PRODUCT MONOGRAPH

PrZEMPLAR®

Paricalcitol Capsules

1 mcg, 2 mcg, 4 mcg

Paricalcitol Injection USP

5 mcg/mL

Vitamin D Analog

AbbVie Corporation
8401 Trans-Canada Highway
St-Laurent, Quebec
H4S 1Z1
Canada

Date of Preparation:
November 1, 2012

Date of Previous Revision:

Date of Revision:

Submission Control No: 158316

Table of Contents

ZEMPLAR®

Paricalcitol Capsules

Paricalcitol Injection USP

PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	Clinically Relevant Nonmedicinal Ingredients
Usual route: Hemodialysis blood line	Solution for injection / 5 mcg/mL	Propylene glycol, 30% (v/v) Alcohol (ethanol), 20% (v/v)
Oral	Soft Gelatin Capsules / 1 mcg, 2 mcg, 4 mcg	Medium chain triglycerides, alcohol, butylated hydroxytoluene, gelatin, glycerin, titanium dioxide, ink, Opacode® WB, black, iron oxide red (2 mcg capsules only), iron oxide yellow (2 and 4 mcg capsules), iron oxide black (1 mcg capsules only), purified water.

INDICATIONS AND CLINICAL USE

ZEMPLAR® (paricalcitol capsules) are indicated for:

- The prevention and treatment of secondary hyperparathyroidism associated with chronic renal insufficiency (chronic kidney disease) Stage 5 patients on hemodialysis (HD) or peritoneal dialysis (PD).

ZEMPLAR® (paricalcitol injection USP) is indicated for:

- The prevention and treatment of secondary hyperparathyroidism associated with chronic renal insufficiency (chronic kidney disease) Stage 5 patients on hemodialysis (HD).

Chronic Renal Impairment: Studies in patients with chronic renal failure on hemodialysis show that paricalcitol suppresses parathyroid hormone (PTH) levels. The serum phosphorus, calcium and calcium x phosphorus product (Ca x P) may increase when paricalcitol is administered, with no significant impact on phosphorus.

Geriatrics (≥ 65 years of age): Of the total number (n=88) of patients with Chronic Kidney Disease (CKD) Stage 5 in the pivotal study of paricalcitol capsules, 28% were age 65 and over, while 6% were 75 and over. No overall differences in safety and effectiveness were observed between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

Pediatrics (< 18 years of age): There is limited experience with the use of paricalcitol injection USP in patients less than 18 years of age (see **CLINICAL TRIALS - Pediatric Patients**).

CONTRAINDICATIONS

- Paricalcitol should not be given to patients with evidence of Vitamin D toxicity, hypercalcemia (defined as two consecutive measurements of > 2.88 mmol/L), or hypersensitivity to any ingredient in this product.

For a complete listing, see the **DOSAGE FORMS, COMPOSITION AND PACKAGING** section of the Product Monograph.

WARNINGS AND PRECAUTIONS

General

Over suppression of PTH may result in elevations of serum calcium levels (defined as two consecutive measurements of > 2.88 mmol/L) and may lead to low-turnover bone disease. Patient monitoring and individualized dose titration is required to reach appropriate physiological endpoints (see **Monitoring and Laboratory Tests**).

ZEMPLAR® (paricalcitol injection USP) contains 20% v/v of ethanol. Dosing is variable dependent on the severity of disease and response to treatment, however each dose may contain up to 1.3 g of ethanol based on the maximum dose seen in clinical trials. Ethanol may be harmful for those suffering from liver disease, alcoholism, epilepsy, brain injury or disease as well as for pregnant women and children, and may modify or increase the effect of other medicines.

Hypercalcemia

During dose adjustment, serum calcium and phosphate levels should be monitored closely (e.g., twice weekly). If hypercalcemia (defined as two consecutive measurements of > 2.88 mmol/L) develops, the dose should be reduced or interrupted. Chronic administration of paricalcitol may place patients at risk of hypercalcemia, elevated Ca x P product, and metastatic calcification. Hypercalcemia related to Vitamin D intoxication may be asymptomatic; however, it may also present with the following signs and symptoms:

Early: Weakness, headache, somnolence, nausea, vomiting, dry mouth, constipation, muscle pain, bone pain and metallic taste.

Late: Anorexia, weight loss, conjunctivitis (calcific), pancreatitis, photophobia, rhinorrhea, pruritus, hyperthermia, decreased libido, elevated urea nitrogen (BUN), hypercholesterolemia, elevated aspartate aminotransferase (AST) and alanine aminotransferase (ALT), ectopic calcification, hypertension, cardiac arrhythmias, somnolence, death, and rarely, overt psychosis.

Treatment of patients with clinically significant hypercalcemia consists of immediate dose reduction or interruption of paricalcitol therapy and includes a low calcium diet, withdrawal of calcium supplements, patient mobilization, attention to fluid and electrolyte imbalances, assessment of electrocardiographic abnormalities (critical in patients receiving digitalis), and hemodialysis or peritoneal dialysis against a calcium-free dialysate, as warranted. Serum calcium levels should be monitored frequently until normocalcemia ensues.

If clinically significant hypercalcemia develops, and the patient is receiving a calcium-based phosphate binder, the dose of the calcium-based phosphate binder should be reduced or interrupted.

Adynamic bone lesions (low-turnover bone disease) may develop if PTH levels are suppressed to abnormal levels.

Acute overdose of paricalcitol may cause hypercalcemia and require emergency attention.

Carcinogenesis and Mutagenesis

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 to 10 mcg/kg (< 1 to 3 times the maximum recommended human weekly dose of 0.72 mcg/kg, based on body surface area, mg/m^2). 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 to 1.5 mcg/kg (≤ 1 times the maximum recommended human weekly dose of 0.72 mcg/kg, based on body surface area, mg/m^2). The increased incidence of pheochromocytomas in rats may be related to the alteration of calcium homeostasis by paricalcitol.

Preclinical effects were observed only at exposures considered sufficiently in excess of the maximum human exposure indicating little relevance to clinical use.

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 the highest recommended human dose (0.24 mcg/kg) based on surface area, mg/m^2].

Neurologic

Paricalcitol injection USP contains 30% v/v of propylene glycol as an excipient. Isolated cases of central nervous system depression, hemolysis and lactic acidosis have been reported as toxic effect associated with propylene glycol administration at high doses. Although they are not expected to be found with paricalcitol injection administration as propylene glycol is eliminated during the hemodialysis process, the risk of toxic effects in overdosing situations has to be taken into account.

Special Populations

Pregnant Women: There are no adequate and well-controlled studies in pregnant women. Animal studies have shown reproductive toxicity. Potential risk in human use is not known. Paricalcitol should be used during pregnancy only if the potential benefit to the mother outweighs the potential risk for the fetus (see **TOXICOLOGY**).

Paricalcitol (20 mcg/kg) has been shown to cross the placental barrier in rats, however the concentration of paricalcitol in the rat fetus was lower than in maternal plasma, suggesting some degree of placental barrier.

There is no experience of exposure in pregnancy during clinical trials as one of the criteria for inclusion was that the female subjects were not pregnant and were taking contraceptive precautions if they were of child-bearing age at the time of the study.

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

Pediatrics (birth to 18 years of age): There is limited experience with the use of paricalcitol injection USP in patients less than 18 years of age (see **CLINICAL TRIALS, Pediatric Patients**).

Geriatrics (≥ 65 years of age): Of the total number (n=88) of patients with Chronic Kidney Disease (CKD) Stage 5 in the pivotal study of paricalcitol capsules, 28% were age 65 and over, while 6% were 75 and over. No overall differences in safety and effectiveness were observed between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

Of the 40 patients receiving paricalcitol injection USP in the three Phase III placebo-controlled chronic renal failure (CRF) studies, ten patients were 65 years or over. In these studies, no overall differences in efficacy or safety were observed between patients 65 years or older and younger patients.

Monitoring and Laboratory Tests

ZEMPLAR® (paricalcitol capsules)

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 oral paricalcitol therapy or following dose-adjustments in oral paricalcitol therapy, then monthly for 3 months, and at least every 3 months thereafter.

ZEMPLAR® (paricalcitol injection USP)

In placebo-controlled studies, paricalcitol injection USP reduced serum total alkaline phosphatase levels. During dose adjustment and before dosage is established with paricalcitol, laboratory tests such as serum calcium and phosphorus should be measured frequently (possibly twice a week). Once dosage has been established, serum calcium and phosphorus should be measured at least monthly. Measurement of serum or plasma PTH is recommended every three months.

ADVERSE REACTIONS

Adverse Drug Reaction Overview

ZEMPLAR® (paricalcitol capsules)

The safety of ZEMPLAR® (paricalcitol capsules) has been evaluated in one pivotal and three supportive 12-week, double-blind, placebo-controlled, multicenter clinical studies involving 313 patients with Chronic Kidney Disease (CKD) Stage 5.

There were no statistically significant or clinically important differences between paricalcitol capsules and placebo in the types and incidences of adverse events. The proportion of patients who terminated prematurely from the pivotal study due to adverse events was 7% for paricalcitol capsule-treated patients and 7% for placebo patients.

In other clinical studies involving paricalcitol capsules, the most commonly reported adverse reaction for paricalcitol capsule treated patients was rash, occurring in 2% of patients. The proportion of patients who discontinued treatment due to adverse events during the double-blind, placebo-controlled studies was 6% for paricalcitol capsule treated patients and 4% for placebo treated patients. This difference was not statistically significant.

ZEMPLAR® (paricalcitol injection USP)

The safety of ZEMPLAR® (paricalcitol injection USP) has been investigated in 660 patients in Phase II/III/IV clinical trials.

The most common adverse events (> 1%) associated with paricalcitol injection USP therapy were hypercalcemia (defined as two consecutive measurements of > 2.88 mmol/L), hyperphosphatemia, parathyroid disorder, pruritus, and taste perversion occurring in 4.7%, 1.7%, 1.2%, 1.1% and 1.1% of patients, respectively. Hypercalcemia and hyperphosphatemia were mainly dependent on the level of PTH oversuppression and can be minimized by proper dose titration. No adverse events with possible or probable or definite relationship to paricalcitol have been reported in > 2% of patients.

Clinical Trial Adverse Drug Reactions

> *Because clinical trials are conducted under very specific conditions the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse drug reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates*.

ZEMPLAR® (paricalcitol capsules)

The safety of ZEMPLAR® (paricalcitol capsules) has been evaluated in one pivotal and three supportive 12-week, double-blind, placebo-controlled, multicenter clinical study involving 313 patients with Chronic Kidney Disease (CKD) Stage 5. All adverse events at least possibly related to paricalcitol capsules, both clinical and laboratory, are displayed in **Table 1** by body system.

Table 1 Summary of Treatment Emergent Adverse Events in CKD Stage 5 Patients Judged to Be Possibly or Probably Related to Study Drug – All Treated Subjects is Pivotal Study M03-635 and Supportive Studies 2001-013, 2001-014, 2001-015				
	Number (%) of Subjects Study M03-635		Number (%) of Subjects Combined Studies 2001-013, 2001-014, 2001-015	
Body System* COSTART Term	**Paricalcitol Capsules (n=61)**	**Placebo (n=27)**	**Paricalcitol Capsules (n=110)**	**Placebo (n=115)**
Overall	7 (11%)	3 (11%)	8 (7%)	11 (10%)
Body As a Whole				
Abdominal pain	0 (0%)	1 (4%)	0 (0%)	1 (1%)
Asthenia	-	-	1 (1%)	0 (0%)
Pain	-	-	1 (1%)	0 (0%)
Cardiovascular System				
Vasodilation	-	-	0 (0%)	1 (1%)
Digestive System				
Anorexia	1 (2%)	0 (0%)	-	-
Constipation	-	-	0 (0%)	1 (1%)
Diarrhea	1 (2%)	2 (7%)	0 (0%)	1 (1%)
Dyspepsia	-	-	1 (1%)	1 (1%)
Eructation	-	-	1 (1%)	0 (0%)
Gastrointestinal disorder	1 (2%)	1 (4%)	1 (1%)	1 (1%)
Nausea	-	-	3 (3%)	2 (2%)
Vomitting	-	-	2 (2%)	1 (1%)
Metabolic and Nutritional Disorders				
Hypercalcemia	1 (2%)	0 (0%)	4 (4%)	0 (0%)
Hypocalcemia	1 (2%)	0 (0%)	0 (0%)	1 (1%)
Musculoskeletal System				
Arthralgia	-	-	0 (0%)	1 (1%)
Myalgia	-	-	1 (1%)	0 (0%)
Nervous System				
Dizziness	2 (3%)	0 (0%)	-	-
Skin and Appendages				
Acne	1 (2%)	0 (0%)	-	-
Pruritus	-	-	0 (0%)	1 (1%)
Rash	0 (0%)	1 (4%)	0 (0%)	1 (1%)
Skin disorder	-	-	0 (0%)	1 (1%)
Urticaria	-	-	0 (0%)	1 (1%)
Special Senses				
Taste loss	-	-	1 (1%)	0 (0%)
Taste perversion	-	-	0 (0%)	1 (1%)
Urogenital System				
Breast pain	1 (2%)	0 (0%)	-	-

ZEMPLAR® (paricalcitol injection USP)

Adverse Events from Phase II and III Clinical Studies

In four, placebo-controlled, double-blind, multicenter studies, discontinuation of therapy due to any adverse event occurred in 6.5% of 62 patients treated with paricalcitol injection USP (dosage titrated as tolerated, see **CLINICAL PHARMACOLOGY, Clinical Studies**) and 2.0% of 51 patients treated with placebo for one to three months. Adverse events occurring with greater frequency in the paricalcitol group at a frequency of 2% or greater, regardless of causality, are presented in the **Table 2**.

