HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use PARICALCITOL INJECTION safely and effectively. See full prescribing information for PARICALCITOL INJECTION.

PARICALCITOL INJECTION, for intravenous use
Initial U.S. Approval: 1998

----------INDICATIONS AND USAGE----------
Paricalcitol injection is an active vitamin D_2 analog indicated for the prevention and treatment of secondary hyperparathyroidism associated with chronic kidney disease Stage 5 (1).

----------DOSAGE AND ADMINISTRATION----------
- The recommended starting dose is 0.04 mcg/kg to 0.1 mcg/kg (2.8 – 7 mcg)
- Administer Paricalcitol Injection as a bolus through a hemodialysis vascular access port at any time during dialysis. Dosing should not occur more frequently than every other day.
- Do not inject Paricalcitol Injection directly into a vein.
- Paricalcitol Injection dose should be individualized. If a satisfactory PTH lowering response is not observed with the initial dose, the dose may be increased by 2 to 4 mcg at 2- to 4- week intervals based on parathyroid hormone (PTH) levels. (2)

Suggested Dosage Adjustment

PTH Level at Follow-up Visit	Dosage Adjustment
Above target and PTH increased	Increase
Above target and PTH decreased by less than 30%	Increase
Above target and PTH decreased by 30 to 60%	No Change
Above target and PTH decreased by more than 60%	Decrease
At target and PTH stable	No Change

----------DOSAGE FORMS AND STRENGTHS----------
Paricalcitol Injection is available as a single-dose vial in following presentations: 2 mcg per mL and 5 mcg per mL vials (3).
Paricalcitol Injection is available as a multi-dose vial in following presentation: 10 mcg per 2 mL (3).

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

----------WARNINGS AND PRECAUTIONS----------
- Hypercalcemia: The risk may be increased when Paricalcitol Injection is used concomitantly with high dose calcium preparations, thiazide diuretics, or metabolically inactive or active forms of vitamin D. Monitor serum calcium when using Paricalcitol Injection and adjust dose accordingly. Inform patients of symptoms of hypercalcemia. (5.1)
- Digitalis Toxicity: Hypercalcemia increases the risk of digitalis toxicity. In patients using Paricalcitol Injection concomitantly with digitalis compounds, monitor both serum calcium and patients for signs and symptoms of digitalis toxicity and increase frequency of monitoring when initiating or adjusting the dose of Paricalcitol Injection. (5.2)
- Risk of Increased Paricalcitol Levels With Concomitant Use of Strong CYP3A Inhibitors: Use of Paricalcitol Injection with strong CYP3A inhibitors increases the concentration of paricalcitol in the blood. In patients on Paricalcitol Injection who are initiating or discontinuing drugs known to be strong CYP3A inhibitors, monitor serum calcium and PTH more frequently and adjust Paricalcitol Injection dose as required. (5.3)
- Adynamic Bone Disease: May develop if PTH levels are suppressed to abnormally low levels. Monitor PTH levels and adjust Paricalcitol Injection accordingly. (5.4).

----------ADVERSE REACTIONS----------
The most common adverse reactions (greater than 5% and more frequent than placebo) include nausea, vomiting and edema (6.1).

To report SUSPECTED ADVERSE REACTIONS, contact Accord Healthcare Inc. at 1-866-941-7875 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch (6).

----------DRUG INTERACTIONS----------
Co-administration with strong CYP3A inhibitors (e.g. ketoconazole) increases paricalcitol blood levels. See WARNINGS AND PRECAUTIONS (5.3, 7.1).

----------USE IN SPECIFIC POPULATIONS----------
- Pregnancy: Use during pregnancy only if the potential benefit justifies the potential risk (8.1).
- Lactation: A decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother (8.2).

See 17 for PATIENT COUNSELING INFORMATION

Revised: 2/2016

FULL PRESCRIBING INFORMATION: CONTENTS*

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

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

Paricalcitol Injection is an active vitamin D_2 analogue indicated for the prevention and treatment of secondary hyperparathyroidism associated with chronic kidney disease (CKD) Stage 5.

2 DOSAGE AND ADMINISTRATION

For intravenous use through hemodialysis vascular access port only.

The recommended starting dose of Paricalcitol Injection is 0.04 mcg/kg to 0.1 mcg/kg (2.8 to 7 mcg) administered through a hemodialysis vascular access port as a bolus dose at any time during dialysis. Dosing should not occur more frequently than every other day. The drug product should not be injected directly into a vein. Dosage should be individualized. If a satisfactory parathyroid hormone (PTH) lowering response is not observed using the recommended starting dose, the dose may be increased by 2 to 4 mcg every 2 to 4 weeks based on PTH levels (refer to Table 1).

