National Formulary Review
Paricalcitol (Zemplar®) Intravenous and Oral

VHA Pharmacy Benefits Management Strategic Health Care Group and the Medical Advisory Panel

Executive Summary

- **Indications:** Paricalcitol (Zemplar®, Abbott Laboratories) is a synthetic vitamin D analog indicated for the prevention and treatment of secondary hyperparathyroidism (SHPT) in patients with chronic kidney disease (CKD). Paricalcitol is available as an injectable product approved for use in patients with chronic renal failure and a recently approved oral formulation indicated for patients with CKD Stage 3 and 4.

- **Efficacy:** (Injectable paricalcitol) Two short-term randomized, double-blind, placebo-controlled trials in patients with end-stage renal disease (ESRD) on hemodialysis evaluated the effect of injectable paricalcitol on reducing intact parathyroid hormone (iPTH). A trial of 35 patients reported that after 4 weeks treatment, paricalcitol resulted in a decrease in iPTH of $\geq$ 30% from maximum baseline in 68% of patients receiving 0.04-0.24 mcg/kg and in 83% of patients receiving 0.16 or 0.24 mcg/kg (vs. 15.4% on placebo). Another trial of 12 weeks duration reported a reduction in iPTH of $\geq$ 30% in 68% of patients (27/40) on paricalcitol (mean dose 0.12 mcg/kg) compared to 8% (3/38) of those receiving placebo (P<0.001; calculated NNT=2). The long-term effect of injectable paricalcitol has been evaluated in two open-label trials and one retrospective evaluation. In one trial of 13 months duration, the iPTH was reduced from a baseline of 668.4$\pm$47.66 pg/mL to 259.1$\pm$34.13 pg/mL in 67 patients treated with paricalcitol with 52% of these patients achieving a target iPTH of 100-300 pg/mL. The mean dose for all treated patients (N=164) was 0.10 mcg/kg. Another trial reported that a dose ratio of paricalcitol to calcitriol of 4:1 resulted in a rapid decrease in iPTH over 2 months of therapy (baseline 1008$\pm$114 pg/mL to 194$\pm$24 pg/mL), with 50% developing hypercalcemia. The remaining 23 patients were dosed at a 3:1 ratio of paricalcitol to calcitriol. After 16 months of treatment in 33 patients, the iPTH was reduced to 165$\pm$24 pg/mL (P<0.001) compared to a baseline iPTH (just prior to discontinuation of calcitriol) of 901$\pm$58 pg/mL. A retrospective evaluation reported an increase in iPTH from a baseline of 705$\pm$423 pg/mL to 821$\pm$480 pg/mL (P=0.37) in 16 patients treated with a mean dose of paricalcitol of 0.13$\pm$0.12 mcg/kg for a mean of 18 months. The authors reported that 69% of patients had their doses of paricalcitol withheld (majority dosed 4:1 ratio paricalcitol to calcitriol) an average of 17% of the time due to elevations in serum calcium or calcium phosphorus product (Ca X P).

  (Oral paricalcitol) Randomized controlled trials evaluating the efficacy of oral paricalcitol have only been published in abstract form. Pooled results of three double-blind, randomized, multi-center, placebo-controlled trials of 24 weeks duration in 220 patients with CKD Stage 3 and 4 reported two consecutive decreases in iPTH $\geq$ 30% from baseline in 91% of patients treated with oral paricalcitol (mean dose not provided) compared to 13% of patients receiving placebo (P<0.001).

  (Injectable paricalcitol vs. calcitriol) One double-blind, randomized controlled trial reported the reduction in iPTH $\geq$ 50% from baseline was achieved in approximately 60% of patients in a trial of 263 patients with ESRD on hemodialysis receiving either paricalcitol or calcitriol (dose escalation ratio 4:1) for up to 32 weeks of treatment. The mean decrease in iPTH $\geq$ 50% occurred earlier with paricalcitol compared to calcitriol (week 15 vs. 23, respectively). Results for the pre-specified endpoint of hypercalcemia and/or elevated Ca X P > 75 were similar. A retrospective database evaluation of 11,443 patients with ESRD reported that patients on paricalcitol had a reduction in the number of hospital admissions per year compared to calcitriol (2.4 vs. 2.61, respectively). Patients on paricalcitol were also hospitalized for a mean of 17.2 days compared to 19.8 days for patients on calcitriol. According to the intent-to-treat analysis (patients started on paricalcitol or calcitriol), patients on paricalcitol were hospitalized for 6.84 fewer days (P<0.0001) and had 0.642 fewer hospital admissions per year (P<0.0001) compared to calcitriol. Survival was evaluated in a historical cohort study. Based on 36 months of follow-up, treatment with paricalcitol was associated with a mortality rate of 0.180 per person year compared to 0.223 per person year with calcitriol (rate ratio 0.80 95% CI 0.77 to 0.84; P<0.001). The mean doses at 12 months of vitamin D treatment were 1.3$\pm$1.2 mcg calcitriol and 4.3$\pm$2.8 mcg paricalcitol.

- **Safety and Laboratory Monitoring:** Treatment with paricalcitol may result in an elevated calcium and/or Ca X P. Elevations in serum phosphorus may also occur. Patients should be monitored for hypercalcemia, an elevated Ca X P, hyperphosphatemia, and for oversuppression of iPTH. Dose adjustments should be made based on these laboratory parameters. Discontinuation of therapy due to adverse effects occurred in approximately 6% of patients receiving either the oral or injectable formulation of paricalcitol (compared to 2 to 4% on placebo).

- **Dose:** (Injectable) According to the manufacturer, the initial recommended dose is 0.04 mcg/kg to 0.1 mcg/kg (2.8 to 7 mcg), administered during dialysis and not more often than every other day. Dose adjustments should be made according to iPTH measured at 2 to 4 week intervals with a recommended increase by 2 to 4 mcg if the iPTH remains the same, is increased, or decreased by < 30%. Clinical practice guideline recommendations for dosing paricalcitol include 2.5 to 5 mcg if iPTH 300 to 600 pg/mL; 6 to 10 mcg if the iPTH is 600 to 1000 pg/mL; and 10 to 15 mcg per hemodialysis if the iPTH is > 1000 pg/mL.

  (Oral) For patients with CKD Stage 3 or 4 and a baseline iPTH ≤ 500 pg/mL, the initial recommended dose of paricalcitol capsules is 1 mcg daily or 2 mcg administered three times per week; a dose of 2 mcg daily or 4 mcg three times per week is recommended in patients with a baseline iPTH > 500 pg/mL. Dose adjustments should be based on iPTH levels evaluated at 2 to 4 week intervals with a recommended increase by 2 mcg if the iPTH remains the same, is increased, or decreased by < 30%.

- **Drug Cost:** The estimated annual drug cost for oral paricalcitol capsules is approximately $1,000 to $2,000 per patient depending on the dose, and approximately $1,700 to nearly $2,200 for the injectable formulation. According to VA data, there would be an annual increase of approximately $1.5 to $3 million if 25% to 50% of current utilization of oral calcitriol capsules were converted to oral paricalcitol capsules (regardless of the approved indication); and $150,000 to $300,000 if 25% to 50% of the utilization of injectable calcitriol were changed to the injectable formulation of paricalcitol.

