Package Insert

PARICORD (Paricalcitol Injection 5 mcg/ml)

QUALITATIVE AND QUANTITATIVE COMPOSITION

Each ml contains 5 micrograms of paricalcitol.

PARICORD (Paricalcitol Injection 5 mcg/ml) – 1 ml:
Each vial contains 5 micrograms of paricalcitol.

PARICORD (Paricalcitol Injection 5 mcg/ml) – 2 ml:
Each vial contains 10 micrograms of paricalcitol.

PHARMACEUTICAL FORM & PRODUCT DESCRIPTION

Solution for injection
A clear, colourless solution filled in a clear glass vial, when examined under suitable condition visibly, it is free from foreign particles.

INDICATIONS

Paricalcitol injection is indicated for the prevention and treatment of secondary hyperparathyroidism associated with chronic renal insufficiency.

DOSAGE AND ADMINISTRATION

The usual route of administration of paricalcitol solution for injection is via the blood tubing through the hemodialysis access. For patients without hemodialysis access Paricalcitol injections should be given by slow intravenous injection, for not less than 30 seconds, to minimize pain on administration.

Adults

Initial Dose

The maximum dose safely administered in clinical studies was as high as 40 micrograms.

Initial Dose Based on Baseline iPTH levels
An intact PTH [iPTH]) has been used as the measurement of biologically active PTH in patients with chronic renal insufficiency (CKD stage 5). The initial dose is calculated by the following formula and administered as an intravenous (IV) bolus dose no more frequently than every other day at any time during dialysis:

$$\text{Initial dose (micrograms)} = \frac{\text{baseline iPTH level (pg/ml)}}{80}$$

Dose Titration

The currently accepted target range for PTH levels in end-stage renal disease patients undergoing dialysis is no more than 1.5 to 3 times the non-uremic upper limit of normal (150- 300 pg/mL for iPTH). Close monitoring and individual dose titration are necessary to reach appropriate physiological endpoints.

During any dose adjustment period serum calcium (corrected for hypoalbuminemia) and phosphorous levels should be monitored more frequently. If an elevated corrected calcium (Ca) level (>11.2 mg/dL) or persistently elevated phosphorous (P) levels (>6.5 mg/dL) are noted, the drug dosage should be adjusted until these parameters are normalized. If hypercalcemia or a persistently elevated corrected Ca x P product greater than 65 is noted, the drug dosage should be reduced or interrupted until these parameters are normalized. Then, paricalcitol administration 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. Doses may need to be decreased as the PTH levels decrease in response to therapy. Thus, incremental dosing must be individualized.

If a satisfactory response is not observed, the dose may be increased by 2 to 4 mcg at two to four week intervals. If at any time the iPTH level decreases to less than 150 pg/mL, the drug dosage should be decreased.

The following table is a suggested approach for dose titration:

Suggested Dosing Guidelines	
iPTH Level	**Paricalcitol Dose**
same or increasing	increase by 2 to 4 mcg
decreasing by < 30%	increase by 2 to 4 mcg
decreasing by > 30%, < 60%	maintain
decreasing by > 60%	decrease by 2 to 4 mcg
< 150 pg/mL	decrease by 2 to 4 mcg
1.5 to 3 times upper limit of normal (150 to 300 pg/mL)	maintain

Once dosage has been established, serum calcium and phosphate should be measured at least monthly. Serum iPTH measurements are recommended every three months. During dose adjustment with paricalcitol, laboratory tests may be required more frequently.

During treatment with paricalcitol patients should take adequate amounts of calcium either nutritionally or by supplements in line with the RDA.

CONTRAINDICATIONS

Paricalcitol injection should not be given to patients with evidence of Vitamin D toxicity, hypercalcemia, or hypersensitivity to any ingredient in this product.

WARNINGS AND PRECAUTIONS

Acute overdose of paricalcitol may cause hypercalcemia, and require emergency attention. During dose adjustment, serum calcium and phosphorus levels should be monitored closely. If clinically significant hypercalcemia 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.

Chronic hypercalcemia can lead to generalized vascular calcification and other soft- tissue calcification.

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.

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

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

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

Laboratory Tests

During dose adjustment and before dosage is established with paricalcitol, laboratory tests may be required more frequently. 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 (See Dosage and Administration).