Table 2
Adverse Event Incidence Rates for All Treated Patients In All Placebo-Controlled Studies*

Adverse Event	Paricalcitol Injection (n=62) %	Placebo (n=51) %
Overall	71	78
Body as a Whole	45	51
Chills	5	0
Feeling Unwell	3	0
Fever	5	2
Flu	5	4
Sepsis	5	2
Cardiovascular		
Palpitation	3	0
Digestive System		
Dry Mouth	3	2
Gastrointestinal Bleeding	5	2
Nausea	13	8
Vomiting	8	4
Metabolism and Nutritional Disorders		
Edema	7	0
Nervous System		
Light-headedness	5	2
Respiratory System		
Pneumonia	5	0

* A patient who reported the same medical term more than once was counted only once for that medical term.

Safety parameters (changes in mean Ca, P, Ca x P) in an open-label safety study up to thirteen months in duration support the long-term safety of paricalcitol in this patient population.

Adverse Events from Phase IV Clinical Studies

In one Phase IV dose finding study, headache (2%) and taste perversion (2%) were commonly reported (see **CLINICAL STUDIES** for a description of the study).

Less Common Clinical Trial Adverse Drug Reactions

ZEMPLAR® (paricalcitol injection USP)

Uncommon adverse reactions (> 0.1% and < 1 % of patients) associated with paricalcitol injection USP therapy are listed below by body system:

Hematological and Lymphatic System:	Anemia, leukopenia, lymphadenopathy, and increased bleeding time.
Metabolic and Nutritional Disorders:	Hyperkalemia, hypocalcemia, edema, peripheral edema, increased AST, and weight loss.
Nervous System:	Abnormal gait, agitation, confusion, delirium, depersonalization, dizziness, hypesthesia, insomnia, myoclonus, nervousness, paresthesia and stupor.
Special Senses:	Conjunctivitis, ear disorder, and glaucoma.
Cardiovascular System:	Arrhythmia, atrial flutter, cerebral ischemia, cerebrovascular accident, cardiac arrest, hypotension, hypertension, and syncope.
Respiratory System:	Asthma, increased cough, dyspnea, epistaxis, pulmonary edema, pharyngitis, and pneumonia.
Gastrointestinal System:	Anorexia, colitis, constipation, diarrhea, dry mouth, dyspepsia, dysphagia, gastrointestinal disorder, gastritis, nausea, rectal hemorrhage, thirst, and vomiting.
Skin and Appendages:	Alopecia, hirsutism, rash, sweating, and vesiculobullous rash.
Musculoskeletal System:	Arthralgia, myalgia, joint disorder, and twitching.
Urogenital System:	Breast carcinoma, breast pain, impotence, and vaginitis.
Others:	Abdominal pain, aggravation reaction, allergic reaction, asthenia, back pain, chest pain, fever, flu syndrome, infection, injection site pain, lab test abnormal, malaise, pain, and sepsis.

Abnormal Laboratory and Haematological Values

There were no statistically significant differences between the paricalcitol capsules treated patients and placebo patients in the incidence of hypercalcemia (defined as two consecutive measurements of > 2.88 mmol/L) (p > 0.999), hyperphosphatemia (p=0.073) or elevated calcium-phosphorus product (p=0.669). At baseline, 53 (87%) paricalcitol-treated subjects and 26 (96%) placebo subjects were receiving phosphate binders. At the Final Visit, phosphate binder usage was unchanged from baseline for the majority of subjects in both treatment groups. However when hypercalcemia is defined as one measurement greater than 2.63 mmol/L (ie. greater than the laboratory upper limit of normal) hypercalcemia is significantly more common in the paricalcitol treated group as compared with placebo (see **Table 3**).

Table 3
Incidence of Hypercalcemia (defined as one measurement greater than 2.63 mmol/L) in Paricalcitol Capsules Studies

Study	Paricalcitol Capsules	Placebo	p-value[#]
M03-635 (titration assessed in pivotal study)[##]	N=61 9 (14.8%)	N=26 0 (0%)	0.053
2001013 (investigational titration scheme)[###]	N=37 12 (32.4%)	N=39 3 (7.7%)	0.009**
2001014 (investigational titration scheme)[###]	N=36 15 (41.7%)	N=38 4 (10.5%)	0.003**
2001015 (investigational titration scheme)[###]	N=36 21 (58.3%)	N=38 6 (15.8%)	< 0.001***

\# p-value is derived from Fisher's Exact Test
Recommended titration scheme
Investigational titration scheme using fixed rather than individualized dose titration based on PTH
** Statistically significant at p=0.01 level
*** Statistically significant at p=0.001 level

Post-Market Adverse Drug Reactions

The following adverse reactions have been rarely reported in postmarketing experience with paricalcitol injection USP. Adverse reactions are presented by system organ class.

Immune System: allergic reaction, urticaria
Nervous System: taste perversion (metallic taste)
Skin and Subcutaneous Tissue: rash, pruritus, facial and oral edema

DRUG INTERACTIONS

Overview

An *in vitro* study indicates that paricalcitol is not an inhibitor of CYP3A, CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, or CYP2E1 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 the clearance of drugs metabolized by these enzymes.

The pharmacokinetic interaction between paricalcitol capsules (16 mcg) and omeprazole (40 mg; oral) was investigated in a single dose, crossover study in 25 healthy subjects. The pharmacokinetics of paricalcitol were unaffected when co-administered with omeprazole.

Ketoconazole is known to be a nonspecific inhibitor of several cytochrome P450 enzymes. The available *in vivo* and *in vitro* data suggest that ketoconazole may interact with enzymes that are responsible for the metabolism of paricalcitol and other vitamin D analogs. Although not studied with paricalcitol injection, the effect of ketoconazole on the pharmacokinetics of paricalcitol capsules has been studied in 14 healthy subjects. The C_{max} of paricalcitol was minimally affected, but $AUC_{0-\infty}$ approximately doubled in the presence of ketoconazole. The mean $t_{1/2}$ of paricalcitol was 17.0 hours in the presence of ketoconazole as compared to 9.8 hours, when paricalcitol was administered alone. Caution should be taken while dosing paricalcitol with ketoconazole and other strong CYP3A4 inhibitors.

Drug-Drug Interactions

Specific drug-drug interaction studies in humans have not been performed with paricalcitol injection USP.

Table 4
Established or Predicted Drug-Drug Interactions

Proper Name	Ref	Effect	Clinical Comment
Digitalis	T	Possible increase of digitalis concentration	Specific interaction studies were not performed. Digitalis toxicity is potentiated by hypercalcemia* of any cause, so caution should be applied when digitalis compounds are prescribed concomitantly with paricalcitol.
Phosphate or vitamin D-related compounds	T	Increased risk of hypercalcemia* and increase levels of Ca x P product	Phosphate or vitamin D-related compounds should not be taken concomitantly with paricalcitol, due to an increased risk of hypercalcemia* and Ca x P product elevation.
Aluminum-containing preparations (e.g., antacids, phosphate-binders)	T	Increased levels of aluminum	Aluminium-containing preparations (e.g., antacids, phosphate-binders) should not be administered chronically with Vitamin D preparations, as increased blood levels of aluminium and aluminium bone toxicity may occur.
Calcium-containing preparations or thiazide diuretics	T	Increased levels of calcium	High doses of calcium-containing preparations or thiazide diuretics may increase the risk of hypercalcemia*.
Magnesium-containing preparations (e.g., antacids)	T	Increased levels of magnesium	Magnesium-containing preparations (e.g., antacids) should not be taken concomitantly with vitamin D preparations, because hypermagnesemia may occur.

Legend: C = Case Study; CT = Clinical Trial; T = Theoretical;
* Hypercalcemia is defined as two consecutive measurements of > 2.88 mmol/L.

Drug-Food Interactions

Paricalcitol capsules may be taken without regard to food.

DOSAGE AND ADMINISTRATION

Dosing Considerations

Hepatic Insufficiency: Unbound concentrations of ZEMPLAR® (paricalcitol injection USP) in patients with mild to moderate hepatic impairment are similar to healthy subjects and dose adjustment is not necessary in this patient population. There is no experience in patients with severe hepatic impairment.

Pediatric Use: There is limited experience with the use of paricalcitol injection USP in patients less than 18 years of age (see **CLINICAL TRIALS, Pediatric Patients**).

Geriatric Use: Of the total number (n=88) of patients with Chronic Kidney Disease (CKD) Stage 5 in the pivotal study of paricalcitol capsules, 28% were age 65 and over, while 6% were 75 and over. No overall differences in safety and effectiveness were observed between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

There is a limited amount of experience with patients 65 years of age or over receiving paricalcitol injection USP in the Phase III studies. In these studies, no overall differences in efficacy or safety were observed between patients 65 years or older and younger patients.

Recommended Dose and Dosage Adjustment

ZEMPLAR® (paricalcitol capsules)

ZEMPLAR® (paricalcitol capsules) may be taken without regard to food.

Adults: ZEMPLAR® (paricalcitol capsules) are administered three times a week, no more frequently than every other day.

Initial Dose: The initial dose of paricalcitol capsules is based on the following formula:

$$\text{Initial dose (micrograms)} = \frac{\text{most recent iPTH level in pmol/L}}{7}$$

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:

$$\text{Titration dose (micrograms)} = \frac{\text{most recent iPTH level in pmol/L}}{7}$$

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 > 2.8 mmol/L or Ca x P > 5.6 $mmol^2/L^2$, the dose should be decreased by 2 to 4 micrograms lower than that calculated by the most recent iPTH/7 (pmol/L). If further adjustment is required, the dose of paricalcitol capsules should be reduced or interrupted until these parameters are normalized.

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

The mean average TIW dose during the initial week in the clinical study was 11.2 mcg per dose. The mean average overall TIW dose administered in the clinical study was 6.3 mcg per dose. The maximum dose safely administered in the clinical study was 32 mcg per dose.

ZEMPLAR® (paricalcitol injection USP)

Adults: The currently accepted target range for intact parathyroid hormone (iPTH) levels CRF patients is no more than 1.5 to 3 times the non-uremic upper limit of normal (15.9 to 31.8 pmol/L for iPTH).

The recommended initial dose of ZEMPLAR® (paricalcitol injection USP) is 0.04 mcg/kg to 0.1 mcg/kg (2.8 to 7 mcg) administered as a bolus dose no more frequently than every other day at any time during dialysis. Single doses as high as 0.24 mcg/kg (16.8 mcg) have been safely administered.

If a satisfactory response is not observed, the dose may be increased by 2 to 4 mcg at every 2- to 4-week interval. During any dose adjustment period serum calcium and phosphorous levels should be monitored more frequently, possibly 2 times per week, and if an elevated corrected calcium (Ca) level or a Ca x P product greater than 6.1 is noted, the drug dosage should be immediately reduced or interrupted until these parameters are normalized. Then, paricalcitol administration should be reinitiated at a lower dose. Doses may need to be decreased as the PTH levels decrease in response to therapy. Thus, incremental dosing must be individualized.

The following table (**Table 5**) is a suggested approach for dose titration:

Table 5
Suggested Dosing Guidelines

PTH Level	Paricalcitol Dose
the same or increasing	Increase by 2-4 mcg
decreasing by < 30%	Increase by 2-4 mcg
decreasing by > 30%, < 60%	Maintain
decreasing by > 60%	Decrease by 2-4 mcg
one and one-half to three times upper limit of normal	Maintain

The influence of mild to moderately impaired hepatic function on paricalcitol pharmacokinetics is sufficiently small that no dosing adjustment is required.

