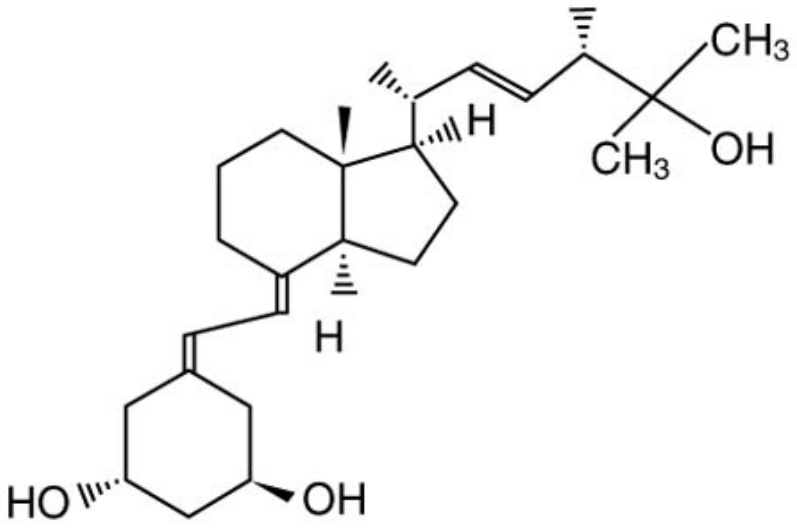
ZEMPLAR®
(paricalcitol) Capsules

DESCRIPTION

Paricalcitol, USP, the active ingredient in Zemplar Capsules, is a synthetically manufactured analog of calcitriol, the metabolically active form of vitamin D indicated for the prevention and treatment of secondary hyperparathyroidism in chronic kidney disease. Zemplar is available as soft gelatin capsules for oral administration containing 1 microgram, 2 micrograms or 4 micrograms of paricalcitol. Each capsule also contains medium chain triglycerides, alcohol, and butylated hydroxytoluene. The medium chain triglycerides are fractionated from coconut oil or palm kernel oil. The capsule shell is composed of gelatin, glycerin, titanium dioxide, iron oxide red (2 microgram capsules only), iron oxide yellow (2 microgram and 4 microgram capsules), iron oxide black (1 microgram capsules only), and water.

Paricalcitol is a white, crystalline powder with the empirical formula of $C_{27}H_{44}O_3$, which corresponds to a molecular weight of 416.64. Paricalcitol is chemically designated as 19-nor-1α,3β,25-trihydroxy-9,10-secoergosta-5(Z),7(E),22(E)-triene and has the following structural formula:



CLINICAL PHARMACOLOGY

Secondary hyperparathyroidism is characterized by an elevation in parathyroid hormone (PTH) associated with inadequate levels of active vitamin D hormone. The source of vitamin D in the body is from synthesis in the skin and from dietary intake. Vitamin D requires two sequential hydroxylations in the liver and the kidney to bind to and to activate the vitamin D receptor (VDR). The endogenous VDR activator, calcitriol [$1,25(OH)_2 D_3$], is a hormone that binds to VDRs that are present in the parathyroid gland, intestine, kidney, and bone to maintain parathyroid function and calcium and phosphorus homeostasis, and to VDRs found in many other tissues, including prostate, endothelium and immune cells. VDR activation is essential for the proper formation and maintenance of normal bone. In the diseased kidney, the activation of vitamin D is diminished, resulting in a rise of PTH, subsequently leading to secondary hyperparathyroidism and disturbances in the calcium and phosphorus homeostasis.[1] Decreased levels of $1,25(OH)_2D_3$ have been observed in early stages of chronic kidney disease. The decreased levels of $1,25(OH)_2 D_3$ and resultant elevated PTH levels, both of which often precede abnormalities in serum calcium and phosphorus, affect bone turnover rate and may result in renal osteodystrophy.

Mechanism of Action

Paricalcitol is a synthetic, biologically active vitamin D analog of calcitriol with modifications to the side chain (D_2) and the A (19-nor) ring. Preclinical and *in vitro* studies have demonstrated that paricalcitol's biological actions are mediated through binding of the VDR, which results in the selective activation of vitamin D responsive pathways. Vitamin D and paricalcitol have been shown to reduce parathyroid hormone levels by inhibiting PTH synthesis and secretion.

Pharmacodynamics

Paricalcitol decreases serum intact parathyroid hormone (iPTH) and increases serum calcium and serum phosphorous in both hemodialysis (HD) and peritoneal dialysis (PD) patients. This observed relationship was quantified using a mathematical model for HD and PD patient populations separately. Computer-based simulations of 100 trials in HD or PD patients (N = 100) using these relationships predict slightly lower efficacy (at least two

consecutive ≥ 30% reductions from baseline iPTH) with lower hypercalcemia rates (at least two consecutive serum calcium ≥ 10.5 mg/dL) for lower iPTH-based dosing regimens. Further lowering of hypercalcemia rates was predicted if the treatment with paricalcitol is initiated in patients with lower serum calcium levels at screening.

