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

DOXERCALCIFEROL injection, for intravenous use
Initial U.S. Approval: 2000

----------INDICATIONS AND USAGE----------

DOXERCALCIFEROL Injection is a synthetic vitamin D_2 analog indicated for treatment of secondary hyperparathyroidism in adult patients with chronic kidney disease on dialysis (1)

----------DOSAGE AND ADMINISTRATION----------

- Ensure serum calcium is within normal limits before initiating (2.1)
- Initiate 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) (2.2)
- Target the maintenance dose to intact parathyroid hormone (PTH) levels within the desired therapeutic range and serum calcium within normal limits (2.2)
- Monitor serum calcium, phosphorus, and intact PTH levels frequently (e.g., weekly) after initiation of therapy or dose adjustment (2.2)
- Titrate the dose based on intact PTH (see Table 1)
- The maximum dose is 18 mcg weekly (2.2)
- Suspend or decrease the dose if serum calcium is consistently above the normal range. If suspended, restart at a dose that is at least 1 mcg lower (2.2)

Table 1: Dose Titration

Dose Titration	
Intact PTH Level	Dosage Adjustment
Decrease by less than 50% and above target	Increase by 1 mcg to 2 mcg at eight-week intervals as necessary
Decrease by more than 50% and above target	Maintain
At target and intact PTH is stable	Maintain
Below the lower limit of the target range	Suspend for one week, then resume at a dose that is at least 1 mcg lower

----------DOSAGE FORMS AND STRENGTHS----------

- Injection: 4 mcg/2 mL (2 mcg/mL) multiple-dose 2 mL vial (3)
- Injection: 10 mcg/5 mL (2 mcg/mL) multiple-dose 5 mL vial (3)

----------CONTRAINDICATIONS----------

- Hypercalcemia (4)
- Vitamin D toxicity (4)
- Known hypersensitivity to doxercalciferol or the inactive ingredients (4)

----------WARNINGS AND PRECAUTIONS----------

- *Hypercalcemia:* Can occur during treatment with Doxercalciferol Injection and can lead to cardiac arrhythmias and seizures. The risk may be increased when used concomitantly with high dose calcium preparations, thiazide diuretics, or vitamin D and its derivatives. 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 both serum calcium and patients for signs and symptoms of digitalis toxicity. Increase the frequency of monitoring when initiating or adjusting the dose of Doxercalciferol Injection (5.2)
- *Serious Hypersensitivity Reactions:* Anaphylaxis with symptoms of angioedema, hypotension, unresponsiveness, chest discomfort, shortness of breath, and cardiopulmonary arrest have been reported in patients on hemodialysis following administration of Doxercalciferol Injection. Monitor patients upon initiation of treatment 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----------

Most common adverse reactions (incidence > 10%): edema, headache, malaise, nausea/vomiting, dyspnea and dizziness (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Pfizer, Inc. at 1-800-438-1985 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)

See 17 for PATIENT COUNSELING INFORMATION.

Revised: 7/2018

FULL PRESCRIBING INFORMATION: CONTENTS*

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

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

Doxercalciferol Injection is indicated for the treatment of secondary hyperparathyroidism in adult patients with chronic kidney disease (CKD) on dialysis.

2 DOSAGE AND ADMINISTRATION

2.1 Important Administration Information

- Ensure serum calcium is within normal limits before initiating treatment *[see Warnings and Precautions (5.1)]*.
- Administer Doxercalciferol Injection intravenously as a bolus dose at the end of dialysis.
- Inspect Doxercalciferol 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, the contents of the multiple-dose vial remain stable up to14 days when stored at room temperature. Discard unused portion of multiple-dose vial after 14 days *[see How Supplied/Storage and Handling (16)]*.

2.2 Starting Dose and Dose Titration

- Initiate Doxercalciferol 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 Doxercalciferol Injection 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 Doxercalciferol Injection based on intact PTH (see Table 1). 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 drug administration if intact PTH falls below 100 pg/mL and restart one week later at a dose that is at least 1 mcg lower than the last administered dose to reduce the risk of adynamic bone disease *[see Warnings and Precautions (5.4)]*.
- Suspend or decrease the dose 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 at a dose that is at least 1 mcg lower.