Administration

The usual route of administration of paricalcitol solution for injection is via a hemodialysis line.

Propylene glycol interacts with heparin and neutralizes its effect. Paricalcitol injection USP contains propylene glycol as an excipient and its administration with heparin must be avoided.

Paricalcitol injection USP should not to be mixed with other medicinal products.

OVERDOSAGE

ZEMPLAR® (paricalcitol capsules)

Excessive administration of ZEMPLAR® (paricalcitol capsules) can cause hypercalcemia (defined as two consecutive measurements of > 2.88 mmol/L) (see **WARNINGS AND PRECAUTIONS**), hypercalciuria, and hyperphosphatemia, and over suppression of PTH.

ZEMPLAR® (paricalcitol injection USP)

Overdosage of ZEMPLAR® (paricalcitol injection USP) may lead to hypercalcemia (defined as two consecutive measurements of > 2.88 mmol/L) (see **WARNINGS AND PRECAUTIONS**). Paricalcitol is not significantly removed by dialysis.

The content of propylene glycol as excipient is eliminated by dialysis.

ACTION AND CLINICAL PHARMACOLOGY

The pharmacology of ZEMPLAR® (paricalcitol injection USP) has been evaluated in healthy subjects, chronic hepatic insufficiency subjects, and in patients on hemodialysis with secondary hyperparathyroidism.

In short-term studies in healthy patients, there were no detectable differences in iPTH levels when paricalcitol injection USP was compared to placebo administration. In patients with secondary hyperparathyroidism, the pharmacodynamic actions of paricalcitol in reducing iPTH levels were as expected of a potent vitamin D analogue.

The pharmacokinetics of paricalcitol appear to be linear for the dose range expected to be used in clinical practice. The half-life of paricalcitol is approximately 5 to 7 hours in healthy adults and 11 to 15 hours in hemodialysis patients. Little or no accumulation of the drug is observed in hemodialysis patients in multiple-dose studies of up to 12 weeks in duration.

Paricalcitol is eliminated primarily by hepatobiliary excretion; 74% of a radiolabelled dose is recovered in feces and only 16% of a dose is detected in urine. 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; this metabolite is less active than paricalcitol in an *in vivo* rat model of PTH suppression. In, *in vitro* studies, paricalcitol had little or no effect on activities catalyzed by CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP2E1 or CYP3A at concentrations up to 50 nM (21 ng/mL). No adjustment of paricalcitol dose appears to be required for subjects with mild to moderate hepatic impairment.

Paricalcitol is not removed by hemodialyis to a significant extent and therefore can be administered before, during, or after a dialysis session.

Mechanism of Action

Vitamin D has a central role in calcium and phosphate homeostasis and the proper formation and maintenance of bone. These classic effects of the hormone are achieved through the actions of 1,25-dihydroxyvitamin D_3 (biologically most active vitamin D) on target cells of the intestine, bone, kidney and parathyroid gland. In the diseased kidney, calcitriol synthesis is diminished. The resultant calcitriol deficiency and altered mineral balance are a major cause of secondary hyperparathyroidism and metabolic bone disease of renal failure.

Vitamin D has broader functions in the body that expand the classic actions to include effects on immunity, muscle and vasculature, reproduction, and the growth and differentiation of many cell types. In addition to the classic target organs, vitamin D receptors (VDR) are found in skin, liver, heart, lungs, lymphoid tissue and other organs, suggesting diverse biological roles for this hormone.

Paricalcitol is a synthetic vitamin D analog of calcitriol with modifications to the side chain (D_2) and the A (19-nor) ring allowing for selective vitamin D receptor (VDR) activation. In rodents, the mechanism of action of paricalcitol appears to differ from calcitriol with respect to the mobilization of calcium and phosphorus from both bone and across the intestine. Paricalcitol does not upregulate the intestinal VDR content in rodents, and is less effective than calcitriol at inducing intestinal calcium and phosphorus absorption. Paricalcitol is also less potent in rodents and in humans than calcitriol in mobilizing calcium and phosphorus from bone. The beneficial effect of paricalcitol in secondary hyperparathyroidism appears to result from correction of vitamin D deficiency, direct inhibition of pre-pro-PTH mRNA synthesis by the parathyroid glands, and anti-proliferative effect on parathyroid cells.

Pharmacodynamics

Secondary hyperparathyroidism is characterized by an elevation in parathyroid hormone (PTH) associated with inadequate levels of active vitamin D hormones. The source of vitamin D is from synthesis in the skin and from dietary intake. Vitamin D requires two sequential hydroxylations in the liver and the kidney to form calcitriol which binds to and to activates 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.[4] 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 result in renal osteodystrophy.

Pharmacokinetics

ZEMPLAR® (paricalcitol capsules) and ZEMPLAR® (paricalcitol injection USP)

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 maximum plasma concentration (C_{max}), time to C_{max} (T_{max}), and area under the concentration time curve ($AUC_{0-\infty}$) were 1.512 pmol/mL, 3 hours and 12.60 pmol•h/mL, respectively. The mean absolute bioavailability of paricalcitol in HD and PD patients is 79% and 86%, respectively, with the upper bound of 95% confidence interval of 93% and 112%, 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. Therefore, paricalcitol capsules may be taken without regard to food.

The C_{max} and $AUC_{0-\infty}$ of paricalcitol increased proportionally over the dose range of 0.06 to 0.48 mcg/kg in healthy subjects. Following multiple dosing, either as daily or three times a week in healthy subjects, steady-state exposure was reached within seven days and remained constant over time.

Distribution: Paricalcitol is extensively bound (> 99.8%) to plasma proteins in healthy subjects (or the plasma free fraction < 0.1%) and the percent bound to plasma proteins is constant over the range of 0.25 to 100 ng/mL. The mean apparent volume of distribution following a 0.24 mcg/kg oral dose of paricalcitol in healthy subjects was 34 L. The protein binding is also very high in CKD Stage 5 subjects. Protein binding results were similar in CKD Stage 5 subjects on HD and CPD. The protein binding was reduced at higher paricalcitol concentrations (50 nM; 21.2 ng/mL) in CKD Stage 5 subjects. However, these high concentrations are highly unlikely in CKD Stage 5 subjects based on the dose recommended for this patient population.

The pharmacokinetics of paricalcitol have been studied in patients with chronic renal failure (CRF) requiring hemodialysis. Paricalcitol injection USP is administered as an intravenous bolus injection. Within two hours after administering doses ranging from 0.04 to 0.24 mcg/kg, concentrations of paricalcitol decreased rapidly; thereafter, concentrations of paricalcitol declined log-linearly with a mean half-life of about 15 hours. No accumulation of paricalcitol was observed with multiple dosing.

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. Approximately 70% of the radioactivity was eliminated in the feces and 18% was recovered in the urine. 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, as well as 24,26- and 24,28-dihydroxylation and direct glucuronidation. 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). Less than two-fold induction was noted for CYP2B6, CYP2C9 and CYP3A4 at similar concentrations of paricalcitol.

Excretion: Paricalcitol is eliminated primarily via hepatobiliary excretion. In healthy subjects, the mean elimination half-life of paricalcitol is five to seven hours over the studies dose range of 0.06 to 0.48 mcg/kg. The degree of accumulation was consistent with the half-life and dosing frequency. Hemodialysis procedure has no effect on paricalcitol elimination.

In healthy subjects, a study was conducted with a single 0.16 mcg/kg intravenous bolus dose of ^{3}H-paricalcitol (n=4), plasma radioactivity was attributed to parent drug. Paricalcitol was eliminated primarily by hepatobiliary excretion, as 74% of the radioactive dose was recovered in feces and only 16% was found in urine.

Special Populations and Conditions

Paricalcitol pharmacokinetics have not been investigated in special populations such as geriatric and pediatric. There is a limited amount of experience with patients 65 years of age or over receiving paricalcitol in Phase III studies. In these studies, no overall differences in efficacy or safety were observed between patients 65 years or older and younger patients.

Age: No age related pharmacokinetic differences have been observed in adult patients studied.

Pediatrics: Paricalcitol pharmacokinetics have not been investigated in pediatric population.

Geriatrics: Paricalcitol pharmacokinetics have not been investigated in geriatric population.

Gender: No gender related pharmacokinetic differences have been observed in adult patients studied. The pharmacokinetics of paricalcitol following single oral doses over 0.06 to 0.48 mcg/kg dose range were gender independent.

Race: Pharmacokinetic differences due to race have not been identified.

Hepatic Insufficiency: Following intravenous administration, the disposition of paricalcitol 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). Following administration of a single dose, the pharmacokinetics of unbound paricalcitol were similar across hepatic function groups. Paricalcitol binding to plasma proteins was very high in all hepatic function groups (mean values > 99.7%). The protein binding of paricalcitol was decreased in subjects with moderate (but not mild) hepatic impairment; total paricalcitol concentrations tended to be lower for subjects with moderate hepatic impairment compared to the other two hepatic function groups.

No dosage 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.

Unbound concentrations of paricalcitol in patients with mild to moderate hepatic impairment is similar to healthy subjects and dose adjustment is not necessary in this patient population.

Table 6 summarizes the pharmacokinetic results from a Phase I pharmacokinetic study in patients with chronic hepatic insufficiency. Considerable inter-individual variation was apparent.

Table 6
Paricalcitol Injection Pharmacokinetic Results in Patients with Mild to Moderate Chronic Hepatic Insufficiency

		Total Paricalcitol				
Hepatic Function	**N**	**C_5 (pmol/mL)**	**$AUC_{0-\infty}$ (pmol•h/mL)**	**$t_{1/2}$† (h)**	**CL (L/h)**	**V_{ss} (L)**
Normal	10	4.46 ± 2.04	13.27 ± 5.73	5.3	4.9 ± 2.8	37.4 ± 17.6
Mild Impairment	5	5.71 ± 2.05	14.87 ± 6.60	6.9	5.0 ± 2.4	38.4 ± 12.4
Moderate Impairment	5	2.48 ± 1.93	9.04 ± 8.67	6.5	12.2 ± 11.7	133.6 ± 154.1
		Unbound Paricalcitol				
Hepatic Function	**N**	**f_u (%)**	**C_5 (pmol/mL)**	**$AUC_{0-\infty}$ (pmol•h/mL)**	**CL (L/h)**	**V_{ss} (L)**
Normal	10	0.16 ± 0.04	0.0070 ± 0.0031	0.021 ± 0.010	2980 ± 1450	22956 ± 9794
Mild Impairment	5	0.14 ± 0.02	0.0082 ± 0.0041	0.022 ± 0.012	3813 ± 2174	28410 ± 11631
Moderate Impairment	5	0.25 ± 0.07	0.0053 ± 0.0034	0.019 ± 0.013	4177 ± 3109	44061 ± 43212

†: Harmonic mean; fu: Free fraction.

Renal Insufficiency:

ZEMPLAR® (paricalcitol capsules)

Paricalcitol pharmacokinetics following single dose oral administration were characterized in patients with Chronic Kidney Disease (CKD) Stage 5 with end-stage renal disease [n = 14 in hemodialysis (HD) and n=8 in peritoneal dialysis (PD)]. Similar to endogenous $1,25(OH)_2$ D_3, the pharmacokinetics of paricalcitol following oral administration were affected significantly by renal impairment, as shown in **Table 7**. Compared to healthy subjects, CKD Stage 5 patients showed decreased CL/F and increased half-life.

Table 7 Comparison of Mean ± SD Pharmacokinetic Parameters in Different Stages of Renal Impairment *versus* Healthy Subjects			
Pharmacokinetic Parameter	**Healthy Subjects**	**CKD Stage 5**	
		HD	**PD**
Number of patients	25	14	8
Dose (mcg/kg)	0.240	0.240	0.240
Oral clearance (CL/F), (L/h)	3.6 ± 1.0	1.8 ± 0.8	1.8 ± 0.8
Half-life ($t_{1/2}$), (h)	5.9 ± 2.8	13.9 ± 5.1	17.7 ± 9.6
Unbound plasma fraction* (f_u), (%)	0.06 ± 0.01	0.09 ± 0.04	0.13 ± 0.08
* Measured at 15 nM paricalcitol concentration			

ZEMPLAR® (paricalcitol injection USP)

In a Phase II study evaluating escalating doses of paricalcitol injection in patients with end stage renal disease (ESRD) undergoing hemodialysis, the paricalcitol pharmacokinetics were in general linear for the dose range of 0.04 to 0.24 mcg/kg. No accumulation of paricalcitol was observed when dosed after each dialysis session. **Table 8** summarizes the paricalcitol pharmacokinetic parameters for the data of the first and the last doses combined.