Based on these simulations, a dosing regimen of iPTH/80 with a screening serum calcium ≤ 9.5 mg/dL, approximately 76.5% (95% CI : 75.6% – 77.3%) of HD patients are predicted to achieve at least two consecutive ≥ 30% reductions from baseline iPTH over a duration of 12 weeks. The predicted incidence of hypercalcemia is 0.8% (95% CI : 0.7% – 1.0%). In PD patients, with this dosing regimen, approximately 83.3% (95% CI : 82.6 – 84.0%) of patients are predicted to achieve at least two consecutive ≥ 30% reductions from baseline iPTH. The predicted incidence of hypercalcemia is 12.4% (95% CI : 11.7% - 13.0 %:). (see **CLINICAL STUDIES; CKD Stage 5** and **DOSAGE AND ADMINISTRATION; CKD Stage 5**)

Pharmacokinetics

Absorption

Paricalcitol is well absorbed. In healthy subjects, following oral administration of paricalcitol at 0.24 mcg/kg, the mean absolute bioavailability was approximately 72%; the mean maximum plasma concentration (C_{max}), time to C_{max} (T_{max}), and area under the concentration time curve ($AUC_{0-\infty}$) were 0.630 ng/mL, 3 hours and 5.25 ng•h/mL, respectively. The mean absolute bioavailability of paricalcitol in CKD Stage 5 patients on hemodialysis (HD) or peritoneal dialysis (PD) was 79% or 86%, respectively. A food effect study in healthy subjects indicated that the C_{max} and $AUC_{0-\infty}$ were unchanged when paricalcitol was administered with a high fat meal compared to fasting. Food delays T_{max} about 2 hours. The $AUC_{0-\infty}$ of paricalcitol increased proportionally over the dose range of 0.06 to 0.48 mcg/kg in healthy subjects. Following multiple dosing, as once daily in CKD Stage 4 patients, the exposure (AUC) was slightly lower than that obtained after a single dose administration.

Distribution

Paricalcitol is extensively bound to plasma proteins (≥ 99.8%). The mean apparent volume of distribution following a 0.24 mcg/kg dose of paricalcitol in healthy subjects was 34 L.

The mean apparent volume of distribution following a 4 mcg dose of paricalcitol in CKD Stage 3 and 3 mcg dose in CKD Stage 4 patients is between 44 and 46 L.

Metabolism

After oral administration of a 0.48 mcg/kg dose of ^{3}H-paricalcitol, parent drug was extensively metabolized, with only about 2% of the dose eliminated unchanged in the feces, and no parent drug found in the urine. Several metabolites were detected in both the urine and feces. Most of the systemic exposure was from the parent drug. Two minor metabolites, relative to paricalcitol, were detected in human plasma. One metabolite was identified as 24(R)-hydroxy paricalcitol, while the other metabolite was unidentified. The 24(R)-hydroxy paricalcitol is less active than paricalcitol in an *in vivo* rat model of PTH suppression.

In vitro data suggest that paricalcitol is metabolized by multiple hepatic and non-hepatic enzymes, including mitochondrial CYP24, as well as CYP3A4 and UGT1A4. The identified metabolites include the product of 24(R)-hydroxylation, 24,26- and 24,28-dihydroxylation and direct glucuronidation.

Elimination

Paricalcitol is eliminated primarily via hepatobiliary excretion; approximately 70% of the radiolabeled dose is recovered in the feces and 18% is recovered in the urine. In healthy subjects, the mean elimination half-life of paricalcitol is 4 to 6 hours over the studied dose range of 0.06 to 0.48 mcg/kg. The pharmacokinetics of paricalcitol capsule have been studied in patients with chronic kidney disease (CKD) Stage 3 and 4 patients. After administration of 4 mcg paricalcitol capsule in CKD Stage 3 patients, the mean elimination half-life of paricalcitol is 17 hours. The mean half-life of paricalcitol is 20 hours in CKD Stage 4 patients when given 3 mcg of paricalcitol capsule.

Table 1. Paricalcitol Capsule Pharmacokinetic Characteristics in CKD Stage 3 and 4 Patients

Pharmacokinetic Parameters	CKD Stage 3 n = 15*	CKD Stage 4 n = 14*
C_{max} (ng/mL)	0.11 ± 0.04	0.06 ± 0.01
$AUC_{0-\infty}$ (ng•h/mL)	2.42 ± 0.61	2.13 ± 0.73

CL/F (L/h)	1.77 ± 0.50	1.52 ± 0.36
V/F (L)	43.7 ± 14.4	46.4 ± 12.4
$t_{1/2}$	16.8 ± 2.65	19.7 ± 7.2

* Four mcg paricalcitol capsule was given to CKD Stage 3 patients; three mcg paricalcitol capsule was given to CKD Stage 4 patients.

Special Populations

Geriatric

The pharmacokinetics of paricalcitol have not been investigated in geriatric patients greater than 65 years (see **PRECAUTIONS**).

Pediatric

The pharmacokinetics of paricalcitol have not been investigated in patients less than 18 years of age.

Gender

The pharmacokinetics of paricalcitol following single doses over 0.06 to 0.48 mcg/kg dose range were gender independent.

Hepatic Impairment

The disposition of paricalcitol (0.24 mcg/kg) was compared in patients with mild (n = 5) and moderate (n = 5) hepatic impairment (as indicated by the Child-Pugh method) and subjects with normal hepatic function (n = 10). The pharmacokinetics of unbound paricalcitol were similar across the range of hepatic function evaluated in this study. No dosing adjustment is required in patients with mild and moderate hepatic impairment. The influence of severe hepatic impairment on the pharmacokinetics of paricalcitol has not been evaluated.

