

Class Review: Vitamin D Analogs

Date of Review: January 2017

Purpose for Class Review:

Oral and intravenous (IV) vitamin D analogs are important treatment options for secondary hyperparathyroidism and low levels of vitamin D associated with chronic kidney disease (CKD). Evidence on effectiveness and harms will be reviewed to make recommendations to the Oregon Health Authority (OHA) on criteria for use.

Research Questions:

1. In children and adult patients with CKD, what is the evidence for differences in efficacy or effectiveness (i.e., parathyroid hormone changes, mortality, cardiovascular outcomes, need for renal replacement therapy) between vitamin D analogs used for the treatment of secondary hyperparathyroidism?
2. In children and adult patients with CKD, what is the evidence for differences in harms (i.e., hypercalcemia, hyperphosphatemia) between drug therapies used for the treatment of secondary hyperparathyroidism?
3. Are there subpopulations (i.e., different stages of chronic kidney disease, dialysis requirements, socioeconomic status, age, race, ethnicities) in which one vitamin D analog may be more effective or associated with less harm than other vitamin D analog for the treatment of secondary hyperparathyroidism?

Conclusions:

- The evidence review on vitamin D analogs found 4 systematic reviews and meta-analyses, 3 randomized-controlled trials and 3 clinical practice guidelines from the U.S. Department of Veterans Affairs/Department of Defense (VA/DoD), National Institute for Health and Care Excellence (NICE), and Kidney Disease Improving Global Outcomes (KDIGO) recommendations for patients with CKD.¹⁻¹⁰ The evidence for vitamin D analogs is limited due to lack of long-term data on clinically meaningful outcomes such as mortality and bone fracture rates, and cardiovascular outcomes. Surrogate endpoints such PTH levels are subject to large variations between assays which make comparisons between clinical trials difficult.
- Evidence for use of vitamin D analogs in children with CKD to impact growth rate, bone fracture rates, electrolyte changes and cardiovascular disease is insufficient.⁹
- Evidence for use of vitamin D analogs in adults with CKD to impact fracture rates, bone pain, parathyroidectomy, cardiovascular outcomes, need for renal replacement therapy is insufficient. Comparative efficacy between the treatments is also insufficient.
- Low quality evidence from small, short-term studies suggest there is no mortality benefit for vitamin D analogs in patients with stage 2-4 CKD (RR 1.40; 95% CI, 0.38 to 5.15).¹ Mortality compared to placebo was not different for older vitamin D analogs (RR 1.49; 95% CI, 0.14 to 15.69) compared to newer vitamin D analogs (RR 1.09; 95% CI, 0.16 to 7.34). In patients on hemodialysis, no difference was observed between patients who received vitamin D analogs or placebo (117 deaths vs. 116 deaths, respectively (p=0.67)) based on low strength of evidence).²

- There is moderate strength of evidence based on 2 studies that newer vitamin D analogs decrease PTH levels more than 30% from baseline in 87.5% of patients compared to 11% of patients on placebo who have CKD not requiring dialysis (RR 7.87; 95% CI 4.87 to 12.73).¹ There was insufficient evidence to compare this surrogate outcome with older, established vitamin D analogs.
- There is moderate strength of evidence in patients requiring dialysis that vitamin D analogs decrease PTH levels more than 30% in 73% of patients compared to 10% in placebo-treated patients (RR 5.90; 95% CI, 3.17 to 10.96).² In a separate analysis between paricalcitol and placebo, paricalcitol was found to suppress PTH levels more than 30% in 73% of patients compared to 10% of placebo-treated patients (RR 6.37; 95% CI, 4.64 to 8.74; P<0.001).³ Low strength of evidence found that in patients requiring dialysis, paricalcitol decreased PTH levels more than 30% from baseline in 61.1% of patients compared to 73.3% of calcitriol treated patients (p=0.29) based on one small randomized-controlled trial.⁴
- Extended-release (ER) calcifediol decreased PTH levels in 2 identical, double-blind, randomized, placebo-controlled, 26-week trials in patients (n= 429) with stage 3 or 4 CKD and SHPT. Low strength of evidence found ER calcifediol to reduce PTH levels by 30% or more from baseline in 33% of patients compared to 8% in the placebo group in the first study (Study A) and by 34% and 7%, respectively, in the second study (Study B) (NNT=4 for both studies).⁵
- There is low quality evidence that paricalcitol decreases proteinuria (RR 1.68; 95% CI, 1.25 to 2.25; P<0.001).⁴
- There is moderate quality evidence to not recommend routinely prescribing vitamin D analogs to patients with CKD unless there is evidence of deficiency or PTH suppression.⁷
- There is moderate quality evidence use of vitamin D analogs result in a statistically significant higher incidence of hypercalcemia than placebo in patients with CKD not requiring dialysis ((5.2% vs. 3.9%, respectively; p=0.022).¹
- There is moderate quality evidence use of newer vitamin D analogs also results in a higher incidence of hypercalcemia than placebo in patients requiring dialysis (39% vs. 5%, respectively).² Established vitamin D analogs had a 31% incidence of hypercalcemia compared to 10% in placebo-treated patients (p=0.26) and newer vitamin D analogs had a 43% risk compared to 0% risk with placebo (p=0.020).
- There is low strength of evidence that there was not a meaningful clinical difference between vitamin D analogs and placebo in risk of hyperphosphatemia.²
- In comparisons in patients requiring dialysis, there was low strength of evidence of no difference for risk of hypercalcemia or hyperphosphatemia between vitamin D analogs.