DRUG INTERACTIONS

Specific interaction studies were not performed with paricalcitol Injection.

A multiple dose drug-drug interaction study with ketoconazole and paricalcitol capsule demonstrated that ketoconazole approximately doubled paricalcitol $AUC_{0-\infty}$. 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.

Prescription-based phosphate or vitamin D-related medicinal products should not be taken concomitantly with paricalcitol due to an increased risk of hypercalcaemia and Ca x P product elevation.

Concomitant administration of high doses of calcium-containing preparations or thiazide diuretics with paricalcitol may increase the risk of hypercalcemia.

Magnesium-containing preparations (e.g. antacids) should not be taken concomitantly with vitamin D preparations, because hypermagnesemia may occur.

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

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.

PREGNANCY AND LACTATION

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, mcg/m2) 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.

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

Lactation

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

There is limited experience with the use of paricalcitol injection in patients less than 18 years of age.

Geriatric Use

Of the 40 patients receiving paricalcitol in the three phase III placebo-controlled Chronic Renal Failure 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.

ADVERSE REACTIONS

Adverse reactions at least possibly related to paricalcitol are displayed by MedDRA System Organ Class, Preferred Term and frequency in Table 2 below. The following frequency groupings are used: Very common (≥ 1/10); common (≥ 1/100, <1/10); uncommon (≥1/1000, <1/100); rare (≥ 1/10,000, <1/1000); very rare (<1/10000), not known (cannot be estimated from the available data).

System Organ Class	Adverse Reaction	Frequency
Infections and infestations	Pneumonia, influenza, upper respiratory tract infection, nasopharyngitis	Uncommon
Neoplasms benign and malignant (including cysts and polyps)	Breast cancer	Uncommon
Blood and lymphatic system disorders	Anemia	Uncommon

Endocrine disorders	Hypoparathyroidism	Uncommon
Metabolism and nutrition disorders	Hypercalcemia	Common
	Hypocalcemia, hyperphosphatemia, decreased appetite	Uncommon
Psychiatric disorders	Delirium, confusional state, agitation, insomnia, nervousness, restlessness	Uncommon
Nervous system disorders	Dysgeusia, headache	Common
	Cerebrovascular accident, syncope,myoclonus, dizziness, hypoesthesia,paresthesia,	Uncommon
Eye disorders	Conjunctivitis	Uncommon
Cardiac disorders	Cardiac arrest, atrial flutter, palpitations*	Uncommon
Vascular disorders	Hypotension, hypertension,	Uncommon
Respiratory, thoracic and mediastinal disorders	Pulmonary edema, dyspnea, orthopnea, cough	Uncommon
Gastrointestinal disorders	Gastrointestinal hemorrhage*, diarrhea, constipation,	Common
	Intestinal ischemia, rectal hemorrhage, vomiting, abdominal discomfort, dry mouth	Uncommon
Skin and subcutaneous tissue disorders	Alopecia, rash pruritic, pruritus, skin burning sensation, blister	Uncommon
Musculoskeletal, connective tissue and bone disorders	Arthralgia, joint stiffness, myalgia, muscle twitching	Uncommon
Reproductive system and breast disorders	Erectile dysfunction, breast pain,	Uncommon
General disorders and administration site conditions	Pyrexia, chills*, injection site pain	Common
	Gait disturbance, swelling, asthenia, malaise, fatigue, condition aggravated	Uncommon
Investigations	Aspartate aminotransferase increased, laboratory test abnormal, weight decreased	Uncommon

* Palpitations, gastrointestinal hemorrhage and chills are adverse events (causality assessment of not related by the investigator) that were observed with a frequency greater than placebo.