Renal Impairment

Following administration of Zemplar Capsules, the pharmacokinetic profile of paricalcitol for CKD Stage 5 on hemodialysis (HD) or peritoneal dialysis (PD) was comparable to that in CKD 3 or 4 patients. Therefore, no special dosing adjustments are required other than those recommended in the Dosage and Administration section (see **DOSAGE AND ADMINISTRATION**).

Drug Interactions

An *in vitro* study indicates that paricalcitol is not an inhibitor of CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP2E1 or CYP3A at concentrations up to 50 nM (21 ng/mL) (approximately 20-fold greater than that obtained after highest tested dose). In fresh primary cultured hepatocytes, the induction observed at paricalcitol concentrations up to 50 nM was less than two-fold for CYP2B6, CYP2C9 or CYP3A, where the positive controls rendered a six- to nineteen-fold induction. Hence, paricalcitol is not expected to inhibit or induce the clearance of drugs metabolized by these enzymes.

Omeprazole

The pharmacokinetic interaction between paricalcitol capsule (16 mcg) and omeprazole (40 mg; oral) was investigated in a single dose, crossover study in healthy subjects. The pharmacokinetics of paricalcitol were unaffected when omeprazole was administered approximately 2 hours prior to the paricalcitol dose.

Ketoconazole

The effect of multiple doses of ketoconazole administered as 200 mg BID for 5 days on the pharmacokinetics of paricalcitol capsule has been studied in healthy subjects. The C_{max} of paricalcitol was minimally affected, but $AUC_{0-\infty}$ approximately doubled in the presence of ketoconazole. The mean half-life of paricalcitol was 17.0 hours in the presence of ketoconazole as compared to 9.8 hours, when paricalcitol was administered alone (see **PRECAUTIONS**).

CLINICAL STUDIES

CKD Stages 3 and 4

The safety and efficacy of Zemplar Capsules were evaluated in three, 24-week, double blind, placebo-controlled, randomized, multicenter, Phase 3 clinical studies in CKD Stage 3 and 4 patients. Two studies used an identical three times a week dosing design, and one study used a daily dosing design. A total of 107 patients received Zemplar Capsules and 113 patients received placebo. The mean age of the patients was 63 years, 68% were male, 71% were Caucasian, and 26% were African-American. The average baseline iPTH was 274 pg/mL (range: 145-856 pg/mL). The average duration of CKD prior to study entry was 5.7 years. At study entry 22% were receiving calcium based phosphate binders and/or calcium supplements. Baseline 25-hydroxyvitamin D levels were not measured.

The initial dose of Zemplar Capsules was based on baseline iPTH. If iPTH was ≤ 500 pg/mL, Zemplar Capsules were administered 1 mcg daily or 2 mcg three times a week, not more than every other day. If iPTH was > 500 pg/mL, Zemplar Capsules were administered 2 mcg daily or 4 mcg three times a week, not more than every other day. The dose was titrated by 1 mcg daily or 2 mcg three times a week every 2 to 4 weeks until iPTH levels were reduced by at least 30% from baseline. The overall average weekly dose of Zemplar Capsules was 9.6 mcg/week in the daily regimen and 9.5 mcg/week in the three times a week regimen.

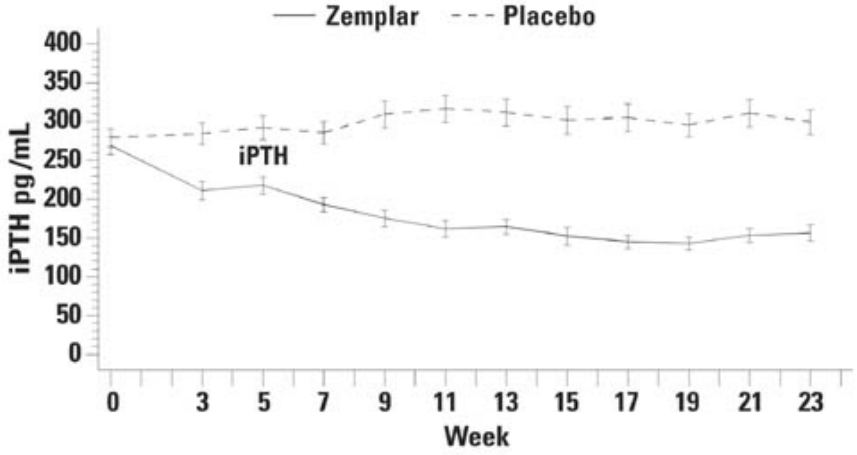
In the clinical studies, doses were titrated for any of the following reasons: if iPTH fell to < 60 pg/mL, or decreased > 60% from baseline, the dose was reduced or temporarily withheld; if iPTH decreased < 30% from baseline and serum calcium was ≤ 10.3 mg/dL and serum phosphorus was ≤ 5.5 mg/dL, the dose was increased; and if iPTH decreased between 30 to 60% from baseline and serum calcium and phosphorus were ≤ 10.3 mg/dL and ≤ 5.5 mg/dL, respectively, the dose was maintained. Additionally, if serum calcium was between 10.4 to 11.0 mg/dL, the dose was reduced irrespective of iPTH, and the dose was withheld if serum calcium was > 11.0 mg/dL. If serum phosphorus was > 5.5 mg/dL, dietary counseling was provided, and phosphate binders could have been initiated or increased. If the elevation persisted, the Zemplar Capsules dose was decreased. Seventy-seven percent (77%) of the Zemplar Capsules treated patients and 82% of the placebo treated patients completed the 24-week treatment. The primary efficacy endpoint of at least two consecutive ≥ 30% reductions from baseline iPTH was

achieved by 91% of Zemplar Capsules treated patients and 13% of the placebo treated patients ($p < 0.001$). The proportion of Zemplar Capsules treated patients achieving two consecutive ≥ 30% reductions was similar between the daily and the three times a week regimens (daily: 30/33, 91%; three times a week: 62/68, 91%).

