

# Findings

## Diet Quality Affects Risk of eGFR Decline in Urban Patients

In a diverse urban population, low dietary quality is associated with an increased risk of declining kidney function among adults with hypertension, reports a study in the *Journal of Renal Nutrition*.

The study included data on 1534 participants in the “Healthy Aging in Neighborhoods of Diversity across the Life Span” (HANDLS) study: African Americans and whites, aged 30 to 64 years, with a baseline estimated glomerular filtration

rate (eGFR) of 60 mL/min/1.73 m<sup>2</sup> or higher. Mean age was 48 years; 59% of participants were African American.

A Dietary Approaches to Stop Hypertension (DASH) score, based on nine target nutrients, was calculated for each participant. Diet score was evaluated for association with rapid decline in kidney function (greater than 3 mL/min/1.73 m<sup>2</sup> per year), incident chronic kidney disease, and eGFR decline greater than 25%.

Accordance with the DASH diet was “minimal”—median score 1.5 on a 0–8 scale. At a median 5 years’ follow-up, rapid eGFR decline occurred in 13.4% of patients overall, 15.2% of those with a DASH score of 1 or less, and 12.0% with a DASH score greater than 1. On adjusted analysis, the association with rapid eGFR decline was significant only for subjects with hypertension: risk ratio 1.68. The DASH score was unrelated to

incident chronic kidney disease or eGFR decline greater than 25%.

Previous studies have linked a healthier diet to a lower risk of kidney disease outcomes, but none of these studies have focused on urban populations. The new results show that a low DASH score is associated with an increased risk of rapid decline in eGFR, among urban adults with hypertension. The investigators conclude: “[D]iet quality may play an important role in determining kidney outcomes among individuals with risk factors for CKD” [Liu Y, et al. *Dietary habits and risk of kidney function decline in an urban population. J Renal Nutr* 2017; 27: 6–25]. ●

### BRIEF SUMMARY CONSULT PACKAGE INSERT FOR FULL PRESCRIBING INFORMATION

**RAYALDEE® (calcifediol) extended-release capsules, for oral use**



#### INDICATIONS AND USAGE:

RAYALDEE® is a vitamin D<sub>3</sub> analog indicated for the treatment of secondary hyperparathyroidism in adult patients with stage 3 or 4 chronic kidney disease and serum total 25-hydroxyvitamin D levels less than 30 ng/mL. RAYALDEE is not indicated for the treatment of secondary hyperparathyroidism in patients with stage 5 chronic kidney disease or in patients with end-stage renal disease on dialysis.

#### CONTRAINDICATIONS:

None

#### WARNINGS AND PRECAUTIONS

Hypercalcemia may occur during RAYALDEE treatment. Acute hypercalcemia may increase the risk of cardiac arrhythmias and seizures and may potentiate the effect of digitalis on the heart. 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. In addition, high intake of calcium and phosphate concomitantly with vitamin D compounds may lead to hypercalcemia and hyperphosphatemia. In these circumstances, frequent serum calcium monitoring and RAYALDEE dose adjustments may be required. Patients with a history of hypercalcemia prior to initiating therapy with RAYALDEE should be monitored more frequently for possible hypercalcemia during therapy.

Patients should be informed about the symptoms of elevated serum calcium, which include feeling tired, difficulty thinking clearly, loss of appetite, nausea, vomiting, constipation, increased thirst, increased urination, and weight loss. Hypercalcemia of any cause, including RAYALDEE, increases the risk of digitalis toxicity. In patients using RAYALDEE concomitantly with digitalis compounds, monitor both serum calcium and patients for signs and symptoms of digitalis toxicity and increase the frequency of monitoring when initiating or adjusting the dose of RAYALDEE.

Adynamic bone disease with subsequent increased risk of fractures may develop if intact PTH levels are suppressed by RAYALDEE to abnormally low levels. Monitor intact PTH levels and adjust RAYALDEE dose, if needed.

