Cinacalcet Tablets

CERACAL™-30/60 xÉUÉM sÉ-30/60

Cinacalcet
CERACAL 30/60

Composition
CERACAL 30
Each film coated tablet contains
Cinacalcet hydrochloride
equivalent to Cinacalcet 30 mg

CERACAL 60
Each film coated tablet contains
Cinacalcet hydrochloride
equivalent to Cinacalcet 60 mg

DESCRIPTION
CERACAL (Cinacalcet) is a calcimimetic that increases the sensitivity of the calcium-sensing receptor to activation by extracellular calcium. Its empirical formula is $C_{22}H_{22}F_3N{\cdot}HCl$ with a molecular weight of 393.9 g/mol (hydrochloride salt) and 357.4 g/mol (free base). It has one chiral center having an R-absolute configuration. The R-enantiomer is the more potent enantiomer and has been shown to be responsible for pharmacodynamic activity.
Cinacalcet is a white to off-white, crystalline solid that is soluble in methanol or 95% ethanol and slightly soluble in water. Cinacalcet is described chemically as N-[1-(R)-(-)-(1-naphthyl)ethyl]-3-[3-(trifluoromethyl)phenyl]-1-aminopropane hydrochloride.

CLINICAL PHARMACOLOGY
Mechanism of Action
Secondary hyperparathyroidism (SHPT) in patients with chronic kidney disease (CKD) is a progressive disease, associated with increases in parathyroid hormone (PTH) levels and derangements in calcium and phosphorus metabolism. Increased PTH stimulates osteoclastic activity resulting in cortical bone resorption and marrow fibrosis. The goals of treatment of secondary hyperparathyroidism are to lower levels of PTH, calcium, and phosphorus in the blood, in order to prevent progressive bone disease and the systemic consequences of disordered mineral metabolism. In CKD patients on dialysis with uncontrolled secondary HPT, reductions in PTH are associated with a favorable impact on bone-specific alkaline phosphatase (BALP), bone turnover and bone fibrosis.

The calcium-sensing receptor on the surface of the chief cell of the parathyroid gland is the principal regulator of PTH secretion. Cinacalcet directly lowers PTH levels by increasing the sensitivity of the calcium-sensing receptor to extracellular calcium. The reduction in PTH is associated with a concomitant decrease in serum calcium levels.

Pharmacokinetics
Absorption and Distribution: After oral administration of Cinacalcet, maximum plasma concentration (C_{max}) is achieved in approximately 2 to 6 hours. A food-effect study in healthy volunteers indicated that the C_{max} and area under the curve (AUC(0-inf)) were increased 82% and 68%, respectively, when Cinacalcet was administered with a high-fat meal compared to fasting. C_{max} and AUC(0-inf) of Cinacalcet were increased 65% and 50%, respectively, when Cinacalcet was administered with a low-fat meal compared to fasting. After absorption, Cinacalcet concentrations decline in a biphasic fashion with a terminal half-life of 30 to 40 hours. Steady-state drug levels are achieved within 7 days. The mean accumulation ratio is approximately 2 with once-daily oral administration. The median accumulation ratio is approximately 2 to 5 with twice-daily oral administration. The AUC and C_{max} of Cinacalcet increase proportionally over the dose range of 30 to 180 mg once daily. The pharmacokinetic profile of Cinacalcet does not change over time with once daily dosing of 30 to 180 mg. The volume of distribution is high (approximately 1000 L), indicating extensive distribution. Cinacalcet is approximately 93 to 97% bound to plasma protein(s). The ratio of blood Cinacalcet concentration to plasma Cinacalcet concentration is 0.80 at a blood Cinacalcet concentration of 10 ng/mL.

