and Precautions (5.4)] or if serum calcium is consistently above the normal range to reduce the risk of hypercalcemia [see Warnings and Precautions (5.1)]. If suspended, the drug should be restarted one week later at a dose that is at least 2.5 mcg lower.

2.4 Important Administration Instructions for HECTOROL Injection

- Administer HECTOROL injection intravenously as a bolus dose at the end of dialysis.
- Inspect HECTOROL injection visually prior to administration; the solution should appear clear and colorless. Do not use if the solution is not clear or particles are present.
- After initial vial use:
  - discard unused portion of the single-dose vial;
  - store opened multiple-dose vial for up to 3 days at 2°C to 8°C (36°F to 46°F). Discard unused portion of multiple-dose vial after 3 days [see How Supplied/Storage and Handling (16)].

2.5 Dosage Recommendations for HECTOROL Injection in Patients with CKD on Dialysis

- Initiate HECTOROL injection at a dose of 4 mcg given by bolus intravenous administration three times weekly at the end of dialysis (no more frequently than every other day).
- Target the maintenance dose of HECTOROL to intact parathyroid hormone (PTH) levels within the desired therapeutic range and serum calcium within normal limits.
- Monitor serum calcium, phosphorus, and intact PTH levels weekly after initiation of therapy or dose adjustment.
- Titrate the dose of HECTOROL injection based on intact PTH. The dose may be increased at 8-week intervals by 1 mcg to 2 mcg if intact PTH is not lowered by 50% and fails to reach the target range. The maximum dose is 18 mcg weekly. Prior to raising the dose, ensure serum calcium is within normal limits.
- Suspend or decrease the dose if intact PTH is persistently and abnormally low to reduce the risk of adynamic bone disease [see Warnings and Precautions (5.4)] or if serum calcium is consistently above the normal range to reduce the risk of hypercalcemia [see Warnings and Precautions (5.1)]. If suspended, the drug should be restarted one week later at a dose that is at least 1 mcg lower.

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 concomitantly with drugs that may increase the risk of hypercalcemia [see Drug Interactions (7)].
- Increased monitoring of both serum calcium and intact PTH as well as dose adjustment of HECTOROL may be necessary when given concomitantly 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 follows:

- 0.5 mcg (salmon color)
- 1 mcg (peach color)
- 2.5 mcg (butter-yellow color)

Injection: clear and colorless solution available as follows:

- 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

4 CONTRAINDICATIONS

HECTOROL is contraindicated in patients with:

- Hypercalcemia [see Warnings and Precautions (5.1)]
- Vitamin D toxicity [see Warnings and Precautions (5.1)]
- Known hypersensitivity to doxercalciferol or any of the inactive ingredients of HECTOROL capsules or HECTOROL injection; serious hypersensitivity reactions including anaphylaxis and angioedema have been reported [see Warnings and Precautions (5.3), Adverse Reactions (6.2)].

5 WARNINGS AND PRECAUTIONS

5.1 Hypercalcemia

Hypercalcemia may occur during HECTOROL treatment. Acute hypercalcemia may increase the risk of cardiac arrhythmias and seizures and may potentiate the effect of digitalis on the heart [see Warnings and Precautions (5.2)]. Chronic hypercalcemia can lead to generalized vascular calcification and other soft-tissue calcification. Severe hypercalcemia may require emergency attention.

Hypercalcemia may be exacerbated by concomitant administration of high doses of calcium-containing preparations, thiazide diuretics, or other vitamin D compounds [see Drug Interactions (7)]. In addition, high intake of calcium and phosphate concomitantly with vitamin D compounds may lead to hypercalciuria and hyperphosphatemia. Patients with a history of hypercalcemia prior to initiating therapy may be at increased risk for development of hypercalcemia with HECTOROL. In these circumstances, frequent serum calcium monitoring and HECTOROL dose adjustments may be required.