#### DOSAGE AND ADMINISTRATION

##### Important Dosage and Administration Information

- Ensure serum calcium is below 9.8 mg/dL before initiating treatment.
- Instruct patients to swallow RAYALDEE capsules whole.
- Instruct patients to skip a missed dose and to resume taking the medicine at the next regularly scheduled time. Do not administer an extra dose.

##### Starting Dose and Dose Titration

- The initial dose of RAYALDEE is 30 mcg administered orally once daily at bedtime.
- The maintenance dose of RAYALDEE should target serum total 25-hydroxyvitamin D levels between 30 and 100 ng/mL, intact parathyroid hormone (PTH) levels within the desired therapeutic range, serum calcium (corrected for low albumin) within the normal range and serum phosphorus below 5.5 mg/dL.
- Monitor serum calcium, serum phosphorus, serum total 25-hydroxyvitamin D and intact PTH levels at a minimum of 3 months after initiation of therapy or dose adjustment, and subsequently at least every 6 to 12 months.
- Increase the dose to 60 mcg orally once daily at bedtime after approximately 3 months, if intact PTH remains above the desired therapeutic range. Prior to raising the dose, ensure serum calcium is below 9.8 mg/dL, serum phosphorus is below 5.5 mg/dL and serum total 25-hydroxyvitamin D is below 100 ng/mL.
- Suspend dosing if intact PTH is persistently and abnormally low to reduce the risk of adynamic bone disease [see Warnings and Precautions], if serum calcium is consistently above the normal range to reduce the risk of hypercalcemia [see Warnings and Precautions], or if serum total 25-hydroxyvitamin D is consistently above 100 ng/mL. Restart at a reduced dose after these laboratory values have normalized.

#### USE IN SPECIFIC POPULATIONS

**Teratogenic Effects - Pregnancy Category C:** Calcifediol has been shown to be teratogenic in rabbits when given in doses of 8 to 16 times the human dose of 60 mcg/day, based on body surface area. There are no adequate and well-controlled studies in pregnant women. RAYALDEE should be used during pregnancy only if the potential benefit justifies potential risk to the fetus. When calcifediol was given orally to bred rabbits on the 6th through the 18th day of gestation, gross visceral and skeletal examination of pups indicated that the

compound was teratogenic at doses of 25 and 50 mcg/kg/day. A dose of 5 mcg/kg/day was not teratogenic. In a similar study in rats, calcifediol was not teratogenic at doses up to and including 60 mcg/kg/day.

#### Carcinogenesis, Mutagenesis, Impairment of Fertility

No neoplastic changes attributable to calcifediol were observed at subcutaneous doses of 3, 10 and 33 mcg/kg/day in a 26-week rasH2 transgenic mouse study. In vitro or in vivo mutagenicity studies have not been performed with RAYALDEE. No genotoxic or mutagenic effects have been reported with calcifediol. Calcifediol has not been shown to have significant effects on fertility in rats.

**Labor and Delivery:** The effect of this drug on the mother and fetus during labor and delivery is not known.

**Nursing Mothers:** Limited available evidence indicates that calcifediol is poorly excreted in human milk. Caution should be exercised when RAYALDEE is administered to a nursing woman.

**Pediatric Use:** The safety and efficacy of RAYALDEE have not been established in pediatric patients.

**Geriatric Use:** Of the total number of subjects in phase 3 placebo-controlled clinical studies of RAYALDEE, 63% were ≥65 years of age and 22% were ≥75 years of age. No overall differences in the safety or efficacy of RAYALDEE were observed between subjects older than 65 years and younger subjects.

#### Renal Impairment

No difference in efficacy was observed between patients with stage 3 chronic kidney disease or those with stage 4 disease in subgroup analysis. Safety outcomes were similar in these subgroups. The safety and efficacy of RAYALDEE in the treatment of secondary hyperparathyroidism in patients with stage 2 or stage 5 chronic kidney disease and patients with end-stage renal disease on dialysis have not been established [see Indications and Usage].

#### Overdosage

Excessive administration of RAYALDEE can cause hypercalcemia, hyperphosphatemia, or oversuppression of intact PTH. Common symptoms of vitamin D overdosage may include constipation, decreased appetite, dehydration, fatigue, irritability, muscle weakness, or vomiting.