Metabolism and Excretion: Cinacalcet is metabolized by multiple enzymes, primarily CYP3A4, CYP2D6 and CYP1A2. After administration of a 75 mg radiolabeled dose to healthy volunteers, Cinacalcet was rapidly and extensively metabolized via: 1) oxidative N-dealkylation to hydrocinnamic acid and hydroxy-hydrocinnamic acid, which are further metabolized via β-oxidation and glycine conjugation; the oxidative N dealkylation process also generates metabolites that contain the naphthalene ring; and 2) oxidation of the naphthalene ring on the parent drug to form dihydrodiols, which are further conjugated with glucuronic acid. The plasma concentrations of the major circulating metabolites including the cinnamic acid derivatives and glucuronidated dihydrodiols markedly exceed parent drug concentrations. The hydrocinnamic acid metabolite was shown to be inactive at concentrations up to 10 μM in a cell-based assay measuring calcium-receptor activation. The glucuronide conjugates formed after Cinacalcet oxidation were shown to have a potency approximately 0.003 times that of Cinacalcet in a cell-based assay measuring a calcimimetic response. Renal excretion of metabolites was the primary route of elimination of radioactivity. Approximately 80% of the dose was recovered in the urine and 15% in the feces.

Special Populations
Hepatic Insufficiency: The disposition of a 50 mg Cinacalcet single dose was compared in patients with hepatic impairment and subjects with normal hepatic function. Cinacalcet exposure, AUC(0-inf), was comparable between healthy volunteers and patients with mild hepatic impairment. However, in patients with moderate and severe hepatic impairment (as indicated by the Child-Pugh method), Cinacalcet exposures as defined by the AUC(0-inf) were 2.4 and 4.2 times higher, respectively, than that in normals. The mean half-life of Cinacalcet is prolonged by 33% and 70% in patients with moderate and severe hepatic impairment, respectively. Protein binding of Cinacalcet is not affected by impaired hepatic function.

Renal Insufficiency: The pharmacokinetic profile of a 75 mg Cinacalcet single dose in patients with mild, moderate, and severe renal insufficiency, and those on hemodialysis or peritoneal dialysis is comparable to that in healthy volunteers.
Geriatric Patients: The pharmacokinetic profile of Cinacalcet in geriatric patients (age ≥65) is similar to that for patients who are < 65 years of age.
Pediatric Patients: The pharmacokinetics of Cinacalcet have not been studied in patients < 18 years of age.

INDICATIONS AND USAGE
Cinacalcet is indicated for the treatment of secondary hyperparathyroidism in patients with Chronic Kidney Disease on dialysis. Cinacalcet is indicated for the treatment of hypercalcemia in patients with parathyroid carcinoma.

CONTRAINDICATIONS
Cinacalcet is contraindicated in patients with hypersensitivity to any component(s) of this product.

WARNINGS
Seizures
In three clinical studies of CKD patients on dialysis, 5% of the patients in both the Cinacalcet and placebo groups reported a history of seizure disorder at baseline. During the trials, seizures (primarily generalized or tonic-clonic) were observed in 1.4% (9/656) of Cinacalcet-treated patients and 0.4% (2/470) of placebo-treated patients. Five of the nine Cinacalcet-treated patients had a history of a seizure disorder and two were receiving anti-seizure medication at the time of their seizure. Both placebo-treated patients had a history of seizure disorder and were receiving anti-seizure medication at the time of their seizure. While the basis for the reported difference in seizure rate is not clear, the threshold for seizures is lowered by significant reductions in serum calcium levels. Therefore, serum calcium levels should be closely monitored in patients receiving Cinacalcet, particularly in patients with a history of a seizure disorder

Hypotension and/or Worsening Heart Failure
In postmarketing safety surveillance, isolated, idiosyncratic cases of hypotension, worsening heart failure, and/or arrhythmia have been reported in patients with impaired cardiac function, in which a causal relationship to Cinacalcet could not be completely excluded and which may be mediated by reductions in serum calcium levels. Clinical trial data showed hypotension occurred in 7% of Cinacalcet-treated patients and 12% of placebo-treated patients, heart failure occurred in 2% of both Cinacalcet- and placebo treated patients.