Table 8 Pharmacokinetic Parameters of Paricalcitol from the First and Last Doses Administered in a Phase II Study Evaluating Escalating Doses of Paricalcitol Injection USP in Patients with End Stage Renal Disease (ESRD) Undergoing Hemodialysis				
	Dose (mcg/kg)			
Parameter	**0.04***	**0.08†**	**0.16‡**	**0.24§**
C_{max} (pmol/mL)	0.61 ± 0.22	3.97 ± 3.88	10.96	4.44 ± 1.59
$AUC_{0-\infty}$ (pmol•h/mL)	14.63 ± 6.56	34.56 ± 27.22	43.76	65.72 ± 19.75
CL (L/h)	0.69 ± 0.27	0.58 ± 0.29	0.91	0.72 ± 0.24
$t_{1/2}$ (h)††	32.0 ± 18.3	11.3 ± 16.2	25.0	13.6 ± 1.9
V_{ss} (L)	34 ± 9	9 ± 5	31	6 ± 2
*: N=6, 12 observations for C_{max}; n=3 patients, 4 observations for all other parameters. †: N=3 patients, 3 observations for C_{max}; n=2 patients, 2 observations for all other parameters. ‡: N=1 patient, 1 observation for all parameters. §: N=6 patients, 11 observations for C_{max}; n=5 patients, 7 observations for all other parameters. ††: Harmonic means and pseudo standard deviations; the arithmetic means ± SD after doses of 0.04, 0.08, and 0.24 mcg/kg were 40.6 ± 24.9, 17.0 ± 14.0, and 13.9 ± 2.2 hours, respectively.				

In three (3) Phase III studies evaluating the safety and efficacy of paricalcitol injection USP in end stage renal disease patients undergoing hemodialysis (refer to **Table 11** in **CLINICAL TRIALS** for more information), the distribution of paricalcitol appeared to be essentially complete within 2 hours after the dose. Concentrations of paricalcitol at 2, 24, and 44 hours after the dose also appeared to have declined log-linearly in these studies. **Table 9** summarizes the paricalcitol plasma concentrations and half-lives after multiple dosing for these studies.

Table 9
Paricalcitol Plasma Concentrations and Half-Lives After Multiple Dosing in Three Phase III Studies Evaluating the Safety and Efficacy of Paricalcitol Injection USP in End Stage Renal Disease Patients Undergoing Hemodialysis

	Study 2 **Mean Plasma Concentrations (pmol/mL ± SD) at Time After Dose**						
Dose (mcg/mL)	**2 hours**	**N**	**24 hours**	**N**	**44 hours**	**N**	**$t_{1/2}$ (hours)**
0.04	0.509 ± 0.396	2	0.178 ± 0.307*	3	0.065 ± 0.130*	4	15.0 ± 5.2†
0.08	0.718 ± 0.130	4	0.322 ± 0.154	5	0.072 ± 0.101*	5	
0.16	1.092 ± 0.302	2	0.408 ± 0.293	2	0.187 ± 0.264*	2	
0.24	2.506	1	0.598	1	0.233	1	

*: Values based on at least one sample concentration of 0 pmol/mL.
†: Based on 9 patients for whom a $t_{1/2}$ could be calculated; mean ± pseudo standard deviation.
Note: Most samples were collected after a dose during the 12th week of dosing. Two patients did not complete the study and had samples collected during Weeks 9 and 8, respectively.

	Study 3 **Mean Plasma Concentrations (pmol/mL ± SD) at Time After Dose**						
Dose (mcg/mL)	**2 hours**	**N**	**24 hours**	**N**	**44 hours**	**N**	**$t_{1/2}$ (hours)**
0.04	NS	-	0	1	0	1	11.6 ± 3.3‡
0.08	0.595 ± 0.202	3	0.288 ± 0.178	2	0.050 ± 0.086*	3	
0.12	1.219 ± 0.622	3	0.427 ± 0.360	3	0.055 ± 0.096*	3	
0.16	0.948 ± 0.449	2	0.055 ± 0.079*	2	0	2	
0.20	1.481 ± 0.384	2	0.401 ± 0.252	2	0.0048	2	

*: Values based on at least one sample concentration of 0 pmol/mL.
‡: Based on 8 patients for whom a $t_{1/2}$ could be calculated; mean ± pseudo standard deviation.
NS: No samples were collected.

	Study 4 **Mean Plasma Concentrations (pmol/mL ± SD) at Time After Dose**						
Dose (mcg/mL)	**2 hours**	**N**	**24 hours**	**N**	**44 hours**	**N**	**$t_{1/2}$ (hours)**
0.08	0.478	1	0.235 ± 0.055	2	0.072 ± 0.101*	2	14.8 ± 9.4§
0.12	0.754	1	0.214 ± 0.031	2	0.065 ± 0.091*	2	
0.16	0.691	1	0.113	1	0	1	
0.20	0.890	1	0.511	1	0.209	1	

*: Values based on at least one sample concentration of 0 pmol/mL.
§: Based on 4 patients for whom a $t_{1/2}$ could be calculated; mean ± pseudo standard deviation.

STORAGE AND STABILITY

ZEMPLAR® (paricalcitol capsules) should be stored between 15 and 25ºC.

ZEMPLAR® (paricalcitol injection USP) should be stored between 15 and 25ºC. Protect from light, freezing and excessive heat.

SPECIAL HANDLING INSTRUCTIONS

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration whenever solution and container permit.

Discard unused portion.

DOSAGE FORMS, COMPOSITION AND PACKAGING

ZEMPLAR® (paricalcitol capsules)

ZEMPLAR® (paricalcitol 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 ⊐ and ZA. The 2 mcg capsule is an oval, orange-brown, soft gelatin capsule imprinted with ⊐ and ZF. The 4 mcg capsule is an oval, gold soft gelatin capsule imprinted with ⊐ and ZK. The capsules are available in high-density polyethylene (HDPE) bottles closed with polypropylene caps in the following package sizes:

- Bottles containing 30 capsules.

Listing of Non-Medicinal Ingredients

In addition to the active ingredient paricalcitol, ZEMPLAR® capsules also contain the following non-medicinal ingredients: medium chain triglycerides, alcohol, butylated hydroxytoluene, gelatin, glycerin, titanium dioxide, ink, Opacode® WB, black, iron oxide red (2 mcg capsules only), iron oxide yellow (2 and 4 mcg capsules), iron oxide black (1 mcg capsules only), purified water.

ZEMPLAR® (paricalcitol injection USP)

ZEMPLAR® (paricalcitol injection USP) containing 5 mcg/mL paricalcitol is presented in single dose Type I glass ampoule or Flip-top vials as follows:

- Ampoules containing 1 mL or 2 mL
- Fliptop vials containing 1 mL or 2 mL

Listing of Non-Medicinal Ingredients

In addition to the active ingredient paricalcitol, ZEMPLAR® (paricalcitol injection USP) contains the following non-medicinal ingredients: ethanol (20 % v/v), propylene glycol (30% v/v), water for injection.

Propylene glycol interacts with heparin and neutralizes its effect. Paricalcitol injection USP contains propylene glycol as an excipient and its administration with heparin must be avoided.

Paricalcitol injection USP should not to be mixed with other medicinal products.

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

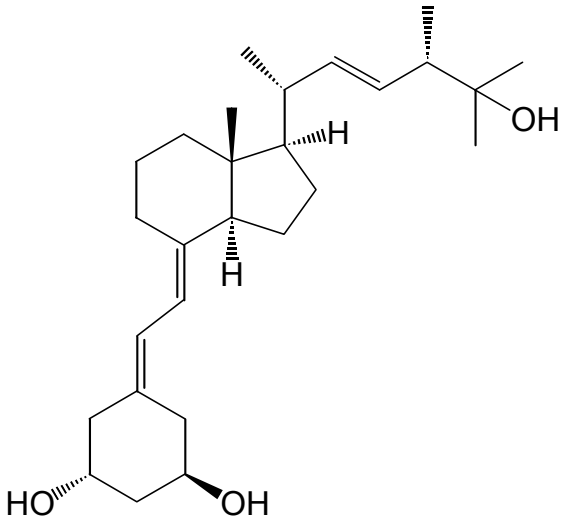
Drug Substance

Proper name: Paricalcitol

Chemical name: (1α,3β,7*E*,22*E*)-19-Nor-9,10-secoergosta-5,7,22-triene-1,3,25-triol

Molecular formula: $C_{27}H_{44}O_3$

Structural formula:



Molecular mass: 416.64

Physical form: Paricalcitol is a white crystalline powder.

Solubility: Paricalcitol is a non-polar compound and is insoluble in water at room temperature, but soluble in most polar solvents e.g., ether, methanol, ethanol, etc.

CLINICAL TRIALS

Study Demographics and Trial Design

ZEMPLAR® (paricalcitol capsules)

Table 10
Summary of Patient Demographics for Clinical Trials in End Stage Renal Disease Patients Undergoing Hemodialysis or Peritoneal Dialysis

Study #	Trial Design	Dosage/route of administration and duration	Study Subjects (n=number)	Mean Age (Range)	Gender
1	Phase III, double-blind, placebo-controlled, randomized, multi-investigator study	Initial dose: Based on iPTH/7 Max. Dose: 32 mcg Oral 12 Weeks	88 treated (61 paricalcitol, 27 placebo)	56.8 (29-92)	55M, 29F

ZEMPLAR® (paricalcitol injection USP)

Table 11
Summary of Patient Demographics for Clinical Trials in End Stage Renal Disease Patients Undergoing Hemodialysis

Study #	Trial Design	Dosage/route of administration and duration	Study Subjects (n=number)	Mean Age (Range)	Gender
Adult Patients					
1	Phase II, double-blind, placebo-controlled, randomized, multi-investigator study	Initial dose: Group 1: 0.04 mcg/kg Group 2: 0.08 mcg/kg Group 3: 0.16 mcg/kg Group 4: 0.24 mcg/kg Group 5: 0.32 mcg/kg given 3 times weekly Intravenous dose 4 Weeks	35 treated (22 paricalcitol, 13 placebo)	50 (18-84)	18M, 17F

Table 11
Summary of Patient Demographics for Clinical Trials in End Stage Renal Disease Patients Undergoing Hemodialysis

Study #	Trial Design	Dosage/route of administration and duration	Study Subjects (n=number)	Mean Age (Range)	Gender
2	Phase III, double-blind, placebo-concurrent controlled, randomized, multi-investigator study	Initial Dose: 0.04 mcg/kg 3 times weekly Dose Titration: 0.04 mcg/kg to 0.24 mcg/kg (depending on dose level) 3 times weekly Intravenous dose 12 Weeks	31 treated	55 (29-90)	16M, 15F
3	Phase III, double-blind, placebo-concurrent controlled, randomized, multi-investigator study	Initial Dose: 0.04 mcg/kg 3 times weekly Dose Titration: 0.04 mcg/kg to 0.24 mcg/kg (depending on dose level) 3 times weekly Intravenous dose 12 Weeks	31 treated	55 (22-86)	16M, 15F
4	Phase III, double-blind, placebo-concurrent controlled, randomized, multi-investigator study	Initial Dose: 0.04 mcg/kg 3 times weekly Dose Titration: 0.04 mcg/kg to 0.24 mcg/kg (depending on dose level) 3 times weekly Intravenous dose 12 Weeks	16 treated	51.0 (28.3-79.2)	8M, 8F
5	Phase III, comparative, double-blind, randomized, multi-center study	Initial paricalcitol dose: 0.04 mcg/kg 3 times weekly Initial calcitriol dose: 0.01 mcg/kg 3 times weekly Intravenous dose 12 to 32 Weeks	263 treated (130 paricalcitol, 133 calcitriol)	56.6 (22.8-89.2)	150M, 113F

Table 11 Summary of Patient Demographics for Clinical Trials in End Stage Renal Disease Patients Undergoing Hemodialysis					
Study #	**Trial Design**	**Dosage/route of administration and duration**	**Study Subjects (n=number)**	**Mean Age (Range)**	**Gender**
6	Phase III, comparative, double-blind, randomized, multi-center study	Initial paricalcitol dose: 0.04 mcg/kg 3 times weekly Max. Dose: 0.24 mcg/kg Initial calcitriol dose: 0.01 mcg/kg 3 times weekly Max. Dose: 0.06 mcg/kg Intravenous dose 24 Weeks	197 treated (98 paricalcitol, 99 calcitriol)	53.8 (19.3-88.8)	paricalcitol: (48M, 50F) calcitriol: (53M, 46F)
7	Phase IV, double-blind, randomized, multi-center, active controlled study.	Initial paricalcitol dose: 0.04 mcg/kg or based on PTH/80 3 times weekly Intravenous dose 12 Weeks	125 treated (64 PTH/80, 61 0.04 mcg/kg)	56.1 (21.1-81.0)	PTH/80: (36M, 28F) paricalcitol 0.04 mcg/kg: (29M, 32 F)
Pediatric Patients					
8	Phase IV, double-blind, placebo-controlled, randomized, multi-investigator study	Initial dose paricalcitol: iPTH < 500 pg/mL = 0.04 mcg/kg; iPTH ≥ 500 pg/mL = 0.08 mcg/kg 3 times weekly Intravenous dose 12 Weeks	29 treated (15 paricalcitol, 14 placebo)	paricalcitol: 13.6 yrs (5-19)	22M, 7F

Study Results

ZEMPLAR® (paricalcitol capsules)

The safety and efficacy of paricalcitol capsules were evaluated in a Phase III, 12-week, double blind, placebo-controlled, randomized, multicenter study in patients with Chronic Kidney Disease (CKD) Stage 5 on HD or PD. The study used a three times a week dosing design. A total of 61 received paricalcitol 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 80.6 pmol/L (range: 24.1-215.9 pmol/L). The average time since first dialysis across all subjects is 3.26 years.