Treatment of acute accidental overdosage with RAYALDEE should consist of general supportive measures. If the overdosage is discovered within a short time, induce emesis or perform gastric lavage to prevent further absorption. Obtain serial serum and urine calcium measurements, and assess any electrocardiographic abnormalities due to hypercalcemia. Discontinue supplemental calcium. Treat with standard medical care if persistent and markedly elevated serum calcium levels occur.

Calcifediol is not significantly removed by dialysis.

#### ADVERSE REACTIONS

The data in Table 1 are derived from two pivotal studies described below. These data reflect exposure of 285 subjects to RAYALDEE 30 or 60 mcg daily for up to 6 months (mean 24 weeks, range 1 to 31 weeks). The mean age of the study population was 66 years old (range 25-85 years). Half of the subjects were male, 65% were White, and 32% were African-American or Black. At baseline, subjects had secondary hyperparathyroidism, stage 3 (52%) or 4 (48%) chronic kidney disease without macroalbuminuria and serum total 25-hydroxyvitamin D levels less than 30 ng/mL. The most common causes of chronic kidney disease were diabetes and hypertension and the mean estimated GFR at baseline was 31 mL/min/1.73 m<sup>2</sup>. At baseline, mean plasma intact PTH was 148 pg/mL, mean serum calcium was 9.2 mg/dL, mean serum phosphorus was 3.7 mg/dL and mean serum 25-hydroxyvitamin D was 20 ng/mL.

Table 1 shows common adverse reactions associated with the use of RAYALDEE in the pooled placebo-controlled trials. These adverse reactions were not present at baseline, occurred more commonly on RAYALDEE than on placebo, and occurred in at least 1.4% of patients treated with RAYALDEE.

**Table 1. Common Adverse Reactions in Placebo-controlled Trials Reported in ≥1.4% of RAYALDEE-Treated Subjects**

Adverse Reaction	Placebo	RAYALDEE
	N=144	N=285
	%	%
Anemia	3.5	4.9
Nasopharyngitis	2.8	4.9
Blood creatinine increased	1.4	4.9
Dyspnea	2.8	4.2
Cough	2.1	3.5
Cardiac failure congestive	0.7	3.5
Constipation	2.8	3.2
Bronchitis	0.7	2.8
Hyperkalemia	0.7	2.5
Osteoarthritis	0.7	2.1
Hyperuricemia	0.7	1.8
Cantusis	0.0	1.8
Pneumonia	0.7	1.4
Chronic obstructive pulmonary disease	0.0	1.4

**Increase in Serum Calcium:** Patients randomized to RAYALDEE experienced a greater mean (SE) increase in serum calcium (P<0.001) than patients randomized to placebo [i.e., 0.2 (0.02) mg/dL on RAYALDEE versus 0.1 (0.03) mg/dL on placebo from baseline to trial end]. Six subjects (2%) in the RAYALDEE treatment group and no subjects (0%) in the placebo group required dose reductions for protocol-defined hypercalcemia (two consecutive serum calcium values greater than 10.3 mg/dL). A total of 4.2% of RAYALDEE treated subjects and 2.1% of placebo treated subjects experienced at least 1 elevation in serum calcium above the upper limit of normal (10.5 mg/dL).

**Increase in Serum Phosphorus:** Patients randomized to RAYALDEE experienced a greater mean (SE) increase in serum phosphorus than patients randomized to placebo [i.e., 0.2 (0.03) mg/dL on RAYALDEE versus 0.1 (0.04) mg/dL on placebo from baseline to trial end]. One subject (0.4%) in the RAYALDEE treatment group met protocol-defined hyperphosphatemia (two consecutive serum phosphorus values >5.5 mg/dL deemed to be study drug related) compared to no subjects in the placebo group. A total of 45% of RAYALDEE treated subjects and 44% of placebo treated subjects experienced at least one elevation in serum phosphorus above the upper limit of normal (4.5 mg/dL).

