DOXERCALCIFEROL- doxercalciferol capsule
REMEDYREPACK INC.

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

DOXERCALCIFEROL capsules, for oral use
Initial U.S. Approval: 1999

INDICATIONS AND USAGE

Doxercalciferol Capsules is a synthetic vitamin D_2 analog:

- Doxercalciferol 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)

DOSAGE AND ADMINISTRATION

- Before initiating treatment, ensure serum calcium is not above the upper limit of normal. (2.1)
- Dosage for doxercalciferol 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)
- Target the maintenance dose of doxercalciferol 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 (3)

CONTRAINDICATIONS

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

WARNINGS AND PRECAUTIONS

- Hypercalcemia:Can occur during treatment with doxercalciferol 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 doxercalciferol. (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 doxercalciferol. 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 Avet Pharmaceuticals Inc. at 1-866-901-DRUG (3784) 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 doxercalciferol capsules. Administer doxercalciferol 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 doxercalciferol capsules. Administer doxercalciferol 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: 4/2026

FULL PRESCRIBING INFORMATION: CONTENTS*

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

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

- Doxercalciferol 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.

2 DOSAGE AND ADMINISTRATION

2.1 Prior to Initiation of Doxercalciferol Capsules

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

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

- Initiate doxercalciferol capsules at a dose of 1 mcg orally once daily.
- Target the maintenance dose of doxercalciferol 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 doxercalciferol 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 doxercalciferol 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 Doxercalciferol Capsules in Patients with CKD on Dialysis

- Initiate doxercalciferol 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 doxercalciferol 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 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 doxercalciferol 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.

2.6 Drug Interactions that May Require Dosage Adjustments of Doxercalciferol

- Increased monitoring of serum calcium and dose adjustment of doxercalciferol 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 doxercalciferol may be necessary when given concomitantly with cytochrome P450 inhibitors or enzyme inducers *[see Drug Interactions (7)].*

3 DOSAGE FORMS AND STRENGTHS

- 0.5 mcg – White, opaque, oval shaped soft gelatin capsules. Each capsule is imprinted with **"HP 538"**in black ink.

4 CONTRAINDICATIONS

Doxercalciferol 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 doxercalciferol capsules; 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 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. In these circumstances, frequent serum calcium monitoring and doxercalciferol dose adjustments may be required.

When initiating doxercalciferol or adjusting doxercalciferol 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 doxercalciferol until serum calcium is normal *[see Dosage andAdministration (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 can cause hypercalcemia *[see Warnings and Precautions (5.1)]* which increases the risk of digitalis toxicity. In patients using doxercalciferol 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 *[see Drug Interactions (7)].*

5.3 Serious Hypersensitivity Reactions

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 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 to abnormally low levels. Monitor intact PTH levels to avoid oversuppression and adjust the doxercalciferol 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.

Adverse reactions in patients with stage 3 or 4 CKD

Doxercalciferol 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 doxercalciferol capsules (n=27) or placebo (n=28) *[seeClinical Studies (14.1)]* . Adverse reactions occurring in the doxercalciferol 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% Doxercalciferol Capsule-Treated Patients with CKD on Predialysis and Greater than Placebo in Two Double-Blind Clinical Studies

Adverse Reaction *	**Doxercalciferol (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

Doxercalciferol capsules have been evaluated in two placebo-controlled, double-blind studies in patients with CKD on hemodialysis. Patients were treated with doxercalciferol 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 doxercalciferol capsules in an open-label fashion for 16 weeks followed by a double-blind period of 8 weeks during which patients received either doxercalciferol capsules or placebo. Adverse reactions occurring in the doxercalciferol 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% Doxercalciferol Capsule-Treated Patients with CKD on Dialysis and Greater than Placebo in Two Double-Blind 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
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.

6.2 Postmarketing Experience

The following adverse reactions have been identified during postapproval use of doxercalciferol. 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 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 doxercalciferol.

Table 3: Clinically Significant Drug Interactions with Doxercalciferol 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 doxercalciferol 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 doxercalciferol in patients receiving digitalis compounds *[see Warnings andPrecautions (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 doxercalciferol 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 may be necessary. Monitor intact PTH and serum calcium concentrations closely.
Magnesium-containing Products	
Clinical Impact	Concomitant administration of doxercalciferol 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 doxercalciferol in patients on chronic renal dialysis.