The initial dose of paricalcitol capsules was based on baseline iPTH/7, up to a maximum initial dose of 32 mcg. Subsequent dose adjustments were based on iPTH/7 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/7. If the serum calcium level was > 2.75 mmo/L or Ca x P > 22.6 $mmol^2/L^2$ or iPTH < 16.8 pmol/L, the previous week's dose was decreased by 2 mcg or 4 mcg. Paricalcitol capsules were administered three times a week, not more than every other day. The overall average three times a week dose of paricalcitol capsules was 6.3 mcg/dose.

Eighty-two percent (82%) of the paricalcitol capsule treated patients and 78% of the placebo patients completed the 12-week treatment. The primary efficacy endpoint of at least two consecutive ≥ 30% reductions from baseline iPTH was achieved by 88% of paricalcitol capsule treated patients and 13% of the placebo patients ($p < 0.001$).

There were no statistically significant differences between the paricalcitol capsules treated patients and placebo patients in the incidence of hypercalcemia (defined as two consecutive measurements of > 2.88 mmol/L) ($p > 0.999$), hyperphosphatemia ($p=0.073$) or elevated calcium-phosphorus product ($p=0.669$). At baseline, 53 (87%) paricalcitol-treated subjects and 26 (96%) placebo subjects were receiving phosphate binders. At the Final Visit, phosphate binder usage was unchanged from baseline for the majority of subjects in both treatment groups. However when hypercalcemia is defined as one measurement greater than 2.63 mmol/L (ie. greater than the laboratory upper limit of normal) hypercalcemia is significantly more common in the paricalcitol treated group as compared with placebo (see **Table 12)**.

Table 12
Incidence of Hypercalcemia (defined as one measurement greater than 2.63 mmol/L) in Paricalcitol Capsules Studies

Study	Paricalcitol Capsules	Placebo	p-value[#]
M03-635 (titration assessed in pivotal study)[##]	N=61 9 (14.8%)	N=26 0 (0%)	0.053
2001013 (investigational titration scheme)[###]	N=37 12 (32.4%)	N=39 3 (7.7%)	0.009**
2001014 (investigational titration scheme)[###]	N=36 15 (41.7%)	N=38 4 (10.5%)	0.003**
2001015 (investigational titration scheme)[###]	N=36 21 (58.3%)	N=38 6 (15.8%)	< 0.001***

\# p-value is derived from Fisher's Exact Test
\## Recommended titration scheme
\### Investigational titration scheme using fixed rather than individualized dose titration based on PTH
** Statistically significant at p=0.01 level
*** Statistically significant at p=0.001 level

The mean values for serum iPTH, calcium, and phosphorus over time are shown in

Figure 1, and the pattern of change in the mean values for serum iPTH during the study are shown in
Figure 2. The mean changes from baseline to final treatment visit in serum iPTH, calcium, phosphorus, and Ca x P shown in **Table 13**.

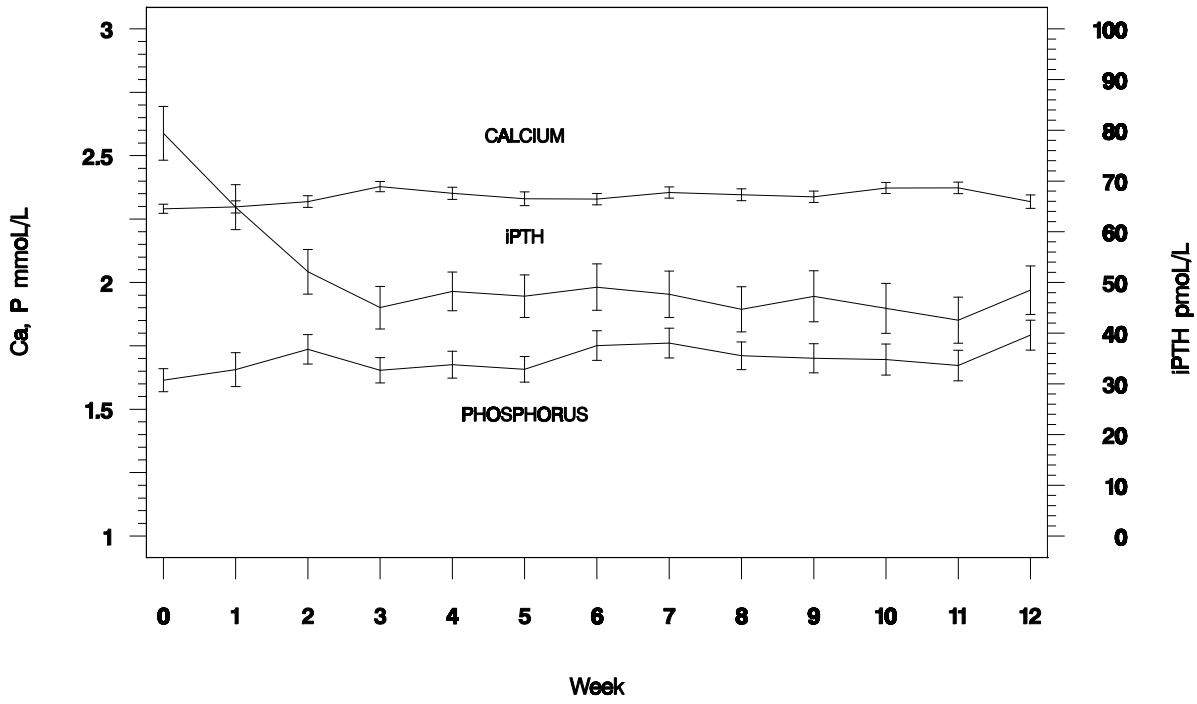


Figure 1
Mean Values for Serum iPTH, Calcium, and Phosphorus Over Time in a Phase 3 Double-Blind, Placebo-Controlled CKD Stage 5 Study

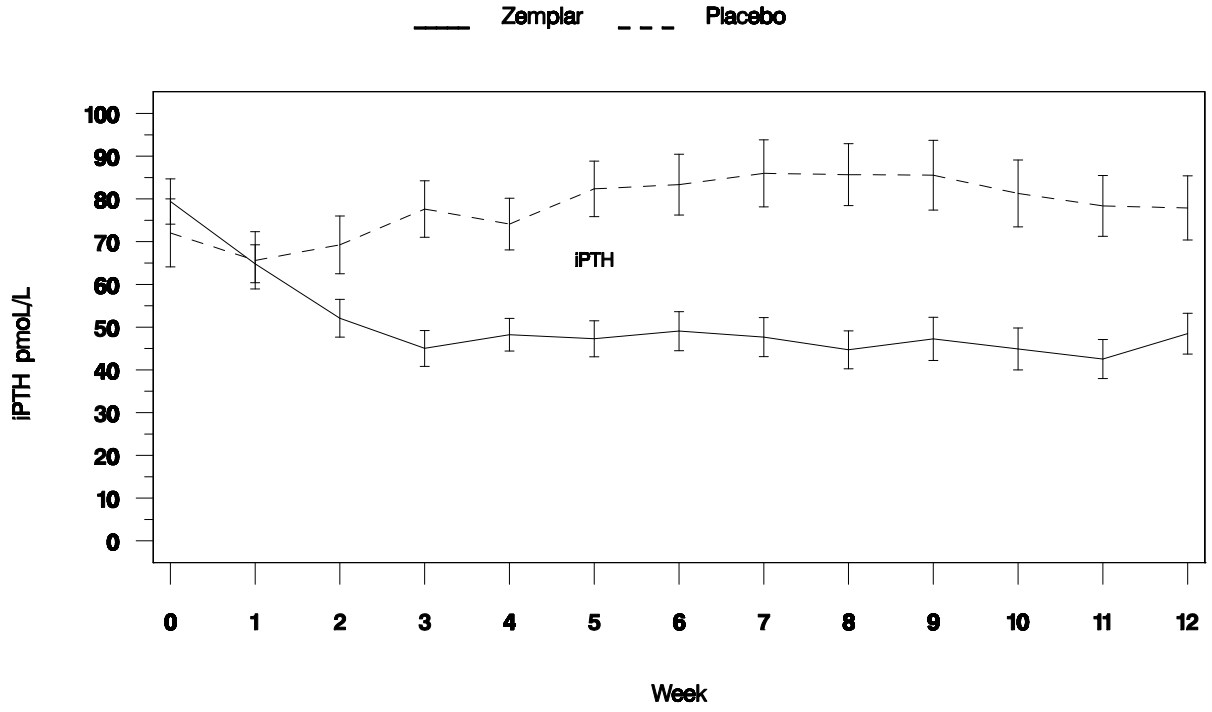


Figure 2
Mean Values for Serum iPTH Over Time in a Phase 3 Double-Blind, Placebo-Controlled CKD Stage 5 Study

Table 13 Mean Changes from Baseline to Final Treatment Visit in Serum iPTH, Bone Specific Alkaline Phosphatase, Calcium, Phosphorus, and Calcium Phosphorus Product in a Phase 3 Double-Blind, Placebo- Controlled CKD Stage 5 Study		
	Paricalcitol Capsules	**Placebo**
iPTH (pmol/L)	N=60	N=26
Mean Baseline Value	80.6	70.0
Mean Final Treatment Value	53.0	84.3
Mean Change from Baseline (SE)	-27.6 (4.2)	+14.2 (6.4)
Bone Specific Alkaline Phosphatase (mcg/L)	N=55	N=23
Mean Baseline Value	34.9	30.0
Mean Final Treatment Value	24.3	39.9
Mean Change from Baseline (SE)	-10.5 (1.88)	+9.9 (2.90)
Calcium (mmol/L)	N=60	N=26
Mean Baseline Value	2.29	2.28
Mean Final Treatment Value	2.33	2.22
Mean Change from Baseline (SE)	+0.04 (0.02)	-0.05 (0.03)
Phosphorus (mmol/L)	N=60	N=26
Mean Baseline Value	1.60	1.52
Mean Final Treatment Value	1.85	1.62
Mean Change from Baseline (SE)	+0.24 (0.05)	+0.10 (0.08)
Calcium x Phosphorus Product ($mmol^2/L^2$)	N=60	N=26
Mean Baseline Value	3.66	3.46
Mean Final Treatment Value	4.27	3.62
Mean Change from Baseline (SE)	+0.61 (0.11)	+0.15 (0.17)

ZEMPLAR® (paricalcitol injection USP)

Adult Patients

In one Phase II, placebo-controlled study (Study 1) designed to investigate the dose of paricalcitol injection required to achieve at least a 30% decrease in the maximal PTH baseline level in at least 75% of patients undergoing regular hemodialysis demonstrated that patients treated with paricalcitol achieved the PTH endpoint within 2 to 21 days. **Table 14** shows the main results of the study. The results showed that increasing the dose of paricalcitol meant a greater and more consistent suppression of PTH.

Table 14 Results of Study 1 in End Stage Renal Disease Patients Undergoing Hemodialysis							
Treatment Arm	**Efficacy Results**						
	Patients achieving 30% reduction in iPTH	**Patients with elevated Ca before, at, and after iPTH endpoint**			**Patients with elevated Ca x P product before, at, and after iPTH endpoint**		
		Before	**At**	**After**	**Before**	**At**	**After**
Placebo	2/13	0	0	0	1	0	0
1: 0.04 mcg/kg	4/6	0	0	0	0	0	0
2: 0.08 mcg/kg	1/4	0	0	0	0	0	0
3: 0.16 mcg/kg	5/6	0	1*	2	1	1	3
4: 0.32 mcg/kg	5/6	0	0	1	2	0	0
* patient achieved a 48% iPTH reduction.							