- **Recommendations:** Due to the lack of evidence from head to head prospective randomized controlled trials demonstrating a benefit of paricalcitol over the formulary agent, calcitriol, it has been recommended that paricalcitol (both injectable and oral formulations) not be added to the VA National Formulary. Although not confirmed in prospective randomized controlled trials with another vitamin D analog as the comparator, a nonformulary vitamin D analog (doxercalciferol, paricalcitol) may be considered in patients with hypercalcemia despite dosage adjustment of the formulary agent (calcitriol).

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Introduction[1-6]

Paricalcitol (Zemplar®, Abbott Laboratories) is a synthetic vitamin D analog available in injectable (FDA approved April 1998) and oral formulations (FDA approved May 2005). Both formulations of paricalcitol are indicated for the prevention and treatment of secondary hyperparathyroidism (SHPT) in patients with chronic kidney disease (CKD); the injectable formulation is approved for use in patients with chronic renal failure, and the oral formulation is indicated for patients with stage 3 and 4 CKD.[1,2] A request for VA national formulary (VANF) addition has been made for both the injectable and oral formulations of paricalcitol.

There has been interest in vitamin D analogs such as paricalcitol and doxercalciferol due to the concern of hypercalcemia or impaired kidney function with calcitriol;[3] however, this has yet to be confirmed in long-term, randomized controlled comparison trials in humans. Of the vitamin D analogs (calcitriol, doxercalciferol, paricalcitol), all are available as injectable and oral formulations (refer to table with FDA approved indications below and Appendix 3 for VA utilization). Both oral and injectable formulations of calcitriol are listed on the VANF. All formulations of doxercalciferol and paricalcitol are available through the nonformulary process.

FDA Approved Indications for the Vitamin D Analogs in Patients with SHPT and CKD

	Calcitriol	Doxercalciferol	Paricalcitol
Description	Synthetic vitamin D analog and active form of vitamin D_3	Synthetic analog of vitamin D_2 requiring activation in the liver but not the kidneys	Synthetic vitamin D analog and activator of the vitamin D receptor
FDA Indication	**Oral:** Management of SHPT and resultant metabolic bone disease in patients with moderate to severe chronic renal failure (CrCl 15-55 mL/min) not yet on dialysis and for the management of hypocalcemia and resultant metabolic bone disease in patients on chronic renal dialysis	**Oral:** Treatment of SHPT associated with CKD Stage 3 and 4 and in patients with CKD on dialysis	**Oral:** Prevention and treatment of SHPT associated with CKD Stage 3 and 4
	Injectable: Management of hypocalcemia in patients on chronic renal dialysis	**Injectable:** Prevention of excessive PTH production in patients with chronic renal failure on dialysis	**Injectable:** Prevention and treatment of SHPT associated with chronic renal failure

Low levels of 25-hydroxyvitamin D, or 25(OH)D, are common in patients with CKD and those on dialysis, possibly due to less exposure to sunlight, reduced endogenous synthesis of vitamin D_3 in the skin after sunlight exposure, and decreased intake of vitamin D in the diet. In addition, there may be a higher need for vitamin D in patients with CKD due to urinary loss of 25(OH)D, high levels of vitamin D binding protein, and a low calcium diet that can lead to conversion of $25(OH)_2$ to 1,25-dihydroxyvitamin D_3 ($1,25(OH)_2D_3$).[3] Patients with CKD often have an increase in parathyroid hormone (PTH) that is thought to be due to a reduced serum calcium and/or to a decrease in $1,25(OH)_2D_3$.[3,4] Possible explanations for the hypocalcemia include: phosphate retention; skeletal resistance to the calcemic action of PTH; and altered metabolism of vitamin D. As kidney function declines, the number of vitamin D receptors and calcium-sensing receptors in the parathyroid gland decrease, making them more resistant to the effects of vitamin D and calcium.[3] The effect of $1,25(OH)_2D_3$ on the parathyroid gland may be via direct suppression of the parathyroid gland; making the parathyroid gland more susceptible to calcium; and decreasing the production of PTH through an increase in the degradation of PTH mRNA.[3]

Secondary hyperparathyroidism is reported to be common in patients with CKD with a glomerular filtration rate (GFR) < 60 mL/min/1.73m^2 (CKD Stage 3 to 5). Secondary hyperparathyroidism may lead to metabolic bone disease, with osteitis fibrosa seen in patients with intact PTH (iPTH) levels over 400 pg/mL, although high-turnover bone lesions may also occur at lower levels.[3]

Based on the National Kidney Foundation Kidney Disease Outcomes Quality Initiative (K/DOQI) Clinical Practice Guidelines for Bone Metabolism and Disease in Chronic Kidney Disease,[3] recommendations for patients with SHPT include restriction of dietary phosphate, the use of phosphate-binders, and vitamin D sterols in patients with an inadequate response or with iPTH levels > 300 pg/mL. The calcimimetics (e.g., cinacalcet) are a new class of agents that decrease secretion of PTH and are also approved for the treatment of patients with SHPT.[5]

As the GFR falls below 60 mL/min/1.73m^2, PTH levels begin to increase. Target levels of iPTH according to the GFR (or by CKD Stage) are as follows:[3]

Stage CKD	GFR (mL/min/1.73m^2)	Target iPTH (pg/mL)
3	30-59	35-70
4	15-29	70-110
5	< 15 or dialysis	150-300

Recommendations for the use of active vitamin D sterols in the treatment of SHPT are also according to CKD Stage and for patients with Stage 3 or 4 CKD, are according to the following parameters:[3]

Stage CKD	GFR (mL/min/1.73m^2)	25(OH)-Vitamin D (ng/mL)	iPTH (pg/mL)	Corrected Total Calcium (mg/dL)	Serum Phosphorus (mg/dL)
3	30-59	> 30	> 70	< 9.5	< 4.6
4	15-29	> 30	> 110	< 9.5	< 4.6

Monitor serum calcium and phosphorus at least monthly after starting therapy for the first 3 months, and then every 3 months. Plasma PTH should be monitored at least every 3 months for the first 6 months, then every 3 months during chronic therapy.