When initiating HECTOROL or adjusting HECTOROL dose, measure serum calcium frequently (weekly in patients with CKD on dialysis or every 2 weeks for patients with stage 3 or 4 CKD). Once a maintenance dose has been established, measure serum calcium monthly for 3 months and then every 3 months. If hypercalcemia occurs, reduce the dose or discontinue HECTOROL until serum calcium is normal [see Dosage and Administration (2)].

Inform patients about the symptoms of elevated calcium (feeling tired, difficulty thinking clearly, loss of appetite, nausea, vomiting, constipation, increased thirst, increased urination and weight loss) and instruct them to report new or worsening symptoms when they occur.

5.2 Digitalis Toxicity

HECTOROL can cause hypercalcemia [see Warnings and Precautions (5.1)] which increases the risk of digitalis toxicity. In patients using HECTOROL concomitantly with digitalis compounds, monitor both serum calcium and patients for signs and symptoms of digitalis toxicity. Increase the frequency of monitoring when initiating or adjusting the dose of HECTOROL [see Drug Interactions (7)].

5.3 Serious Hypersensitivity Reactions

Serious hypersensitivity reactions, including fatal outcome, have been reported post marketing 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, and cardiopulmonary arrest. These reactions may occur separately or together.

Monitor patients receiving HECTOROL upon initiation of treatment for hypersensitivity reactions. Should a hypersensitivity reaction occur, discontinue HECTOROL, monitor and treat if indicated [see Contraindications (4)].

5.4 Adynamic Bone Disease

Adynamic bone disease with subsequent increased risk of fractures may develop if intact PTH levels are suppressed by HECTOROL to abnormally low levels. Monitor intact PTH levels to avoid oversuppression and adjust the HECTOROL dose, if needed [see Dosage and Administration (2)].

6 ADVERSE REACTIONS

The following adverse reactions are discussed in greater detail in another section of the label:

- Hypercalcemia [see Warnings and Precautions (5.1)]
- Serious Hypersensitivity Reactions [see Warnings and Precautions (5.3)]
- Adynamic Bone Disease [see Warnings and Precautions (5.4)]

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

HECTOROL Capsules

Adverse reactions in patients with stage 3 or 4 CKD

HECTOROL capsules have been evaluated in two placebo-controlled, double-blind 24 week studies in patients with Stage 3 or 4 CKD. Patients were treated with HECTOROL capsules (n=27) or placebo (n=28) [see Clinical Studies (14.1)]. Adverse reactions occurring in the HECTOROL capsules group at a frequency of 5% or greater and more frequently than in the placebo group are presented in Table 1.

Table 1: Adverse Reactions Occurring in ≥5% HECTOROL Capsule-Treated Patients with CKD on Predialysis and Greater than Placebo in Two Double-Blind Clinical Studies

Adverse Reaction*	**HECTOROL (n=27) %**	**Placebo (n=28) %**
Infection/bacterial infection/viral infection	30	25
Constipation	26	11
Rhinitis	22	11
Anemia	19	4
Cough	19	4
Dyspnea	19	11
Paresthesia	15	11
Asthenia	15	11
Insomnia	15	4
Hypertonia	11	4
Angina pectoris	8	0
Dehydration	7	4
Depression	7	0
Dyspepsia	7	4
Edema	7	4
Urinary tract infection	7	4
Leukopenia	7	0
Chest pain	7	4
Pruritus	7	4
Sinusitis	7	4

* Pooled data on adverse reactions from clinical study reports (Studies BCI-CH-115 and BCI-CH-119).

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

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

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

HECTOROL Injection

Adverse reactions in patients with CKD on hemodialysis

HECTOROL injection has been studied in 70 patients with CKD on hemodialysis in two 12-week, open-label, single-arm, multicenter studies [see Clinical Studies (14.3)]. The incidence of hypercalcemia and hyperphosphatemia increased during therapy with HECTOROL injection. Patients with higher pretreatment serum levels of calcium (>10.5 mg/dL) or phosphorus (>6.9 mg/dL) were more likely to experience hypercalcemia or hyperphosphatemia.

