(Nos. 4637, 1658)
NEW

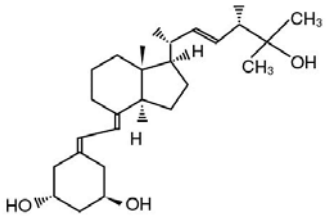
Zemplar®
(paricalcitol) Injection

Fliptop Vial
R_x only

DESCRIPTION

Paricalcitol, USP, the active ingredient in Zemplar Injection, is a synthetically manufactured analog of calcitriol, the metabolically active form of vitamin D indicated for the prevention and treatment of secondary hyperparathyroidism associated with chronic kidney disease(CKD) Stage 5. Zemplar is available as a sterile, clear, colorless, aqueous solution for intravenous injection. Each mL contains paricalcitol, 2 mcg or 5 mcg; propylene glycol, 30% (v/v); and alcohol, 20% (v/v).

Paricalcitol is a white powder chemically designated as 19-nor-1α,3β,25-trihydroxy-9,10-secoergosta-5(Z),7(E),22(E)-triene and has the following structural formula:



Molecular formula is $C_{27}H_{44}O_3$.
Molecular weight is 416.64.

CLINICAL PHARMACOLOGY

Secondary hyperparathyroidism is characterized by an elevation in parathyroid hormone (PTH) associated with inadequate levels of active vitamin D hormone. The source of vitamin D in the body is from synthesis in the skin and from dietary intake. Vitamin D requires two sequential hydroxylations in the liver and the kidney to bind to and to activate the vitamin D receptor (VDR). The endogenous VDR activator, calcitriol [1,25$(OH)_2$ D_3], is a hormone that binds to VDRs that are present in the parathyroid gland, intestine, kidney, and bone to maintain parathyroid function and calcium and

phosphorus homeostasis, and to VDRs found in many other tissues, including prostate, endothelium and immune cells. VDR activation is essential for the proper formation and maintenance of normal bone. In the diseased kidney, the activation of vitamin D is diminished, resulting in a rise of PTH, subsequently leading to secondary hyperparathyroidism, and disturbances in the calcium and phosphorus homeostasis.[1] The decreased levels of $1,25(OH)_2$ D_3 and resultant elevated PTH levels, both of which often precede abnormalities in serum calcium and phosphorus, affect bone turnover rate and may result in renal osteodystrophy.

Mechanism of Action

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

Pharmacokinetics

Within two hours after administering Zemplar intravenous doses ranging from 0.04 to 0.24 mcg/kg, concentrations of paricalcitol decreased rapidly; thereafter, concentrations of paricalcitol declined log-linearly. No accumulation of paricalcitol was observed with multiple dosing.

Distribution

Paricalcitol is extensively bound to plasma proteins (≥99.8%). In healthy subjects, the steady state volume of distribution is approximately 23.8 L. The mean apparent volume of distribution following a 0.24 mcg/kg dose of paricalcitol in CKD Stage 5 subjects requiring hemodialysis (HD) and peritoneal dialysis (PD) is between 31 and 35 L.

Metabolism

After IV administration of a 0.48 mcg/kg dose of ^{3}H-paricalcitol, parent drug was extensively metabolized, with only about 2% of the dose eliminated unchanged in the feces and no parent drug found in the urine. Several metabolites were detected in both the urine and feces. Most of the systemic exposure was from the parent drug. Two minor metabolites, relative to paricalcitol, were detected in human plasma. One metabolite was identified as 24(R)-hydroxy paricalcitol, while the other metabolite was unidentified. The 24(R)-hydroxy paricalcitol is less active than paricalcitol in an *in vivo* rat model of PTH suppression.
In vitro data suggest that paricalcitol is metabolized by multiple hepatic and non-hepatic enzymes, including mitochondrial CYP24, as well as CYP3A4 and UGT1A4. The

identified metabolites include the product of 24(R)-hydroxylation (present at low levels in plasma), as well as 24,26- and 24,28-dihydroxylation and direct glucuronidation.