Table 1: Dose Titration

Dose Titration	
Intact PTH Level	Dosage Adjustment
Decrease by less than 50% and above target intact PTH	Increase by 1 mcg to 2 mcg at eight-week intervals as necessary
Decrease by more than 50% and above target	Maintain
At target and intact PTH is stable	Maintain
Below the lower limit of the target range	Suspend for one week, then resume at a dose that is at least 1 mcg lower

3 DOSAGE FORMS AND STRENGTHS

Injection: clear and colorless solution available as follows:

- 4 mcg/2 mL (2 mcg/mL) multiple-dose 2 mL vial
- 10 mcg/5 mL (2 mcg/mL) multiple-dose 5 mL vial

4 CONTRAINDICATIONS

Doxercalciferol Injection is contraindicated in patients with:

- Hypercalcemia
- Vitamin D toxicity
- Known hypersensitivity to doxercalciferol or any of the inactive ingredients; 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 Doxercalciferol Injection 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 Doxercalciferol Injection. In these circumstances, frequent serum calcium monitoring and Doxercalciferol Injection dose adjustments may be required.

When initiating Doxercalciferol Injection or adjusting Doxercalciferol Injection dose, measure serum calcium frequently (e.g., weekly). Once a maintenance dose has been established, measure serum calcium at least monthly. If hypercalcemia occurs, reduce the dose or discontinue Doxercalciferol Injection until serum calcium is normal *[see Dosage and Administration (2.2)]*.

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

Doxercalciferol Injection can cause hypercalcemia *[see Warnings and Precautions (5.1)]* which increases the risk of digitalis toxicity. In patients using Doxercalciferol Injection 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 Doxercalciferol Injection *[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 Doxercalciferol 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 Doxercalciferol Injection upon initiation of treatment for hypersensitivity reactions. Should a hypersensitivity reaction occur, discontinue doxercalciferol, 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 Doxercalciferol Injection to abnormally low levels. Monitor intact PTH levels to avoid oversuppression and adjust the Doxercalciferol Injection dose, if needed *[see Dosage and Administration (2.2)]*.

6 ADVERSE REACTIONS

The following serious adverse reactions are described below and elsewhere in the labeling:

- 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 clinical practice.

Doxercalciferol Injection has been studied in 70 patients with chronic renal disease on hemodialysis in two 12-week, open-label, single-arm, multi-centered studies. The incidence of hypercalcemia and hyperphosphatemia increased during therapy with Doxercalciferol Injection. 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.

Because there was no placebo group included in the studies of Doxercalciferol Injection, Table 2 provides the adverse reaction rates from placebo-controlled studies of oral doxercalciferol.

Table 2: Adverse Reactions Reported by ≥2% of Doxercalciferol Treated Patients and More Frequently Than Placebo During the Double-blind Phase of Two Clinical Studies

Adverse Reaction	Doxercalciferol (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
Constipation	3	3
Abscess	3	0
Sleep disorder	3	0

Adverse reactions associated with Doxercalciferol Injection are similar to those encountered with excessive vitamin D intake and hypercalcemia which 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.

6.2 Postmarketing Experience
The following adverse reactions have been identified during post-approval use of Doxercalciferol Injection. 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 following administration of Doxercalciferol Injection. Hypersensitivity reactions included 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

Table 3 includes clinically significant drug interactions with doxercalciferol.