In three 12-week, placebo-controlled, Phase III studies (Studies 2, 3 and 4) in chronic renal failure patients on dialysis, the dose of paricalcitol injection was started at 0.04 mcg/kg three times per week. The dose was increased by 0.04 mcg/kg every two weeks until intact parathyroid hormone (iPTH) levels were decreased at least 30% from baseline or a fifth escalation brought the dose to 0.24 mcg/kg, or iPTH fell to less than 10.6 pmol/L, or the Ca x P product was greater than 6.1 within any two week period, or serum calcium became greater than 2.88 mmol/L at any time.

There was a clear response in PTH suppression in patients treated with paricalcitol for 12 weeks. PTH endpoint results are summarized in **Table 15** and **Table 16.**

Table 15 Results of Studies 2, 3 & 4 in End Stage Renal Disease Patients Undergoing Hemodialysis					
	Paricalcitol Injection		**Placebo**		
Parameter	**Number**	**%**	**Number**	**%**	**p-value†**
At least one 30% decrease in iPTH	35/40	87.5%	23/38	60.5%	0.009**
A 30% decrease in iPTH for al least one consecutive period of 4 lab draws	27/40	67.5%	3/38	7.9%	<0.001***
A 30% decrease in iPTH at the final lab draw	32/40	80.0%	11/38	28.9%	<0.001***
† p-value based upon a 2 x 2 Fisher's Exact test. ** indicates statistical significance (2-tailed) at the 0.01 level. *** indicates statistical significance (2-tailed) at the 0.001 level.					

Sixty-eight percent (27/40) of active patients had a 30% greater decrease in iPTH levels for 4 consecutive laboratory draws. Eight percent (3/38) of placebo patients demonstrated a similar response. A statistically significant difference ($p<0.001$) was observed between treatment groups.

Patients treated with paricalcitol achieved a mean iPTH reduction of 30% within six weeks. In these studies, there was no significant difference in the incidence of hypercalcemia, as defined in the protocol as 2.88 mmol/L, or hyperphosphatemia between paricalcitol and placebo treated patients. The results from these studies are summarized in **Table 16**.

Table 16
Change from Baseline in iPTH, Alkaline Phosphatase, Calcium, Phosphorus, and Ca x P Product in All Phase III Placebo-Concurrent Controlled Studies

	Group (# of patients)	Baseline Mean (Range)	Mean (SE) Change from Baseline to Final Evaluation
iPTH (pmol/L)	Paricalcitol (n=40) Placebo (n=38)	83.0 (31-220) 79.0 (34-177)	-40.2 (4.63) -7.4 (4.75)
Alkaline Phosphatase (U/L)	Paricalcitol (n=31) Placebo (n=34)	149.74 (40.00 - 600.00) 168.56 (56.00 - 911.00)	-41.48 (10.59) 2.59 (10.11)
Calcium (mmol/L)	Paricalcitol (n=40) Placebo (n=38)	2.31 (1.80-2.60) 2.26 (1.95-2.68)	0.12 (0.03) 0.01 (0.03)
Phosphorus (mmol/L)	Paricalcitol (n=40) Placebo (n=38)	1.87 (1.20-3.29) 1.94 (0.90-2.84)	0.15 (0.08) -0.15 (0.08)
Calcium x Phosphorus Product ($mmol^2/L^2$)	Paricalcitol (n=40) Placebo (n=38)	4.34 (2.57-6.25) 4.36 (2.10-6.25)	0.64 (0.18) -0.31 (0.19)
Note: results based upon a one-way ANOVA			

Studies 5 and 6 were designed to investigate if paricalcitol injections induce less incidence of hypercalcemia (defined as two consecutive measurements of > 2.88 mmol/L) and Ca x P product episodes than calcitriol injections when using similar starting doses (dose ratio of 4:1, 0.04 mcg/kg for paricalcitol and 0.01 mcg/kg for calcitriol). Study 5 evaluated the drugs for a duration of 12 to 32 weeks, while Study 6 evaluated therapy for 24 weeks. Results of these studies are summarized in **Table 17** and **Table 18**.

Table 17
Results of Study 5 in End Stage Renal Disease Patients Undergoing Hemodialysis

	Paricalcitol Injection (N=130)		Calcitriol (N=133)		
Parameter	**Number**	**%**	**Number**	**%**	**p-value†**
Incidence(s) of Hypercalcemia for two consecutive lab draws and/or elevated Ca x P product for 4 consecutive lab draws	24	18%	44	33%	0.008**
At least one 50% decrease in iPTH	108	83%	111	83%	1.000
A 50% decrease in iPTH for at least one consecutive period of 4 lab draws	80	62%	72	54%	0.261
A 50% decrease in iPTH at the final lab draw	80	62%	76	57%	0.530

† p-value comparing the proportions between treatment groups are from a 2 x 2 Fisher's Exact test.
** indicates statistical significance (2-tailed) at the 0.01 and 0.001 level.

Additional analysis of iPTH results indicated that consecutive 50% reductions from baseline iPTH levels occurred in significantly less time in all-treated patients receiving paricalcitol (87 days) than in calcitriol-treated patients (108 days) (p=0.025, Kaplan-Meier survival analysis). The findings suggest that in applications of up to 32 weeks, paricalcitol reduces iPTH levels more rapidly than calcitriol.

Table 18
Results of Study 6 in End Stage Renal Disease Patients Undergoing Hemodialysis

	Paricalcitol Injection (N=98)		Calcitriol (N=99)		
Parameter	**Number**	**%**	**Number**	**%**	**p-value†**
Incidence(s) of Hypercalcemia for two consecutive lab draws and/or elevated Ca x P (> 6.1) product for 4 consecutive lab draws	31	32%	32	32%	1.000
At least one 50% decrease in iPTH	83	84.7%	75	75.8%	0.152
A 50% decrease in iPTH for at least one consecutive period of 4 lab draws	56	57.1%	52	52.5%	0.568
A 50% decrease in iPTH at the final lab draw	60	61.2%	51	51.5%	0.197

† p-value comparing the proportions between treatment groups are from a 2 x 2 Fisher's Exact test.

Paricalcitol injection reduced iPTH to levels similar to those achieved with calcitriol in ESRD patients on hemodialysis without evidence of a clinically significant difference in its effect on calcium and/or Ca x P product profiles. In addition, the 50% iPTH reduction criterion was met 6 weeks earlier for the paricalcitol group. Also, a statistically significant greater reduction of percent change in iPTH at weeks 11 through 14 occurred in the paricalcitol group.

In a Phase IV, double-blind, randomized, multicenter, 12 week study, (Study 7) paricalcitol injection was administered at an initial dose of either 0.04 mcg/kg or baseline iPTH/8 (using intact PTH expressed as pmol/L) three times weekly to chronic renal failure patients on dialysis. The dose was increased by 2 mcg every two weeks until iPTH levels fell between 30% to 60% from baseline, or iPTH fell to less than 10.6 pmol/L, or the Ca x P product was greater than 6.1 for two consecutive occurrences, or serum calcium became greater than 2.88 mmol/L at anytime. This represents a value that is 11% above the published K/DOQI (Kidney Disease Outcomes Quality Initiative) guidelines for the upper limit of normal serum calcium. Patients completed the study by reducing iPTH > 30% from baseline levels for four consecutive measurements, or by having a single incidence of hypercalcemia (defined as two consecutive measurements of > 2.88 mmol/L), or by completing twelve weeks of treatment.

No incidence of hypercalcemia was seen for any patients in either treatment group. Both dosing methods were shown to be safe and effective. Results are presented in **Table 19**.

Table 19 Results of Study 7 in End Stage Renal Disease Patients Undergoing Hemodialysis		
Parameter	**iPTH/8† (n=64)**	**0.04 mcg/kg (n=61)**
Incidence(s) of Hypercalcemia	0	0
Median Days to First of 4 ≥ 30% iPTH Decreases	31*	45
Median Number of Dose Adjustments to first of 4 ≥ 30% iPTH Decreases	2	3
Incidences of Ca x P > 6.1	5 (7.8%)	2 (3.3%)
* Statistically significant (p=0.0306) † Baseline iPTH/8 (using intact PTH expressed as pmol/L)		

A long-term, open-label safety study of 164 CRF patients (mean dose of 7.5 mcg three times per week), demonstrated that mean serum Ca, P, and Ca x P remained within clinically appropriate ranges with PTH reduction (mean decrease of 43.4 pmol/L at 13 months) as demonstrated in **Figure 3**.

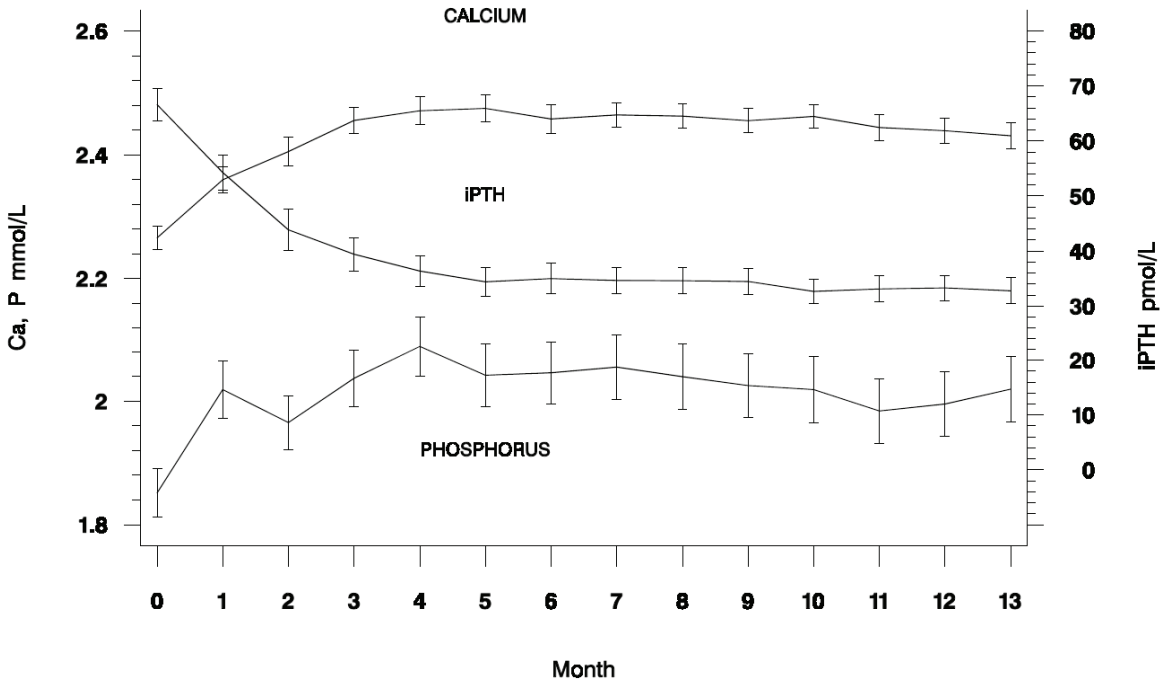


Figure 3
Plot of Mean ± SEM for iPTH, Calcium and Phosphorus by Month
(All-Treated Patient; N=164)

Pediatric Patients

The safety and effectiveness of paricalcitol injection were examined in a 12-week randomized, double blind, placebo-controlled study of 29 pediatric patients, aged 5 to19 years, with end-stage renal disease on hemodialysis (Study 8). Nearly all patients had received some form of vitamin D prior to the study. Seventy-six percent of the patients were male, 52% were Caucasian and 45% were African-American. The initial dose of paricalcitol was 0.04 mcg/kg 3 times a week, based on baseline iPTH level of < 53 pmol/L, or 0.08 mcg/kg 3 times a week based on baseline iPTH level of ≥ 53 pmol/L, respectively. The dose of paricalcitol was adjusted in 0.04 mcg/kg increments based on the levels of serum iPTH, calcium, and Ca x P. The mean baseline levels of iPTH were 89.1 pmol/L for the 15 paricalcitol-treated patients and 78.4 pmol/L for the 14 placebo-treated patients. The mean dose of paricalcitol administered was 4.6 mcg (range: 0.8 mcg to 9.6 mcg). Ten of the 15 (67%) paricalcitol-treated patients and 2 of the 14 (14%) placebo-treated patients completed the trial. Ten of the placebo treated patients (71%) were discontinued due to excessive elevations in iPTH levels as defined by 2 consecutive iPTH levels > 74.2 pmol/L and greater than baseline after 4 weeks of treatment In the primary efficacy analysis, 9 of 15 (60%) patients in the paricalcitol group had 2 consecutive 30% decreases from baseline iPTH compared with 3 of 14 (21%) patients in the placebo group (95% CI for the difference between groups –1%, 63%). No patients in either the paricalcitol group or placebo group developed hypercalcemia (defined as at least one calcium value 2.8 mmol/L) during the study.