Elimination

Paricalcitol is excreted primarily by hepatobiliary excretion. Approximately 63% of the radioactivity was eliminated in the feces and 19% was recovered in the urine in healthy subjects. In healthy subjects, the mean elimination half-life of paricalcitol is about five to seven hours over the studied dose range of 0.04 to 0.16 mcg/kg. The pharmacokinetics of paricalcitol has been studied in CKD Stage 5 subjects requiring hemodialysis (HD) and peritoneal dialysis (PD). The mean elimination half-life of paricalcitol after administration of 0.24 mcg/kg paricalcitol IV bolus dose in CKD Stage 5 HD and PD patients is 13.9 and 15.4 hours, respectively (Table 1).

Table 1 Mean ± SD Paricalcitol Pharmacokinetic Parameters in CKD Stage 5 Subjects Following Single 0.24 mcg/kg IV Bolus Dose

	CKD Stage 5-HD (n=14)	CKD Stage 5-PD (n=8)
C_{max} (ng/mL)	1.680 ± 0.511	1.832 ± 0.315
$AUC_{0-\infty}$ (ng·h/mL)	14.51 ± 4.12	16.01 ± 5.98
β (1/h)	0.050 ± 0.023	0.045 ± 0.026
$t_{1/2}$ (h) †	13.9 ± 7.3	15.4 ± 10.5
CL (L/h)	1.49 ± 0.60	1.54 ± 0.95
Vd_{β} (L)	30.8 ± 7.5	34.9 ± 9.5

†: harmonic mean ± pseudo standard deviation, HD: hemodialysis, PD: peritoneal dialysis

The degree of accumulation was consistent with the half-life and dosing frequency.

Special Populations

Geriatric

The pharmacokinetics of paricalcitol have not been investigated in geriatric patients greater than 65 years.

Pediatrics

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

Gender

The pharmacokinetics of paricalcitol were gender independent.

Hepatic Impairment

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

Renal Impairment

The pharmacokinetics of paricalcitol have been studied in CKD Stage 5 subjects requiring hemodialysis (HD) and peritoneal dialysis (PD). Hemodialysis procedure has essentially no effect on paricalcitol elimination. However, compared to healthy subjects, CKD Stage 5 subjects showed a decreased CL and increased half-life (see **Pharmacokinetics**, Elimination).

Drug Interactions

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

Drug interactions with paricalcitol injection have not been studied.

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

Ketoconazole: Although no data are available for the drug interaction between paricalcitol injection and ketoconazole, the effect of multiple doses of ketoconazole administered as 200 mg BID for 5 days on the pharmacokinetics of paricalcitol capsule has been studied in healthy subjects. The C_{max} of paricalcitol was minimally affected, but $AUC_{0-\infty}$ approximately doubled in the presence of ketoconazole. The mean half-life of paricalcitol was 17.0 hours in the presence of ketoconazole as compared to 9.8 hours, when paricalcitol was administered alone (See **PRECAUTIONS**).

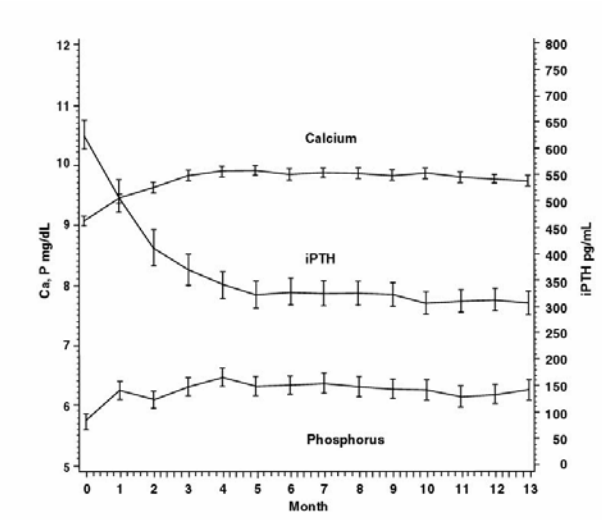
Clinical Studies

In three 12-week, placebo-controlled, phase 3 studies in chronic kidney disease Stage 5 patients on dialysis, the dose of Zemplar was started at 0.04 mcg/kg 3 times per week. The dose was increased by 0.04 mcg/kg every 2 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 100 pg/mL, or the Ca x P product was greater than 75 within any 2 week period, or serum calcium became greater than 11.5 mg/dL at any time.