Table 1 Suggested Dosage Adjustment

PTH Level at Follow-up Visit	Dosage Adjustment
Above target and PTH increased	Increase
Above target and PTH decreased by less than 30%	Increase
Above target and PTH decreased by 30 to 60%	No Change
Above target and PTH decreased by more than 60%	Decrease
At target and PTH stable	No Change

When initiating Paricalcitol Injection or adjusting Paricalcitol Injection dose, measure serum calcium and phosphorus frequently (e.g., twice weekly) and PTH every 2 to 4 weeks. Once a maintenance dose has been established, serum calcium and phosphorus should be measured at least monthly and plasma PTH every 3 months.

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

3 DOSAGE FORMS AND STRENGTHS

Paricalcitol is available in two strengths, 2 mcg/mL and 5 mcg/mL, as clear, colorless solutions. Both strengths are available as single-dose presentation in 1 mL vials. The 5 mcg/mL strength is also available as a multi-dose presentation, 10 mcg/2 mL in 2 mL vials.

4 CONTRAINDICATIONS

Paricalcitol Injection is contraindicated in patients with evidence of:

- Hypercalcemia [see *Warnings and Precautions (5.1)*]
- Vitamin D toxicity [see *Warnings and Precautions (5.1)*] or
- Hypersensitivity to paricalcitol or any inactive ingredient in this product [*see Adverse reactions (6.2)*].

5 WARNINGS AND PRECAUTIONS

5.1 Hypercalcemia

Hypercalcemia may occur during Paricalcitol Injection treatment and may be exacerbated by concomitant administration of high doses of calcium containing preparations, thiazide diuretics, or vitamin D (i.e., all forms). Acute hypercalcemia may exacerbate tendencies for cardiac arrhythmias and seizures and may potentiate the effect of digitalis on the heart. Chronic hypercalcemia can lead to generalized vascular calcification and other soft-tissue calcification. Hypercalcemia may be so severe as to require emergency attention.

High intake of calcium and phosphate concomitantly with vitamin D compounds may lead to hypercalcemia, hypercalciuria, and hyperphosphatemia. Prevention of such adverse reactions requires frequent serum calcium monitoring and careful Paricalcitol Injection dose adjustments.

Concomitant use with other active vitamin D analogues should be avoided during Paricalcitol Injection treatment to prevent hypercalcemia.

Patients also should be informed about the symptoms of elevated calcium, which include feeling tired, difficulty thinking clearly, loss of appetite, nausea, vomiting, constipation, increased thirst, increased urination and weight loss.

5.2 Digitalis Toxicity

Hypercalcemia of any cause increases the risk of digitalis toxicity. In patients using Paricalcitol Injection concomitantly with digitalis compounds, monitor both serum

calcium and patients for signs and symptoms of digitalis toxicity and increase frequency of monitoring when initiating or adjusting the dose of Paricalcitol Injection *[see Dosage and Administration (2)]*.

5.3 Risk of Increased Paricalcitol Levels With Concomitant Use of Strong CYP3A Inhibitors

Concomitant use of Paricalcitol Injection with strong CYP3A inhibitors will increase the levels of paricalcitol in the blood. In patients on Paricalcitol Injection who are initiating or discontinuing therapy with drugs known to be strong CYP3A inhibitors, monitor serum calcium and PTH more frequently and adjust Paricalcitol Injection dose as required *[see Drug Interactions (7.1), Clinical Pharmacology (12.3)]*.

5.4 Adynamic Bone Disease

Adynamic bone disease with subsequent increased risk of fractures may develop if PTH levels are suppressed to abnormally low levels. Monitor PTH levels and adjust Paricalcitol Injection dose [see Dosage and Administration (2)].