The initial oral dose for calcitriol is 0.25 mcg per day and for doxercalciferol is 2.5 mcg three times per week.[3] The manufacturer of paricalcitol recommends an initial oral dose of either 1 mcg daily or 2 mcg three times per week for patients with an iPTH ≤ 500 pg/mL and 2 mcg daily or 4 mcg three times per week for those patients with a serum iPTH > 500 pg/mL.[2] Recommendations for adjusting oral vitamin D sterols are in the table below.[3]

If iPTH Below Target for Stage CKD (above)	If Corrected Total Calcium > 9.5 mg/dL	If Serum Phosphorus > 4.6 mg/dL
Hold until iPTH increases to within target range, then continue at half dose (if lowest dose, use alternate day therapy)	Hold until calcium < 9.5, then continue at half dose (if lowest dose, use alternate day therapy)	Hold vitamin D, begin or increase phosphate binder until phosphorus ≤ 4.6, then continue vitamin D at previous dose

Patients with Stage 5 CKD (GFR < 15 mL/min/1.73m^2) or those on dialysis, with iPTH > 300 pg/mL, should be treated with vitamin D therapy according to the following recommendations:[3]

iPTH (pg/mL)	Serum Calcium (mg/dL)	Serum Phosphorus (mg/dL)	Ca X P	Calcitriol (per HD)	Doxercalciferol (per HD)	Paricalcitol (per HD)
300-600	< 9.5	< 5.5	< 55	IV: 0.5-1.5 mcg PO: 0.5-1.5 mcg	IV: 2 mcg PO: 5 mcg	IV: 2.5-5.0 mcg PO: NA
600-1000	< 9.5	< 5.5	< 55	IV: 1.0-3.0 mcg PO: 1-4 mcg	IV: 2-4 mcg PO: 5-10 mcg	IV: 6.0-10 mcg PO: NA
> 1000	< 10	< 5.5	< 55	IV: 3.0-5.0 mcg PO: 3-7 mcg	IV: 4-8 mcg PO: 10-20 mcg	IV: 10-15 mcg PO: NA

After starting therapy or dosage change, monitor serum calcium and phosphorus at least every 2 weeks for 1 month, then every month. Plasma PTH should be monitored monthly for at least 3 months, then every 3 months once at target levels.
HD=hemodialysis treatment; patients receiving peritoneal dialysis can be given oral calcitriol (0.5-1.5 mcg) or doxercalciferol (2.5-5 mcg) 2 to 3 times per week or oral calcitriol 0.25 mcg daily
NA=oral dose not approved for use in patients with Stage 5 CKD

Pharmacology[1,2]

Paricalcitol (19-nor-1α-25 dihydroxyvitamin D_2) is a synthetic vitamin D analog. Through binding of the vitamin D receptor, paricalcitol activates the vitamin D pathway, thereby reducing elevated PTH levels through inhibiting synthesis and secretion of PTH in patients with SHPT due to CKD.

Pharmacokinetics[1,2]

Paricalcitol Formulation	C_{max}	Protein Binding	t½	Metabolism	Elimination	Excretion	Food Effect
Oral	0.11±0.04 ng/mL[a] (4 mcg dose) 0.06±0.01 ng/mL[b] (3 mcg dose)	≥ 99.8%	4-6 hrs[d] 17 hrs[a] 20 hrs[b]	Hepatic and non-hepatic enzymes including CYP24, CYP3A4, UGT1A4	Hepatobiliary	70% feces 18% urine	High fat meal C_{max} and AUC unchanged[d] Food effect T_{max} delayed 2 hrs
Injectable	1850±664 pg/mL[c] (0.24 mcg/kg)	> 99.9%	15 hrs[c]	Several unknown metabolites	Hepatobiliary	74% feces 18% urine	NA

[a] Patients with stage 3 CKD
[b] Patients with stage 4 CKD
[c] Patients with chronic renal failure
[d] Healthy patients

FDA Approved Indication(s)[1,2]

Both formulations of paricalcitol are indicated for the prevention and treatment of SHPT in patients with CKD; the injectable formulation is approved for use in patients with chronic renal failure, and the oral formulation is indicated for patients with stage 3 and 4 CKD.

Dosage and Administration (Manufacturer Recommendations)[1,2]

Oral capsules are available in 1 mcg, 2 mcg, and 4 mcg doses to be administered daily or three times per week (with similar total weekly dose). The oral capsules may be given without regard to meals.

iPTH	Daily Dose	Dose Given 3x/wk[a]
Baseline		
≤ 500 pg/mL	Initial: 1 mcg	Initial: 2 mcg
> 500 pg/mL	Initial: 2 mcg	Initial: 4 mcg
Titration		
Same, ↑, or ↓ by < 30%[b]	Increase by 1 mcg	Increase by 2 mcg
↓ by ≥ 30% or ≤ 60%[b]	Maintain initial dose	Maintain initial dose
↓ by > 60% or iPTH < 60 pg/mL[b]	Decrease by 1 mcg	Decrease by 2 mcg

[a] Not to be administered more often than every other day
[b] Evaluated at 2 to 4 week intervals

Injectable formulation is available in 2 mcg/mL (1 mL), 5 mcg/mL (1 mL), and 5 mcg/mL (2 mL). The injectable formulation should be administered as a bolus dose. Any unused portion should be discarded.

Initial recommended dose is 0.04 mcg/kg to 0.1 mcg/kg (2.8 to 7 mcg) any time during dialysis and not to be administered more often than every other day.

iPTH	Titration
Same, ↑, or ↓ by < 30%[a]	Increase by 2 to 4 mcg
↓ by > 30% or < 60%; or iPTH 1.5 to 3 times ULN[b]	Maintain dose
↓ by > 60%	Decrease dose

[a] Evaluated at 2 to 4 week intervals
[b] ULN=upper limit normal

Adverse Events[1,2]

Adverse Event[a]	Placebo (n=113)	Paricalcitol Oral (n=107)	Placebo (n=51)	Paricalcitol Inj. (n=62)
Overall	76%	82%	78%	71%
Body as a Whole	35%	46%		
Accidental injury	9%	7%		
Pain	7%	6%		
Viral infection	7%	7%		
Allergic reaction	6%	2%		
Headache	5%	4%		
Chills			0%	5%
Fever			2%	5%
Flu			4%	5%
Sepsis			2%	5%
Cardiovascular	17%	25%		
Hypertension	7%	4%		
Hypotension	5%	3%		
Digestive	27%	27%		
Diarrhea	7%	4%		
Nausea	6%	4%	8%	13%
Vomiting	6%	4%	4%	8%
Gastrointestinal bleeding			2%	5%
Metabolic/Nutritional	30%	22%		
Edema	7%	4%	0%	7%
Uremia	7%	8%		
Musculoskeletal	8%	11%		
Arthritis	5%	1%		
Nervous	11%	17%		
Dizziness	5%	4%		
Vertigo	5%	0%		
Light-headedness			2%	5%
Respiratory	22%	24%		
Pharyngitis	10%	11%		
Rhinitis	5%	4%		
Pneumonia			0%	5%
Skin and Appendages	9%	16%		
Rash	6%	3%		
DC due to AE	4%	6%	2%	6.5%

[a]Adverse events reported in double-blind, placebo-controlled trials that occurred at an incidence of ≥ 5% with paricalcitol (injectable: 4 studies of patients with chronic renal failure; oral: 3 studies of ~ 6 months in duration in patients with CKD Stage 3 or 4)

Post-marketing experience (injectable formulation): Adverse events including taste perversion (i.e., metallic taste) and allergic reactions (i.e., rash, urticaria, pruritus) have been reported rarely.

Look-alike/Sound-alike Error Risk Potential

As part of a pilot program, the VA PBM and Center for Medication Safety queried a multi-attribute drug product search engine for similar sounding and appearing drug names based on orthographic and phonological similarities, as well as similarities in dosage form, strength and route of administration. By incorporating similarity scores as well as clinical judgment, it was determined that the following drug names may pose as potential sources of drug name confusion.