PRECAUTIONS
General
Hypocalcemia
Cinacalcet lowers serum calcium, and therefore patients should be carefully monitored for the occurrence of hypocalcemia. Potential manifestations of hypocalcemia include paresthesias, myalgias, cramping, tetany, and convulsions.

Cinacalcet treatment should not be initiated if serum calcium is less than the lower limit of the normal range (8.4 mg/dL). Serum calcium should be measured within 1 week after initiation or dose adjustment of Cinacalcet. Once the maintenance dose has been established, serum calcium should be measured approximately monthly. If serum calcium falls below 8.4 mg/dL but remains above 7.5 mg/dL, or if symptoms of hypocalcemia occur, calcium-containing phosphate binders and/or vitamin D sterols can be used to raise serum calcium. If serum calcium falls below 7.5 mg/dL, or if symptoms of hypocalcemia persist and the dose of vitamin D cannot be increased, withhold administration of Cinacalcet until serum calcium levels reach 8.0 mg/dL, and/or symptoms of hypocalcemia have resolved. Treatment should be re-initiated using the next lowest dose of Cinacalcet. Cinacalcet is not indicated for CKD patients not on dialysis. In CKD patients withsecondary HPT not on dialysis, the long-term safety and efficacy of Cinacalcet have not been established. Clinical studies indicate that Cinacalcet-treated CKD patients not on dialysis have an increased risk for hypocalcemia compared to Cinacalcet-treated CKD patients on dialysis, which may be due to lower baseline calcium levels

Adynamic Bone Disease
Adynamic bone disease may develop if iPTH levels are suppressed below 100 pg/mL. One clinical study evaluated bone histomorphometry in patients treated with Cinacalcet for one year. Three patients with mild hyperparathyroid bone disease at the beginning of the study developed adynamic bone disease during treatment with Cinacalcet. Two of these patients had iPTH levels below 100 pg/mL at multiple time points during the study. In the three 6-month, phase 3 studies conducted in CKD patients on dialysis, 11% of patients treated with Cinacalcet had mean iPTH values below 100 pg/mL during the efficacy-assessment phase. If iPTH levels decrease below the NKF-K/DOQI recommended target range (150-300 pg/mL) 1 in patients treated with Cinacalcet, the dose of Cinacalcet and/or vitamin D sterols should be reduced or therapy discontinued.

Biocon

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Hepatic Insufficiency
Cinacalcet exposure as assessed by AUC(0-inf) in patients with moderate and severe hepatic impairment (as indicated by the Child-Pugh method) were 2.4 and 4.2 times higher, respectively, than that in normals. Patients with moderate and severe hepatic impairment should be monitored throughout treatment with Cinacalcet .
Information for Patients
It is recommended that Cinacalcet be taken with food or shortly after a meal. Tablets should be taken whole and should not be divided.

Laboratory Tests
Patients with CKD on Dialysis with Secondary Hyperparathyroidism Serum calcium and serum phosphorus should be measured within 1 week and iPTH should be measured 1 to 4 weeks after initiation or dose adjustment of Cinacalcet. Once the maintenance dose has been established, serum calcium and serum phosphorus should be measured approximately monthly, and PTH every 1 to 3 months . In patients with end-stage renal disease, testosterone levels are often below the normal range. In a placebo-controlled trial in patients with CKD on dialysis, there were reductions in total and free testosterone in male patients following six months of treatment with Cinacalcet. Levels of total testosterone decreased by a median of 15.8% in the Cinacalcet-treated patients and by 0.6% in the placebo-treated patients. The clinical significance of these reductions in serum testosterone is unknown.