Recommendations:

- Add a PDL class for Vitamin D analogs on the Oregon Health Plan (OHP) fee-for-service practitioner-managed prescription drug plan.
- Designate paricalcitol, doxercalciferol and calcifediol non-preferred and subject to prior authorization (PA) criteria (Appendix 3).
- Recommend to continue to keep calcitriol as the preferred vitamin D analog.

Background:

Mineral metabolism can be altered in patients with CKD and are associated with increased morbidity and mortality.¹¹ Altered levels of calcium, phosphorus and PTH are hallmarks of the disease due to the inability of the kidney to remove phosphorous from the blood and to activate vitamin D to allow for the absorption of calcium.¹ These disturbances in mineral homeostasis cause stimulation of the parathyroid gland that may lead to secondary hyperparathyroidism. Abnormal bone turnover, mineralization, growth, strength and vascular and other soft tissue calcification may result. Supplementation to correct disturbances is recommended by the National Kidney Foundation when there is suspected or documented deficiency.⁷ When vitamin D supplements fail to correct PTH levels then vitamin D analogs are initiated.⁵ Vitamin D analogs are thought to be more selective and less likely to cause hypercalcemia and hypophosphatemia than vitamin D compounds, while still suppressing PTH secretion; however, dose limiting effects of vitamin D analogs are increased calcium and phosphate levels

which have been linked to increased cardiovascular disease and mortality.^{2,11} Contraindications to vitamin D analogs are phosphorous concentrations >5.5 mg/dL and serum calcium >9.5 mg/dL due to the increase risk of metastatic and vascular calcification when levels are high.^{1,2}

There are four vitamin D analogs available; calcifediol, calcitriol, doxercalciferol, and paricalcitol (Table 1).¹²⁻¹⁵ Studies have shown the oral and IV formulations of calcitriol to be similar in PTH suppression and adverse events. Adynamic bone disease may also occur if vitamin D analogs and calcitriol are used when PTH levels are <150 pg/mL and therefore it is not recommended.

Table 1. Indications and Dosing¹²⁻¹⁵

Drug Name	Indication(s)	Strength/Route	Dose and Frequency
Calcitriol	<ul style="list-style-type: none"> - Secondary hyperparathyroidism in patients with moderate to severe chronic renal failure (CrCl 15 to 55 mL/min) not on dialysis - Hypocalcemia/metabolic bone disease in patients undergoing chronic renal dialysis or postsurgical hypoparathyroidism, idiopathic hypoparathyroidism and pseudohypoparathyroidism 	0.25 mcg or 0.50 mcg oral capsules 1 mcg/mL oral solution	Capsules and solution should be started at the lowest dose and should be increased according to serum calcium levels taken twice weekly while titrating dose and once monthly when on maintenance dose Dialysis patients: initial dose of 0.25 mcg/day and increased by 0.25 mcg/day every 4 to 8 weeks if needed Hypoparathyroidism: initial dose 0.25 mcg/day given in the morning. Dose titration may occur at every 2-4 weeks Pre-dialysis: initial dose of 0.25 mcg/day in patients 3 years and older and 10-15 ng/kg/day in patients under 3
Calcifediol	<ul style="list-style-type: none"> - Secondary hyperparathyroidism in adults with stage 3 or 4 chronic kidney disease and serum total 25-hydroxyvitamin D levels less than 30 ng/mL - Not for patients with stage 5 chronic kidney disease or end-stage renal disease on dialysis 	30 mg extended release oral capsules	30 mcg once daily at bedtime initially, the dose can be increased to 60 mcg once daily if needed. Adjustments should be made after 3 months of therapy and with proper monitoring
Doxercalciferol	<ul style="list-style-type: none"> - IV: secondary hyperparathyroidism in patients with chronic kidney disease on dialysis - Oral: secondary hyperparathyroidism in patients with Stage 3 or 4 chronic kidney disease 	2.0 mcg and 4.0 mcg IV 1 mcg and 2 mcg capsules	IV: 4.0 mcg three times weekly at the end of dialysis. Dose may be increased at 8-week intervals by 1.0-2.0 mcg Oral Dialysis patients: 10 mcg three times a week. Increase by 2.5 mcg at 8 week intervals if needed (max dose of 60 mcg/week) Pre-dialysis: 1 mcg/day. Increases may be done at 2-week intervals by 0.5 mcg (max dose of 3.5 mcg/day)

Paricalcitol	<ul style="list-style-type: none"> - IV formulation: secondary hyperparathyroidism associated with chronic kidney disease stage 5 - Oral capsules: secondary hyperparathyroidism associated with chronic kidney disease Stage 3 and 4 	<p>0.04 mcg/kg to 0.1 mcg/kg given IV</p> <p>1 mcg, 2 mcg, and 4 mcg capsules</p>	<p>IV: given as a bolus dose no more frequently than every other day during dialysis. Increase 2-4 mcg at 2-4 week intervals if needed</p> <p>Oral: 1-2 mcg, dependent upon PTH levels, given daily or 3 times a week. Increase every 2-4 weeks if needed</p>
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Parathyroid hormone levels are often used to monitor therapeutic efficacy of vitamin D analogs; however, because inactive and active fragments are measured, assays often have large variations.⁹ Levels of intact parathyroid hormone (iPTH) for patients requiring dialysis are recommended to be 150 to 300 pg/mL. Other important outcomes are: fractures, bone pain, muscle weakness, parathyroidectomy, cardiovascular disease, mortality, and need for renal replacement therapy. Patients should also be monitored for adverse effects of vitamin D analogs, which include hyperphosphatemia and hypercalcemia. Recommended serum phosphorous levels are 3.5 to 5.5 mg/dL and serum corrected total calcium levels of 8.4 to 9.5 mg/dL.¹

Vitamin D analog utilization by the majority of fee-for-service patients in the OHP is calcitriol.