**To report SUSPECTED ADVERSE REACTIONS, contact OPKO Pharmaceuticals, LLC at 1-844-729-2539 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch**

#### DRUG INTERACTIONS

##### CYP3A Inhibitors

Cytochrome P450 inhibitors, such as ketoconazole, atazanavir, clarithromycin, indinavir, itraconazole, nefazodone, nelfinavir, ritonavir, saquinavir, telithromycin or voriconazole, may inhibit enzymes involved in vitamin D metabolism (CYP24A1 and CYP27B1), and may alter serum levels of calcifediol. Dose adjustment of RAYALDEE may be required, and serum 25-hydroxyvitamin D, intact PTH and serum calcium concentrations should be closely monitored if a patient initiates or discontinues therapy with a strong CYP3A4 inhibitor.

##### Thiazides

Thiazides are known to induce hypercalcemia by reducing excretion of calcium in the urine. Concomitant administration of thiazides with RAYALDEE may cause hypercalcemia. Patients may require more frequent serum calcium monitoring in this setting.

##### Cholestyramine

Cholestyramine has been reported to reduce intestinal absorption of fat-soluble vitamins and may impair the absorption of calcifediol, the active ingredient in RAYALDEE. Dose adjustment of RAYALDEE may be required, and serum total 25-hydroxyvitamin D, intact PTH and serum calcium concentrations should be closely monitored if a patient initiates or discontinues therapy with cholestyramine.

##### Other Agents

Phenobarbital or other anticonvulsants or other compounds that stimulate microsomal hydroxylation reduce the half-life of calcifediol, the active ingredient in RAYALDEE. Dose adjustment of RAYALDEE may be required, and serum total 25-hydroxyvitamin D, intact PTH and serum calcium concentrations should be closely monitored if a patient initiates or discontinues therapy with phenobarbital or other anticonvulsants.

#### HOW SUPPLIED

RAYALDEE is supplied as 30 mcg calcifediol in blue, oval extended-release capsules, imprinted O.

Bottles of 30 [NDC 70301-1001-1]

Bottles of 60 [NDC 70301-1001-2]

#### STORAGE AND HANDLING

Store at 20-25°C (68-77°F); excursions permitted to 15-30°C (59-86°F) [see USP Controlled Room Temperature].

RAYALDEE is a registered trademark of OPKO Ireland Global Holdings Ltd.

Patent: <http://www.opko.com/products/patents/>

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## OPKO RENAL

Manufactured for:

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## Mortality Differs by Reason for Starting Dialysis

Among patients initiating dialysis, mortality is higher for those with a primary indication of volume overload or hypertension, suggests a study in the *American Journal of Kidney Diseases*.

The retrospective analysis included 461 patients who initiated hemodialysis or peritoneal dialysis (24 patients) from 2004 through 2012 at 14 facilities. All-cause mortality was analyzed for patients with differing primary indications for dialysis initiation: laboratory evidence of kidney function decline (reference category), uremic symptoms, volume overload, hypertension, or “other/unknown.”

At a median follow-up of 2.4 years, 40% percent of patients had died. Crude mortality was 21.7 per 100 patient-years for patients with volume overload or hypertension, compared to 10.0 for those with kidney function decline, 12.7 with uremic symptoms, and 12.2 for the “other/unknown” category.

On adjusted analysis, volume overload or hypertension was the only category associated with increased mortality: hazard ratio 1.69. Among patients using a permanent dialysis access, the risk of death was eight times higher for those in the volume overload/hypertension group, compared to those with decreased kidney function.

The results suggest increased mortality among patients initiating dialysis due to volume overload, relative to those with laboratory evidence of kidney function decline. The researchers write: “Improved understanding of symptoms and clinical decision making at the time of the transition to dialysis therapy has the potential to lead to innovation in identifying the optimal timing for the initiation of maintenance dialysis therapy” [Rivara MB, et al. Indication for dialysis initiation and mortality in patients with chronic kidney failure: a retrospective cohort study. *Am J Kidney Dis* 2017; 69:41–50]. ●