Table 3: Clinically Significant Drug Interactions with Doxercalciferol

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 Doxercalciferol Injection dose as needed *[see Warnings and Precautions (5.1)]*.
Digitalis Compounds	
Clinical Impact	Doxercalciferol Injection 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 Doxercalciferol Injection 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-hydroxtlation 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 Doxercalciferol Injection 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 Doxercalciferol Injection may be necessary. Monitor intact PTH and serum calcium concentrations closely.
Magnesium Containing Products	
Clinical Impact	Concomitant administration of Doxercalciferol Injection and high doses of magnesium containing products may increase the risk of hypermagnesemia.
Examples	Magnesium containing products such as antacids
Intervention	Monitor serum magnesium concentrations more frequently and adjust Doxercalciferol Injection dose as needed.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

There are no human data with Doxercalciferol Injection in pregnant women 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 animal 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, still birth, and low birth weight infants.

Data

Animal Data

There were no adverse effects on fetal growth or survival at doses up to 20 mcg/kg/day, when doxercalciferol was administered to pregnant female rats during organogenesis. When administered to pregnant female rabbits during organogenesis, there were no adverse effects on fetal growth or survival at doses up to 0.3 mcg/kg/day.

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 Doxercalciferol Injection 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 Doxercalciferol Injection and any potential adverse effects on the breastfed child from Doxercalciferol Injection 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

Safety and efficacy of Doxercalciferol Injection in pediatric patients have not been established.

8.5 Geriatric Use

Clinical studies of Doxercalciferol Injection 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 Doxercalciferol Injection appropriately. More frequent monitoring of intact PTH, calcium, and phosphorus levels should be done in patients with hepatic impairment.

10 OVERDOSAGE

Overdosage of Doxercalciferol Injection may lead to hypercalcemia, hypercalciuria, hyperphosphatemia, and oversuppression of PTH *[see Warnings and Precautions (5.1, 5.4)]*.

The treatment of acute overdosage should consist of supportive measures, discontinuation of Doxercalciferol Injection administration and supplemental calcium, and institution of a low calcium diet. Serum calcium levels should be measured until normal.

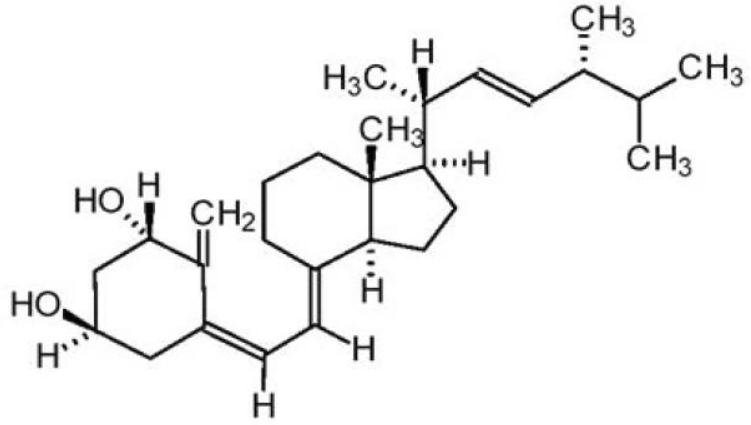
Based on similarities between Doxercalciferol Injection and its active metabolite, $1\alpha,25\text{-}(OH)_2D_2$, it is expected that Doxercalciferol Injection is not removed from the blood by dialysis.

11 DESCRIPTION

Doxercalciferol is a synthetic vitamin D_2 analog that undergoes metabolic activation *in vivo* to form $1\alpha,25$-dihydroxy vitamin D_2 ($1\alpha,25\text{-}(OH)_2D_2$), a naturally occurring, biologically active form of vitamin D_2. Doxercalciferol injection is a sterile, clear, colorless aqueous solution for intravenous injection.

Doxercalciferol is a colorless crystalline compound with a calculated molecular weight of 412.65 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 and has the structural formula presented in Figure 1.

Figure 1: Chemical Structure of Doxercalciferol



Other names frequently used for doxercalciferol are 1α-hydroxyvitamin D_2, 1α-OH-D_2, and 1α-hydroxyergocalciferol.