Drug Name	Potential Name Confusion	Potential Severity	Probability	SAC[a]
Paricalcitol (generic)	Calcitriol	Minor	Uncommon	1
	Ergocalciferol	Minor	Remote	1
	Paclitaxel	Minor	Remote	1
Zemplar (brand)	Remular	Minor	Remote	1
	Tempra	Minor	Remote	1
	Gemzar	Minor	Remote	1
	Zanosar	Minor-Moderate	Remote	1

[a] SAC=Safety Assessment Code (3=highest risk; 2=intermediate risk; 1=lowest risk)

Contraindications[1,2]

Paricalcitol is contraindicated in patients with vitamin D toxicity, hypercalcemia, or hypersensitivity to any component of the drug.

Warnings/Precautions[1,2]

Overdosage of paricalcitol may result in hypercalcemia requiring emergency intervention. Early signs and symptoms of vitamin D intoxication include: weakness, headache, somnolence, nausea, vomiting, dry mouth, constipation, muscle or bone pain, or a metallic taste. The following can be late signs or symptoms of intoxication: anorexia, weight loss, calcific conjunctivitis, pancreatitis, photophobia, rhinorrhea, pruritus, hyperthermia, decreased libido, increased BUN, hypercholesterolemia, increased AST and ALT, ectopic calcification, hypertension, arrhythmias, somnolence, death, or overt psychosis (rare).

General: Concomitant administration of paricalcitol with digitalis compounds should be used with caution as hypercalcemia may potentiate digitalis toxicity. Oversuppression of PTH may result in adynamic bone disease.

Patient Information: The patient and caregiver should be informed of the importance of adherence to the medication regimen, and to dietary instructions including phosphorus restriction. Although phosphate binders may be prescribed, patients should avoid excessive use of products containing aluminum. The symptoms of hypercalcemia should be discussed with the patient and caregiver.

Carcinogenesis, Mutagenesis, Fertility Impairment: In mice, there was an increase in the incidence of uterine leiomyoma and leiomyosarcoma with subcutaneous doses of paricalcitol of 1 to 10 mcg/kg (<1-3 times the maximum recommended weekly dose in humans) in a study of 104 weeks, and was significant compared to controls at the highest dose. In rats, there was an increase in the incidence of benign adrenal pheochromocytoma with subcutaneous doses of paricalcitol of 0.15 to 1.5 mcg/kg ($\leq$1 times the maximum recommended weekly dose in humans) in a study of 104 weeks. Paricalcitol did not show an effect on the incidence of tumors in carcinogenic studies in rodents, except for benign lesions associated with chronic hypercalcemia. Paricalcitol tested negative for mutagenic activity in *in vitro* and *in vivo* studies. In male or female rats, fertility was not affected with paricalcitol at intravenous doses of 13 times the maximum recommended dose in humans.

Pregnancy Category C: Paricalcitol should only be used in pregnant women if the benefit outweighs the risk to the fetus. There have not been any adequate well-controlled studies in pregnant women. In rabbits, there was a minimal decrease in fetal viability of 5% when paricalcitol was given at a dose 0.5 times the human dose; and in rats at two times the dose given to humans. In rats, there was a significant increase in fetal mortality when administered at 13 times the human dose. There were no teratogenic or other developmental effects on the offspring.

Nursing Mothers: Paricalcitol has been found in the milk during studies with rats. It is not known whether the drug is excreted in human milk. Since many drugs are excreted in human milk, it is recommended that the risk versus benefit be taken into consideration when determining whether to discontinue nursing or discontinue the drug.

Demographics (Age): In clinical trials with paricalcitol, there was no difference in the overall safety or effectiveness between patients 65 years of age or older compared to younger patients. Forty-nine percent of patients included in the clinical trials with paricalcitol capsules were 65 years of age or older, and17% of patients were 75 years of age or older. The use of paricalcitol capsules in pediatric patients has not been studied. The safety and effectiveness of the injectable form of paricalcitol was studied in 29 patients aged 5 to 19 years with end stage renal disease (ESRD) on hemodialysis. It was reported that 60% of patients on paricalcitol had a 30% decrease in iPTH from baseline on two consecutive evaluations compared with 21% of patients in the placebo group. A lower percent of patients experienced at least one serum calcium level > 10.3 mg/dL in the paricalcitol group vs. placebo (23% vs. 31%, respectively, although a higher percent had at least one Ca X P > 72 mg/dL^2 (40% vs. 14%, respectively).

Drug Interactions[1,2]

As digitalis toxicity is potentiated by hypercalcemia, digitalis compounds should be used with caution in patients on paricalcitol. A drug interaction study with paricalcitol capsules in healthy patients on ketoconazole showed that the $AUC_{0-\infty}$ of paricalcitol was approximately doubled. The mean half-life was also increased to 17.0 hours, compared to 9.8 hours without concomitant ketoconazole. Dosage adjustments or monitoring of iPTH and calcium is recommended in patients initiated on strong inhibitors of CYP3A4, or when therapy is discontinued. Other strong inhibitors of CYP3A (e.g., atazanavir, clarithromycin, indinavir, itraconazole, nefazodone, nelfinavir, ritonavir, saquinavir, telithromycin, voriconazole) should be used with caution if prescribed with paricalcitol. According to the manufacturer, paricalcitol should not inhibit drugs metabolized by CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP2E1, or CYP3A; and should not induce drugs metabolized by CYP2B6, CYP2C9, or CYP3A. The absorption of paricalcitol capsules may be impaired if taken with medications such as cholestyramine that interfere with the absorption of fat-soluble vitamins.

Efficacy Measures

The efficacy measures relating to the effect of injectable paricalcitol on laboratory values in two publications of short-term randomized, placebo-controlled trials[7-8] included the primary endpoints: reduction of serum iPTH; and secondary endpoints: effect on serum calcium levels, phosphorus levels, Ca X P, and alkaline phosphatase.

Other trials reporting the effects of paricalcitol on the above laboratory parameters included two long-term, open label trials[9-10] and one retrospective evaluation[11] with injectable paricalcitol, and one trial with oral paricalcitol (published in abstract form).[12] Comparison trials of injectable paricalcitol and calcitriol reported results on serum iPTH,[13] hospitalizations,[14] and survival.[15] Published randomized controlled trials are not available comparing doxercalciferol with either calcitriol or paricalcitol.

Clinical Trial Data[7-15]

Injectable Paricalcitol (reduction in serum iPTH)

Short-term trials

Two publications of randomized, double-blind, placebo-controlled trials in patients with ESRD on hemodialysis were identified that evaluated the effect of paricalcitol on reducing serum iPTH :[7-8] one was a dose escalation study of 4 weeks duration with a primary endpoint of a decrease in serum iPTH of $\geq$ 30% from maximum baseline in 75% of patients;[7] the other reported results of three studies that randomized patients to 12 weeks of treatment with paricalcitol or placebo, with a primary endpoint of reduction in serum iPTH of $\geq$ 30% or maximum 5 dose increases.[8]

In the trial enrolling 35 patients by Llach et al,[7] the primary endpoint was achieved in patients receiving paricalcitol 0.16 mcg/kg and 0.24 mcg/kg treatment groups (reduction in iPTH of $\geq$ 30% in 83.3% of patients in both treatment groups). Overall, 68% of patients receiving paricalcitol achieved a reduction in iPTH of $\geq$ 30% compared to 15% of patients in the placebo treatment group.