Patients with Parathyroid Carcinoma
Serum calcium should be measured within 1 week after initiation or dose adjustment of Cinacalcet. Once maintenance dose levels have been established, serum calcium should be measured every 2 months

Carcinogenesis, Mutagenesis, and Impairment of Fertility
Carcinogenicity: Standard lifetime dietary carcinogenicity bioassays were conducted in mice and rats. Mice were given dietary doses of 15, 50, 125 mg/kg/day in males and 30, 70, 200 mg/kg/day in females (exposures up to 2 times those resulting with a human oral dose of 180 mg/day based on AUC comparison). Rats were given dietary doses of 5, 15, 35 mg/kg/day in males and 5, 20, 35 mg/kg/day in females (exposures up to 2 times those resulting with a human oral dose of 180 mg/day based on AUC comparison). No increased incidence of tumors was observed following treatment with Cinacalcet. Mutagenicity: Cinacalcet was not genotoxic in the Ames bacterial mutagenicity assayor in the Chinese Hamster Ovary (CHO) cell HGPRT forward mutation assay and CHOcell chromosomal aberration assay, with and without metabolic activation or in the invivo mouse micronucleus assay. Impairment of Fertility: Female rats were given oral gavage doses of 5, 25, 75 mg/kg/day beginning 2 weeks before mating and continuing through gestation day 7. Male rats were given oral doses 4 weeks prior to mating, during mating (3 weeks) and 2 weeks post-mating. No effects were observed in male or female fertility at 5 and 25 mg/kg/day (exposures up to 3 times those resulting with a human oral dose of 180 mg/day based on AUC comparison). At 75 mg/kg/day, there were slight adverse effects(slight decreases in body weight and food consumption) in males and females.

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

Lactating Women
Studies in rats have shown that Cinacalcet is excreted in the milk with a high milk-to plasma ratio. It is not known whether this drug is excreted in human milk. Considering these data in rats and because many drugs are excreted in human milk and because of the potential for clinically significant adverse reactions in infants from Cinacalcet, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the lactating woman.

Pediatric Use
The safety and efficacy of Cinacalcet in pediatric patients have not been established.

Geriatric Use
Of the 1136 patients enrolled in the Cinacalcet phase 3 clinical program, 26% were ≥65 years old, and 9% were ≥75 years old. No differences in the safety and efficacy of Cinacalcet were observed in patients greater or less than 65 years of age .

DRUG INTERACTIONS
An in vitro study indicates that Cinacalcet is a strong inhibitor of CYP2D6, but not of CYP1A2, CYP2C9, CYP2C19, and CYP3A4. In vitro induction studies indicate that Cinacalcet is not an inducer of CYP450 enzymes.
Ketoconazole: Cinacalcet AUC(0-inf) and Cmax increased 2.3 and 2.2 times, respectively, when a single 90 mg Cinacalcet dose on Day 5 was administered to subjects treated with 200 mg ketoconazole twice daily for 7 days compared to 90 mg Cinacalcet given alone Calcium Carbonate: No significant pharmacokinetic interaction was observed when a single dose of 1500 mg calcium carbonate was coadministered with 100 mg Cinacalcet. Pantoprazole: No significant pharmacokinetic interaction was observed when Cinacalcet 90 mg was administered to subjects treated with 80 mg pantoprazole daily for 3 days. Sevelamer HCl: No significant pharmacokinetic interaction was observed when 2400 mg sevelamer HCl was coadministered with 90 mg Cinacalcet tablet. Desipramine: The effect of Cinacalcet (90 mg) on the pharmacokinetics of desipramine (50 mg) has been studied in healthy subjects who were CYP2D6 extensive metabolizers. The AUC and Cmax of desipramine increased by 3.6 (296.5-446.7%) and 1.75 (157.5-194.9%) fold, respectively, in the presence of Cinacalcet. This indicates that Cinacalcet is a strong in vivo inhibitor of CYP2D6 and can increase the blood concentrations of drugs metabolized by CYP2D6. Amitriptyline: Concurrent administration of 25 mg or 100 mg Cinacalcet with 50 mg amitriptyline increased amitriptyline exposure and nortriptyline (active metabolite) exposure by approximately 20% in CYP2D6 extensive metabolizers. Warfarin: R- and S-warfarin pharmacokinetics and warfarin pharmacodynamics were not affected in subjects treated with warfarin 25 mg who received Cinacalcet 30 mg twice daily. The lack of effect of Cinacalcet on the pharmacokinetics of R- and S-warfarin and the absence of auto-induction upon multiple dosing in patients indicates that Cinacalcet is not an inducer of CYP2C9 in humans.
Midazolam: There were no significant differences in the pharmacokinetics of midazolam, a CYP3A4 and CYP3A5 substrate, in subjects receiving 90 mg Cinacalcet once daily for 5 days and a single dose of 2 mg midazolam on day 5 as compared to those of subjects receiving 2 mg midazolam alone. This suggests that Cinacalcet would not affect the pharmacokinetics of drugs predominantly metabolized by CYP3A4 and CYP3A5