The incidence of hypercalcemia (defined as two consecutive serum calcium values > 10.5 mg/dL), hyperphosphatemia and elevated Ca x P product in Zemplar Capsules treated patients was similar to placebo. There were no treatment related adverse events associated with hypercalcemia or hyperphosphatemia in the Zemplar Capsules group. No increases in urinary calcium or phosphorous were detected in Zemplar Capsules treated patients compared to placebo.

The pattern of change in the mean values for serum iPTH during the studies are shown in Figure 1.

Figure 1. Mean Values for Serum iPTH Over Time in the Three Double-Blind, Placebo-Controlled, Phase 3, CKD Stage 3 and 4 Studies Combined



The mean changes from baseline to final treatment visit in serum iPTH, calcium, phosphorus, calcium-phosphorus product (Ca x P), and bone-specific alkaline phosphatase are shown in Table 2.

Table 2. Mean Changes from Baseline to Final Treatment Visit in Serum iPTH, Bone Specific Alkaline Phosphatase, Calcium, Phosphorus, and Calcium x Phosphorus Product in Three Double-Blind, Placebo-Controlled, Phase 3, CKD Stage 3 and 4 Studies Combined

	Zemplar Capsules	Placebo

iPTH (pg/mL)	n = 104	n = 110
Mean Baseline Value	266	279
Mean Final Treatment Value	162	315
Mean Change from Baseline (SE)	-104 (9.2)	+35 (9.0)
Bone Specific Alkaline Phosphatase (mcg/L)	n = 101	n = 107
Mean Baseline	17.1	18.8
Mean Final Treatment Value	9.2	17.4
Mean Change from Baseline (SE)	-7.9 (0.76)	-1.4 (0.74)
Calcium (mg/dL)	n = 104	n = 110
Mean Baseline	9.3	9.4
Mean Final Treatment Value	9.5	9.3
Mean Change from Baseline (SE)	+0.2 (0.04)	-0.1 (0.04)
Phosphorus (mg/dL)	n = 104	n = 110
Mean Baseline	4.0	4.0
Mean Final Treatment Value	4.3	4.3
Mean Change from Baseline (SE)	+0.3 (0.08)	+0.3 (0.08)
Calcium x Phosphorus Product (mg^2/dL^2)	n = 104	n = 110
Mean Baseline	36.7	36.9
Mean Final Treatment Value	40.7	39.7
Mean Change from Baseline (SE)	+4.0 (0.74)	+2.9 (0.72)

CKD Stage 5

The safety and efficacy of Zemplar Capsules were evaluated in a Phase 3, 12-week, double blind, placebo-controlled, randomized, multicenter study in patients with CKD Stage 5 on HD or PD. The study used a three times a week dosing design. A total of 61 patients received Zemplar Capsules and 27 patients received placebo. The mean age of the patients was 57 years, 67% were male, 50% were Caucasian, 45% were African-American, and 53% were diabetic. The average baseline iPTH was 701 pg/mL (range: 216-1933 pg/mL). The average time since first dialysis across all subjects was 3.3 years.

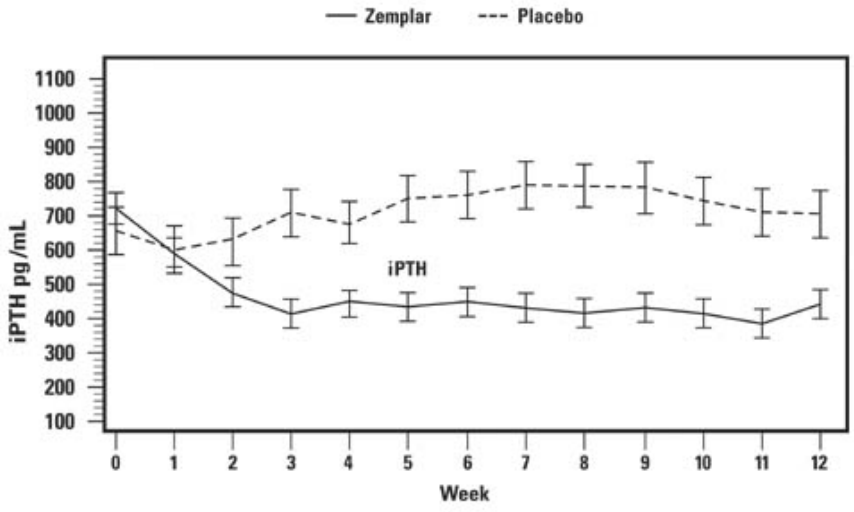
The initial dose of Zemplar Capsules was based on baseline iPTH/60. Subsequent dose adjustments were based on iPTH/60 as well as primary chemistry results that were measured once a week. Starting at Treatment Week 2, study drug was maintained, increased or decreased weekly based on the results of the previous week's calculation of

iPTH/60. Zemplar Capsules were administered three times a week, not more than every other day.