Results of the studies published by Martin et al.[8] reported that 68% of patients (27/40) on paricalcitol (mean dose 0.12 mcg/kg) achieved a reduction in iPTH of $\geq$ 30% compared to 8% (3/38) of those receiving placebo ($P<0.001$).

Patients in the paricalcitol treatment groups experienced a greater change in serum calcium from baseline compared to patients on placebo,[7] and a significant increase from baseline[8] although within the therapeutic range.

Long-term trials

Two open-label trials[9-10] and one retrospective evaluation[11] reported the long-term effects of paricalcitol in decreasing iPTH levels compared to baseline in patients with ESRD on hemodialysis.

Of those patients who achieved 13 months of treatment with paricalcitol (n=67) in the trial published by Lindberg et al.,[9] the iPTH was reduced from a baseline of 668.4±47.66 pg/mL to 259.1±34.13 pg/mL (statistical significance not reported), with 52% of these patients achieving a target iPTH of 100-300 pg/mL. The mean dose for all treated patients (N=164) was 0.10 mcg/kg. Ten percent of all patients treated were reported to have a serum calcium of ≥ 11.5 mg/dL and 5% had a phosphorus level ≥ 6.5 mg/dL.

In the trial published by Llach et al.,[10] 14 patients were initially given a dose of paricalcitol at a 4:1 ratio compared to their previous dose of calcitriol. This dose resulted in a rapid decrease in iPTH over 2 months of therapy (baseline 1008±114 pg/mL to 194±24 pg/mL), with 50% of these patients developing hypercalcemia. The following 23 patients were dosed at a 3:1 ratio of paricalcitol to calcitriol. In all patients, the baseline iPTH (just prior to discontinuation of calcitriol) was 901±58 pg/mL. After 16 months of treatment in 33 patients, the iPTH was reduced to 165±24 pg/mL (P<0.001). At the end of treatment, calcium and phosphorus levels were not statistically significantly increased compared to baseline.

A retrospective evaluation published by Barton Pai et al.[11] reported an increase in iPTH from a baseline of 705±423 pg/mL to 821±480 pg/mL (P=0.37) in 16 patients treated with a mean dose of paricalcitol of 0.13±0.12 mcg/kg for a mean of 18 months. Fourteen of the 16 patients were on calcitriol prior to being switched to paricalcitol at a conversion dose of 4:1 paricalcitol to calcitriol. It was reported that 69% of patients had their doses of paricalcitol withheld an average of 17% of the time (usually for 4 weeks) due to elevations in serum calcium or Ca X P. A serum calcium ≥ 11.5 mg/dL, phosphorus ≥ 6.5 mg/dL, and Ca X P ≥ 70 mg^2/dL^2 was reported in 75%, 94%, and 82% of patients receiving paricalcitol, respectively.

Oral Paricalcitol (reduction in serum iPTH)

Abstract

Pooled results of three double-blind, randomized, multi-center, placebo-controlled trials (two trials evaluating paricalcitol capsules administered 3 times per week; one with paricalcitol dosed once daily) in patients with CKD Stage 3 and 4 were presented at the European Dialysis and Transplant Association Congress in June 2005. The reduction in serum iPTH in 107 patients on paricalcitol capsules was compared to 113 patients receiving placebo. After 24 weeks of treatment, it was reported that 91% of patients treated with paricalcitol (initial dose based on iPTH ≤ 500 vs. > 500 pg/mL; dose titrations based on iPTH, calcium, and phosphorus levels) achieved the primary efficacy endpoint (two consecutive decreases in iPTH ≥ 30% from baseline) compared to 13% of patients receiving placebo (P<0.001). It was reported that there were no differences in efficacy based on the dosing regimen. It was also reported that there was a similar incidence of hypercalcemia (defined as > 10.5 mg/dL), elevated phosphorus (> 5.5 mg/dL), or increased Ca X P (> 55) in patients treated with paricalcitol and placebo (details not provided in the abstract). Bone-specific alkaline phosphatase levels were reduced with paricalcitol compared to placebo (P<0.001). Treatment related adverse events occurred in 10% of patients treated with paricalcitol compared to 11% of patients on placebo.[12]

Comparison of Injectable Paricalcitol to Injectable Calcitriol

Efficacy (reduction in iPTH)

The primary endpoint of decreasing iPTH ≥ 50% from baseline was evaluated in a randomized, double-blind trial published by Sprague et al.[13] comparing paricalcitol to calcitriol (with a dose escalation ratio of 4:1) for 12 to 32 weeks of treatment in 263 patients with ESRD on hemodialysis. It was reported that approximately 60% of patients in each treatment group achieved the primary endpoint at the last blood draw (mean duration of treatment not provided). The mean decrease in iPTH ≥ 50% was also reported to have been achieved with paricalcitol at week 15

compared to calcitriol at week 23. There was no significant difference in the pre-specified endpoint of calcium > 11.5 mg/dL and/or Ca X P > 75 at least once during treatment. Upon additional analysis, hypercalcemia and/or a Ca X P > 75 for four consecutive laboratory evaluations was lower with paricalcitol compared to calcitriol (18% vs. 33%, respectively; P=0.008).

Hospitalizations

Dobrez et al.[14] published the effect of treatment with paricalcitol on hospitalizations compared to treatment with calcitriol in a retrospective database evaluation of 11,443 patients with ESRD who were new to hemodialysis and received at least 10 doses of a vitamin D analog. Results of a descriptive evaluation (summary of hospital use for patients started on either paricalcitol or calcitriol) reported that patients on paricalcitol had 2.4 hospital admissions per year compared to 2.61 hospitalizations for patients on calcitriol. Patients on paricalcitol were also hospitalized for a mean of 17.2 days compared to 19.8 days for patients on calcitriol. According to the intent-to-treat analysis (patients started on paricalcitol or calcitriol), patients on paricalcitol were hospitalized for 6.84 fewer days (P<0.0001) and had 0.642 fewer hospital admissions per year (P<0.0001) compared to calcitriol. According to the multivariate analysis, treatment with paricalcitol reduced the risk of first hospitalization by 14% compared to calcitriol.

Survival

Based on 36 months of follow-up in a historical cohort study published by Teng et al.,[15] treatment with paricalcitol was associated with a mortality rate of 0.180 per person year (3417 deaths per 19,031 person years) compared to 0.223 per person year (6805 deaths per 30,471 person years) with calcitriol (rate ratio 0.80 95% CI 0.77 to 0.84; P<0.001). The mean doses at 12 months of vitamin D treatment were 1.3±1.2 mcg calcitriol and 4.3±2.8 mcg paricalcitol. During the evaluation, 14,862 patients with ESRD on hemodialysis were switched from calcitriol to paricalcitol, while 1,621 patients were switched from paricalcitol to calcitriol.