6 ADVERSE REACTIONS

6.1 Clinical Trials Experience

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

Safety has been evaluated in clinical studies conducted with another paricalcitol injection product in 609 patients with CKD Stage 5. 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 (dosage titrated as tolerated, [*see Clinical Studies (14)*]) and 2.0% of 51 patients treated with placebo for 1 to 3 months. Adverse reactions occurring with greater frequency in the paricalcitol group and at a frequency of 2% or greater are presented in the following table:

Table 2: Adverse Reactions Occurring at a Rate* of 2% or Greater in CKD Stage 5 Patients In Four Placebo-Controlled Studies

Adverse Reaction	**Placebo (n = 51) %**	**Paricalcitol Injection (n = 62) %**
Cardiac Disorders		
Palpitations	0.0	3.2
Gastrointestinal Disorders		
Nausea	7.8	12.9

Vomiting	5.9	8.1
Gastrointestinal Hemorrhage	2.0	4.8
Dry Mouth	2.0	3.2
General Disorders and Administration Site Conditions		
Edema	0.0	6.5
Chills	2.0	4.8
Pyrexia	2.0	4.8
Malaise	0.0	3.2
Infections and Infestations		
Pneumonia	0.0	4.8
Sepsis	2.0	4.8
Influenza	3.9	4.8
Musculoskeletal and Connective Tissue Disorders		
Arthralgia	3.9	4.8
*A patient who reported the same medical term more than once was counted only once for that medical term.		

Specific laboratory parameters [i.e., changes in mean Calcium (Ca), Phosphorus (P), and Calcium Phosphorus product (Ca x P)] were followed in an open-label safety study conducted with another paricalcitol injection product for up to 13 months in duration in this patient population and results are shown below [*see Clinical Studies (14)*].

Other Adverse Reactions Associated with Paricalcitol Injection Use

The following adverse reactions, occurred in less than 2% of the paricalcitol-treated patients in the above mentioned double-blind, placebo-controlled clinical trials and in additional double-blind, active-controlled and open-label studies:

Blood and Lymphatic System Disorders: Anemia, lymphadenopathy

Cardiac Disorders: Arrhythmia, atrial flutter, cardiac arrest

Ear and Labyrinth Disorders: Ear discomfort

Endocrine Disorders: hypoparathyroidism

Eye Disorders: Conjunctivitis, glaucoma, ocular hyperemia

Gastrointestinal Disorders: Abdominal discomfort, constipation, diarrhea, dysphagia, gastritis, intestinal ischemia, rectal hemorrhage

General Disorders and Administration Site Conditions: Asthenia, chest discomfort, chest pain, condition aggravated, edema peripheral, fatigue, feeling abnormal, gait disturbance, injection site extravasation, injection site pain, pain, swelling, thirst

Infections and Infestations: Nasopharyngitis, upper respiratory tract infection, vaginal infection

Laboratory Investigations and Vital Signs: Increased Aspartate aminotransferase, prolonged bleeding time, irregular heart rate, decreased weight

Metabolism and Nutrition Disorders: Decreased appetite, hypercalcemia, hyperkalemia, hyperphosphatemia, hypocalcemia

Musculoskeletal and Connective Tissue Disorders: Joint stiffness, muscle twitching, myalgia

Neoplasms Benign, Malignant and Unspecified: Breast cancer

Nervous System Disorders: Cerebrovascular accident, dizziness, dysgeusia, headache, hypoesthesia, myoclonus, paresthesia, syncope, unresponsive to stimuli

Psychiatric Disorders: Agitation, confusional state, delirium, insomnia, nervousness, restlessness

Reproductive System and Breast Disorders: Breast pain, erectile dysfunction

Respiratory, Thoracic and Mediastinal Disorders: Cough, dyspnea, orthopnea, pulmonary edema, wheezing

Skin and Subcutaneous Tissue Disorders: Alopecia, blister, hirsutism, night sweats, rash pruritic, pruritus, skin burning sensation

Vascular Disorders: Hypertension, hypotension

6.2 Postmarketing Experience

The following adverse reactions have been identified during post-approval use of another paricalcitol injection product. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Allergic reactions including rash, urticaria, and angioedema (including laryngeal edema) have been reported.

7 DRUG INTERACTIONS

7.1 Strong CYP3A Inhibitors

Paricalcitol is partially metabolized by CYP3A. Paricalcitol blood levels will be increased when paricalcitol is co-administered with strong CYP3A inhibitors. If a patient initiates or discontinues therapy with a strong CYP3A inhibitor, monitor both PTH and serum calcium more frequently and adjust Paricalcitol Injection dose as required [see *Clinical Pharmacology (12.3)*].

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

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. Paricalcitol Injection should be used during pregnancy only if the potential benefit to the mother justifies the potential risk to the fetus.