The proportion of patients achieving at least two consecutive ≥ 30% reductions from baseline iPTH was achieved by 88% of Zemplar Capsules treated patients and 13% of the placebo treated patients. The proportion of patients achieving at least two consecutive ≥ 30% reductions from baseline iPTH was similar for HD and PD patients.

The incidences of hypercalcemia (defined as two consecutive serum calcium values > 10.5 mg/dL) in patients treated with Zemplar Capsules was 6.6% as compared to 0% for patients given placebo. In PD patients the incidences of hypercalcemia in patients treated with Zemplar Capsules was 21% as compared to 0% for patients given placebo. The pattern of change in the mean values for serum iPTH during the studies are shown in Figure 2. The rate of hypercalcemia with Zemplar Capsules may be reduced with a lower dosing regimen based on the iPTH/80 formula as shown by computer simulations. The hypercalcemia rate can be further predicted to decrease, if the treatment is initiated in only those with baseline serum calcium ≤ 9.5 mg/dL. (see **CLINICAL PHARMACOLOGY; Pharmacodynamics** and **DOSAGE AND ADMINISTRATION; CKD Stage 5**)

Figure 2. Mean Values for Serum iPTH Over Time in a Phase 3, Double-Blind, Placebo-Controlled CKD Stage 5 Study



INDICATIONS AND USAGE

Zemplar Capsules are indicated for the prevention and treatment of secondary hyperparathyroidism associated with chronic kidney disease (CKD) Stage 3 and 4, and CKD Stage 5 patients on hemodialysis (HD) or peritoneal dialysis (PD).

CONTRAINDICATIONS

Zemplar Capsules should not be given to patients with evidence of vitamin D toxicity, hypercalcemia, or hypersensitivity to any ingredient in this product (see **WARNINGS**).

WARNINGS

Excessive administration of vitamin D compounds, including Zemplar Capsules, can cause over suppression of PTH, hypercalcemia, hypercalciuria, hyperphosphatemia, and adynamic bone disease. Progressive hypercalcemia due to overdosage of vitamin D and its metabolites may be so severe as to require emergency attention. Acute hypercalcemia may exacerbate tendencies for cardiac arrhythmias and seizures and may potentiate the action of digitalis. Chronic hypercalcemia can lead to generalized vascular calcification and other soft-tissue calcification. High intake of calcium and phosphate concomitant with vitamin D compounds may lead to similar abnormalities and patient monitoring and individualized dose titration is required.

Pharmacologic doses of vitamin D and its derivatives should be withheld during Zemplar treatment to avoid hypercalcemia.

PRECAUTIONS

General

Digitalis toxicity is potentiated by hypercalcemia of any cause, so caution should be applied when digitalis compounds are prescribed concomitantly with Zemplar Capsules.

Information for Patients

The patient or guardian should be informed about compliance with dosage instructions, adherence to instructions about diet and phosphorus restriction, and avoidance of the use

of unapproved nonprescription drugs. Phosphate-binding agents may be needed to control serum phosphorus levels in patients, but excessive use of aluminum containing compounds should be avoided. Patients also should be informed about the symptoms of elevated calcium (see **ADVERSE REACTIONS**).

Laboratory Tests

During the initial dosing or following any dose adjustment of medication, serum calcium, serum phosphorus, and serum or plasma iPTH should be monitored at least every two weeks for 3 months after initiation of Zemplar therapy or following dose-adjustments in Zemplar therapy, then monthly for 3 months, and every 3 months thereafter.

Drug Interactions

Paricalcitol is not expected to inhibit the clearance of drugs metabolized by cytochrome P450 enzymes CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP2E1 or CYP3A nor induce the clearance of drugs metabolized by CYP2B6, CYP2C9 or CYP3A.

A multiple dose drug-drug interaction study demonstrated that ketoconazole approximately doubled paricalcitol $AUC_{0-\infty}$ (see **CLINICAL PHARMACOLOGY**). Since paricalcitol is partially metabolized by CYP3A and ketoconazole is known to be a strong inhibitor of cytochrome P450 3A enzyme, care should be taken while dosing paricalcitol with ketoconazole and other strong P450 3A inhibitors including atazanavir, clarithromycin, indinavir, itraconazole, nefazodone, nelfinavir, ritonavir, saquinavir, telithromycin or voriconazole. Dose adjustment of Zemplar Capsules may be required, and iPTH and serum calcium concentrations should be closely monitored if a patient initiates or discontinues therapy with a strong CYP3A4 inhibitor such as ketoconazole.

Drugs that impair intestinal absorption of fat-soluble vitamins, such as cholestyramine, may interfere with the absorption of Zemplar Capsules.

Carcinogenesis, Mutagenesis, Impairment of Fertility

In a 104-week carcinogenicity study in CD-1 mice, an increased incidence of uterine leiomyoma and leiomyosarcoma was observed at subcutaneous doses of 1, 3, 10 mcg/kg

given three times weekly (2 to 15 times the AUC at a human dose of 14 mcg, equivalent to 0.24 mcg/kg based on AUC). The incidence rate of uterine leiomyoma was significantly different than the control group at the highest dose of 10 mcg/kg. In a 104-week carcinogenicity study in rats, there was an increased incidence of benign adrenal pheochromocytoma at subcutaneous doses of 0.15, 0.5, 1.5 mcg/kg (< 1 to 7 times the exposure following a human dose of 14 mcg, equivalent to 0.24 mcg/kg based on AUC). The increased incidence of pheochromocytomas in rats may be related to the alteration of calcium homeostasis by paricalcitol. Paricalcitol did not exhibit genetic toxicity *in vitro* with or without metabolic activation in the microbial mutagenesis assay (Ames Assay), mouse lymphoma mutagenesis assay (L5178Y), or a human lymphocyte cell chromosomal aberration assay. There was also no evidence of genetic toxicity in an *in vivo* mouse micronucleus assay. Paricalcitol had no effect on fertility (male or female) in rats at intravenous doses up to 20 mcg/kg/dose (equivalent to 13 times a human dose of 14 mcg based on surface area, mcg/m^2).