A summary of relevant drug information is available in **Appendix 1**, which includes pharmacology and pharmacokinetic characteristics of these drugs, contraindications, warnings and precautions, including any Black Boxed Warnings and Risk Evaluation Mitigation Strategies.

Table 2. Summary of Direct Comparative Studies Completed

Study	Comparison	Population	Primary Outcome	Results
Coyne, et al ⁶ 24 weeks	paricalcitol 1 mcg/day* vs. calcitriol 0.25 mcg/day*	Patients with Stage 3-4 CKD and secondary hyperparathyroidism	Number of patients with confirmed hypercalcemia (≥ 10.5 mg/dL)	paricalcitol 3 (6%) calcitriol: 1 (2%) P=0.36
Ong, et al ⁴ 24 weeks	paricalcitol vs. calcitriol	Patients (n=66) dialysis patients with secondary hyperthyroidism	Number of patients with a $\geq 30\%$ reduction in iPTH	paricalcitol: 22 (61.1%) calcitriol: 22 (73.3%) P=0.29

* Initial dose

Methods:

A Medline literature search for new systematic reviews and randomized controlled trials (RCTs) assessing clinically relevant outcomes to active controls, or placebo if needed, was conducted. The Medline search strategy used for this review is available in **Appendix 2**, which includes dates, search terms and limits used. The OHSU Drug Effectiveness Review Project, Agency for Healthcare Research and Quality (AHRQ), Cochrane Collection, National Institute for Health and Clinical Excellence (NICE), Department of Veterans Affairs, BMJ Clinical Evidence, and the Canadian Agency for Drugs and Technologies in Health (CADTH) resources were manually searched for high quality and relevant systematic reviews. When necessary, systematic reviews are critically appraised for quality using the AMSTAR tool and clinical practice guidelines using the AGREE tool. The FDA website was searched for new drug approvals, indications, and pertinent safety alerts. Finally, the AHRQ National Guideline Clearinghouse (NGC) was searched for updated and recent evidence-based guidelines.

The primary focus of the evidence is on high quality systematic reviews and evidence-based guidelines. Randomized controlled trials will be emphasized if evidence is lacking or insufficient from those preferred sources.

Systematic Reviews:

Cochrane – Vitamin D Compounds and Chronic Kidney Disease

In a 2009 review Cochrane Systematic Reviews looked at the use of vitamin D compounds in suppressing PTH in patients with chronic kidney disease that are not on dialysis.¹ Drugs included in the review are: calcitriol (5 studies), alfacalcidol (3 studies), 24, 25(OH)₂ vitamin D₃, doxercalciferol (1 study), maxacalcitol, paricalcitol (1 study), and falecalcitriol. The newly approved calcifediol was not available at the time of this review. Sixteen randomized controlled trials on oral or IV formulations were found to meet the inclusion criteria. Ten studies were placebo-controlled. Most studies were small (less than 50 participants) and lasted less than 12 months. All patients had CKD; 2 studies with stage 2 or lower, eight studies enrolled stage 3 or lower and 3 studies were in stage 4 or lower. The overall quality was rated poor for most of the studies.

Vitamin D compounds were found to not change the most important outcomes of mortality reduction (RR 1.40; 95% CI, 0.38 to 5.15) and dialysis prevention (RR 0.76; 95% CI, 0.36 to 1.62).¹ PTH levels were reduced by vitamin D analogs compared to placebo by MD -49.34 pg/mL (95% CI, -85.70 to 12.97 pg/mL), based on 4 studies. Vitamin D compounds were also associated with increased phosphorous levels, MD 0.37 mg/dL (95% CI, 0.09 to 0.66) and increased serum calcium MD 0.20 mg/dL (95% CI, 0.17 to 0.23 mg/dL). Evidence on fracture, parathyroidectomy and bone pain was insufficient to draw conclusions. Of the 9 studies which reported harms, one study found nausea and vomiting with paricalcitol which was similar to placebo. There was insufficient comparative evidence between calcitriol and newer vitamin D compounds. Limitations to the analysis are small study sizes which suggests insufficient power to detect a difference between treatments if one did exist.

Cochrane – Vitamin D Compounds and Chronic Kidney Disease in Patients Requiring Dialysis

A second Cochrane Systematic Review was done to determine the role of vitamin D compounds in patients with CKD requiring dialysis.² The effect of vitamin D compounds on mortality, PTH and bone was investigated. Sixty studies met the inclusion criteria. The following included drugs were compared to placebo: calcitriol (7 studies), alfacalcidol (2 studies), 24,25 dihydroxyvitamin D₃, maxacalcitol (1 study), doxercalciferol (1 study) and paricalcitol (6 studies). Head to head studies involved 13 studies; however, only 2 studies evaluated drugs available in the U.S. (n=294). Majority of studies enrolled less than 75 participants. Pediatric patients were represented in six studies. The majority of studies (n=50) enrolled patients on hemodialysis and 7 studies included patients with peritoneal dialysis. Most studies were deemed to be poor quality.