There was no placebo group included in the studies of HECTOROL injection. Adverse reactions in patients with CKD on hemodialysis receiving HECTOROL injection are expected to be similar to those reported in placebo-controlled studies of HECTOROL capsules presented in Table 2.

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, cardiopulmonary 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

Drugs that May Increase the Risk of Hypercalcemia	
Clinical Impact	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.
Examples	Calcium-containing products, other vitamin D compounds or thiazide diuretics
Intervention	Monitor serum calcium concentrations more frequently and adjust HECTOROL dose as needed [see Warnings and Precautions (5.1)].
Digitalis Compounds	
Clinical Impact	Doxercalciferol can cause hypercalcemia which can potentiate the risk of digitalis toxicity.
Intervention	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)].
Cytochrome P450 Inhibitors	
Clinical Impact	Doxercalciferol is activated by CYP 27 in the liver. Cytochrome P450 inhibitors may inhibit the 25-hydroxylation of doxercalciferol and thus reduce the formation of active doxercalciferol moiety [see Clinical Pharmacology (12.3)].
Examples	Ketoconazole and erythromycin
Intervention	If a patient initiates or discontinues therapy with a cytochrome P450 inhibitor, dose adjustment of HECTOROL may be necessary. Monitor intact PTH and serum calcium concentrations closely.
Enzyme Inducers	
Clinical Impact	Doxercalciferol is activated by CYP 27 in the liver. Enzyme inducers may affect the 25-hydroxylation of doxercalciferol [see Clinical Pharmacology (12.3)].
Examples	Glutethimide and phenobarbital
Intervention	If a patient initiates or discontinues therapy with an enzyme inducer, dose adjustment of HECTOROL may be necessary. Monitor intact PTH and serum calcium concentrations closely.
Magnesium-containing Products	
Clinical Impact	Concomitant administration of HECTOROL and high doses of magnesium-containing products may increase the risk of hypermagnesemia.
Examples	Magnesium-containing products such as antacids
Intervention	Avoid use of magnesium-containing products and HECTOROL in patients on chronic renal dialysis.

Table 4: Clinically Significant Drug Interactions with HECTOROL Capsules

Cholestyramine	
Clinical Impact	Cholestyramine has been reported to reduce intestinal absorption of fat-soluble vitamins. Therefore, it may impair intestinal absorption of HECTOROL capsules.
Intervention	Administer HECTOROL capsules at least 1 hour before or 4 to 6 hours after taking cholestyramine.
Mineral Oil or other Substances that May Affect Absorption of Fat	
Clinical Impact	The use of mineral oil or other substances that may affect absorption of fat may influence the absorption and availability of HECTOROL.
Intervention	Administer HECTOROL capsules at least 1 hour before or 4 to 6 hours after taking mineral oil or other substances that may affect absorption of fat.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

The limited available data with HECTOROL in pregnant women are insufficient to identify a drug-associated risk for major birth defects, miscarriage or adverse maternal or fetal outcomes. There are risks to the mother and fetus associated with chronic kidney disease in pregnancy [see Clinical Considerations]. In reproduction studies in rats and rabbits administered doxercalciferol during organogenesis at up to 20 mcg/kg/day and 0.1 mcg/kg/day, respectively (approximately 25 times (rats) and less than (rabbits) the maximum recommended human oral dose of 60 mcg/week based on mcg/m^2 body surface area), no adverse developmental effects were observed [see Data].

The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2%-4% and 15%-20%, respectively.

Clinical Considerations

Disease-associated maternal and/or embryo/fetal 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.

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 breastfed child from HECTOROL or from the underlying maternal condition.

Clinical Considerations

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.

8.4 Pediatric Use

The safety and efficacy of HECTOROL have not been established for the treatment of secondary hyperparathyroidism in pediatric patients with Stage 3 or Stage 4 chronic kidney disease (CKD) and with CKD on dialysis.

Effectiveness was not demonstrated in a 12-week randomized, open-label trial in fourteen HECTOROL-treated patients, aged 5 to 17 years with chronic kidney disease (not on dialysis) and secondary hyperparathyroidism.

