HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use ZEMPLAR safely and effectively.
See full prescribing information for ZEMPLAR.
ZEMPLAR (paricalcitol) capsules
Initial U.S. Approval: 1998

-------RECENT MAJOR CHANGES-------
Warnings and Precautions, Laboratory tests (5.3) 8/2014

-------INDICATIONS AND USAGE-------
Zemplar is a vitamin D analog indicated for the prevention and treatment of secondary hyperparathyroidism associated with

- Chronic kidney disease (CKD) Stages 3 and 4 (1.1).
- CKD Stage 5 in patients on hemodialysis (HD) or peritoneal dialysis (PD) (1.2).

-------DOSAGE AND ADMINISTRATION-------

- CKD Stages 3 and 4: Zemplar Capsules may be administered once daily or every other day, three times a week (2.1).
- CKD Stage 5: Zemplar Capsules are dosed every other day, three times a week (2.2). To minimize the risk of hypercalcemia patients should be treated only after their baseline serum calcium has been reduced to 9.5 mg/dL or lower.

Initial Dosage

CKD Stages 3, 4		CKD Stage 5
Baseline intact parathyroid (iPTH) Level	Starting Dose	Dose in micrograms is based on baseline iPTH level (pg/mL)/80. Dose three times a week (e.g. every other day).
≤ 500 pg/mL	1 mcg daily or 2 mcg three times a week (e.g. every other day)	
> 500 pg/mL	2 mcg daily or 4 mcg three times a week (e.g. every other day)	

Dose Titration

CKD Stages 3, 4		CKD Stage 5
iPTH Level Relative to Baseline	Dosing Recommendation	Dose in micrograms is based on most recent iPTH level (pg/mL)/80 with adjustments based on serum calcium and phosphorous levels. Dose three times a week (e.g. every other day).
Decreased by < 30%	Increase dose by 1 mcg daily or 2 mcg three times a week (e.g. every other day)	
Decreased by ≥ 30% and ≤ 60%	Maintain dose	
Decreased by > 60% or iPTH < 60 pg/mL	Decrease dose by 1 mcg daily or 2 mcg three times a week (e.g. every other day)	

-------DOSAGE FORMS AND STRENGTHS-------
Capsules: 1 mcg, 2 mcg, and 4 mcg (3).

-------CONTRAINDICATIONS-------
Evidence of hypercalcemia or vitamin D toxicity (4).

-------WARNINGS AND PRECAUTIONS-------

- Hypercalcemia: Excessive administration of Zemplar Capsules can cause over suppression of PTH, hypercalcemia, hypercalciuria, hyperphosphatemia, and adynamic bone disease. Prescription-based doses of vitamin D and its derivatives should be withheld during Zemplar treatment (5.1).
- Digitalis toxicity: Potentiated by hypercalcemia of any cause. Use caution when Zemplar Capsules are prescribed concomitantly with digitalis compounds (5.2).
- Laboratory tests: Monitor serum calcium, serum phosphorus, and serum or plasma iPTH during initial dosing or following any dose adjustment. Zemplar Capsules may increase serum creatinine and therefore decrease the estimated GFR (eGFR) (5.3).
- Aluminum overload and toxicity: Avoid excessive use of aluminum containing compounds (5.4).

-------ADVERSE REACTIONS-------
The most common adverse reactions (> 5% and more frequent than placebo) include diarrhea, hypertension, dizziness and vomiting.
To report SUSPECTED ADVERSE REACTIONS, contact AbbVie Inc. at 1-800-633-9110 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch

-------DRUG INTERACTIONS-------

- Strong CYP3A inhibitors (e.g. ketoconazole) will increase the exposure of paricalcitol. Use with caution (7.1).
- Cholestyramine, Mineral Oil: Intestinal absorption of Zemplar may be reduced if administered simultaneously with mineral oil or cholestyramine (7.2,7.3).