Meta-analysis capability was limited due to heterogeneity in outcomes. In comparisons of vitamin D analogs to placebo and effect on mortality, no difference was found (RR 1.34; 95% CI, 0.34 to 5.24).² Rates of fracture, bone pain, and effects on stature were found to have similar risks for vitamin D analogs and placebo; however, the number of outcomes were too low to draw meaningful conclusions. Vitamin D was found to lower PTH levels; however, efficacy comparisons between the different vitamin D analogs was limited. One study found newer analogs to be similar in PTH lowering as established vitamin D analogs (MD 19.0 pg/mL; 95% CI, -96.2 to 134.2). Eight additional studies reported PTH levels but not in a way that allowed for a meta-analysis calculation to be done. Placebo controlled comparisons found vitamin D analogs to lower PTH more than placebo MD -196.05 pg/mL; 95% CI, -298.43 to -93.66). The ability of vitamin D analogs to suppress PTH levels \geq 30% was more effective than placebo (RR 5.90; 95% CI, 3.17 to 10.96). Studies of established vitamin D analogs found them to be more effective at suppressing PTH levels \geq 30% than placebo (RR 2.72, 95% CI, 1.12 to 6.61) and similar findings for the newer analogs (RR 7.05; 95% CI, 3.82 to 13.04).

Serum phosphorous levels were significantly increased with vitamin D analogs in data available from 2 studies (MD 0.70 mg/dL; 95% CI, 0.08 to 1.33) and hypercalcemia was more common but did not meet statistical significance.² Newer vitamin D analogs were associated with a higher incidence of hypercalcemia compared to placebo (serum phosphorous data was not reported). Evidence suggests that IV vitamin D lowers PTH more than oral formulations but evidence is insufficient to draw strong conclusions. There was insufficient evidence on the effect of different dosing strategies on outcomes.

In head to head comparisons of vitamin D analogs no difference in mortality outcomes was found based on data from 94 patients.² There was insufficient evidence to draw conclusions on fracture and bone pain. One study of PTH levels found no difference between the newer vitamin D analogs on PTH suppression. Phosphorous levels were also found to be similar between agents. Serum calcium levels were found to be similar between older and newer vitamin D analogs based on one study (MD 0.30 mg/dL; 95% CI, -0.11 to 0.71). For patients with IP outcome data was insufficient to make conclusions.

Robust harms data was not available. One study of with calcitriol compared to no treatment found hypercalcemia-related adverse events such as insomnia, pruritus, irritation, conjunctival congestion and eosinophilia. Paricalcitol was found to be associated with cough, rash, headache and infection in 1-3 patients, depending on the study.²

Cochrane – Interventions for Metabolic Bone Disease in Children with Chronic Kidney Disease

The topic of a 2015 Cochrane Systematic Review was the role of interventions for metabolic bone disease in children with Stage 2 to Stage 5D CKD.⁹ Eighteen studies were identified involving 576 children up to the age of 21. Interventions included in the study were; dietary, vitamin D or metabolites, calcimimetic and phosphate binding agents.

Changes in PTH levels were the most commonly investigated outcome, with little evidence on growth or bone deformities. Most of the included studies had a high risk of performance bias. Two studies compared oral versus intraperitoneal (IP) calcitriol. One study was too small to draw meaningful conclusions (n=7) and the second found no difference between the types of administration for the outcomes of PTH levels, hyperphosphatemia, hypercalcemia or of bone histology. Intermittent compared to once daily dosing of calcitriol was evaluated in 3 studies (n=104).⁹ PTH levels, height, hypercalcemia or hyperphosphatemia were not statistically different between groups. Six studies compared vitamin D analogs. In placebo-controlled comparisons, IV formulations of calcitriol and paricalcitol were more effective at lowering PTH levels and risk of hypercalcemia was not statistically different when compared to placebo. One head to head compared doxercalciferol and calcitriol combined with either sevelamer or calcium carbonate found no significant differences in parameters of bone health. Studies evaluating ergocalciferol and phosphate binders will not be discussed since they aren't the focus of this review. Limitations to this review is the insufficient evidence available on growth rates, fractures, cardiovascular calcification or calcium and phosphorous changes. Additionally, many studies were too small to detect a treatment difference if one did exist.

Paricalcitol Use in CKD – Systematic Review and Meta-Analysis

The efficacy and safety of paricalcitol was evaluated in a systematic review and meta-analysis of available randomized controlled trials in patients with Stage 2-5 CKD.³ The Jadad scale score (0-5) and risk of bias was used to evaluate the quality of the included trials. Efficacy outcomes studied were: effects on proteinuria, PTH, serum calcium and phosphorous levels. Nine placebo comparison trials were included (n=832). The majority of studies were of good quality with a Jadad score of >3. Five trials were in patients on hemodialysis and 4 trials were in patients with stage 2-4 CKD. Trial durations were from 4 weeks to 6 months. The primary outcomes were either changes in intact PTH levels, proteinuria or urine albumin/creatinine ratio changes.