Acquisition Cost

Current VA prices and estimated cost per patient are shown below:

Vitamin D analog	Price Per Unit	Monthly Cost/Patient	Annual Cost/Patient	Annual VA Cost (per units dispensed)[f]
Calcitriol Injectable[a]				
1 mcg/mL (1 mL)	6.000	$72.00	$864.00	$470,850
Calcitriol Oral[b]				
0.25 mcg capsule	0.7293	$21.88	$262.55	$1,465,873
0.5 mcg capsule	1.1661	$34.98	$419.80	$322,750
1 mcg/mL (15 mL) oral solution	6.26/mL	$187.80	$2,253.60	
Doxercalciferol Injectable[a]				
2 mcg/mL (2 mL)	7.4334 (2 mL)	$89.20	$1070.41	$508,073
Doxercalciferol Oral[b]				
0.5 mcg capsule	1.6982	$101.89[c]	$1,222.70[c]	
2.5 mcg capsule	4.1714	$125.14	$1,501.70	$8,384,401
Paricalcitol Injectable[a]				
2 mcg/mL (1 mL)	6.1733	$148.16[d]	$1,777.91[d]	
5 mcg/mL (1 mL)	15.4323	$185.19	$2,222.25	$1,054,798
5 mcg/mL (2 mL)	15.0374			
Paricalcitol Oral[b]				
1 mcg capsule	2.944	$88.32 (vs. $70.66[e])	$1,059.84 (vs. $847.87[e])	$5,917,361
2 mcg capsule	5.888	$176.64	$2,119.68	$1,629,663
4 mcg capsule[a]	11.776	$141.31	$1,695.74	

[a] Assume administered three times per week
[b] Based on once daily dosing
[c] Based on 2 capsules per day
[d] Based on 2 doses administered three times per week
[e] Price for 2 mcg administered three times per week
[f] Estimated cost based on VA calcitriol utilization (oral per outpatient prescription data 6/2004-5/2005; injectable per prime vendor purchase data FY05), regardless of FDA approved indication

Cost Analysis

Results of a budget impact model for paricalcitol capsules are presented in the manufacturer's dossier (confidential information available from manufacturer) based on the estimated prevalence of CKD Stage 3 and 4 in the U.S. As both the oral formulations of calcitriol and doxercalciferol are indicated for treatment in patients with CKD Stage 3 and 4, it would be possible to use the VA database to construct a budget impact model with current utilization data; however, this would most likely be an overestimation of oral paricalcitol use as the oral formulations of calcitriol and doxercalciferol are also approved for use in patients with ESRD on dialysis whereas oral paricalcitol is not. Similar comparisons can be done with the injectable formulations for patients with ESRD on dialysis. According to the VA data, there would be an annual increase of approximately $1.5 to $3 million if 25% to 50% of current utilization of oral calcitriol capsules (based on outpatient prescription data) were converted to oral paricalcitol capsules; and $150,000 to $300,000 if 25% to 50% of the utilization of injectable calcitriol (based on prime vendor purchase data) were changed to the injectable formulation of paricalcitol. Ideally, the impact of treating patients with paricalcitol compared to another vitamin D analog would include long-term outcomes from prospective, randomized controlled trials; however, these data are only available in a retrospective database evaluation on hospitalizations and a historical cohort study evaluating survival, both in patients with ESRD on hemodialysis receiving injectable paricalcitol compared with calcitriol. Hospitalization and mortality data are available within the VA and could be used to develop a pharmacoeconomic model that would better reflect the long-term outcomes of vitamin D therapy in our healthcare system. As this is a lengthy and labor intensive process, the VA budget impact model will be used for cost comparison with the available vitamin D products.

Data Compilation Table

Primary Endpoint	Reduction iPTH
Results: Paricalcitol (injectable)	27/40 (68%)
Results: Placebo	3/38 (8%)
Treatment duration	12 weeks
Absolute Benefit Increase (95% CI)	60% (43 to 77)
NNT (95% CI)	2 (1.3 to 2.3)

Conclusions

Injectable paricalcitol has been reported to significantly reduce iPTH in patients with CKD on dialysis compared to placebo in two published, short-term, randomized, placebo-controlled trials. The long-term effect of injectable paricalcitol in patients with CKD on dialysis has also been evaluated in two open-label trials and one retrospective evaluation. The efficacy of oral paricalcitol compared to placebo in patients with CKD Stage 3 and 4 has only been published in abstract form.

The injectable formulations of paricalcitol and calcitriol were compared in one randomized, double-blind trial that reported a similar percentage of patients in each treatment group achieved the primary endpoint of reduction in iPTH, although this endpoint was achieved earlier with paricalcitol compared to calcitriol. There was no significant difference in the pre-specified endpoint of hypercalcemia or elevated Ca X P although a lower incidence of sustained hypercalcemia and/or elevated Ca X P was seen upon further analysis of the data. The reduction in hospitalizations and mortality with paricalcitol compared to patients treated with calcitriol requires confirmation in long-term, prospective, randomized, controlled trials. The long-term skeletal or cardiovascular effects of treatment with paricalcitol compared to other vitamin D analogs have yet to be established. Published randomized controlled trials are needed to confirm the comparable efficacy and to determine the long-term consequence of potential differences in calcium levels or Ca X P between treatments with the vitamin D analogs used in patients with SHPT.

Recommendations

Due to the lack of evidence from head to head prospective randomized controlled trials demonstrating a benefit of paricalcitol over the formulary agent, calcitriol, it has been recommended that paricalcitol (both injectable and oral formulations) not be added to the VA National Formulary. Although not confirmed in prospective randomized controlled trials with another vitamin D analog as the comparator, a nonformulary vitamin D analog (doxercalciferol, paricalcitol) may be considered in patients with hypercalcemia despite dosage adjustment of the formulary agent (calcitriol).

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Appendix 1: Paricalcitol (Injectable) Placebo-Controlled Trials