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

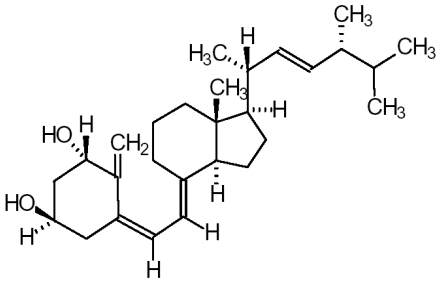
Overdosage of HECTOROL may lead to hypercalcemia, hypercalciuria, and hyperphosphatemia [see Warnings and Precautions (5.1)]. The treatment of acute overdosage should consist of supportive measures and discontinuation of HECTOROL administration. Serum calcium levels should be measured until normal.

Based on similarities between doxercalciferol and its active metabolite, $1\alpha,25\text{-}(OH)_2D_2$, it is expected that doxercalciferol is not removed from the blood by dialysis.

11 DESCRIPTION

HECTOROL contains doxercalciferol, which is a synthetic vitamin D_2 analog. Doxercalciferol undergoes metabolic activation *in vivo* to form 1α,25-dihydroxyvitamin D_2 ($1\alpha,25\text{-}(OH)_2D_2$), a naturally occurring, biologically active form of vitamin D_2.

Doxercalciferol is a colorless crystalline compound with a calculated molecular weight of 412.66 and a molecular formula of $C_{28}H_{44}O_2$. It is soluble in oils and organic solvents, but is relatively insoluble in water. Chemically, doxercalciferol is (1α,3β,5Z,7E,22E)-9,10-secoergosta-5,7,10(19),22-tetraene-1,3-diol. 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, glycerin, 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/2 mL (2 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).

HECTOROL injection 2 mL multiple-dose vials contain 4 mcg/2 mL (2 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% (0.075 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 D_2 analog that requires metabolic activation to form the active $1\alpha,25\text{-}(OH)_2D_2$ 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.

12.3 Pharmacokinetics

Absorption

In healthy volunteers, peak blood levels of $1\alpha,25\text{-}(OH)_2D_2$, 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 doses.

Elimination

The mean elimination half-life of $1\alpha,25\text{-}(OH)_2D_2$ 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 $1\alpha,25\text{-}(OH)_2D_2$ (major metabolite) and $1\alpha,24$-dihydroxyvitamin D_2 (minor metabolite). Activation of doxercalciferol does not require the involvement of the kidneys.

Specific Populations

Patients with renal impairment

The mean elimination half-life of 1α,25-$(OH)_2D_2$ in patients with end-stage renal disease (ESRD) and in healthy volunteers appears to be similar following an oral dose. Hemodialysis causes a temporary increase in 1α,25-$(OH)_2D_2$ mean concentrations, presumably due to volume contraction. 1α,25-$(OH)_2D_2$ is not removed from blood during hemodialysis.

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 and malignant adrenal pheochromocytomas 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/week based on mcg/m^2 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 chromatid and chromosome aberrations in an *in vitro* human lymphocyte clastogenicity assay with metabolic activation. However, doxercalciferol was negative in an *in vivo* mouse micronucleus clastogenicity assay.

Doxercalciferol had no effect on male or female fertility in rats at oral doses up to 2.5 mcg/kg/day (approximately 3 times the maximum recommended human oral dose of 60 mcg/week based on mcg/m^2 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, 40% 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: <5 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 dosage of HECTOROL capsules was adjusted 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 intact PTH fell below 15 pg/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 pg/mL in the HECTOROL capsules group and by 4 pg/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 two (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 138 patients with CKD on hemodialysis. Patients in Study A were an average age 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 3 occasions. Eighty-seven (63%) patients had plasma intact PTH levels <150 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

		Intact PTH (pg/mL)	
		means ± SD (n)* p-value vs Baseline p-value vs Placebo	
		HECTOROL Capsules	Placebo
Study A	Baseline	797.2 ± 443.8 (30) NA 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) NA 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.
NA = not applicable

HECTOROL capsules treatment resulted in a statistically significant reduction from baseline in mean intact PTH levels during 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 near baseline in the placebo group.