SIDE EFFECTS
Secondary Hyperparathyroidism in patients with Chronic Kidney Disease on dialysis: In clinical studies the most frequently reported events with Cinacalcet were nausea and vomiting. Other adverse effects observed were diarrhea, myalgia, hypertension, dizziness, rashes, asthenia, anorexia, chest pain (non cardiac) and access infection.

Parathyroid Carcinoma
The most frequent adverse events in this patient group were nausea and vomiting.

OVERDOSAGE
Doses titrated up to 300 mg once daily have been safely administered to patients on dialysis. Overdosage of Cinacalcet may lead to hypocalcemia. In the event of overdosage, patients should be monitored for signs and symptoms of hypocalcemia and appropriate measures taken to correct serum calcium level. Since Cinacalcet is highly protein bound, hemodialysis is not an effective treatment for overdosage of Cinacalcet

DOSAGE AND ADMINISTRATION
Cinacalcet tablets should be taken whole and should not be divided. Cinacalcet should be taken with food or shortly after a meal.

Dosage must be individualized.
Secondary Hyperparathyroidism in Patients with Chronic Kidney Disease on Dialysis: The recommended starting oral dose of Cinacalcet is 30 mg once daily. Serum calcium and serum phosphorus should be measured within 1 week and PTH should be measured 1 to 4 weeks after initiation or dose adjustment of Cinacalcet. Cinacalcet should be titrated no more frequently than every 2 to 4 weeks through sequential doses of 60, 90, 120, and 180 mg once daily to target iPTH consistent with the NKF-K/DOQI recommendation for CKD patients on dialysis of 150-300 pg/mL. PTH levels should be assessed no earlier than 12 hours after dosing with Cinacalcet.

Cinacalcet can be used alone or in combination with vitamin D sterols and/or phosphate binders. During dose titration, serum calcium levels should be monitored frequently and if levels decrease below the normal range, appropriate steps should be taken to increase serum calcium levels, such as by providing supplemental calcium, initiating or increasing the dose of calcium-based phosphate binder, initiating or increasing the dose of vitamin D sterols, or temporarily withholding treatment with Cinacalcet.

Parathyroid Carcinoma
The recommended starting oral dose of Cinacalcet is 30 mg twice daily. The dosage of Cinacalcet should be titrated every 2 to 4 weeks through sequential doses of 30 mg twice daily, 60 mg twice daily, 90 mg twice daily, and 90 mg three or four times daily as necessary to normalize serum calcium levels.

Special Populations
Geriatric patients: Age does not alter the pharmacokinetics of Cinacalcet; no dosage adjustment is required for geriatric patients.
Patients with renal impairment: Renal impairment does not alter the pharmacokinetics of Cinacalcet; no dosage adjustment is necessary for renal impairment.

Patients with hepatic impairment: Cinacalcet exposures, as assessed by AUC(0-inf), in patients with moderate and severe hepatic impairment (as indicated by the Child-Pugh method) were 2.4 and 4.2 times higher, respectively, than in normals. In patients with moderate and severe hepatic impairment, PTH and serum calcium concentrations should be closely monitored throughout treatment with Cinacalcet.

Storage
Store in a cool, dry place. Protect from light

Presentation
CERACAL 30/60 are available in 10 tablets per blister

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