Pregnancy

Pregnancy Category C

Paricalcitol has been shown to cause minimal decreases in fetal viability (5%) when administered daily to rabbits at a dose 0.5 times a human dose of 14 mcg or 0.24 mcg/kg (based on body surface area, mcg/m^2), and when administered to rats at a dose two times the 0.24 mcg/kg human dose (based on body surface area, mcg/m^2). At the highest dose tested, 20 mcg/kg administered three times per week in rats (13 times the 14 mcg human dose based on surface area, mcg/m^2), there was a significant increase in the mortality of newborn rats at doses that were maternally toxic and are known to produce hypercalcemia in rats. No other effects on offspring development were observed. Paricalcitol was not teratogenic at the doses tested.

Paricalcitol (20 mcg/kg) has been shown to cross the placental barrier in rats. There are no adequate and well-controlled clinical studies in pregnant women. Zemplar Capsules should be used during pregnancy only if the potential benefit to the mother justifies the potential risk to the fetus.

Nursing Mothers

Studies in rats have shown that paricalcitol is present in the milk. It is not known whether paricalcitol is excreted in human milk. In the nursing patient, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Geriatric Use

Of the total number (n = 220) of CKD Stages 3 and 4 patients in clinical studies of Zemplar Capsules, 49% were age 65 and over, while 17% were age 75 and over. Of the total number (n = 88) of CKD Stage 5 patients in the pivotal study of Zemplar Capsules, 28% were age 65 and over, while 6% were age 75 and over. No overall differences in safety and effectiveness were observed between these patients and younger patients, and other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

Pediatric Use

Safety and efficacy of Zemplar Capsules in pediatric patients have not been established.

ADVERSE REACTIONS

CKD Stages 3 and 4

The safety of Zemplar Capsules has been evaluated in three 24-week (approximately six-month), double-blind, placebo-controlled, multicenter clinical studies involving 220 CKD Stage 3 and 4 patients. Six percent (6%) of Zemplar Capsules treated patients and 4% of placebo treated patients discontinued from clinical studies due to an adverse event. All reported adverse events occurring in at least 2% in either treatment group are presented in Table 4.

Table 4. Treatment-Emergent Adverse Events by Body System Occurring in ≥ 2% of Subjects in the Zemplar-Treated Group of Three, Double-Blind, Placebo-Controlled, Phase 3, CKD Stage 3 and 4 Studies; All Treated Patients

Body System[a] COSTART V Term	Number (%) of Subjects Zemplar Capsules (n = 107)		Placebo (n = 113)	
Overall	**88**	**(82%)**	**86**	**(76%)**
Body as a Whole	**49**	**(46%)**	**40**	**(35%)**
Accidental Injury	10	(9%)	8	(7%)
Pain	8	(7%)	7	(6%)
Viral Infection	8	(7%)	8	(7%)
Allergic Reaction	6	(6%)	2	(2%)
Headache	5	(5%)	5	(4%)
Abdominal Pain	4	(4%)	2	(2%)
Back Pain	4	(4%)	1	(1%)
Infection	4	(4%)	4	(4%)
Asthena	3	(3%)	2	(2%)
Chest Pain	3	(3%)	1	(1%)
Fever	3	(3%)	1	(1%)
Infection Fungal	3	(3%)	0	(0%)
Cyst	2	(2%)	0	(0%)
Flu Syndrome	2	(2%)	1	(1%)
Infection Bacterial	2	(2%)	1	(1%)
Cardiovascular	**27**	**(25%)**	**19**	**(17%)**
Hypertension	7	(7%)	4	(4%)
Hypotension	5	(5%)	3	(3%)
Syncope	3	(3%)	1	(1%)
Cardiomyopathy	2	(2%)	0	(0%)
Congestive Heart Failure	2	(2%)	5	(4%)
Myocardial Infarct	2	(2%)	0	(0%)
Postural Hypotension	2	(2%)	0	(0%)
Digestive	**29**	**(27%)**	**31**	**(27%)**
Diarrhea	7	(7%)	5	(4%)
Nausea	6	(6%)	4	(4%)
Vomiting	6	(6%)	5	(4%)
Constipation	4	(4%)	4	(4%)
Gastroenteritis	3	(3%)	3	(3%)
Dyspepsia	2	(2%)	2	(2%)
Gastritis	2	(2%)	4	(4%)