Patients treated with Zemplar achieved a mean iPTH reduction of 30% within 6 weeks. In these studies, there was no significant difference in the incidence of hypercalcemia or hyperphosphatemia between Zemplar and placebo-treated patients. The results from these studies are as follows:

	Group (No. of Pts.)	**Baseline Mean (Range)**	**Mean (SE) Change From Baseline to Final Evaluation**
iPTH (pg/mL)	Zemplar (n=40)	783 (291 – 2076)	-379 (43.7)
	placebo (n=38)	745 (320 – 1671)	-69.6 (44.8)
Alkaline Phosphatase (U/L)	Zemplar (n=31)	150 (40 – 600)	-41.5 (10.6)
	placebo (n=34)	169 (56 – 911)	+2.6 (10.1)
Calcium (mg/dL)	Zemplar (n=40)	9.3 (7.2 – 10.4)	+0.47 (0.1)
	placebo (n=38)	9.1 (7.8 – 10.7)	+0.02 (0.1)
Phosphorus (mg/dL)	Zemplar (n=40)	5.8 (3.7 – 10.2)	+0.47 (0.3)
	placebo (n=38)	6.0 (2.8 – 8.8)	-0.47 (0.3)
Calcium x Phosphorus Product	Zemplar (n=40)	54 (32 – 106)	+7.9 (2.2)
	placebo (n=38)	54 (26 – 77)	-3.9 (2.3)

A long-term, open-label safety study of 164 CKD Stage 5 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 319 pg/mL at 13 months).



INDICATIONS AND USAGE

Zemplar is indicated for the prevention and treatment of secondary hyperparathyroidism associated with chronic kidney disease Stage 5.

CONTRAINDICATIONS

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

WARNINGS

Acute overdose of Zemplar may cause hypercalcemia, and require emergency attention. During dose adjustment, serum calcium and phosphorus levels should be monitored closely (e.g., twice weekly). If clinically significant hypercalcemia develops, the dose should be reduced or interrupted. Chronic administration of Zemplar may place patients at risk of hypercalcemia, elevated Ca x P product, and metastatic calcification.

Treatment of patients with clinically significant hypercalcemia consists of immediate dose reduction or interruption of Zemplar 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), hemodialysis or peritoneal dialysis against a calcium-free dialysate, as warranted. Serum calcium levels should be monitored frequently until normocalcemia ensues.

Phosphate or vitamin D-related compounds should not be taken concomitantly with Zemplar.

PRECAUTIONS

General

Digitalis toxicity is potentiated by hypercalcemia of any cause, so caution should be applied when digitalis compounds are prescribed concomitantly with Zemplar. Adynamic bone lesions may develop if PTH levels are suppressed to abnormal levels.

Information for the Patient

The patient should be instructed that, to ensure effectiveness of Zemplar therapy, it is important to adhere to a dietary regimen of calcium supplementation and phosphorus restriction. Appropriate types of phosphate-binding compounds may be needed to control serum phosphorus levels in patients with chronic kidney disease (CKD) Stage 5, but excessive use of aluminum containing compounds should be avoided. Patients should also be carefully informed about the symptoms of elevated calcium (See **ADVERSE REACTIONS**).

Laboratory Tests

During the initial phase of medication, serum calcium and phosphorus should be determined frequently (e.g., twice weekly). Once dosage has been established, serum calcium and phosphorus should be measured at least monthly. Measurements of serum or plasma PTH are recommended every 3 months. An intact PTH (iPTH) assay is recommended for reliable detection of biologically active PTH in patients with CKD Stage 5. During dose adjustment of Zemplar, laboratory tests may be required more frequently.

Drug Interactions

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

Specific interaction studies were not performed with Zemplar Injection.

A multiple dose drug-drug interaction study with ketoconazole and paricalcitol capsule demonstrated that ketoconazole approximately doubled paricalcitol $AUC_{0-\infty}$ (see **CLINICAL PHARMACOLOGY**). Since paricalcitol is partially metabolized by CYP3A and ketoconazole is known to be a strong inhibitor of cytochrome P450 3A enzyme, care should be taken while dosing paricalcitol with ketoconazole and other strong P450 3A inhibitors including atazanavir, clarithromycin, indinavir, itraconazole, nefazodone, nelfinavir, ritonavir, saquinavir, telithromycin or voriconazole.