8.2 Lactation

Risk Summary

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

8.4 Pediatric Use

The safety and effectiveness of paricalcitol injection were examined with another paricalcitol injection product in a 12-week randomized, double-blind, placebo-controlled study of 29 pediatric patients, aged 5 to 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 paricalcitol injection 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 paricalcitol injection 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 paricalcitol injection-treated patients and 740 pg/mL for the 14 placebo-treated subjects. The mean dose of paricalcitol injection administered was 4.6 mcg (range: 0.8 mcg to 9.6 mcg). Ten of the 15 (67%) paricalcitol injection-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 paricalcitol injection 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 paricalcitol injection vs. 31% of placebo patients had at least one serum calcium level > 10.3 mg/dL, and 40% vs. 14% of paricalcitol injection 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 paricalcitol injection 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 paricalcitol injection group and 7% in the placebo group. No subjects in either the paricalcitol injection group or placebo group developed hypercalcemia (defined as at least one calcium value > 11.2 mg/dL) during the study.

8.5 Geriatric Use

Clinical studies of paricalcitol injection did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

10 OVERDOSAGE

Overdosage of Paricalcitol Injection may lead to hypercalcemia, hypercalciuria, hyperphosphatemia, and over suppression of PTH resulting in adynamic bone disease. [*see Warnings and Precautions (5.1, 5.4)*].

10.1 Treatment of Overdosage and Hypercalcemia

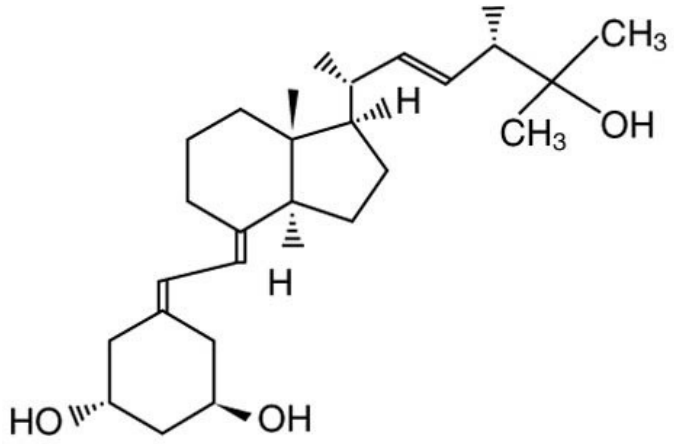
The treatment of acute overdosage should consist of general supportive measures, discontinuation of drug administration and supplemental calcium, institution of a low

calcium diet. Serum calcium levels should be measured until normocalcemia ensues. When serum calcium levels have returned to within normal limits, Paricalcitol Injection may be reinitiated at a lower dose.

Paricalcitol is not significantly removed by dialysis.

11 DESCRIPTION

Paricalcitol, USP, the active ingredient in Paricalcitol Injection, is a synthetically manufactured active vitamin D_2 analog. It 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:



Paricalcitol Injection is available as a sterile, clear, colorless, aqueous solution for intravenous injection. Each mL contains paricalcitol, 2 mcg or 5 mcg and the following inactive ingredients: alcohol, 35 % (v/v) and propylene glycol, 30 % (v/v).

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Preclinical and *in vitro* studies have demonstrated that paricalcitol's biological actions are mediated through binding of the vitamin D receptor (VDR), which results in the selective activation of vitamin D responsive pathways. Vitamin D and paricalcitol have been shown to reduce parathyroid hormone levels by inhibiting PTH synthesis and secretion.

12.3 Pharmacokinetics

Within two hours after administering paricalcitol 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 three times a week dosing.

Distribution: Paricalcitol is extensively bound to plasma proteins ($\geq$ 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 intravenous 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 a radioactive dose was recovered 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 intravenous bolus dose in CKD Stage 5 HD and PD patients is 13.9 and 15.4 hours, respectively (Table 3).

Table 3: Mean ± SD Paricalcitol Pharmacokinetic Parameters in CKD Stage 5 Subjects Following Single 0.24 mcg/kg Intravenous 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.

Specific Populations

Geriatric: The pharmacokinetics of paricalcitol has not been investigated in geriatric patients greater than 65 years.

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

Gender: The pharmacokinetics of paricalcitol was gender independent.

Hepatic Impairment: The disposition of intravenous 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 has 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.

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. The following studies have been performed with oral paricalcitol capsules.

Omeprazole

The pharmacokinetic interaction between paricalcitol capsule (16 mcg) and omeprazole (40 mg; oral), a strong inhibitor of CYP2C19, was investigated in a single dose,

crossover study in healthy subjects. The pharmacokinetics of paricalcitol was unaffected when omeprazole was administrated approximately 2 hours prior to the paricalcitol dose.

Strong CYP3A Inhibitors

Ketoconazole

Although no data are available for the drug interaction between Paricalcitol Injection and ketoconazole, a strong inhibitor of CYP3A, 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 Drug Interactions (7.1)*].