Four studies (n=469) evaluated the effect of paricalcitol compared to placebo on reducing residual albuminuria in patients with CKD. Use of oral paricalcitol 1-2mcg/day was shown to reduce proteinuria (defined as at least a 10% reduction in proteinuria by trials end) (RR 1.68; 95% CI, 1.25 to 2.25; P<0.001).³ Paricalcitol was shown to decrease PTH levels more than placebo (RR 6.37; 95% CI, 4.64 to 8.74; P<0.001) based on 5 trials enrolling 563 patients. Hypercalcemia was found to be more common with paricalcitol compared to placebo (RR 2.25; 95% CI, 0.81 to 6.26; P=0.12). Phosphorous levels were only reported in one trial, so relative risk calculations were not done. Risk of harms were reported in 6 trials and events were not statistically different between paricalcitol and placebo (58 vs. 28; RR 1.28; 95% CI, 0.84 to 1.94; P=0.26). Limitations include the inclusion of studies with different primary endpoints, oral and intravenous routes of paricalcitol administration and lack of evidence on long-term outcomes, such as progression of renal disease, fractures and mortality.

Guidelines:

Kidney Disease: Improving Global Outcomes (KDIGO)

In 2012 the KDIGO recommendations were published to assist in the management, evaluation and treatment of patients with CKD.⁷ This guideline updates the 2002 recommendations. The GRADE system was used to evaluate the literature and assign a strength of recommendation to the quality of evidence. Guidance pertaining to vitamin D analogs will be presented. Recommendations for patients with CKD and GFR <45 ml/min/1.73 m² are baseline serum calcium, phosphate, PTH and alkaline phosphatase levels (low quality evidence). Low evidence recommends maintaining phosphorous levels within the normal range for patients with CKD. Patients with elevated PTH levels should be tested for hyperphosphatemia, hypocalcemia, and vitamin D deficiency. Moderate evidence supports the recommendation of not routinely adding vitamin D supplements or vitamin D analogs without documentation of deficiency or to suppress PTH levels in patients with CKD and not on dialysis.

National Institute for Health and Care Excellence

Recommendations for adults with CKD were updated by NICE in 2014.¹⁰ Recommendations related to CKD and vitamin D analogs were the following: measurement of calcium, phosphorous, PTH and vitamin D levels should be done only in patients with a GFR <30 ml/min/1.73 m²; routine vitamin D supplementation should not be used to manage CKD-mineral and bone disorders; colecalciferol or ergocalciferol are recommended to treat vitamin D deficiency and CKD; if symptoms of CKD-mineral and bone disorders persist after correction of vitamin D deficiency, offer alfacalcidol (not available in the US) or calcitriol to patients with a GFR <30 ml/min/1.73 m²; serum phosphate and calcium levels should be monitored in patients receiving supplements.

VA/DOD Clinical Practice Guideline for the Management of Chronic Kidney Disease in Primary Care

An update of the 2007 Department of Veteran Affairs (VA)/Department of Defense (DoD) guideline on the management of CKD in primary care was published in 2014.⁸ Clinical management strategies pertaining to the use of vitamin D analogs or calcitriol are weakly recommended to not be used in patients with Stage 3 and 4 CKD with elevated PTH by primary care physicians. This recommendation is based on the lack of evidence of kidney, bone or cardiovascular benefit. Referral to a nephrologist is recommended for management of vitamin D analogs.

New Drug Evaluation

Clinical Efficacy: ER calcifediol was studied in two identical placebo-controlled, double-blind randomized controlled trials in a total of 429 patients with stage 3 or 4 CKD and SHPT.⁵ Patients were randomized to ER calcifediol 30 or 60 mcg daily at bedtime or placebo. Patients were an average of 66 years old with a mean iPTH level of 147.2 pg/ml. The primary outcome was a 30% reduction in PTH levels from baseline after 26 weeks. Important secondary outcomes were incidence of hypercalcemia, defined as 2 consecutive serum Ca values >10.3 mg/dl, and hyperphosphatemia, defined as 2 consecutive serum phosphorous levels > 5.5

mg/dl deemed to be study drug related. Study A found reductions in PTH levels in > 30% of patients in 33% of patients taking ER calcifediol compared to 8% taking placebo (p< 0.001, CI not provided) (Table 4). The NNT for this endpoint was 4 patients being treated for 26 weeks. Study B found 34% of patients in the ER calcifediol group and 7% in the placebo group obtained the primary endpoint (p < 0.001, NNT 4)(Table 4).⁵ Lack of details on study methodology limit strength of the findings of these trials and suggest the potential for bias in the results. Long-term studies of health outcomes (i.e., mortality, fractures, parathyroidectomy) would be more helpful to determine the benefit of ER calcifediol.

Clinical Safety:

Discontinuations due to adverse events was 5.7% in the ER calcifediol group compared to 2.8% in the placebo group.⁵ In study B discontinuations due to adverse events was 4.9% in the ER calcifediol group and 5.6% in the placebo group.⁵ Adverse events occurring more commonly with ER calcifediol compared to placebo are presented in Table 3. Six patients taking ER calcifediol experienced hypercalcemia compared to none in the placebo group in a pooled data analysis from study A and B. Utilizing the same pooled analysis, the incidence of hyperphosphatemia was 0.4% in the ER calcifediol group compared to none in the placebo group.

