Zemplar™

(paricalcitol injection)

Ampul
Fliptop Vial

DESCRIPTION

Zemplar™ (paricalcitol injection) is a synthetically manufactured vitamin D analog. It is available as a sterile, clear, colorless, aqueous solution for intravenous injection. Each mL contains paricalcitol, 5 mcg, propylene glycol, 30% (v/v); and alcohol, 20% (v/v).

Paricalcitol is a white powder chemically designated as

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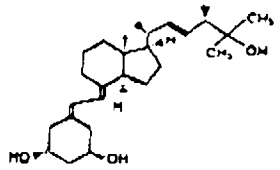
19-nor-1α,3β,25-trihydroxy-9,10-secoergosta-5(Z),7(E),22(E)-triene and has the following structural formula:



Molecular formula is $C_{27}H_{44}O_3$.
Molecular weight is 416.65.

CLINICAL PHARMACOLOGY

Mechanism of Action

Paricalcitol is a synthetic vitamin D analog. Vitamin D and paricalcitol have been shown to reduce parathyroid hormone (PTH) levels.

Pharmacokinetics

Distribution

The pharmacokinetics of paricalcitol have been studied in patients with chronic renal failure (CRF) requiring hemodialysis. Zemplar™ 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.

Elimination

In healthy subjects, plasma radioactivity after a single 0.16 mcg/kg intravenous bolus dose of ^{3}H-paricalcitol ($n=4$) 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.

Metabolism

Several unknown metabolites were detected in both the urine and feces, with no detectable paricalcitol in the urine. These metabolites have not been characterized and have not been identified. Together, these metabolites contributed 51% of the urinary radioactivity and 58% of the fecal radioactivity. *In vitro* plasma protein binding of paricalcitol was extensive (>99.8%) and nonsaturable over the concentration range of 1 to 100 ng/mL.

Paricalcitol Pharmacokinetic Characteristics in CRF Patients (0.24 mcg/kg dose)

Parameter	n	Values (Mean ± SD)
C_{max} (5 min. after bolus)	6	1850 ± 884 (pg/mL)
$AUC_{0-\infty}$	5	27382 ± 8230 (pg•hr/mL)
CL	5	0.72 ± 0.24 (L/hr)
V_{ss}	5	6 ± 2 (L)

Laboratory Tests

In placebo-controlled studies, paricalcitol reduced serum total alkaline phosphatase levels.

Special Populations

Paricalcitol pharmacokinetics have not been investigated in special populations (geriatric, pediatric, hepatic insufficiency), or for drug-drug interactions. Pharmacokinetics were not gender-dependent.

Clinical Studies

In three 12-week, placebo-controlled, phase 3 studies in chronic renal failure 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
PTH (pg/mL)	Zemplar™ (n=40)	783 (291 – 2078)	-378 (43.7)
	placebo (n=38)	745 (320 – 1871)	-58.6 (44.8)
Alkaline Phosphatase (U/L)	Zemplar™ (n=31)	130 (40 – 605)	+1.5 (10.6)
	placebo (n=34)	169 (58 – 811)	+2.8 (10.1)
Calcium (mg/dL)	Zemplar™ (n=40)	9.3 (7.2 – 10.4)	+0.47 (0.1)
	placebo (n=38)	9.1 (7.6 – 10.7)	+0.03 (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 – 9.8)	-0.07 (0.3)
Calcium x Phosphorus Product	Zemplar™ (n=40)	54 (32 – 105)	+1.9 (2.2)
	placebo (n=38)	54 (28 – 77)	-3.9 (2.3)

INDICATIONS AND USAGE

Zemplar™ is indicated for the prevention and treatment of secondary hyperparathyroidism associated with chronic renal failure. Studies in patients with chronic renal failure show that Zemplar™ suppresses PTH levels with no significant difference in the incidence of hypercalcemia or hyperphosphatemia when compared to placebo. However, the serum phosphorus, calcium and the calcium x phosphorus product (Ca x P) may increase when Zemplar™ is administered.

CONTRAINDICATIONS

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

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. 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.

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), and 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 renal failure (CRF), but excessive use of aluminum containing compounds should be avoided. Patients should also be carefully informed about the symptoms of elevated calcium.

Essential 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 CRF. During dose adjustment of

Zemplar™, laboratory tests may be required more frequently.

Drug Interactions: 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 Zemplar™.

Carcinogenesis, Mutagenesis, Impairment of Fertility. Long-term studies in animals to evaluate the carcinogenic potential of paricalcitol have not been completed. 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/m²).

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/m²) 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 justifies the potential risk to the fetus.

Nursing Mothers: It is not known whether paricalcitol is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when Zemplar™ is administered to a nursing woman.

Pediatric Use: Safety and efficacy of Zemplar™ in pediatric patients have not been established.

Geriatric Use: Of the 40 patients receiving Zemplar™ in the three phase 3 placebo-controlled CRF 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 270 CRF 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 one to three 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) number of events, %	Placebo (n=51) number of events, %
Overall	71	78
Body as a Whole		
Chills	5	0
Feeling unwell	3	0
Fever	5	2
Flu	5	4
Sepsis	6	2
Cardiovascular System		
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.

OVERDOSAGE

Overdosage of Zemplar™ may lead to hypercalcemia (see **WARNINGS**).

DOSAGE AND ADMINISTRATION

The currently accepted target range for iPTH levels in CRF 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 – 7.0 mcg) administered as a bolus dose no more frequently than every other day at any time during dialysis. 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 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. 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

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™ (paricalcitol injection) 5 mcg/mL is supplied as a single dosage strength in 1, 2, and 5 mL single-dose ampuls or Fliptop Vials.

List No.	Volume/Container	Concentration	Total Content
1858	1 mL/Fliptop Vial	5 mcg/mL	5 mcg
1658	2 mL/Fliptop Vial	5 mcg/mL	10 mcg
1858	5 mL/Fliptop Vial	5 mcg/mL	25 mcg
3043	1 mL/ampul	5 mcg/mL	5 mcg
3043	2 mL/ampul	5 mcg/mL	10 mcg
3043	5 mL/ampul	5 mcg/mL	25 mcg

Store at 25°C (77°F). Excursions permitted to 15° – 30°C (59° – 86°F).

℞ only

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