Rectal Disorder	2	(2%)	0	(0%)
Hemic and Lymphatic System	**4**	**(4%)**	**10**	**(9%)**
Hypervolemia	2	(2%)	4	(4%)
Ecchymosis	2	(2%)	4	(4%)
Metabolic and Nutritional Disorders	**24**	**(22%)**	**34**	**(30%)**
Edema	7	(7%)	5	(4%)
Uremia	7	(7%)	9	(8%)
Gout	4	(4%)	6	(5%)
Dehydration	3	(3%)	1	(1%)
Acidosis	2	(2%)	1	(1%)
Hyperkalemia	2	(2%)	3	(3%)
Hyperphosphatemia	2	(2%)	4	(4%)
Hypoglycemia	2	(2%)	4	(4%)
Hypokalemia	2	(2%)	1	(1%)
Musculoskeletal	**12**	**(11%)**	**9**	**(8%)**
Arthritis	5	(5%)	1	(1%)
Leg Cramps	3	(3%)	0	(0%)
Myalgia	2	(2%)	5	(4%)
Nervous	**18**	**(17%)**	**12**	**(11%)**
Dizziness	5	(5%)	5	(4%)
Vertigo	5	(5%)	0	(0%)
Depression	3	(3%)	0	(0%)
Insomnia	2	(2%)	2	(2%)
Neuropathy	2	(2%)	1	(1%)
Respiratory	**26**	**(24%)**	**25**	**(22%)**
Pharyngitis	11	(10%)	12	(11%)
Rhinitis	5	(5%)	4	(4%)
Bronchitis	3	(3%)	1	(1%)
Cough Increased	3	(3%)	2	(2%)
Sinusitis	3	(3%)	1	(1%)
Epistaxis	2	(2%)	1	(1%)
Pneumonia	2	(2%)	0	(0%)
Skin and Appendages	**17**	**(16%)**	**10**	**(9%)**
Rash	6	(6%)	3	(3%)
Pruritus	3	(3%)	3	(3%)
Skin Ulcer	3	(3%)	0	(0%)

Skin Hypertrophy	2	(2%)	0	(0%)
Vesiculobullous Rash	2	(2%)	1	(1%)
Special Senses	**9**	**(8%)**	**11**	**(10%)**
Amblyopia	2	(2%)	0	(0%)
Retinal Disorder	2	(2%)	0	(0%)
Urogenital System	**10**	**(9%)**	**10**	**(9%)**
Urinary Tract Infection	3	(3%)	1	(1%)
Kidney Function Abnormal	2	(2%)	1	(1%)

a. Includes all patients with events in that body system.

CKD Stage 5

The safety of Zemplar Capsules has been evaluated in one 12-week, double-blind, placebo-controlled, multicenter clinical study involving 88 CKD Stage 5 patients. Sixty-one patients received Zemplar Capsules and 27 patients received placebo.

The proportion of patients who terminated prematurely from the study due to adverse events was 7% for Zemplar Capsules treated patients and 7% for placebo patients.

Adverse events occurring in the Zemplar Capsules group at a frequency of 2% or greater and more frequently than in the placebo group are as follows:

Table 5. Treatment-Emergent Adverse Events by Body System Occurring in ≥ 2% of Subjects in the Zemplar-Treated Group , Double-Blind, Placebo-Controlled, Phase 3, CKD Stage 5 Study;

All Treated Patients

	Number (%) of Subjects			
Body System[a] **COSTART V Term**	**Zemplar Capsules (n = 61)**		**Placebo (n = 27)**	
Overall	**43**	**(70%)**	**19**	**(70%)**
Body as a Whole	**27**	**(44%)**	**8**	**(30%)**
Infection	9	(15%)	3	(11%)
Asthenia	3	(5%)	0	(0%)
Peritonitis	3	(5%)	0	(0%)
Accidental Injury	2	(3%)	0	(0%)
Headache	2	(3%)	0	(0%)

Digestive	**18**	**(30%)**	**4**	**(15%)**
Diarrhea	7	(11%)	3	(11%)
Constipation	3	(5%)	0	(0%)
Nausea and Vomiting	3	(5%)	0	(0%)
Dyspepsia	2	(3%)	0	(0%)
Hemic and Lymphatic System	**6**	**(10%)**	**0**	**(0%)**
Hypervolemia	3	(5%)	0	(0%)
Ecchymosis	2	(3%)	0	(0%)
Metabolic and Nutritional Disorders	**7**	**(11%)**	**0**	**(0%)**
Hypoglycemia	2	(3%)	0	(0%)
Peripheral Edema	2	(3%)	0	(0%)
Uremia	2	(3%)	0	(0%)
Nervous	**12**	**(20%)**	**2**	**(7%)**
Dizziness	4	(7%)	0	(0%)
Insomnia	3	(5%)	0	(0%)
Anxiety	2	(3%)	0	(0%)
Respiratory	**8**	**(13%)**	**4**	**(15%)**
Sinusitis	2	(3%)	0	(0%)
Urogenital System	**6**	**(10%)**	**4**	**(15%)**
Urinary Tract Infection	2	(3%)	0	(0%)

OVERDOSAGE

Excessive administration of Zemplar Capsules can cause hypercalcemia, hypercalciuria, and hyperphosphatemia, and over suppression of PTH (see **WARNINGS**).

Treatment of Overdosage

The treatment of acute overdosage of Zemplar Capsules should consist of general supportive measures. If drug ingestion is discovered within a relatively short time, induction of emesis or gastric lavage may be of benefit in preventing further absorption. If the drug has passed through the stomach, the administration of mineral oil may promote its fecal elimination. Serial serum electrolyte determinations (especially calcium), rate of urinary calcium excretion, and assessment of electrocardiographic abnormalities due to

hypercalcemia should be obtained. Such monitoring is critical in patients receiving digitalis. Discontinuation of supplemental calcium and institution of a low-calcium diet are also indicated in accidental overdosage. Due to the relatively short duration of the pharmacological action of paricalcitol, further measures are probably unnecessary. If persistent and markedly elevated serum calcium levels occur, there are a variety of therapeutic alternatives that may be considered depending on the patient's underlying condition. These include the use of drugs such as phosphates and corticosteroids, as well as measures to induce an appropriate forced diuresis.