See 17 for PATIENT COUNSELING INFORMATION

Revised: 08/2014

FULL PRESCRIBING INFORMATION: CONTENTS*

* Sections or subsections omitted from the full prescribing information are not listed

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

1.1 Chronic Kidney Disease Stages 3 and 4

Zemplar Capsules are indicated for the prevention and treatment of secondary hyperparathyroidism associated with Chronic Kidney Disease (CKD) Stages 3 and 4.

1.2 Chronic Kidney Disease Stage 5

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

2 DOSAGE AND ADMINISTRATION

2.1 Chronic Kidney Disease 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 not more frequently than every other day. The total weekly doses for both daily and three times a week dosage regimens are similar [*see Clinical Studies (14.1)*].

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 Stages 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 to dose 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, increased or decreased by < 30%	Increase dose by	1 mcg	2 mcg
Decreased by ≥ 30% and ≤ 60%	Maintain dose	-	-

Decreased by > 60% or iPTH < 60 pg/mL	Decrease dose by	1 mcg	2 mcg
* To be administered not more often than every other day			

If a patient is taking the lowest dose, 1 mcg, 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 restarted at a lower dosing frequency. If a patient is on a calcium-based phosphate binder, the phosphate-binder dose may be decreased or withheld, or the patient may be switched to a non-calcium-based phosphate binder. If hypercalcemia is observed, the dose of Zemplar should be reduced or withheld until these parameters are normalized.

Serum calcium and phosphorus levels should be closely monitored after initiation of Zemplar Capsules, during dose titration periods and during co-administration with strong CYP3A inhibitors [see *Warnings and Precautions (5.3)*, *Drug Interactions (7)* and *Clinical Pharmacology (12.3)*].

2.2 Chronic Kidney Disease Stage 5

Zemplar Capsules are to be administered three times a week, not 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 (12.2)* and *Clinical Studies (14.2)*].

Dose Titration

Subsequent dosing should be individualized and based on iPTH, serum calcium and phosphorus levels. A suggested dose titration of Zemplar 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 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 is 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 withheld 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 (e.g., iPTH/100) may be warranted.

3 DOSAGE FORMS AND STRENGTHS

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

- 1 mcg: oval, gray capsule imprinted with the “a” logo and “ZA”
- 2 mcg: oval, orange-brown capsule imprinted with the “a” logo and “ZF”
- 4 mcg: oval, gold capsule imprinted with the “a” logo and “ZK”

4 CONTRAINDICATIONS

Zemplar Capsules should not be given to patients with evidence of

- hypercalcemia or
- vitamin D toxicity [see *Warnings and Precautions (5.1)*].

5 WARNINGS AND PRECAUTIONS

Excessive administration of vitamin D compounds, including Zemplar Capsules, can cause over suppression of PTH, hypercalcemia, hypercalciuria, hyperphosphatemia, and adynamic bone disease.

5.1 Hypercalcemia

Progressive hypercalcemia due to overdosage of vitamin D and its metabolites may be so severe as to require emergency attention [see *Overdosage (10)*]. 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. Concomitant administration of high doses of calcium-containing preparations or thiazide diueretics with Zemplar may increase the risk of hypercalcemia. High intake of calcium and phosphate concomitant with vitamin D compounds may lead to serum abnormalities requiring more frequent patient monitoring and individualized dose titration. Patients also should be informed about the symptoms of elevated calcium, which include feeling tired, difficulty thinking clearly, loss of appetite, nausea, vomiting, constipation, increased thirst, increased urination and weight loss.

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

5.2 Digitalis Toxicity

Digitalis toxicity is potentiated by hypercalcemia of any cause. Use caution when Zemplar Capsules are prescribed concomitantly with digitalis compounds.

5.3 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, then monthly for 3 months, and every 3 months thereafter.

In pre-dialysis patients, Zemplar Capsules may increase serum creatinine and therefore decrease the estimated GFR (eGFR). Similar effects have also been seen with calcitriol.