Table 3. Adverse Events Occurring in ≥ 1.4% of Patients Treated with ER Calcifediol Compared to Placebo¹²

Adverse Reaction	Placebo (n=144)	ER Calcifediol (n=285)
Anemia	3.5%	4.9%
Nasopharyngitis	2.8%	4.9%
Blood creatinine increase	1.4%	4.9%
Dyspnea	2.8%	4.2%
Cough	2.1%	3.5%

Table 4. Comparative Evidence Table

Ref./ Study Design	Drug Regimens/ Duration	Patient Population	N	Efficacy Endpoints	ARR/NNT	Safety Outcomes	ARR/ NNH	Risk of Bias/ Applicability
1. Sprague, et al – Study A ⁵ RCT, DB, PC, MC 26 weeks	1. ER Calcifediol 30 or 60 mcg daily (C)* 2. Placebo daily (P) ER Calcifediol dose was 30 mcg for 12 weeks and then 30-60 mcg for 14 weeks. Dose was based on iPTH, vitamin D and calcium levels	<u>Demographics:</u> Age: 65 years Male: 52% White: 63% eGFR: 31.3 ml/min/1.73 m2 iPTH: 144.5 pg/ml 25-Hydroxyvitamin D: 19.7 ng/dl <u>Key Inclusion Criteria:</u> - iPTH >70 pg/ml - serum 25-hydroxyvitamin D <30 ng/ml - stage 3-4 CKD - ≥ 18 years - eGFR ≥15 to < 60 ml/min/1.73m2 - 25-hydroxyvitamin D ≥ 10 - plasma iPTH ≥ 85 and < 500 pg/ml - serum Ca ≥ 8.4 to < 9.8 mg/dl - P ≥ 2.0 to < 5.0 mg/dl <u>Key Exclusion Criteria:</u> - Ca:Cr ratio >0.2 - Nephrotic proteinuria (> 3 mg/ml Cr) - Parathyroidectomy for SHPT - Renal transplant	<u>ITT:</u> C: 141 P: 72 <u>PP:</u> not reported <u>Attrition:</u> 17% total	<u>Primary Endpoint:</u> Reduction in iPTH levels by at least 30%: C: 47 (33%) P: 8 (8%) (CI not provided) p < 0.001	25%/4	Hypercalcemia*: C: 6 (2%) P: 0 (0%) p-value not provided Hyperphosphatemia*: C: 1 (0.4%) P: 0 (0%) p-value not provided Discontinuations due to AE: C: 8 (5.7%) P: 2 (2.8%) p-value not reported Anemia*: C: 7 (4.9%) P: 3 (3.5%) p-value not reported Increased blood Cr*: C: 7 (4.9%) P: 1 (1.4%) p-value not reported * Only pooled data from Study A and B was reported	NA NA NA NA	Risk of Bias (low/high/unclear): <u>Selection Bias:</u> (unclear) randomized 2:1, process not described <u>Performance Bias:</u> (low) blinding of subjects and staff described. Allocation concealment was described. <u>Detection Bias:</u> (unclear) details on outcome assessment was not provided. <u>Attrition Bias:</u> (unclear) 17% of patients from both studies discontinued but details were not provided. ITT analysis was used and dropouts were categorized as non-responders. <u>Reporting Bias:</u> Pre-specified outcomes reported. Study funded by manufacturer. Applicability: <u>Patient:</u> Nutritional vitamin D was used in 14.4% in ER calcifediol group and 13.2% in placebo group (pooled data from Study A and B). <u>Intervention:</u> Labeled dose administered. <u>Comparator:</u> Placebo comparison appropriate. <u>Outcomes:</u> pre-specified surrogate outcomes measured. Outcomes such as mortality and fractures would help to better inform treatment decisions. <u>Setting:</u> Eighty-nine US sites.

<p>2. Sprague, et al – Study B⁵</p> <p>RCT, DB, PC, MC</p> <p>26 weeks</p>	<p>1. ER Calcifediol 30 or 60 mcg daily (C)*</p> <p>2. Placebo daily (P)</p> <p>ER Calcifediol dose was 30 mcg for 12 weeks and then 30-60 mcg for 14 weeks. Dose was based on iPTH, vitamin D and calcium levels</p>	<p>Demographics: Age: 66 years Male: 48% White: 66% eGFR: 31.35 ml/min/1.73 m² iPTH: 151.6 pg/ml 25-Hydroxyvitamin D: 19.6 ng/dl</p> <p>Key Inclusion Criteria:</p> <ul style="list-style-type: none"> - iPTH >70 pg/ml - serum 25-hydroxyvitamin D <30 ng/ml - stage 3-4 CKD - ≥ 18 years - eGFR ≥15 to < 60 ml/min/1.73m² - 25-hydroxyvitamin D ≥ 10 - plasma iPTH ≥ 85 and < 500 pg/ml - serum Ca ≥ 8.4 to < 9.8 mg/dl - P ≥ 2.0 to < 5.0 mg/dl <p>Key Exclusion Criteria:</p> <ul style="list-style-type: none"> - Ca:Cr ratio >0.2 - Nephrotic proteinuria (> 3 mg/ml Cr) - Parathyroidectomy for SHPT - Renal transplant 	<p>ITT: C: 144 P: 72</p> <p>PP: not reported</p> <p>Attrition: 17% total</p>	<p>Primary Endpoint: Reduction in iPTH levels by at least 30%: C: 49 (34%) P: 5 (7%) (CI not reported) P < 0.001</p>	<p>27%/4</p>	<p>Hypercalcemia*: C: 6 (2%) P: 0 (0%) p-value not provided</p> <p>Hyperphosphatemia*: C: 1 (0.4%) P: 0 (0%) p-value not provided</p> <p>Discontinuations due to AE: C: 7 (4.9%) P: 4 (5.6%) p-value not reported</p> <p>Anemia*: C: 7 (4.9%) P: 3 (3.5%) p-value not reported</p> <p>Increased blood Cr*: C: 7 (4.9%) P: 1 (1.4%) p-value not reported</p> <p>* Only pooled data from Study A and B was reported</p>	<p>NA</p> <p>NA</p> <p>NA</p> <p>NA</p> <p>NA</p>	<p>Risk of Bias (low/high/unclear): Selection Bias: (unclear) randomized 2:1, process not described Performance Bias: (low) blinding of subjects and staff described. Allocation concealment was described. Detection Bias: (unclear) details on outcome assessment was not provided. Attrition Bias: (unclear) 17% of patients from both studies discontinued but details were not provided. ITT analysis was used and dropouts were categorized as non-responders. Reporting Bias: Pre-specified outcomes reported. Study funded by manufacturer.</p> <p>Applicability: Patient: Nutritional vitamin D was used in 14.4% in ER calcifediol group and 13.2% in placebo group (pooled data from Study A and B). Intervention: Labeled dose administered. Comparator: Placebo comparison appropriate. Outcomes: Outcomes: pre-specified surrogate outcomes measured. Outcomes such as mortality and fractures would help to better inform treatment decisions. Setting: Eighty-nine US sites.</p>
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Abbreviations [alphabetical order]: ARR = absolute risk reduction; Ca = calcium; CI = confidence interval; CKD = chronic kidney disease; Cr = creatinine; eGFR = estimated glomerular filtration rate; iPTH = intact parathyroid hormone; ITT = intention to treat; MC – multi-center; mITT = modified intention to treat; MR = modified release; N = number of subjects; NA = not applicable; NNH = number needed to harm; NNT = number needed to treat; P = phosphorous; PP = per protocol; SHPT = secondary hyperparathyroidism.

