PDL DRUG REVIEW

Proprietary Name: Rayaldee®
Common Name: calcifediol, extended-release
PDL Category: Hyperparathyroid Treatment - Vitamin D Analogs

Comparable Products	Preferred Drug List Status
Calcitriol	Preferred

Summary

Pharmacology: Calcifediol, the active ingredient of Rayaldee®, is synthetically manufactured as calcifediol monohydrate. Calcifediol is also known as calcidiol, 25-hydroxycholecalciferol, or 25-hydroxyvitamin D3. Calcifediol is a pro-hormone of the active form of vitamin D3, calcitriol. It is converted to calcitriol by cytochrome P450 27B1 (CYP27B1), also called 1-alpha hydroxylase. Calcitriol binds to vitamin D receptors in target tissues and activates vitamin D responsive pathways that cause an increased intestinal absorption of calcium and phosphorus, as well as reduced parathyroid hormone synthesis.

Indications and Usage: A vitamin D3 analog indicated for the treatment of secondary hyperparathyroidism in adult patients with stage 3 or 4 chronic kidney disease (CKD) and serum total 25-hydroxyvitamin D levels <30ng/ml. It is not indicated for the treatment of secondary hyperparathyroidism in patients with stage 5 CKD or in patients with end-stage renal disease on dialysis.

This is a pregnancy category C medication. The safety and efficacy of use in children under the age of 18 years have not been established.

Dosage Forms: Extended-release capsules: 30mcg

Recommended Dosage: Prior to starting treatment, it is recommended to ensure that serum calcium is below 9.8mg/dL. Take one capsule once daily at bedtime to start. The maintenance dose should target serum total 25-hydroxyvitamin D levels between 30 and 100ng/ml, intact parathyroid hormone (PTH) levels within the desired therapeutic range, serum calcium within the normal range, and serum phosphorus below 5.5mg/dL.

It is recommended to monitor serum calcium, serum phosphorus, serum total 25-hydroxyvitamin D, and intact PTH levels at a minimum of 3 months after starting therapy or after dose adjustment, and then at least every 6-12 months thereafter.

Increase to 60mcg QHS after 3 months, if intact PTH remains above the desired therapeutic range. Before increasing the dose, ensure serum calcium is below 9.8mg/dL, serum phosphorus is below 5.5mg/dL, and serum total 25-hydroxyvitamin D is below 100ng/mL. If intact PTH is persistently and abnormally low, if serum calcium is consistently above the normal range, or if serum total 25-hydroxyvitamin D is consistently above 100ng/ml, it is recommended to suspend dosing.

Drug Interactions: Concomitant use of thiazides with Rayaldee® may cause hypercalcemia. It is recommended to monitor serum calcium more frequently in this setting. It is recommended to monitor both serum calcium and signs/symptoms of digitalis toxicity if use Rayaldee® concomitantly with digitalis compounds.

Cholestyramine has been reported to reduce intestinal absorption of fat-soluble vitamins and it may impair the absorption of calcifediol. Phenobarbital or other anticonvulsants or other compounds that stimulate microsomal hydroxylation reduce the half-life of calcifediol. CYP3A inhibitors (such as ketoconazole, atazanavir, clarithromycin, indinavir, itraconazole, nefazodone, nelfinavir, ritonavir, saquinavir, telithromycin, or voriconazole) may alter serum levels of calcifediol. Concomitant use of Rayaldee® with any of these agents may require dose adjustments of Rayaldee®. In addition, serum calcium, intact PTH, and serum total 25-hydroxyvitamin D should be monitored closely.

Common Adverse Drug Reactions: *Listed % incidence for adverse drug reactions= reported % incidence for drug (Rayaldee®) minus reported % incidence for placebo. Please note that an incidence of 0% means the incidence was the same as or that the active drug was less than its comparator.* The most frequently reported adverse events included anemia (1.4%), nasopharyngitis (2.1%), blood creatinine increased (3.5%), dyspnea (1.4%), cough (1.4%), cardiac failure congestive (2.8%), constipation (0.4%), bronchitis (2.1%), hyperkalemia (1.8%), osteoarthritis (1.4%), hyperuricemia (1.1%), contusion (1.8%), pneumonia (0.7%), and chronic obstructive pulmonary disease (1.4%).

In clinical trials, patients randomized to Rayaldee® had a greater mean increase in serum calcium as compared to placebo (0.2mg/dl vs 0.1mg/dl respectively; p<0.001). More in the Rayaldee® group had at least 1 elevation in serum calcium above the upper limit of normal as compared with placebo (4.2% vs 2.1%). Hypercalcemia may occur during treatment, and acute hypercalcemia may increase the risk of cardiac arrhythmias and seizures, as well as potentiate the effects of digitalis on the heart. Those with a history of hypercalcemia prior to starting Rayaldee® treatment should be monitored more frequently for possible hypercalcemia.

In clinical trials, patients randomized to Rayaldee® had a greater mean increase in serum phosphorus compared to placebo (0.2mg/dl vs 0.1mg/dl). More in the Rayaldee® group had at least 1 elevation in serum phosphorus above the upper limit of normal as compared with placebo (45% vs 44%).

Adynamic bone disease with subsequent increased risk of fractures may occur if intact PTH levels are suppressed by Rayaldee® to abnormally low levels. It is recommended to monitor intact PTH levels and adjust Rayaldee® dose if needed.

Contraindications: There are currently no contraindications listed with this product.

Manufacturer: OPKO Pharmaceuticals

Analysis: The safety and efficacy of Rayaldee® were assessed in two identical multicenter, randomized, placebo-controlled, double-blind studies in patients with secondary hyperparathyroidism, stage 3 or 4 CKD, and serum total 25-hydroxyvitamin D levels between 10 and 30ng/mL. Subjects were stratified by CKD and randomized to Rayaldee® 30mcg QD for the first 12 weeks and either 30 or 60mcg QD for the last 14 weeks or a matching placebo. Trial 1 included 213 patients and trial 2 included 216 patients.

The primary outcome compared the proportion of subjects who experienced an at least 30% reduction in plasma intact PTH from baseline to the end of the study. Results suggested that a larger proportion in the Rayaldee® group had an at least 30% reduction in plasma intact PTH from baseline as compared to placebo in both trials (Trial 1: 33% vs 8%, p<0.001; Trial 2: 34% vs 7%, p<0.001). Serum total 25-hydroxyvitamin D levels increased to at least 30ng/mL in more patients treated with Rayaldee® vs placebo (Trial 1: 80% vs 3%, p<0.001; Trial 2: 83% vs 7%, p<0.001).

Place in Therapy: Rayaldee® is indicated for the treatment of secondary hyperparathyroidism in adult patients with stage 3 or 4 chronic kidney disease (CKD) and serum total 25-hydroxyvitamin D levels <30ng/ml. Compared with placebo, it was found to be significantly more effective for obtaining an at least 30% reduction in plasma intact

parathyroid hormone from baseline in two registration trials (NNT 4 in study 1; NNT 4 in study 2). Comparator trials with extended-release calcifediol were not found.

There is no evidence at this time to support that Rayaldee® is safer or more effective than the currently available, more cost effective medications. It is therefore recommended that Rayaldee® remain non-preferred and require prior authorization and be available to those who are unable to tolerate or who have failed on preferred medications.

PDL Placement:

- ☐ **Preferred**
- ☒ **Non-Preferred**
- ☐ **Preferred with Conditions**

References

[1] Rayaldee [package insert]. Miami, FL: OPKO Pharmaceuticals, LLC; 2016.