DETAILED PHARMACOLOGY

Two primary pharmacodynamics studies demonstrated in 5/6 nephrectomized rats that paricalcitol (19-nor-1,25-$(OH)_2D_2$) has advantages over calcitriol (1,25-$(OH)_2D_3$) at doses that give equivalent or greater reduction of serum PTH. No increase in serum ionized calcium and no increase in serum phosphorus were observed with paricalcitol. In addition there was a reduction of endogenous serum calcitriol levels, a reduction in intestinal vitamin D receptor content and a decrease in parathyroid gland growth.

There was also a similar reduction of pre-pro PTH messenger RNA compared with uremic controls.

The primary pharmacological activity of paricalcitol was also demonstrated during the repeat dose toxicity evaluations. Pronounced reductions in serum intact PTH occurred at most dosages in all species in subchronic and chronic toxicology studies of paricalcitol. Typically this response was dosage-related, with serum PTH levels approaching zero at higher dosages.

In the secondary pharmacodynamic study, it was concluded that paricalcitol is approximately seven-fold less potent than calcitriol in promoting bone mobilization in this animal model. These results support the conclusion of other investigators, using the same animal model but a different statistical method of comparison that the difference in potencies of the two vitamin D analogs was approximately 10-fold.

Based on the cumulative information from animal toxicity studies in rodents and dogs and the 8-10 fold exposure margins achieved in dogs relative to the therapeutic range, the lack of effect of paricalcitol on vital organ function has been well documented in these studies.

TOXICOLOGY

Single Dose Toxicity Study

The acute intravenous toxicity of paricalcitol was evaluated in Crl:CD-1® (ICR)BR mice and Crl:CD® BR rats of both sexes. No adverse effects were observed in mice and rats treated with paricalcitol at dose levels of 24 and 16 mcg/kg, respectively.

Long- Term Toxicity

Repeat dose toxicity studies of paricalcitol are listed in **Table 20**. To mimic the clinical dosing regimen, doses were intravenously administered three times per week, two or three days apart, in all of these studies. The toxicology assessment of paricalcitol requires that a distinction be made between effects that were directly or indirectly related its pharmacological actions (suppression of PTH and elevation of serum calcium) and other effects of the vitamin D analog.

Table 20
Long-Term Toxicity Summaries

Species / strain	Method of administration	Dose/Duration of dosing/ Number of animals used	Noteworthy findings
Mouse/ Crl:CD®-1 (ICR) BR	Subcutaneous injection	0, 0.1, 0.5, 3.0 or 10.0 mcg/kg/dose 3 months 155 males, 155 females	Nephrocalcinosis was observed predominantly in male mice, especially those treated with 3.0 or 10.0 mcg/kg/dose. Therefore, a dosage of 3.0 mcg/kg/dose, and possibly a dosage of 10.0 mcg/kg/dose, was regarded as tolerated in this study. Neither of these two dosages caused significant physiological dysfunctions and likely would be compatible with long-term survival.
Rat/ Crl:CD® (SD) BR	Subcutaneous injection	0, 0.1, 0.5 or 3.0 mcg/kg/dose 13 weeks 50 males, 50 females	Decreased body weight gains and tissue changes related to the pharmacologic activity of the vitamin D_2 analog were observed at the highest dosage, 3.0 mcg/kg/dose, with the effects being greater in males than females. The mid-dosage, 0.5 mcg/kg/dose, was tolerated without apparent significant physiological dysfunction and likely would be compatible with long-term survival.

Table 20 Long-Term Toxicity Summaries			
Species / strain	**Method of administration**	**Dose/Duration of dosing/ Number of animals used**	**Noteworthy findings**
Rat/ Crl:CD® (SD)BR	Intravenous bolus	0, 0.3, 3.0 or 20.0 mcg/kg/dose approx. 4 weeks 50 males, 50 females	Undesirable pharmacologic effects of the analog, hypercalcemia and tissue mineralization, were observed at dosages of 3.0 and 20.0 mcg/kg/dose. All effects except tissue mineralization were reversible within the two-week recovery period. The maximum no-toxic effect dosage for the vitamin D_2 analog in rats was 0.3 mcg/kg/dose.
Rat/ Crl:CD® (SD)BR	Intravenous bolus	0, 0.1, 0.5 or 3.0 mcg/kg/dose approx. 13 weeks 75 males, 75 females	Evidence of toxicity, including extensive soft tissue mineralization and hyperostosis, was observed in some rats treated with calcitriol, but not in rats treated with the same dosage of 19-nor-1α, 25 dihydroxyvitamin D_2 or in control rats. The maximum no-toxic effect dosage for the vitamin D_2 analog in rats was 3.0 mcg/kg/dose.
Rat/ Crl:CD® (SD)BR	Intravenous bolus	0, 0.1, 0.5 or 3.0 mcg/kg/dose 6 months 100 males, 100 females	The effects at the low-and mid-dosages (0.1 and 0.5 mcg/kg/dose) were related to the pharmacologic activity of the D_2 and/or were not considered toxicologically meaningful. Thus, the maximum no-toxic effect dosage for the vitamin D_2 analog in rats was 0.5 mcg/kg/dose when administered intravenously three times per week for six months.
Dogs/ purebred beagles	Intravenous bolus	0, 0.1, 0.3, 0.6 or 1.0 mcg/kg/dose approx. 4 weeks 19 males, 19 females	Adverse effects were negligible at the lowest dosage, but minimal renal tubular regeneration and dilatation were observed in a single low-dosage dog. Therefore, 0.1 mcg/kg/dose was considered to approximate the No-Toxic-Effect dosage
Dogs/ purebred beagles	Intravenous bolus	0, 0.02, 0.1 or 0.3 mcg/kg/dose 3 months 20 males, 20 females	Changes in the dogs that received 0.02 mcg/kg/dose of the vitamin D_2 analog were limited to a moderate decrease in parathyroid hormone in the female and hypercalcemia and hypercalciuria in a single male. The calcitriol-treated dogs and the high dosage vitamin D_2 analog-treated dogs were terminated after one and two months of treatment, respectively. Based on these findings, it was determined that a dosage of 0.02 mcg/kg/dose of the vitamin D_2 analog given three times per week for three months was not toxic. The vitamin D_2 analog was found to be less toxic than calcitriol at a dosage of 0.30 mcg/kg/dose.
Dogs/ purebred beagles	Intravenous bolus	0, 0.02, 0.06 or 0.2 mcg/kg/dose 6 months 20 males, 20 females	Since nearly all of the drug-related effects were directly or indirectly attributable to an exaggeration of the Vitamin D_2 analog's calcemic activity, the mid-dosage, 0.06 mcg/kg/dose, was considered the maximum no-toxic effect dosage in this study.

Table 20 Long-Term Toxicity Summaries			
Species / strain	**Method of administration**	**Dose/Duration of dosing/ Number of animals used**	**Noteworthy findings**
Dogs/ purebred beagles	Intravenous bolus	0, 0.02, 0.06 or 0.2 mcg/kg/dose 1 year 20 males, 20 females	The 0.02 mcg/kg dose has no obvious or statistically significant effects under conditions of this study.

The effects seen in repeat-dose toxicity studies in rodents and dogs fell into two general categories: those related and those unrelated to paricalcitol's calcemic activity.

Effects not clearly related to hypercalcemia included decreased white blood cell counts and thymic atrophy in dogs, and altered activated partial thromboplastin time (APTT) values (increased in dogs, decreased in rats). Except for reductions in white blood cell counts (WBCs), similar effects were seen in rats and dogs treated with calcitriol. Such WBC changes were not observed in clinical trials of paricalcitol.

Reproductive Toxicity

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

Mutagenicity and Carcinogenicity

Refer to **WARNINGS AND PRECAUTIONS**.

Limitations of the animal models (animals without renal insufficiency) precluded the administration of high doses of paricalcitol in studies on repeated dose toxicity, reproductive toxicity and carcinogenicity. Doses administered and/or systemic exposures to paricalcitol were slightly higher than therapeutic doses/systemic exposures.

REFERENCES

1. Goldenberg MM. Paricalcitol, a new agent for the management of secondary hyperparathyroidism in patients undergoing chromic renal dialysis. *Clin Therap* 1999;21:432-41.

2. Drüeke TB, McCarron DA. Paricaclitol as compared with calcitriol in patients undergoing hemodialysis. An Editorial. *N Eng J Med* 2003;349(5):496-9.

3. Llach F. Paricalcitol: An updated review and guidelines for use. *Dialysis & Transplant* 2001;30:654-664.

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

5. Sprague SM, Lerma E, McCormick D, Abraham M, Batlle D. Suppression of parathyroid hormone secretion in hemodialysis patients: Comparison of paricalcitol with calcitriol. *Am J Kidney Dis* 2001;38(5 Suppl 5):S51-6.

6. Sprague SM, Llach F, Amdahl M, Taccetta C, Battle D. Paricalcitol versus calcitriol in the treatment of secondary hyperparathyroidism. *Kidney International* 2003; 63:1483-1490.

7. Lindberg J, Martin KJ, Gonzalez EA, Acchiardo SR, Valdin JR, Soltanek. A long-term multicentere study of the efficacy and safety of paricalcitol in end-stage renal disease. *Clin Nephrol* 2001;56:315-23.

8. Slatopolsky E, Finch JL, Ritter C, et al., A new Analog of calcitriol, 19-nor-1α, 25-(OH)2D_2, suppresses parathyroid hormone secretion in uremic rats in the absence of hypercalcemia. *Am J Kidney Dis*, 1995; 26(5):852-860.

9. Takahashi F, Finch JL, Denda M, et al., A new analog of 1,25-(OH)2D_2, 19-nor-1,25-(OH)2D_2, suppresses serum PTH and parathyroid gland growth in uremic rats without elevation of intestinal vitamin D receptor content. *Am J Kidney Dis* 1997; 30(1): 105-122.

10. Finch JL, Brown AJ, Slatopolsky E. Differential effects of 1α, 25-dihydroxyvitamin D_3 and 19-nor-1α,25-dihydroxyvitamin D_2 on calcium and phosphorous resorption in bone. *J Am Soc Nephrol* 1999;10(5):980-991.

11. Brown AJ. Vitamin D analogues. *Am J Kidney Dis* 1998;32(2 Suppl 2):S25-39.

PART III: CONSUMER INFORMATION

PrZEMPLAR®
Paricalcitol Capsules

This leaflet is part III of a three-part "Product Monograph" published when ZEMPLAR® Capsules was approved for sale in Canada and is designed specifically for Consumers. This leaflet is a summary and will not tell you everything about ZEMPLAR® Capsules. Contact your doctor or pharmacist if you have any questions about the drug.

ABOUT THIS MEDICATION

What the medication is used for:
ZEMPLAR® Capsules are used in the prevention and treatment of secondary hyperparathyroidism (high levels of parathyroid hormone which can cause bone problems) in chronic renal failure patients on peritoneal or hemodialysis (Chronic Kidney Disease Stage 5).

What it does:
ZEMPLAR® Capsules are a synthetic vitamin D analogue and are used to replace the body's naturally produced active form of vitamin D. In healthy people, the active form of vitamin D is naturally produced by the kidneys but in kidney failure, the production of the active vitamin is reduced which can cause low levels of calcium and high levels of parathyroid hormone in the blood.

When it should not be used:
ZEMPLAR® Capsules should not be used:

- If you are allergic to vitamin D or have developed evidence of vitamin D toxicity. Symptoms which can occur after receiving too much vitamin D include: confusion, feeling sleepy, weakness, muscle pain, bone pain, constipation, nausea, vomiting, stomach pains, itchy skin, increased thirst, and increased urination.
- If you suffer from hypercalcemia (high levels of calcium in your blood)
- If you are allergic to any of the product's ingredients

What the medicinal ingredient is:
The active substance is paricalcitol.

What the important nonmedicinal ingredients are:
ZEMPLAR® Capsules also contains medium chain triglycerides, alcohol, butylated hydroxytoluene, gelatin, glycerin, titanium dioxide, ink, Opacode® WB, black, iron oxide red (2 mcg capsules only), iron oxide yellow (2 mcg and 4 mcg capsules), iron oxide black (1 mcg capsules only), purified water.