5.4 Aluminum Overload and Toxicity

Aluminum-containing preparations (e.g., antacids, phosphate binders) should not be administered chronically with Zemplar, as increased blood levels of aluminum and aluminum bone toxicity may occur.

6 ADVERSE REACTIONS

Because clinical studies are conducted under widely varying conditions, adverse reaction rates observed in the clinical studies of a drug cannot be directly compared to rates in the clinical studies of another drug and may not reflect the rates observed in practice.

6.1 Clinical Trials Experience

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 Stages 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. Adverse events occurring in the Zemplar Capsules group at a frequency of 2% or greater and more frequently than in the placebo group are presented in Table 1:

Table 1. 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 Stages 3 and 4 Studies; All Treated Patients

	Number (%) of Subjects			
Adverse Event[a]	**Zemplar Capsules (n = 107)**		**Placebo (n = 113)**	
Overall	**88**	**(82%)**	**86**	**(76%)**
Ear and Labyrinth Disorders				
Vertigo	5	(4.7%)	0	(0.0%)
Gastrointestinal Disorders				
Abdominal Discomfort	4	(3.7%)	1	(0.9%)
Constipation	4	(3.7%)	4	(3.5%)
Diarrhea	7	(6.5%)	5	(4.4%)
Nausea	6	(5.6%)	4	(3.5%)
Vomiting	5	(4.7%)	5	(4.4%)
General Disorders and Administration Site Conditions				
Chest Pain	3	(2.8%)	1	(0.9%)
Edema	6	(5.6%)	5	(4.4%)
Pain	4	(3.7%)	4	(3.5%)
Immune System Disorders				
Hypersensitivity	6	(5.6%)	2	(1.8%)
Infections and Infestations				
Fungal Infection	3	(2.8%)	0	(0.0%)
Gastroenteritis	3	(2.8%)	3	(2.7%)
Infection	3	(2.8%)	3	(2.7%)

Sinusitis	3	(2.8%)	1	(0.9%)
Urinary Tract Infection	3	(2.8%)	1	(0.9%)
Viral Infection	8	(7.5%)	8	(7.1%)
Metabolism and Nutrition Disorders				
Dehydration	3	(2.8%)	1	(0.9%)
Musculoskeletal and Connective Tissue Disorders				
Arthritis	5	(4.7%)	0	(0.0%)
Back Pain	3	(2.8%)	1	(0.9%)
Muscle Spasms	3	(2.8%)	0	(0.0%)
Nervous System Disorders				
Dizziness	5	(4.7%)	5	(4.4%)
Headache	5	(4.7%)	5	(4.4%)
Syncope	3	(2.8%)	1	(0.9%)
Psychiatric Disorders				
Depression	3	(2.8%)	0	(0.0%)
Respiratory, Thoracic and Mediastinal Disorders				
Cough	3	(2.8%)	2	(1.8%)
Oropharyngeal Pain	4	(3.7%)	0	(0.0%)
Skin and Subcutaneous Tissue Disorders				
Pruritus	3	(2.8%)	3	(2.7%)
Rash	4	(3.7%)	1	(0.9%)
Skin Ulcer	3	(2.8%)	0	(0.0%)
Vascular Disorders				
Hypertension	7	(6.5%)	4	(3.5%)
Hypotension	5	(4.7%)	3	(2.7%)
a. Includes only events more common in the Zemplar treatment group.				

The following adverse reactions, with a causal relationship to Zemplar, occurred in <2% of the Zemplar treated patients in the above double-blind, placebo-controlled clinical trial data set.