Study	Population	N	Treatment	Duration	Results	Adverse Events	Comments
Short-term trials							
Llach et al. 1998[7] R, DB, PC, MC Dose escalation	ESRD on HD iPTH > 300 pg/mL Ca 8 to 10 mg/dL P ≤ 6 mg/dL	35	Paricalcitol 3x/wk (N=22) 0.04 mcg/kg 0.08 mcg/kg 0.16 mcg/kg 0.24 mcg/kg vs. Placebo (N=13)	4 wks	**Primary Endpoint:** ↓ iPTH ≥ 30% from maximum baseline in 75% patients on paricalcitol per tx group **Treatment** / **Baseline iPTH** / **Primary Endpoint** Paricalcitol — 691 pg/mL 0.04 mcg/kg — 66.7% (4/6) 0.08 mcg/kg — 25.0% (1/4) 0.16 mcg/kg — 83.3% (5/6) 0.24 mcg/kg — 83.3% (5/6) Placebo — 728 pg/mL — 15.4% (2/13) **Overall:** Mean percent change from baseline iPTH (P<0.01) with paricalcitol, no significant change with placebo; 68% (15/22) ↓ iPTH ≥ 30% on paricalcitol vs. 15% (2/13) on placebo **Phosphorus:** No significant difference (P=0.625) in change from baseline between groups **Calcium:** Greater change from baseline with paricalcitol vs. placebo (P<0.001)	Withdrew or completed study early: Paricalcitol (1 rash, 3 hypercalcemia, 3 Ca X P > 70); placebo (1 withdrew consent) **AE** / **PAR** / **PL** ≥ 1 AE — 77% — 77% Tx AE — 2[a] — 3[b] Ca 11.6-12.5 — 4 — 0 [a]pruritic rash, intermittent dry cough [b]intermittent headache, cough, left rib pain	Enrolled exceptions to inclusion criteria (N=10)
Martin et al. 1998[8] R, DB, PC, MC 3 trials	ESRD on HD iPTH ≥ 400 pg/mL Ca 8 to 10 mg/dL Ca X P < 75	78	Paricalcitol 3x/wk (N=40) 0.04 mcg/kg, increase by 0.04 mcg/kg every 2 wks Max 0.24 mcg/kg vs. Placebo (N=38)	12 wks	**Primary Endpoint:** ↓ iPTH ≥ 30% or maximum 5 dose increases; 68% (27/40) ↓ iPTH ≥ 30% vs. 8% (3/38) on placebo (P<0.001) **Mean paricalcitol dose:** 0.12 mcg/kg **Treatment** / **Baseline** / **Endpoint** iPTH (pg/mL) Paricalcitol — 795±86 — 406±106[a] Placebo — 680±45 — 592±4 Ca (mg/dL) Paricalcitol — 9.24±0.12 — 9.56±0.15[b] Placebo — 9.06±0.1 — 9.02±0.15 P (mg/dL) Paricalcitol — 5.88±0.24 — 6.35±0.32 Placebo — 6.00±0.26 — 5.48±0.27 Alk Phos (U/L) Paricalcitol — 148±23 — 101±14[a] Placebo — 120±9 — 130±11 [a]P<0.001 baseline vs. endpoint; P<0.001 change from baseline paricalcitol vs. placebo [b]P<0.02 baseline vs. endpoint	**Labs** / **PAR**[a/b] / **PL**[a/b] Ca X P > 75 — 45/395 — 16/412 Ca > 10.5 — 27/401 — 14/417 [a]number of occurrences [b]number of lab determinations	

Long-term trials							
Lindberg et al. 2001[9] Open-label, MC	ESRD on HD iPTH ≥ 300 pg/mL Ca < 11.5 mg/dL Ca X P ≤ 75	164	Paricalcitol 2-3x/wk (N=40) 0.04-0.24 mcg/kg, increase by 0.04 mcg/kg every wk until iPTH 100-300 pg/mL	13 months (N=67)	**Primary Endpoint:** ↓ iPTH (pre-tx vs. tx); 52% (of N=67) achieved iPTH 100-300 pg/mL **Mean paricalcitol dose:** 0.10 mcg/kg **Baseline** / **Endpoint (N=67)** iPTH (pg/mL): 668.4±47.66 (N=67) / 259.1±34.13 Ca (mg/dL): 9.06±0.08 (N=164) / 9.62±0.11 P (mg/dL): 5.73±0.12 (N=164) / 6.08±0.25 Ca X P: 51.73±1.09 (N=164) / 58.84±2.47	Withdrawal due to AEs: 9% (15/164) **AE** / **Tx** Tx AE: 26% (43/164) ↑ Ca (> 11.5 mg/dL): 10% (17/164) ↑ P (> 6.5 mg/dL): 5% (9/164) iPTH (< 100 pg/mL): 22% (15/67) Death: 10 patients (4 during treatment phase; 6 post-study)	295 patients enrolled; 164 entered treatment phase; 67 completed 13 months treatment
Llach et al. 2001[10] Open-label	ESRD on HD iPTH ≥ 600 pg/mL on calcitriol Ca < 11.5 mg/dL Ca X P ≤ 75	37	Initial doses: 1:4 calcitriol:paricalcitol (N=14) 1:3 calcitriol:paricalcitol (N=23); dose adjusted based on Ca (> 11.5 mg/dL), P (> 7.5 mg/dL), Ca X P (> 75); goal iPTH 100-200 pg/mL	16 months (N=33) mean 14.9±4.3 months	**Primary Endpoint:** Decrease serum iPTH (baseline vs. treatment) **Mean initial paricalcitol dose:** 16±3 mcg (N=14), 7±4 mcg (N=23); by 16 months, dose reduced to 3 mcg in patients with baseline iPTH > 800 pg/mL (N=13) and 1.5 mcg with baseline iPTH 600-800 pg/mL (N=24) **Baseline** / **Endpoint** / **P value** iPTH (pg/mL): 901±58 / 165±24 / <0.001 Ca (mg/dL): 9.4±0.02 / 9.7±0.2 / 0.86 P (mg/dL): 6.1±0.2 / 5.8±0.2 / 0.77 Alk Phos (U/L): 280±27 / 65±12 / <0.001	**Dose** / **Lab (2 months)** Initial 1:4: Ca 12.0+0.2 mg/dL; 50% (7/14) Initial 1:3: Ca 10.7 mg/dL; 4.4% (1/23) Hyperphosphatemia: 6 patients (3 discontinued tx due to recurrences)	Dose last calcitriol tx 3.2±1.6 mcg; 50% developed hypercalcemia with initial 1:4 dose ratio, reduced to 1:3 for remaining patients
Barton Pai et al. 2003[11] Retrospective	ESRD on HD Paricalcitol ≥ 3 months	16	Paricalcitol 3x/wk ≥ 3 months (14/16 on calcitriol with mean dose 0.04±0.02 mcg/kg; 1:4 ratio most often used for conversion to paricalcitol)	Mean 18 months	**Primary Endpoint:** Change serum iPTH (baseline vs. treatment) **Mean paricalcitol dose:** 0.13±0.12 mcg/kg (8.4% > 0.24 mcg/kg) **Baseline** / **Endpoint** / **P value** iPTH (pg/mL): 705±423 / 821±480 / 0.37 Ca (mg/dL): 10.5±1.0 / 10.2±0.8 / NR P (mg/dL): 6.2±2.0 / 6.4±1.6 / NR Ca X P: 65±20 / 65±16 / NR Alk Phos (U/L): 105±58 / 152±100 / <0.05	**Lab** / **Tx** ↑ Ca (≥ 11.5 mg/dL): 75% (12/16) ↑ P (≥ 6.5 mg/dL): 94% (15/16) Ca X P (≥ 70 mg²/dL²): 82% (13/16)	14/16 previously switched from calcitriol due to 43% ↑ iPTH, 36% ↑ Ca, 14% ↑ Ca X P; 69% had paricalcitol doses withheld average 17% of the time due to ↑ Ca, P, or Ca X P

AE=adverse event; Alk Phos=alkaline phosphatase; Ca=calcium; Ca X P=calcium phosphorus product; DB=double-blind; ESRD=end-stage renal disease; HD=hemodialysis; iPTH=intact parathyroid hormone; MC=multi-center; N=number of patients; NR=not reported; P=phosphorus; PC=placebo-controlled; PL=placebo; R=randomized; Tx=treatment; wks=weeks