Each milliliter (mL) of solution contains doxercalciferol, 2 mcg; ethanol, 96%, 0.078 mL; Polysorbate 20, 10 mg; sodium chloride, 1.5 mg; butylated hydroxytoluene, 0.02 mg; sodium phosphate dibasic, heptahydrate, 14.4 mg; sodium phosphate monobasic, monohydrate, 1.8 mg; and disodium edetate, 1.1 mg. The pH of the solution is 7.0-8.0.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Doxercalciferol is a synthetic vitamin D_2 analog that requires metabolic activation to form the active 1α,25-$(OH)_2D_2$ 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 parathyroid hormone (PTH) levels by inhibiting PTH synthesis and secretion.

12.3 Pharmacokinetics

Peak blood concentrations of 1α,25-$(OH)_2D_2$ are reached at 8 ± 5.9 hours (mean ± SD) after a single intravenous dose of 5 mcg of doxercalciferol.

Elimination

The mean elimination half-life of 1α,25-$(OH)_2D_2$ 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. Doxercalciferol Injection is not approved for oral use.

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.

Metabolism

After intravenous administration, doxercalciferol is activated by CYP 27 in the liver to form 1α,25-$(OH)_2D_2$ (major metabolite) and 1α,24-dihydroxyvitamin D_2 (minor metabolite). Activation of doxercalciferol does not require the involvement of the kidneys.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Long-term studies in animals to evaluate the carcinogenic potential of doxercalciferol have not been conducted. 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

The safety and effectiveness of Doxercalciferol 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 Doxercalciferol Capsules in prior clinical studies (Study A and Study B) received Doxercalciferol Injection in an open-label fashion for 12 weeks following an 8-week washout (control) period. Dosing of Doxercalciferol 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 Doxercalciferol Injection was adjusted to achieve intact PTH 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 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, Doxercalciferol Injection was immediately suspended and restarted at a lower dosage the following week.

Results:

Fifty-two of the 70 patients who were treated with Doxercalciferol Injection achieved intact PTH levels ≤ 300 pg/mL. Forty-one of these patients exhibited plasma intact PTH levels ≤ 300 pg/mL on at least 3 occasions. Thirty-six patients had plasma intact PTH 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 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 the table below. Plasma intact PTH levels were measured weekly during the 12-week study.

Table 4: Intact PTH Summary Data for Patients Receiving Doxercalciferol Injection in Two 12 week Open-Label Studies

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

Intact PTH Level	Study C (n=28)	Study D (n=42)	Combined Protocols (n=70)
Change from Baseline†			
Mean (SE)	-292 (55)	-336 (41)	-318 (33)
Median	-274	-315	-304
P-value‡	.004	.001	<.001

* Values were carried forward for the two patients on study for 10 weeks
† Treatment intact PTH minus baseline intact PTH
‡ Wilcoxon one-sample test

Doxercalciferol Injection 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

Doxercalciferol Injection is a clear, colorless solution in multiple-dose amber glass vials supplied as displayed in Table 5. The closure consists of a fluorocarbon-coated chlorobutyl stopper, with an aluminum seal and plastic flip-off cap.

Table 5: Doxercalciferol Injection Strengths and Package Configurations

Total Strength per Total Volume	Strength per mL	Flip-off Cap Color	Vial Count per Carton x Total Vial Volume and Vial Type	Carton NDC	Vial NDC
4 mcg/2 mL	2 mcg/mL	Orange	50 x 2 mL multiple-dose vials	0409-1330-01	0409-1330-11
10 mcg/5 mL	2 mcg/mL	Gray	50 x 5 mL multiple-dose vials	0409-1331-01	0409-1331-11

STORAGE

Store multiple-dose vials at 20°C to 25°C (68°F to 77°F) [see USP controlled room temperature].

Protect from light. Store unopened vial in original carton. Discard vial 14 days after opening.

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 Doxercalciferol Injection *[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 Doxercalciferol Injection. 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 Doxercalciferol Injection if a new medication is prescribed *[see Drug Interactions (7)]*.

This product's label may have been updated. For the current prescribing information, please visit www.pfizer.com.

Manufactured by: Hospira, Inc.
Lake Forest, IL 60045 USA

LAB-0887-1.0