What dosage forms it comes in:
Each capsule contains either 1 mcg, 2 mcg or 4 mcg of paricalcitol. The 1 mcg capsule is an oval, gray, soft gelatin capsule imprinted with ⊐ and ZA. The 2 mcg capsule is an oval, orange-brown, soft gelatin capsule imprinted with ⊐ and ZF. The 4 mcg capsule is an oval, gold soft gelatin capsule imprinted with ⊐ and ZK.

ZEMPLAR® Capsules is available in bottles containing 30 capsules each.

WARNINGS AND PRECAUTIONS

BEFORE you use ZEMPLAR® Capsules talk to your doctor or pharmacist if:

- You are pregnant or if you are breast feeding. Ask your doctor or pharmacist for advice.

INTERACTIONS WITH THIS MEDICATION

Tell your doctor or pharmacist if you are taking or have recently taken any other medicines, including the medicine you can buy without a prescription, natural health products, vitamin or mineral supplements.

Drugs that may interact with ZEMPLAR® Capsules include:

- Products containing phosphate or vitamin D.
- Products which contain aluminum or magnesium, these would include antacids (stomach medicine) or phosphate binders (used to remove phosphate from the blood).
- Digitalis compound e.g., digoxin or digitoxin (medicines used in certain heart conditions), thiazide diuretics (a type of water tablet) or medicines which contain high levels of calcium.
- Products used to treat fungal infections (e.g., ketoconazole).

PROPER USE OF THIS MEDICATION

Usual dose:
The dosage of ZEMPLAR® Capsules varies for each patient. Your doctor will decide on the appropriate dose for you. ZEMPLAR® Capsules are to be taken three times a week (every other day) and may be taken with or without food.

Missed dose:
If you miss a dose, do not take a double dose. The next dose should be taken as usual.

Overdose:
If you take more ZEMPLAR® Capsules than you should, contact your doctor or an emergency room of the nearest hospital.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

The most common side effects experienced: *These might affect between 1 and 10 in every 100 people.* High blood levels of calcium and phosphate; low blood levels of calcium, loss of appetite, diarrhea, dizziness, acne, breast pain, itchy skin and a change in your sense of taste.

Uncommon side effects: *These might affect less than 1 in every 100 people.* Allergic reaction, constipation, dry mouth, indigestion, gastrointestinal disorder or upset stomach (gastritis), dizziness, rash, hives, leg cramps and unusual taste. The results of blood tests may show raised liver enzymes.

Too much ZEMPLAR® Capsules can cause hypercalcemia (higher than normal levels of calcium in the blood, which can be harmful). To help prevent this your blood will be tested frequently early in your treatment, so that your doctor can adjust the dose of ZEMPLAR® Capsules to suit you.

Early signs and symptoms of hypercalcemia associate with vitamin D overdose include weakness, headache, feeling sleepy or sick, vomiting, dry mouth, constipation, muscle pain, bone pain and metallic taste.

Symptoms of hypercalcemia associated with vitamin D overdose which may develop over a longer period include a lack of appetite, feeling sleepy, weight loss, sore eyes, runny nose, itchy skin, feeling hot and feverish, decreased sex drive, calcium deposits and severe abdominal pain (due to an inflamed pancreas).

If you experience any other unusual or unexpected symptoms while receiving ZEMPLAR® Capsules tell your doctor immediately.

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM

Symptom / effect		Talk with your doctor or pharmacist		Stop taking drug and call your doctor or pharmacist
		Only if severe	In all cases	
Uncommon	Gastrointestinal disorder (diarrhea, abdominal pain)		✓	
	Dizziness		✓	✓

This is not a complete list of side effects. For any unexpected effects while taking ZEMPLAR®, contact your doctor or pharmacist.

HOW TO STORE IT

ZEMPLAR® Capsules should be stored between 15 and 25ºC.

REPORTING SUSPECTED SIDE EFFECTS

To monitor drug safety, Health Canada collects information on serious and unexpected effects of drugs. If you suspect you have had a serious or unexpected reaction to this drug you may notify Health Canada by:

toll-free telephone: 866-234-2345
toll-free fax 866-678-6789
By email: cadrmp@hc-sc.gc.ca

By regular mail:
National AR Centre
Marketed Health Products Safety and Effectiveness Information Division
Marketed Health Products Directorate
Tunney's Pasture, AL 0701C
Ottawa ON K1A 0K9

NOTE: Before contacting Health Canada, you should contact your physician or pharmacist.

MORE INFORMATION

This document plus the full product monograph, prepared for health professionals can be obtained by contacting the sponsor, AbbVie Corporation at 1-800-699-9948.

This leaflet was prepared by AbbVie Corporation.

Last revised: November 1, 2012

PART III: CONSUMER INFORMATION

PrZEMPLAR®
Paricalcitol Injection USP

This leaflet is part III of a three-part "Product Monograph" published when ZEMPLAR® Injection USP was approved for sale in Canada and is designed specifically for Consumers. This leaflet is a summary and will not tell you everything about ZEMPLAR® Injection USP. Contact your doctor or pharmacist if you have any questions about the drug.

ABOUT THIS MEDICATION

What the medication is used for:
ZEMPLAR® Injection USP is used in the prevention and treatment of secondary hyperparathyroidism (high levels of parathyroid hormone which can cause bone problems) in chronic renal failure patients on hemodialysis (Chronic Kidney Disease Stage 5).

What it does:
ZEMPLAR® Injection USP is a synthetic vitamin D analogue and is used to replace the body's naturally produced active form of vitamin D. In healthy people, the active form of vitamin D is naturally produced by the kidneys but in kidney failure, the production of the active vitamin is reduced which can cause low levels of calcium and high levels of parathyroid hormone in the blood.

When it should not be used:
ZEMPLAR® Injection USP should not be used:

- If you are allergic to vitamin D or have developed evidence of vitamin D toxicity. Symptoms which can occur after receiving too much vitamin D include: confusion, feeling sleepy, weakness, muscle pain, bone pain, constipation, nausea, vomiting, stomach pains, itchy skin, increased thirst, and increased urination.
- If you suffer from hypercalcemia (high levels of calcium in your blood)
- If you are allergic to any of the product's ingredients

What the medicinal ingredient is:
The active substance is paricalcitol.

What the important nonmedicinal ingredients are:
ZEMPLAR® Injection USP also contains alcohol (20% v/v), propylene glycol and water for injection.

What dosage forms it comes in:
ZEMPLAR® Injection USP is available as a liquid (containing 5 micrograms of paricalcitol per 1 mL) and packaged in ampoules or Fliptop vials as follows:

- Ampoules containing 1 mL or 2 mL
- Fliptop vials containing 1 mL or 2 mL

WARNINGS AND PRECAUTIONS

This product contains 20% ethanol. The amount of ZEMPLAR® Injection USP given to you could contain up to 1.3 grams of alcohol. This could be harmful to people who suffer from liver disease, alcoholism, epilepsy, brain injury or disease as well as for pregnant women and children. It may modify or increase the effect of other medicines.

BEFORE you use ZEMPLAR® Injection USP talk to your doctor or pharmacist if:

- You are pregnant or if you are breast feeding. Ask your doctor or pharmacist for advice.
- You have liver disease
- You drink alcohol
- You have seizures (epilepsy or brain injury)

INTERACTIONS WITH THIS MEDICATION

Tell your doctor or pharmacist if you are taking or have recently taken any other medicines, including the medicine you can buy without a prescription, natural health products, vitamin or mineral supplements.

Drugs that may interact with ZEMPLAR® Injection USP include:

- Products containing phosphate or vitamin D.
- Products which contain aluminum or magnesium, these would include antacids (stomach medicine) or phosphate binders (used to remove phosphate from the blood).
- Digitalis compound e.g., digoxin or digitoxin (medicines used in certain heart conditions), thiazide diuretics (a type of water tablet) or medicines which contain high levels of calcium.
- Products used to treat fungal infections (e.g., ketoconazole)**.**

PROPER USE OF THIS MEDICATION

Usual dose:
The dosage of ZEMPLAR* Injection USP varies for each patient. Your doctor will decide on the appropriate dose for you. ZEMPLAR* Injection USP will be injected into your vein through the hemodialysis line. You should not receive ZEMPLAR* Injection USP any more frequently than every other day during dialysis.

Overdose:
If you think you are given too much ZEMPLAR® Injection USP than you should, talk to your nurse, doctor, or contact an emergency room of the nearest hospital.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

The most common side effects experienced: *These might affect between 1 and 10 in every 100 people.* High blood levels of calcium and phosphate; parathyroid disorder; itchy skin and a change in your sense of taste.

Uncommon side effects: *These might affect less than 1 in every 100 people.* Blood disorders; enlargement of lymph nodes; taking longer for your blood to clot; blood pressure problems; irregular heart beat; heart attack; stroke; fainting; tissue swelling; fluid retention; loss of appetite; weight loss; constipation; dry mouth; feeling thirsty; diarrhea; feeling sick; vomiting; bleeding from your bottom; difficulty swallowing; indigestion. The results of blood tests may show raised liver enzymes. Unsteadiness; confusion; sleep disturbance; feeling anxious; dizziness; behavioural disorders; shaking; muscle twitches; numbness; eye (glaucoma); breathing difficulties; cough; nose bleeds; fluid on the lungs; chest infection; asthma; sore throat; rash; altered hair growth; sweating; feeling tired; joint pain; muscle pain; twitching; breast cancer; breast pain; impotence; inflammation of vagina; allergic reaction; aches and pains; feeling tired; fever; pain around the injection site; infections; flu-like symptoms, swelling of the face and mouth.

Too much ZEMPLAR® Injection USP can cause hypercalcemia (higher than normal levels of calcium in the blood, which can be harmful). To help prevent this your blood will be tested frequently early in your treatment, so that your doctor can adjust the dose of ZEMPLAR® Injection USP to suit you.

Early signs and symptoms of hypercalcemia associate with vitamin D overdose include weakness, headache, feeling sleepy or sick, vomiting, dry mouth, constipation, muscle pain, bone pain and metallic taste.

Symptoms of hypercalcemia associated with vitamin D overdose which may develop over a longer period include a lack of appetite, feeling sleepy, weight loss, sore eyes, runny nose, itchy skin, feeling hot and feverish, decreased sex drive, calcium deposits and severe abdominal pain (due to an inflamed pancreas).

The results of blood and urine tests may show high cholesterol, urea nitrogen (BUN) and raised levels of liver enzymes. Your blood pressure may be affected and heart beat irregularities can occur. ZEMPLAR® Injection USP may rarely cause mental changes including confusion, drowsiness, insomnia or nervousness.

If you experience any other unusual or unexpected symptoms while receiving ZEMPLAR® Injection USP tell your doctor immediately.

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM

Symptom / effect		Talk with your doctor or pharmacist		Stop taking drug and call your doctor or pharmacist
		Only if severe	In all cases	
Uncommon	Back pain		✓	
	Fever		✓	
	Headache	✓		
	Heart attack		✓	
	High blood pressure		✓	
	Irregular heart beat		✓	✓
	Stroke		✓	
	Gastrointestinal disorder (diarrhea, abdominal pain, low blood flow to the intestine)		✓	
	Nausea		✓	
	Rectal bleeding		✓	
	Vomiting		✓	
	Confusion		✓	✓
	Dizziness		✓	✓
	Impaired thinking (Not thinking clearly)		✓	
	Asthma (wheezing)		✓	
	Increased cough	✓		
	Shortness of breath		✓	

This is not a complete list of side effects. For any unexpected effects while taking ZEMPLAR® Injection USP, contact your doctor or pharmacist.

HOW TO STORE IT

ZEMPLAR® Injection USP should be stored between 15 and 25ºC. Protect from light, freezing and excessive heat.

REPORTING SUSPECTED SIDE EFFECTS

To monitor drug safety, Health Canada collects information on serious and unexpected effects of drugs. If you suspect you have had a serious or unexpected reaction to this drug you may notify Health Canada by:

toll-free telephone: 866-234-2345
toll-free fax 866-678-6789
By email: cadrmp@hc-sc.gc.ca

By regular mail:
National AR Centre
Marketed Health Products Safety and Effectiveness Information Division
Marketed Health Products Directorate
Tunney's Pasture, AL 0701C
Ottawa ON K1A 0K9

NOTE: Before contacting Health Canada, you should contact your physician or pharmacist.

MORE INFORMATION

This document plus the full product monograph, prepared for health professionals can be obtained by contacting the sponsor, AbbVie Corporation at 1-800-699-9948.

This leaflet was prepared by AbbVie Corporation.

Last revised: November 1, 2012