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

Carcinogenesis, Mutagenesis, Impairment of Fertility

In a 104-week carcinogenicity study in CD-1 mice, an increased incidence of uterine leiomyoma and leiomyosarcoma was observed at subcutaneous doses of 1, 3, 10 mcg/kg (2 to 15 times the AUC at a human dose of 14 mcg, equivalent to 0.24 mcg/kg based on AUC). The incidence rate of uterine leiomyoma was significantly different than the control group at the highest dose of 10 mcg/kg.

In a 104-week carcinogenicity study in rats, there was an increased incidence of benign adrenal pheochromocytoma at subcutaneous doses of 0.15, 0.5, 1.5 mcg/kg (<1 to 7 times the exposure following a human dose of 14 mcg, equivalent to 0.24 mcg/kg based on AUC). The increased incidence of pheochromocytomas in rats may be related to the alteration of calcium homeostasis by paricalcitol.

Paricalcitol did not exhibit genetic toxicity *in vitro* with or without metabolic activation in the microbial mutagenesis assay (Ames Assay), mouse lymphoma mutagenesis assay (L5178Y), or a human lymphocyte cell chromosomal aberration assay. There was also no evidence of genetic toxicity in an *in vivo* mouse micronucleus assay. Zemplar 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].

Pregnancy

Pregnancy Category C.

Paricalcitol has been shown to cause minimal decreases in fetal viability (5%) when administered daily to rabbits at a dose 0.5 times the 0.24 mcg/kg human dose (based on surface area, mg/m^2) and when administered to rats at a dose 2 times the 0.24 mcg/kg human dose (based on plasma levels of exposure). At the highest dose tested (20 mcg/kg 3 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.

There are no adequate and well-controlled studies in pregnant women. Zemplar should be used during pregnancy only if the potential benefit to the mother justifies the potential risk to the fetus.

Nursing Mothers

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

Pediatric Use

The safety and effectiveness of Zemplar were examined in a 12-week randomized, double-blind, placebo-controlled study of 29 pediatric patients, aged 5-19 years, with end-stage renal disease on hemodialysis and nearly all 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 Zemplar was 0.04 mcg/kg 3 times per week, based on baseline iPTH level of less than 500 pg/mL, or 0.08 mcg/kg 3 times a week based on baseline iPTH level of ≥ 500 pg/mL, respectively. The dose of Zemplar 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 841 pg/mL for the 15 Zemplar-treated patients and 740 pg/mL for the 14 placebo-treated subjects. The mean dose of Zemplar administered was 4.6 mcg (range: 0.8 mcg – 9.6 mcg). Ten of the 15 (67%) Zemplar-treated patients and 2 of the 14 (14%) placebo-treated patients completed the trial. Ten of the placebo patients (71%) were discontinued due to excessive elevations in iPTH levels as defined by 2 consecutive iPTH levels > 700 pg/mL and greater than baseline after 4 weeks of treatment.

In the primary efficacy analysis, 9 of 15 (60%) subjects in the Zemplar 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%). Twenty-three percent of Zemplar vs. 31% of placebo patients had at least one serum calcium level > 10.3 mg/dL, and 40% vs. 14% of Zemplar vs. placebo subjects had at least one Ca x P ion product > 72 $(mg/dL)^2$. The overall percentage of serum calcium measurements > 10.3 mg/dL was 7% in the Zemplar group and 7% in the placebo group; the overall percentage of patients with Ca x P product > 72 $(mg/dL)^2$ was 8% in the Zemplar group and 7% in the placebo group. No subjects in either the Zemplar group or placebo group developed hypercalcemia (defined as at least one calcium value > 11.2 mg/dL) during the study.

Geriatric Use

Of the 40 patients receiving Zemplar in the three phase 3 placebo-controlled CKD Stage 5 studies, 10 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.