References:

1. Palmer SC, McGregor DO, Craig JC, Elder G, Macaskill P, Strippoli GF. Vitamin D compounds for people with chronic kidney disease not requiring dialysis. *Cochrane Database Syst Rev*. 2009;(4):CD008175. doi:10.1002/14651858.CD008175.
2. Palmer SC, McGregor DO, Craig JC, Elder G, Macaskill P, Strippoli GF. Vitamin D compounds for people with chronic kidney disease requiring dialysis. *Cochrane Database Syst Rev*. 2009;(4):CD005633. doi:10.1002/14651858.CD005633.pub2.
3. Cheng J, Zhang W, Zhang X, Li X, Chen J. Efficacy and Safety of Paricalcitol Therapy for Chronic Kidney Disease: A Meta-Analysis. *CJASN*. 2012;7(3):391-400. doi:10.2215/CJN.03000311.
4. Ong LM, Narayanan P, Goh HK, et al. Randomized controlled trial to compare the efficacy and safety of oral paricalcitol with oral calcitriol in dialysis patients with secondary hyperparathyroidism. *Nephrology*. 2013;18(3):194-200. doi:10.1111/nep.12029.
5. Sprague SM, Crawford PW, Melnick JZ, et al. Use of Extended-Release Calcifediol to Treat Secondary Hyperparathyroidism in Stages 3 and 4 Chronic Kidney Disease. *Am J Nephrol*. 2016;44(4):316-325. doi:10.1159/000450766.
6. Coyne DW, Goldberg S, Faber M, Ghossein C, Sprague SM. A randomized multicenter trial of paricalcitol versus calcitriol for secondary hyperparathyroidism in stages 3-4 CKD. *Journal of The American Society of Nephrology*. 2014;9(9):1620-1626. doi:10.2215/CJN.10661013.
7. 3b2b_npg_kisup_3_1_fmiii 3..3 - KDIGO_2012_CKD_GL.pdf. http://www.kdigo.org/clinical_practice_guidelines/pdf/CKD/KDIGO_2012_CKD_GL.pdf. Accessed November 8, 2016.
8. VA. VA/DoD clinical practice guideline for the management of chronic kidney disease in primary care. | National Guideline Clearinghouse. <https://www.guideline.gov/summaries/summary/48951/vadod-clinical-practice-guideline-for-the-management-of-chronic-kidney-disease-in-primary-care?q=vitamin+d+analogs>. Accessed November 8, 2016.
9. Hahn D, Hodson EM, Craig JC. Interventions for metabolic bone disease in children with chronic kidney disease. *Cochrane Database Syst Rev*. 2015;(11):CD008327. doi:10.1002/14651858.CD008327.pub2.
10. Chronic kidney disease in adults: assessment and management | Guidance and guidelines | NICE. <https://www.nice.org.uk/guidance/cg182?unlid=616689932016111443858>. Accessed December 5, 2016.
11. Block GA, Klassen PS, Lazarus JM, Ofsthun N, Lowrie EG, Chertow GM. Mineral Metabolism, Mortality, and Morbidity in Maintenance Hemodialysis. *JASN*. 2004;15(8):2208-2218. doi:10.1097/01.ASN.0000133041.27682.A2.
12. Rayaldee (calcifediol) [Prescribing Information]. Miami, FL: OPKO Pharmaceuticals, LLC, 2016.
13. Zemplar (paricalcitol) [Prescribing Information]. North Chicago, IL: AbbVie Inc., October 2016.
14. Hectoral® (doxercalciferol) [Prescribing Information]. North Chicago, IL: Abbott Laboratories, May 2005.
15. Rocaltrol® (calcitriol) [Prescribing Information]. Parsippany, NJ: Validus Pharmaceuticals LLC, August 2010.