Gastrointestinal Disorders: Dry mouth

Investigations: Hepatic enzyme abnormal

Nervous System Disorders: Dysgeusia

Skin and Subcutaneous Tissue Disorders: Urticaria

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 2. 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			
Adverse Events[a]	**Zemplar Capsules (n=61)**		**Placebo (n = 27)**	
Overall	**43**	**(70%)**	**19**	**(70%)**
Gastrointestinal Disorders				
Constipation	3	(4.9%)	0	(0.0%)
Diarrhea	7	(11.5%)	3	(11.1%)
Vomiting	4	(6.6%)	0	(0.0%)
General Disorders and Administration Site Conditions				
Fatigue	2	(3.3%)	0	(0.0%)
Edema Peripheral	2	(3.3%)	0	(0.0%)
Infections and Infestations				
Nasopharyngitis	5	(8.2%)	2	(7.4%)
Peritonitis	3	(4.9%)	0	(0.0%)
Sinusitis	2	(3.3%)	0	(0.0%)
Urinary Tract Infection	2	(3.3%)	0	(0.0%)
Metabolism and Nutrition Disorders				
Fluid Overload	3	(4.9%)	0	(0.0%)
Hypoglycemia	2	(3.3%)	0	(0.0%)
Nervous System Disorders				
Dizziness	4	(6.6%)	0	(0.0%)
Headache	2	(3.3%)	0	(0.0%)
Psychiatric Disorders				
Anxiety	2	(3.3%)	0	(0.0%)
Insomnia	3	(4.9%)	0	(0.0%)
Renal and Urinary Disorders				
Renal Failure Chronic	2	(3.3%)	0	(0.0%)

a. Includes only events more common in the Zemplar treatment group.

The following adverse reactions, with a causal relationship to Zemplar, occurred in <2% of the Zemplar treated patients in the above double-blind, placebo-controlled clinical trial data set.

Gastrointestinal Disorders: Gastroesophageal reflux disease

Metabolism and Nutrition Disorders: Decreased appetite, hypercalcemia, hypocalcemia

Reproductive System and Breast Disorders: Breast tenderness

Skin and Subcutaneous Tissue Disorders: Acne

6.2 Postmarketing Experience

The following additional adverse reactions have been reported during post-approval use and post-approval clinical trials with the active ingredient in Zemplar capsules:

Immune System Disorders: Angioedema (including laryngeal edema)

Metabolism and Nutrition Disorders: Hypercalcemia

Investigations: Blood creatinine increased

7 DRUG INTERACTIONS

7.1 CYP3A Inhibitors

Since paricalcitol is partially metabolized by CYP3A, exposure of paricalcitol will be increased while paricalcitol is co-administered with strong CYP3A inhibitors including the following drugs but not limited to: ketoconazole, 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 [see *Clinical Pharmacology (12.3)*].

7.2 Cholestyramine

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

7.3 Mineral Oil

The use of mineral oil or other substances that may affect absorption of fat may influence the absorption of Zemplar Capsules.

8 USE IN SPECIFIC POPULATIONS

8.1 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.

8.3 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.

8.4 Pediatric Use

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

8.5 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.

10 OVERDOSAGE

Excessive administration of Zemplar Capsules can cause hypercalcemia, hypercalciuria, and hyperphosphatemia, and over suppression of PTH [see *Warnings and Precautions (5.1)*].

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.