Table 4: Clinically Significant Drug Interactions with Doxercalciferol Capsules

Cholestyramine	
Clinical Impact	Cholestyramine has been reported to reduce intestinal absorption of fat-soluble vitamins. Therefore, it may impair intestinal absorption of

	doxercalciferol capsules.
Intervention	Administer doxercalciferol 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 doxercalciferol.
Intervention	Administer doxercalciferol 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 doxercalciferol 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% to 4% and 15% to 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 doxercalciferol 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 and any potential adverse effects on the breastfed child from doxercalciferol or from the underlying maternal condition.

Clinical Considerations

Monitoring of serum calcium in the infant should be considered.

8.4 Pediatric Use

The safety and efficacy of doxercalciferol 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 doxercalciferol-treated patients, aged 5 to 17 years with chronic kidney disease (not on dialysis) and secondary hyperparathyroidism.

8.5 Geriatric Use

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

10 OVERDOSAGE

Overdosage of doxercalciferol 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 doxercalciferol administration. Serum calcium levels should be measured until normal.

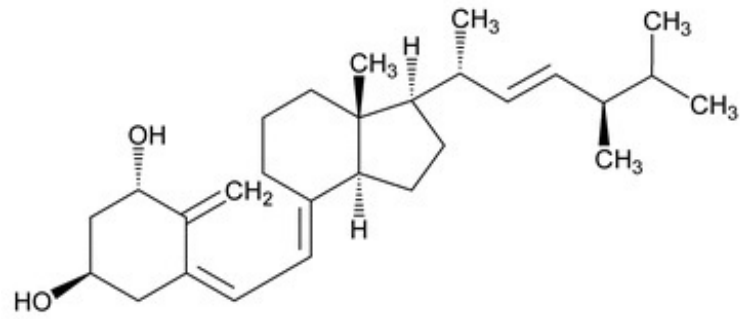
Based on similarities between doxercalciferol and its active metabolite, 1α,25-$(OH)_2D_2$, it is expected that doxercalciferol is not removed from the blood by dialysis.

11 DESCRIPTION

Doxercalciferol Capsules contains doxercalciferol, which is a synthetic vitamin D_2analog. Doxercalciferol undergoes metabolic activation *in vivo*to form 1α,25-dihydroxyvitamin D_2(1α,25-$(OH)_2D_2$), 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:



Doxercalciferol 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 medium-chain triglycerides. The capsule shells contain gelatin, glycerin, iron oxide black and titanium dioxide. In addition, the 0.5 mcg capsule shells contain shellac glaze, the 1 mcg capsule shells contain FD&C Blue No. 1, FD&C Yellow No. 6, shellac and the 2.5 mcg capsule shells contain FD&C Red No. 40 and shellac.

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 PTH levels by inhibiting PTH synthesis and secretion.

12.3 Pharmacokinetics

Absorption

In healthy volunteers, peak blood levels of 1α,25-$(OH)_2D_2$, the major metabolite of doxercalciferol, are attained at 8 hours after a single intravenous dose of doxercalciferol and at 11 to 12 hours following capsule doses.

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.

Metabolism

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.

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) $_2$D $_2$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 Doxercalciferol Capsules in Patients with Stage 3 or 4 CKD

The safety and effectiveness of doxercalciferol 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 doxercalciferol capsules and the other placebo during the double-blind period of 24 weeks. The initial dose of doxercalciferol capsules was 1 mcg per day. The dosage of doxercalciferol 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, doxercalciferol 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 doxercalciferol capsules group and by 4 pg/mL in the placebo group ($p<0.001$). Twenty (74%) of 27 subjects in the doxercalciferol 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 Doxercalciferol Capsules in Patients with CKD on Dialysis

The safety and effectiveness of doxercalciferol 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 doxercalciferol capsules in an open-label fashion for 16 weeks followed by a double-blind period of 8 weeks during which patients received either doxercalciferol capsules or placebo. The initial dose of doxercalciferol 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 doxercalciferol 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, doxercalciferol 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 doxercalciferol 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 Doxercalciferol Capsules in Studies A and B

		Intact PTH (pg/mL)	
		means± SD (n)* p-value vs Baseline p-value vs Placebo	
		Doxercalciferol 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	526.5 ± 872.2 (29) <0.001

		0.72	–
	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

Doxercalciferol 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 doxercalciferol capsules treatment group compared to a return to near baseline in the placebo group.