Appendix 2: Paricalcitol vs. Calcitriol (Injectable) Trials

Study	Population	N	Treatment	Duration	Results	Adverse Events/Labs	Comments
Efficacy							
Sprague et al. 2003[13] R, DB, MC	ESRD on HD iPTH ≥ 300 pg/mL Ca < 11.5 mg/dL Ca X P ≤ 75	263	Paricalcitol 3x/wk (N=130) 0.04 mcg/kg, increase by 0.04 mcg/kg every 4 wks Max 0.24 mcg/kg vs. Calcitriol 3x/wk (N=133) 0.01 mcg/kg, increase by 0.01 mcg/kg every 4 wks Max 0.06 mcg/kg	32 wks	**Primary Endpoint:** Decrease serum iPTH ≥ 50% from baseline (but not < 100 pg/mL); baseline iPTH (paricalcitol 675±35.0 vs. calcitriol 648±30.5 pg/mL) • mean ↓ with paricalcitol wk 15 vs. calcitriol wk 23 • 1st of 4 consecutive ↓ iPTH 50% (median days) paricalcitol (87) vs. calcitriol (108) (P=0.025) • ~60% in each group achieved endpoint at final blood draw **Alk Phos:** Mean reductions from baseline were 37.4 U/L for paricalcitol and 44.0 U/L with calcitriol **Mean treatment doses:** Dose escalation 4:1 ratio paricalcitol:calcitriol; mean doses not reported	Ca > 11.5 mg/dL and/or Ca X P > 75 at least 1 time during treatment (pre-specified endpoint): Calcitriol 68% (90/133) vs. Paricalcitol 64% (83/130) (P=0.519)	476 enrolled, 266 randomized
Hospitalizations							
Dobrez et al. 2004[14] Retrospective database evaluation	ESRD new HD ≥ 10 doses vitamin D	11,443	Injectable vitamin D therapy with calcitriol or paricalcitol	Data from 1/1999-11/2001	**Primary Endpoints:** 1) total number all-cause hospitalizations; 2) total number hospitalization days; 3) time to first hospitalization after vitamin D therapy initiated **Baseline iPTH > 300 pg/mL:** Calcitriol 59.2%; Paricalcitol 70.4% **Mean treatment doses:** Not reported **Treatment / Endpoint[a] / PAR vs. CAL** Number hospitalizations per year (mean) Calcitriol 2.61 Paricalcitol 2.4 -0.642[b] Hospitalization days per year (mean) Calcitriol 19.8 Paricalcitol 17.2 -6.84[b] Time (days) to first admission (median) Calcitriol 135 Paricalcitol 159 Risk of first hospitalization PAR vs. CAL RRR 14% HR 0.863[b] [a]Descriptive analysis [b]P<0.0001 intent-to-treat analysis	Influence of independent variables (paricalcitol vs. calcitriol) **Variable[a] / # Hosp** iPTH 301-600 pg/mL -0.179[b] iPTH ≥ 601 pg/mL -0.370[c] Ca < 8.5 mg/dL 0.340[c] [a]vs. normal values [b]P<0.05 [c]P<0.0001	Patients on doxercalciferol excluded due to limited number (N=50); 94.4% on paricalcitol and 58.7% on calcitriol remained on these agents, respectively; significant differences in baseline

Survival							
Teng et al. 2003[15] Historical cohort evaluation	ESRD on HD	67,399	Injectable vitamin D therapy with calcitriol or paricalcitol	36 months (Data from 1/1/1999-12/31/2001)	**Primary Endpoint:** Mortality rate **Baseline iPTH (pg/mL):** Calcitriol 413±336 vs. paricalcitol 496±364 (P<0.01) **Mean treatment doses at 12 months:** Calcitriol 1.3±1.2 mcg; paricalcitol 4.3±2.8 mcg **Tx** / **Deaths/ Person Year** / **Rate Ratio (95%CI)** CAL: 6805/30,471 (0.223/py) PAR: 3417/19,031 (0.180/py) PAR vs. CAL 0.80 (0.77 to 0.84) P<0.001 Survival benefit regardless of Ca or iPTH level	**Lab**[a] / **CAL** / **PAR** ↓ **iPTH** 5% 15% ↑ **Ca** 8.2% 6.7% ↑ **P** 13.9% 11.9% [a]mean change within 6.1 to 12 months after starting tx	14,862 were switched from calcitriol to paricalcitol, with 1,621 switched from paricalcitol to calcitriol; significant differences in baseline

AE=adverse event; Alk Phos=alkaline phosphatase; Ca=calcium; Ca X P=calcium phosphorus product; CAL=calcitriol; DB=double-blind; ESRD=end-stage renal disease; HD=hemodialysis; Hosp=hospitalization; HR=hazard ratio; iPTH=intact parathyroid hormone; MC=multicenter; N=number of patients; P=phosphorus; PAR=paricalcitol; PC=placebo-controlled; PL=placebo; py=person year; R=randomized; RRR=relative risk reduction; Tx=treatment; wks=weeks

Appendix 3: VA Utilization of the Vitamin D Analogs

VA Utilization of the Vitamin D Analogs (based on outpatient prescription data 6/2004-5/2005)

Vitamin D Analog[a]	Units Dispensed	30 Day Rx	Uniques	Average Daily Dose	Total Cost
Calcitriol Injectable					
1 mcg/mL (1 mL)	9,132	560	175		$92,097
2 mcg/mL (1 mL)	139	4	3		$2,677
Calcitriol Oral					
0.25 mcg capsule	2,009,973	57,632	8,480	0.2936	$1,362,895
0.5 mcg capsule	276,777	7,996	1,278	0.5857	$313,192
1 mcg/mL (15 mL) soln	883	33	10		$6,226
Doxercalciferol Injectable					
2 mcg/mL (1 mL)	581	30	18		$1,642
Doxercalciferol Oral					
0.5 mcg capsule	610	11	3	1.0	$849
2.5 mcg capsule	57,844	2,351	352	2.1	$65,016
Paricalcitol Injectable					
2 mcg/mL (1 mL)	122	5	3		$705
5 mcg/mL (1 mL)	9,722	583	128		$149,517

[a] No utilization oral paricalcitol (1 mcg, 2 mcg, 4 mcg capsules) during this time due to recent FDA approval

VA Utilization of the Vitamin D Analogs (based on prime vendor purchase data FY2005)

Vitamin D Analog[a]	NDC Units	Package	Total Dollars
Calcitriol Injectable			
1 mcg/mL (1 mL)	1,367	50	$389,530
	405	25	$91,310
2 mcg/mL (1 mL)	15	25	$7,460
Calcitriol Oral			
0.25 mcg capsule	20,874	100	$1,267,622
	557	30	$11,517
0.5 mcg capsule	1,141	100	$135,954
1 mcg/mL (15 mL) soln	27	1	$3,193
Doxercalciferol Injectable			
2 mcg/mL (2 mL)	179	50	$48,332
Doxercalciferol Oral			
0.5 mcg capsule	32	50	$2,234
2.5 mcg capsule	1,190	50	$76,409
Paricalcitol Injectable			
2 mcg/mL (1 mL)	151	25	$21,405
5 mcg/mL (1 mL)	3,195	25	$1,133,742
5 mcg/mL (2 mL)	197	25	139,819

[a] No utilization oral paricalcitol (1 mcg, 2 mcg, 4 mcg capsules) during this time due to recent FDA approval