14.3 Clinical Studies of HECTOROL Injection in Patients with CKD on Dialysis

The safety and effectiveness of HECTOROL injection were evaluated in two open-label, single-arm, multicenter clinical studies (Study C and Study D) in a total of 70 patients with CKD on hemodialysis. Patients in Study C were an average age of 54 years (range: 23 to 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 to 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 to achieve intact PTH levels (measured weekly) within a targeted range of 150 pg/mL to 300 pg/mL. The dosage was increased by 2 mcg per dialysis session after 8 weeks of treatment if the intact PTH levels remained above 300 pg/mL and were greater than 50% of baseline levels. The maximum dosage was limited to 18 mcg per week. If at any time

during the study intact PTH fell below 150 pg/mL, HECTOROL injection was immediately suspended and restarted at a lower dosage the following week. Mean weekly doses ranged from 9 mcg to 13 mcg in Study C and ranged from 9 mcg to 12 mcg in Study D.

Fifty-two (74%) of the 70 patients who were treated with HECTOROL injection achieved intact PTH levels ≤300 pg/mL. Forty-one (59%) of these patients exhibited plasma intact PTH levels ≤300 pg/mL on at least 3 occasions. Thirty-six (51%) patients had plasma intact PTH levels <150 pg/mL on at least one occasion during 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 period and are displayed in Table 6.

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

Intact PTH Level	Study C (n=28)	Study D (n=42)	Combined Protocols (n=70)
Baseline (Mean of Weeks -2, -1, and 0)			
Mean (SE)	698 (60)	762 (65)	736 (46)
Median	562	648	634
On-treatment (Week 12*)			
Mean (SE)	406 (63)	426 (60)	418 (43)
Median	311	292	292
Change from Baseline†			
Mean (SE)	-292 (55)	-336 (41)	-318 (33)
Median	-274	-315	-304
P-value‡	0.004	0.001	<0.001

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

16 HOW SUPPLIED/STORAGE AND HANDLING

How Supplied

HECTOROL capsules are oval, soft gelatin capsules supplied as follows.

Strength	Capsule Color	Imprint Code	Package size	NDC
0.5 mcg	salmon	g	bottle of 50 capsules	58468-0120-1
1 mcg	peach	g	bottle of 50 capsules	58468-0124-1
2.5 mcg	butter-yellow	g	bottle of 50 capsules	58468-0121-1

HECTOROL injection is a clear, colorless solution supplied in 2 mL amber glass vials as follows.

Total Strength per Total Volume	Strength per mL	Flip-off Cap Color	Vial Count per Carton × Total Vial Volume and Vial Type	Carton NDC	Vial NDC
2 mcg/mL	2 mcg/mL	Green	50 × 1 mL single-dose vials	58468-0126-1	58468-0126-0
4 mcg/2 mL	2 mcg/mL	Yellow	50 × 2 mL single-dose vials	58468-0123-1	58468-0123-0
4 mcg/2 mL	2 mcg/mL	Orange	50 × 2 mL multiple-dose vials	58468-0127-1	58468-0127-0

Storage and Handling

Dosage Form	Storage temperature	Excursions permitted to	In-use storage
Capsule	25°C (77°F)	15°C to 30°C (59°F to 86°F) [see USP controlled room temperature]	–
Single-dose vial*	25°C (77°F)	15°C to 30°C (59°F to 86°F) [see USP controlled room temperature]	Discard unused portion
Multiple-dose vial*	25°C (77°F)	15°C to 30°C (59°F to 86°F) [see USP controlled room temperature]	2°C to 8°C (36°F to 46°F), Discard 3 days after opening

* Protect from light. Store unopened vial in original carton.

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)].

HECTOROL Capsules

Manufactured for:

Genzyme Corporation
Cambridge, MA 02141
A SANOFI COMPANY

HECTOROL Injection

Manufactured by:
Genzyme Corporation
Cambridge, MA 02141
A SANOFI COMPANY