16 HOW SUPPLIED/STORAGE AND HANDLING

Doxercalciferol capsules are oval, soft gelatin capsules supplied as follows

0.5 mcg, Capsule Color: White, Opaque, Imprint Code: HP 538

NDC: 70518-4642-00

NDC: 70518-4642-01

OUTER PACKAGING: 50 in 1 BOX

PACKAGING: 1 in 1 POUCH

Store at 25°C (77°F); excursions permitted to 15° to 30°C (59° to 86°F)

[see USP Controlled Room Temperature.]

Repackaged and Distributed By:

Remedy Repack, Inc.

625 Kolter Dr. Suite #4 Indiana, PA 1-724-465-8762

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 *[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. 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 *[seeDosage and Administration (2), Drug Interactions (7)]* .

DrugInteractions

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

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625 Kolter Drive, Indiana, PA 15701

(724) 465-8762

DRUG: Doxercalciferol

GENERIC: Doxercalciferol

DOSAGE: CAPSULE

ADMINSTRATION: ORAL

NDC: 70518-4642-0

NDC: 70518-4642-1

COLOR: white

SHAPE: OVAL

SCORE: No score

SIZE: 8 mm

IMPRINT: HP538

PACKAGING: 1 in 1 POUCH

OUTER PACKAGING: 50 in 1 BOX

ACTIVE INGREDIENT(S):
- DOXERCALCIFEROL 0.5ug in 1

INACTIVE INGREDIENT(S):
- BUTYLATED HYDROXYANISOLE
- ALCOHOL
- MEDIUM-CHAIN TRIGLYCERIDES
- GELATIN

- GLYCERIN
- FERROSOFERRIC OXIDE
- SHELLAC
- TITANIUM DIOXIDE

Doxercalciferol Capsule

MFG NDC: 23155-0538-25
MFG: Avet Pharma, East Brunswick, NJ 08816

Usual Dosage: See Insert

Keep this and all medication out o the reach of children
Store at 20-25°C (68-77°F); excursions permitted to 15-30°C (59-86°F) [See USP]

0.5 mcg

QTY: 50 Per Box
NDC #: **70518-4642-00**
LOT #:
Expires:
Oval WHITE HP538

remedy repack

RX ONLY

Repackaged By: RemedyRepack Inc.,
Indiana, PA 15701, 724.465.8762

Doxercalciferol Capsule

MFG NDC: 23155-0538-25
MFG: Avet Pharma, East Brunswick, NJ 08816

Usual Dosage: See Insert

Keep this and all medication out o the reach of children
Store at 20-25°C (68-77°F); excursions permitted to 15-30°C (59-86°F) [See USP]

0.5 mcg

QTY: 1 Capsule
NDC #: **70518-4642-01**
LOT #:
Expires:
Oval WHITE HP538

remedy repack

RX ONLY

Repackaged By: RemedyRepack Inc.,
Indiana, PA 15701, 724.465.8762

DOXERCALCIFEROL

doxercalciferol capsule

Product Information			
Product Type	HUMAN PRESCRIPTION DRUG	**Item Code (Source)**	NDC:70518-4642(NDC:23155-538)
Route of Administration	ORAL		

Active Ingredient/Active Moiety		
Ingredient Name	**Basis of Strength**	**Strength**

DOXERCALCIFEROL (UNII: 3DIZ9LF5Y9) (DOXERCALCIFEROL - UNII:3DIZ9LF5Y9)	DOXERCALCIFEROL	0.5 ug

Inactive Ingredients

Ingredient Name	Strength
BUTYLATED HYDROXYANISOLE (UNII: REK4960K2U)	
ALCOHOL (UNII: 3K9958V90M)	
MEDIUM-CHAIN TRIGLYCERIDES (UNII: C9H2L21V7U)	
GELATIN (UNII: 2G86QN327L)	
GLYCERIN (UNII: PDC6A3C0OX)	
FERROSOFERRIC OXIDE (UNII: XM0M87F357)	
SHELLAC (UNII: 46N107B71O)	
TITANIUM DIOXIDE (UNII: 15FIX9V2JP)	

Product Characteristics

Color	white (WHITE)	**Score**	no score
Shape	OVAL	**Size**	8mm
Flavor		**Imprint Code**	HP538
Contains			

Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:70518-4642-0	50 in 1 BOX	04/28/2026	
1	NDC:70518-4642-1	1 in 1 POUCH; Type 0: Not a Combination Product		

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
ANDA	ANDA205360	04/28/2026	

Labeler - REMEDYREPACK INC. (829572556)

Revised: 4/2026 REMEDYREPACK INC.