Other adverse reactions

Infections and infestations:
Sepsis, vaginal infection

Blood and lymphatic system disorders:
Lymphadenopathy

Immune system disorders:
Hypersensitivity, angioedema, laryngeal edema

Endocrine disorders:
Hyperparathyroidism

Metabolism and nutrition disorders:
Hyperkalemia

Nervous system disorders:
Unresponsive to stimuli

Eye disorders:
Glaucoma, ocular hyperemia

Ear and labyrinth disorders:
Ear discomfort

Cardiac disorders:
Arrhythmia

Respiratory, thoracic and mediastinal disorders:
Wheezing

Gastrointestinal disorders:
Dysphagia, gastritis, nausea

Skin and subcutaneous tissue disorders:
Hirsutism, night sweats, rash, urticaria

General disorders and administration site conditions:
Chest discomfort, chest pain, edema, feeling abnormal, injection site extravasation, edema peripheral, pain, thirst

Investigations:
Bleeding time prolonged, heart rate irregular

OVERDOSAGE

Overdosage of paricalcitol may lead to hypercalcemia, hypercalciuria, hyperphosphatemia, and over suppression of PTH (see Warnings and precautions).

Paricalcitol is not significantly removed by dialysis. 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.

When serum calcium levels have returned to within normal limits, paricalcitol 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.

PHARMACOLOGIC PROPERTIES

Mechanism of Action

Paricalcitol is a synthetic, biologically active vitamin D analog of calcitriol. Preclinical and *in vitro* studies have demonstrated that paricalcitol's biological actions are mediated through binding of the VDR, which results in the selective activation of vitamin D responsive pathways. Vitamin D and paricalcitol have been shown to reduce parathyroid hormone levels by inhibiting PTH synthesis and secretion. Decreased levels of $1,25(OH)_2$ D_3 have been observed in early stages of chronic kidney disease (CKD).

Pharmacodynamics

Secondary hyperparathyroidism is characterized by an elevation in parathyroid hormone (PTH) associated with inadequate levels of active vitamin D hormone. The source of vitamin D in the body is from synthesis in the skin as vitamin D_3 and from dietary intake as either Vitamin D_2 or D_3. Both Vitamin D_2 and D_3 require two sequential hydroxylations in the liver and the kidney to bind to and to activate the vitamin D receptor (VDR). The endogenous VDR activator, calcitriol [$1,25(OH)_2$ 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. 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. In chronic kidney disease (CKD) patients reductions in PTH are associated with a favorable impact on bone-specific alkaline phosphatase, bone turnover and bone fibrosis. In addition to reducing PTH and correcting bone turnover, active vitamin D therapy may prevent or treat other consequences of vitamin D deficiency.

Pharmacokinetics

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.

Distribution

Paricalcitol is extensively bound to plasma proteins (>99%). 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 The pharmacokinetics of paricalcitol have been studied in patients with chronic renal failure CKD Stage 5 requiring hemodialysis. Paricalcitol is administered as an intravenous bolus injection.

Metabolism

Several metabolites were detected in both the urine and feces, with no detectable paricalcitol in the urine. *In vitro* data suggest that paricalcitol is metabolized by multiple hepatic and nonhepatic 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. Paricalcitol is not an inhibitor of CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP2E1 or CYP3A at concentrations up to 50nM (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 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.

Pharmacokinetics in Special Populations

Pediatrics

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

Geriatric

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

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.

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.

Gender

The pharmacokinetics of paricalcitol were gender independent.

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.

Ketoconazole: Although not studied with paricalcitol injection, the effect of of multiple doses of ketoconazole administered as 200 mg BID for 5 days on the pharmacokinetics of paricalcitol capsules has been studied in healthy subjects. The Cmax of paricalcitol was minimally affected, but AUC0-∞ 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.

PHARMACEUTICAL PARTICULARS

List of excipients
Propylene Glycol, Dehydrated alcohol, Water for Injection

Storage Conditions
Do not store above 30 °C.
Discard unused portion of the single-dose vial immediately after use.

Effects on ability to drive and use machines

Dizziness may occur following administration of paricalcitol, which may have a minor influence on the ability to drive and use machines.

Presentation
Paricalcitol Injection 5 mcg/ml is supplied in clear tubular glass vial. 1 labeled vial is packed in carton with package insert.

Pack size

For 1 ml: 1ml is supplied in a 2 ml USP type I clear tubular glass vial and sealed with 13 mm Teflon faced rubber stopper with 13 mm aluminium flip off or plain royal blue seal. Sealed vial is packed in a carton with package insert.

For 2 ml: 2ml is supplied in a 2 ml USP type I clear tubular glass vial and sealed with 13 mm Teflon faced rubber stopper with 13 mm aluminium flip off or plain yellow seal. Sealed vial is packed in a carton with package insert.

Manufacturer
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