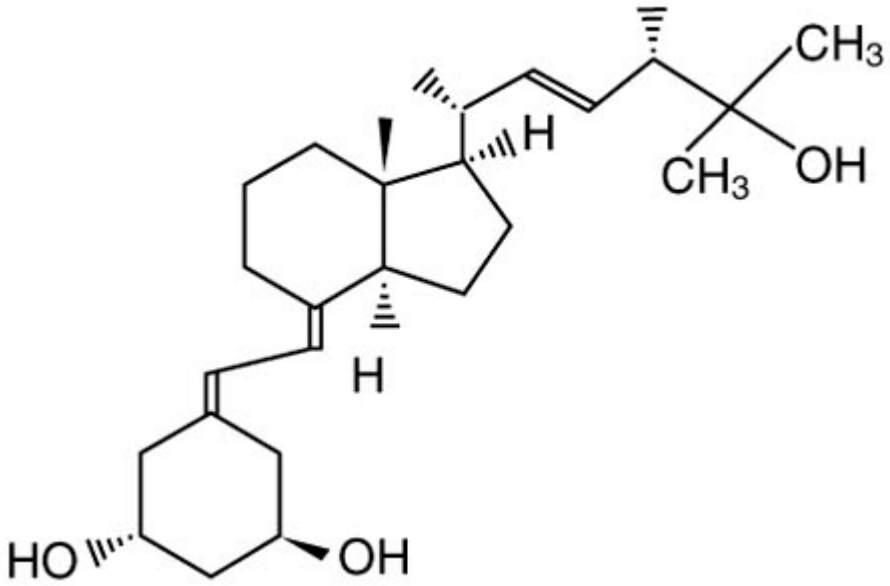
Zemplar is not significantly removed by dialysis.

11 DESCRIPTION

Paricalcitol, USP, the active ingredient in Zemplar Capsules, is a synthetically manufactured, metabolically active vitamin D analog of calcitriol with modifications to the side chain (D_2) and the A (19-nor) ring. Zemplar is 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:



12 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 as vitamin D_3 and from dietary intake as either vitamin D_2 or D_3. Both vitamin D_2 and D_3 require 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 [$1,25(OH)_2D_3$], 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. Decreased levels of $1,25(OH)_2D_3$ have been observed in early stages of chronic kidney disease. The decreased levels of $1,25(OH)_2D_3$ 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.

12.1 Mechanism of Action

Paricalcitol is a synthetic, biologically active vitamin D_2 analog of calcitriol. 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.

12.2 Pharmacodynamics

Paricalcitol decreases serum intact parathyroid hormone (iPTH) and increases serum calcium and serum phosphorous in both HD and 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 weekly ≥ 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 weekly ≥ 30% reductions from baseline iPTH. The predicted incidence of hypercalcemia is 12.4% (95% CI: 11.7% - 13.0%) [*see Clinical Studies (14.2) and Dosage and Administration (2.2)*].

12.3 Pharmacokinetics

Absorption

The mean absolute bioavailability of Zemplar Capsules under low-fat fed condition ranged from 72% to 86% in healthy subjects, CKD Stage 5 patients on HD, and CKD Stage 5 patients on PD. 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 delayed T_{max} by 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.

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 a 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 was 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. While the mean elimination half-life of paricalcitol is 4 to 6 hours in healthy subjects, the mean elimination half-life of paricalcitol in CKD Stages 3, 4, and 5 (on HD and PD) patients ranged from 14 to 20 hours.

Table 3. Paricalcitol Capsule Pharmacokinetic Characteristics in CKD Stages 3, 4, and 5 Patients

Pharmacokinetic Parameters	**CKD Stage 3 n = 15***	**CKD Stage 4 n = 14***	**CKD Stage 5 HD** n = 14**	**CKD Stage 5 PD** n = 8**
C_{max} (ng/mL)	0.11 ± 0.04	0.06 ± 0.01	0.575 ± 0.17	0.413 ± 0.06
$AUC_{0-\infty}$ (ng•h/mL)	2.42 ± 0.61	2.13 ± 0.73	11.67 ± 3.23	13.41 ± 5.48
CL/F (L/h)	1.77 ± 0.50	1.52 ± 0.36	1.82 ± 0.75	1.76 ± 0.77
V/F (L)	43.7 ± 14.4	46.4 ± 12.4	38 ± 16.4	48.7 ± 15.6
$t_{1/2}$	16.8 ± 2.65	19.7 ± 7.2	13.9 ± 5.1	17.7 ± 9.6

* Four mcg paricalcitol capsules were given to CKD Stage 3 patients; three mcg paricalcitol capsules were given to CKD Stage 4 patients.
** CKD Stage 5 HD and PD patients received a 0.24 mcg/kg dose of paricalcitol as capsules.