ADVERSE REACTIONS

Zemplar has been evaluated for safety in clinical studies in 454 CKD Stage 5 patients. 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 Zemplar (dosage titrated as tolerated, see **CLINICAL PHARMACOLOGY, Clinical Studies**) and 2.0% of 51 patients treated with placebo for 1 to 3 months. Adverse events occurring with greater frequency in the Zemplar group at a frequency of 2% or greater, regardless of causality, are presented in the following table:

Adverse Event Incidence Rates For All Treated Patients In All Placebo-Controlled Studies

Adverse Event	Zemplar (n=62) %	Placebo (n=51) %
Overall	71	78
Body as a Whole		
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
Metabolic 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 13 months in duration support the long-term safety of Zemplar in this patient population.

Potential adverse events of Zemplar Injection are, in general, similar to those encountered with excessive vitamin D intake. Signs and symptoms of vitamin D intoxication associated with hypercalcemia include:

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 BUN,

hypercholesterolemia, elevated AST and ALT, ectopic calcification, hypertension, cardiac arrhythmias, somnolence, death, and rarely, overt psychosis.

Adverse events during post-marketing experience: Taste perversion, such as metallic taste, and allergic reactions, such as rash, urticaria, pruritus, facial and oral edema rarely have been reported.

OVERDOSAGE

Overdosage of Zemplar may lead to hypercalcemia, hypercalciuria, hyperphosphatemia, and over suppression of PTH. (see **WARNINGS**).

Treatment of Overdosage and Hypercalcemia

The treatment of acute overdosage should consist of general supportive measures. Serial serum electrolyte determinations (especially calcium), rate of urinary calcium excretion, and assessment of electrocardiographic abnormalities due to hypercalcemia should be obtained. Such monitoring is critical in patients receiving digitalis. Discontinuation of supplemental calcium and institution of a low calcium diet are also indicated in acute overdosage.

General treatment of hypercalcemia due to overdosage consists of immediate suspension of Zemplar therapy, institution of a low calcium diet, and withdrawal of calcium supplements. Serum calcium levels should be determined at least weekly until normocalcemia ensues. When serum calcium levels have returned to within normal limits, Zemplar may be reinitiated at a lower dose. If persistent and markedly elevated serum calcium levels occur, there are a variety of therapeutic alternatives that may be considered. These include the use of drugs such as phosphates and corticosteroids as well as measures to induce diuresis. Also, one may consider dialysis against a calcium-free dialysate.

DOSAGE AND ADMINISTRATION

The currently accepted target range for iPTH levels in CKD Stage 5 patients is no more than 1.5 to 3 times the non-uremic upper limit of normal.

The recommended initial dose of Zemplar is 0.04 mcg/kg to 0.1 mcg/kg (2.8 – 7 mcg) administered as a bolus dose no more frequently than every other day at any time during dialysis.

If a satisfactory response is not observed, the dose may be increased by 2 to 4 mcg at 2- to 4-week intervals. During any dose adjustment period, serum calcium and phosphorus levels should be monitored more frequently, and if an elevated calcium level or a Ca x P product greater than 75 is noted, the drug dosage should be immediately reduced or interrupted until these parameters are normalized. Then, Zemplar should be reinitiated at a lower dose. If a patient is on a calcium-based phosphate binder, the dose

may be decreased or withheld, or the patient may be switched to a non-calcium-based phosphate binder. Zemplar doses may need to be decreased as the PTH levels decrease in response to therapy. Thus, incremental dosing must be individualized.

The following table is a suggested approach in dose titration:

Suggested Dosing Guidelines	
PTH Level	**Zemplar Dose**
the same or increasing	increase
decreasing by < 30%	increase
decreasing by >30%, < 60%	maintain
decreasing by > 60%	decrease
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.

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

Discard unused portion.

HOW SUPPLIED

Zemplar Injection is available as 2 mcg/mL (NDC 0074-4637-01) and 5 mcg/mL (NDC 0074-1658-01 and NDC 0074-1658-02).

List No.	Volume/Container	Concentration	Total Content
4637-01	1 mL/Fliptop Vial	2 mcg/mL	2 mcg
1658-01	1 mL/Fliptop Vial	5 mcg/mL	5 mcg
1658-02	2 mL/Fliptop Vial	5 mcg/mL	10 mcg

Store at 25°C (77°F). Excursions permitted between 15° - 30°C (59° - 86°F)
U.S. patents: 5,246,925; 5,587,497; 6,136,799; 6,361,758

REFERENCES

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

NEW

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