DOSAGE AND ADMINISTRATION

CKD Stages 3 and 4

Zemplar Capsules may be administered daily or three times a week. When dosing three times weekly, the dose should be administered no more frequently than every other day. The average weekly doses for both daily and three times a week dosage regimens are similar (see CLINICAL STUDIES).

Zemplar Capsules may be taken without regard to food. No dosing adjustment is required in patients with mild and moderate hepatic impairment.

Initial Dose

The initial dose of Zemplar Capsules for CKD Stage 3 and 4 patients is based on baseline intact parathyroid hormone (iPTH) levels.

Baseline iPTH Level	Daily Dose	Three Times a Week Dose*
≤ 500 pg/mL	1 mcg	2 mcg
> 500 pg/mL	2 mcg	4 mcg

* To be administered not more often than every other day

Dose Titration

Dosing must be individualized and based on serum or plasma iPTH levels, with monitoring of serum calcium and serum phosphorus. The following is a suggested approach in titration.

		Dose Adjustment at 2 to 4 Week Intervals	
iPTH Level Relative to Baseline	**Zemplar Capsule Dose**	**Daily Dosage**	**Three Times a Week Dosage***
The same or increased	Increase	1 mcg	2 mcg
Decreased by < 30%			
Decreased by ≥ 30%, ≤ 60%	Maintain		
Decreased > 60%	Decrease	1 mcg	2 mcg
iPTH < 60 pg/mL			

* To be administered not more often than every other day

If a patient is taking the lowest dose on the daily regimen and a dose reduction is needed, the dose can be decreased to 1 mcg three times a week. If a further dose reduction is required, the drug should be withheld as needed and can be restarted at a lower dose. If a patient is on a calcium-based phosphate binder, the binder dose may be decreased or withheld, or the patient may be switched to a non-calcium-based phosphate binder. If hypercalcemia or an elevated Ca x P is observed, the dose of Zemplar should be reduced or interrupted until these parameters are normalized.

Serum calcium and phosphorus levels should be closely monitored after initiation of Zemplar Capsules and during dose titration periods and coadministration with strong P450 3A inhibitors (see **CLINICAL PHARMACOLOGY** and **PRECAUTIONS**).

CKD Stage 5

Zemplar Capsules are to be administered three times a week, no more frequently than every other day.

Zemplar Capsules may be taken without regard to food. No dosing adjustment is required in patients with mild and moderate hepatic impairment.

Initial Dose

The initial dose of Zemplar Capsules in micrograms is based on a baseline iPTH level (pg/mL)/80. To minimize the risk of hypercalcemia patients should be treated only after their baseline serum calcium has been adjusted to 9.5 mg/dL or lower (see **CLINICAL PHARMACOLOGY; Pharmacodynamics** and **CLINICAL STUDIES; CKD Stage 5**).

Dose Titration

Subsequent dosing should be individualized and based on iPTH, serum calcium and phosphorus levels. A suggested dose titration of paricalcitol capsules is based on the following formula:

Titration dose (micrograms) = most recent iPTH level (pg/ml)/80

Serum calcium and phosphorus levels should be closely monitored after initiation, during dose titration periods, and with co-administration of strong P450 3A inhibitors. If an elevated serum calcium or elevated Ca x P is observed and the patient is on a calcium-based phosphate binder, the binder dose may be decreased or withheld, or the patient may be switched to a non-calcium-based phosphate binder. If serum calcium or Ca x P are elevated, the dose should be decreased by 2 to 4 micrograms lower than that calculated by the most recent iPTH/80. If further adjustment is required, the dose of paricalcitol capsules should be reduced or interrupted until these parameters are normalized.

As iPTH approaches the target range, small, individualized dose adjustments may be necessary in order to achieve a stable iPTH. In situations where monitoring of iPTH, Ca or P occurs less frequently than once per week, a more modest initial and dose titration ratio may be warranted.

HOW SUPPLIED

Zemplar Capsules are available as 1 mcg, 2 mcg, and 4 mcg capsules.

The 1 mcg capsule is an oval, gray, soft gelatin capsule imprinted with **Abbott “A” logo** and ZA, and is available in the following package size:

Bottles of 30 (NDC 0074-4317-30)

The 2 mcg capsule is an oval, orange-brown, soft gelatin capsule imprinted with **Abbott "A" logo** and ZF, and is available in the following package size:

Bottles of 30 (NDC 0074-4314-30)

The 4 mcg capsule is an oval, gold soft gelatin capsule imprinted with **Abbott "A" logo** and ZK, and is available in the following package size:

Bottles of 30 (NDC 0074-4315-30)

Storage

Store Zemplar Capsules at 25°C (77°F). Excursions permitted between 15°- 30°C (59°- 86°F). See USP Controlled Room Temperature.

U.S. patents: 5,246,925; 5,587,497

REFERENCES

1. K/DOQI Clinical Practice Guidelines for Bone Metabolism and Disease in Chronic Kidney Disease. Am J Kidney Dis 2003; Volume 42(4): Supplement 3.

Abbott Laboratories

North Chicago, IL 60064, U.S.A.