Specific Populations

Geriatric

The pharmacokinetics of paricalcitol has not been investigated in geriatric patients greater than 65 years [*see Use in Specific Populations (8.5)*].

Pediatric

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

Gender

The pharmacokinetics of paricalcitol following single doses over the 0.06 to 0.48 mcg/kg dose range was 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 was similar across the range of hepatic function evaluated in this study. No dose 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 HD or PD was comparable to that in CKD 3 or 4 patients. Therefore, no special dose adjustments are required other than those recommended in the Dosage and Administration section [*see Dosage and Administration (2)*].

Drug Interactions

An *in vitro* study indicates that paricalcitol is neither an inhibitor of CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP2E1 or CYP3A nor an inducer of CYP2B6, CYP2C9 or CYP3A. Hence, paricalcitol is neither expected to inhibit nor induce the clearance of drugs metabolized by these enzymes.

Omeprazole

The effect of omeprazole (40 mg capsule), a strong inhibitor of CYP2C19, on paricalcitol (four 4 mcg capsules) pharmacokinetics was investigated in a single dose, crossover study in healthy subjects. The pharmacokinetics of paricalcitol was not affected when omeprazole was administered approximately 2 hours prior to the paricalcitol dose.

Ketoconazole

The effect of multiple doses of ketoconazole, a strong inhibitor of CYP3A, administered as 200 mg BID for 5 days on the pharmacokinetics of paricalcitol (4 mcg 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 Drug Interactions (7)*].

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis and 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).

14 CLINICAL STUDIES

14.1 Chronic Kidney Disease 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 Stages 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.

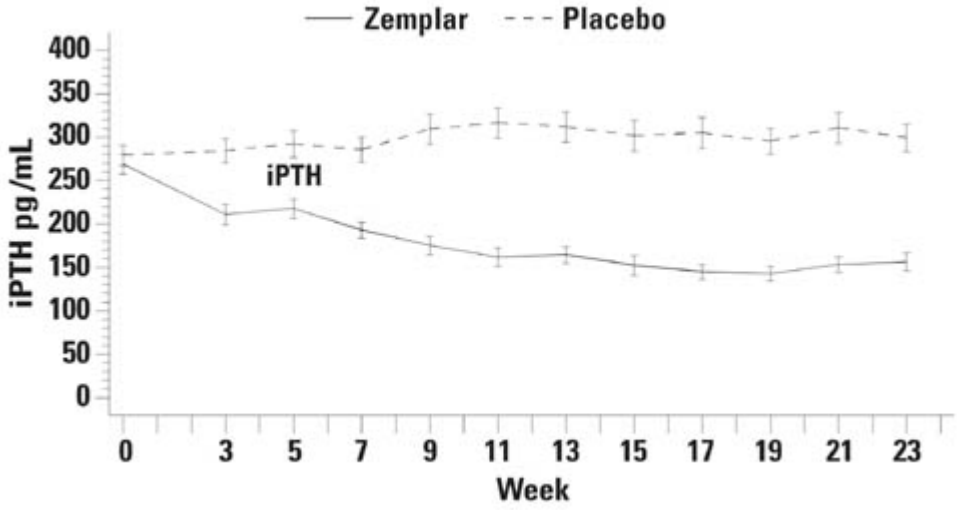
The initial dose of Zemplar Capsules was based on baseline iPTH. If iPTH was ≤ 500 pg/mL, Zemplar Capsules were administered 1 mcg daily or 2 mcg three times a week, not more than every other day. If iPTH was > 500 pg/mL, Zemplar Capsules were administered 2 mcg daily or 4 mcg three times a week, not more than every other day. The dose was increased 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), and hyperphosphatemia 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 is shown in Figure 1.