Appendix 1: Specific Drug Information

Table 5. Clinical Pharmacology and Pharmacokinetics

Drug Name	Mechanism of Action	Absorption	Metabolism/Excretion	Pharmacokinetics (mean)
Calcitriol (Rocaltrol®)	Synthetic vitamin D analog which regulates absorption of calcium from the GI tract and utilization throughout the body.	Rapidly absorbed from the intestine	<ul style="list-style-type: none"> - 24-hydroxylase and hydroxylation - enterohepatic recycling and biliary excretion 	<ul style="list-style-type: none"> • Half-life: 5-8 hours • Cmax: not provided • AUC: 60 pg/mL at 2 • Vd: not provided • 99% protein bound
Doxercalciferol (Hectoral®)	Synthetic vitamin D analog that undergoes activation to the biologically active form of vitamin D2.	Rapidly absorbed from the intestine	<ul style="list-style-type: none"> - Metabolized by CYP27 in the liver and by hydroxylation in the kidney 	<ul style="list-style-type: none"> • Half-life: 32-37 hours • Cmax: at 11-12 hours (levels not provided) • AUC: 60 pg/mL • Vd: not provided
Paricalcitol (Zemplar)	Synthetic vitamin D2 analog of calcitriol resulting in reduced PTH synthesis and secretion.	72-86%	<ul style="list-style-type: none"> - Metabolized by CYP24, CYP3A4 and UGT1A4 - Excreted in the feces 	<ul style="list-style-type: none"> - Half-life: 4-6 hours - Cmax: not provided - AUC: not provided - Vd: 34 L - >98% protein bound
Calcifediol (Rayaldee)	Converted to calcitriol in the kidney resulting in increased intestinal absorption of calcium and phosphorous and decreased PTH synthesis.	Increased absorption with high fat, high calorie meal	<ul style="list-style-type: none"> - Metabolized by CYP450 primarily in the kidney - Excreted by fecal and biliary route 	<ul style="list-style-type: none"> - Half-life: 11 days - Cmax: not provided - AUC: not provided - Vd: 8.8. L - >98% protein bound

Use in Specific Populations:

Calcitriol – use in patients with renal insufficiency (nephrotic syndrome and undergoing dialysis) were found to have lower predose and peak calcitriol levels with at least double the half-life compared to normal subjects. No specific dosing recommendations were provided.

Calcifediol – use in pediatric patients has not been studied.

Doxercalciferol – use in pediatric patients has not been studied. Use with caution in patients with impaired hepatic function.

Paricalcitol – not recommended to be used during breast feeding.

Drug Safety:

Black Boxed Warnings:

There are no black boxed warnings for vitamin D analogs.

Contraindications:

Calcifediol – none

Calcitriol, doxercalciferol and paricalcitol – do not use in patients with hypercalcemia or evidence of vitamin D toxicity.

Table 6. Summary of Warnings and Precautions

Warning/Precaution	Calcitriol	Doxercalciferol	Paricalcitol	Calcifediol
Hypercalcemia	X	X	X	X
Hyperphosphatemia		X		
Adynamic bone disease				X
Digitalis toxicity			X	X
Increased serum creatinine	X			
Oversuppression of PTH		x		
Aluminum overload			X	

Appendix 2: Medline Search Strategy

Database(s): **Ovid MEDLINE(R) without Revisions** 1996 to November Week 3 2016

Search Strategy:

#	Searches	Results	Annotations
1	Calcitriol/	7143	
2	paricalcitol.mp.	478	
3	calcifediol.mp. or Calcifediol/	1918	
4	doxercalciferol.mp.	79	
5	1 or 2 or 3 or 4	9039	
6	limit 5 to (english language and humans)	6488	
7	limit 6 to (clinical trial, all or clinical trial or comparative study or meta analysis or practice guideline or pragmatic clinical trial or randomized controlled trial or systematic reviews)	1561	
8	limit 7 to yr="2007 -Current"	739	

Vitamin D Analogs

Goal(s):

- Restrict use of non-preferred vitamin D analogs to populations in which there is evidence of benefit.

Length of Authorization:

Up to 12 months

Requires PA:

- Non-preferred drugs

Covered Alternatives:

- Current PMPDP preferred drug list per OAR 410-121-0030 at www.orpdl.org
- Searchable site for Oregon FFS Drug Class listed at www.orpdl.org/drugs/

Approval Criteria		
1. What diagnosis is being treated?	Record ICD10 code.	
2. Will the provider switch to a preferred product? Note: Preferred products are reviewed and designated as preferred agents by the Oregon Pharmacy and Therapeutics Committee based on published medical evidence for safety and efficacy. Preferred products are available without a PA.	Yes: Inform prescriber of covered alternatives in the class	No: Go to #3
3. Does the patient have secondary hyperparathyroidism and stage 3 or higher chronic kidney disease or on dialysis?	Yes: Go to #4	No: Pass to RPh. Deny; medical appropriateness
4. Is the request for extended-release calcifediol and the patient has stage 5 chronic kidney disease or is on dialysis?	Yes: Pass to RPh. Deny; medical appropriateness	No: Go to #5

Approval Criteria

5. Has the patients tried and failed calcitriol or have contraindications to this treatment?

Yes: Approve for 12 months

No: Pass to RPh. Deny; recommend trial of calcitriol

P&T Review: 1/17 (KS)
Implementation: TBD

DRAFT