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

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

Paricalcitol did not exhibit genetic toxicity *in vitro* with or without metabolic activation in the microbial mutagenesis assay (Ames Assay), mouse lymphoma mutagenesis assay (L5178Y), or a human lymphocyte cell chromosomal aberration assay. There was also no evidence of genetic toxicity in an *in vivo* mouse micronucleus assay. Paricalcitol had no effect on fertility (male or female) in rats at intravenous doses up to 20 mcg/kg/dose [equivalent to 13 times the highest recommended human dose (0.24 mcg/kg) based on surface area, mg/m^2].

14 CLINICAL STUDIES

In three 12-week, placebo-controlled, phase 3 studies conducted with another paricalcitol injection product in patients with Stage 5 chronic kidney disease on dialysis, the dose of paricalcitol 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.

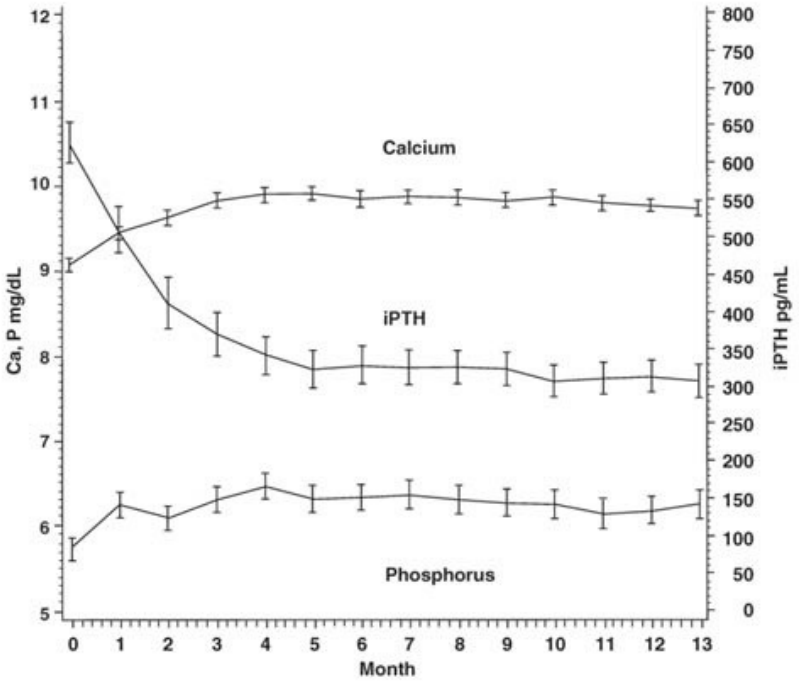
Patients treated with paricalcitol achieved a mean iPTH reduction of 30% within 6 weeks. In these studies, there was no significant difference in the incidence of hypercalcemia or hyperphosphatemia between paricalcitol and placebo-treated patients. The results from these studies are as follows:

Table 4: Mean Changes from Baseline to Final Evaluation in PTH, Alkaline Phosphatase, Phosphorus, and Calcium x Phosphorus Product in CKD Stage 5 Patients in Three Placebo-Controlled, Phase 3 Studies

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

A long-term, open-label safety study of 164 CKD Stage 5 patients conducted with another paricalcitol injection product (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).

Figure 1: Mean Values for Serum iPTH, Calcium and Phosphorus Over Time in CKD Stage 5 Patients in a Phase 3 Study



16 HOW SUPPLIED/STORAGE AND HANDLING

Paricalcitol Injection is available as 2 mcg per mL (**NDC** 16729-310-63), 5 mcg per mL (**NDC** 16729-311-63), and 10 mcg per 2 mL (5 mcg per mL)(**NDC** 16729-311-30) in carton of 1 vial.

NDC No.	Total Content/Concentration	Volume/Container	Vial Type
16729-310-63	2 mcg/mL	1 mL	Single-dose
16729-311-63	5 mcg/mL	1 mL	Single-dose
16729-311-30	10 mcg/2 mL (5 mcg/mL)	2 mL	Multi-dose

Storage

Store at at 20° to 25° C (68° to 77° F) [see USP Controlled Room Temperature].Excursions permitted between 15° to 30°C (59° to 86°F).

Discard unused portion of the single-dose vial.

The opened (in use) should be stored at room temperature 20° to 25° C (68° to 77° F) and protected from light. Discard seven days after being open.

17 PATIENT COUNSELING INFORMATION

Patients should be advised:

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

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