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



The mean changes from baseline to final treatment visit in serum iPTH, calcium, phosphorus, calcium-phosphorus product, and bone-specific alkaline phosphatase are shown in Table 4.

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

	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)

14.2 Chronic Kidney Disease Stage 5

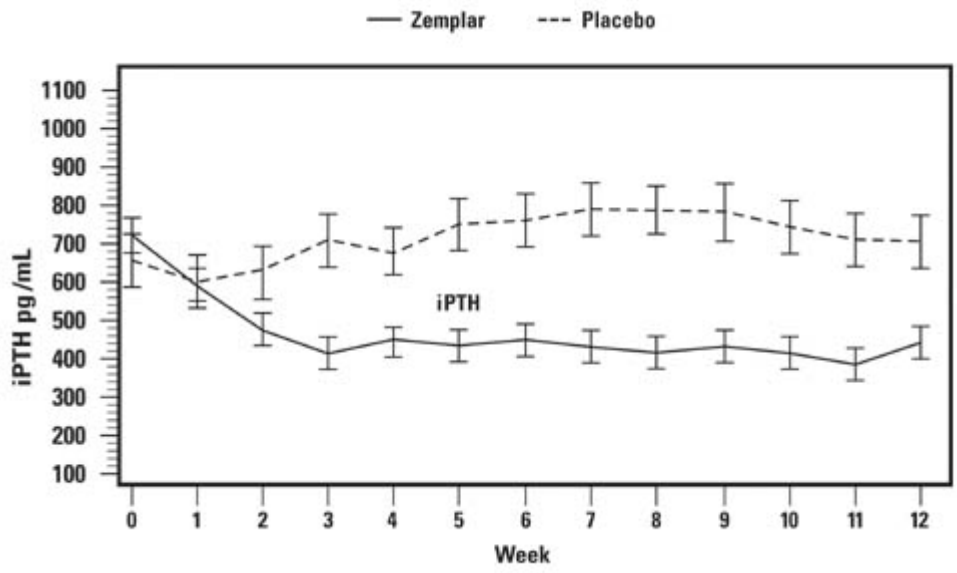
The safety and efficacy of Zemplar Capsules were evaluated in a Phase 3, 12-week, double blind, placebo-controlled, randomized, multicenter study in patients with CKD Stage 5 on HD or PD. The study used a three times a week dosing design. A total of 61 patients received Zemplar Capsules and 27 patients 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 weekly ≥ 30% reductions from baseline iPTH was 88% of Zemplar Capsules treated patients and 13% of the placebo treated patients. The proportion of patients achieving at least two consecutive weekly ≥ 30% reductions from baseline iPTH was similar for HD and PD patients.

The incidence 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 incidence of hypercalcemia in patients treated with Zemplar Capsules was 21% as compared to 0% for patients given placebo. The patterns of change in the mean values for serum iPTH 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 (12.2) and Dosage and Administration (2.2)*].

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



16 HOW SUPPLIED/STORAGE AND HANDLING

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 the **“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 the **“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 the **“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.

17 PATIENT COUNSELING INFORMATION

Patients should be advised:

- of the most common adverse reactions with use of Zemplar Capsules, which include diarrhea, hypertension, dizziness and vomiting.
- to adhere to instructions regarding diet and phosphorus restriction.
- to contact a health care provider if you develop symptoms of elevated calcium, (e.g. feeling tired, difficulty thinking clearly, loss of appetite, nausea, vomiting, constipation, increased thirst, increased urination and weight loss).
- to return to the physician's office for routine monitoring. More frequent monitoring is necessary during the initiation of therapy, following dose changes or when potentially interacting medications are started or discontinued.
- to inform their physician of all medications, including prescription and nonprescription drugs, supplements, and herbal preparations they are taking and any change to their medical condition. Patients should also be advised to inform their physicians prescribing a new medication that they are taking Zemplar Capsules.

Manufactured for

AbbVie Inc.

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

03-AXXX Month, Year