Sensipar™ (cinacalcet) Tablets

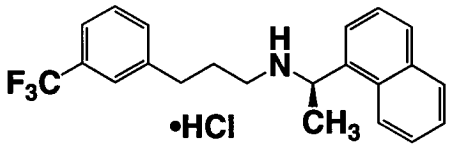
DESCRIPTION

Sensipar™ (cinacalcet) is a calcimimetic agent 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.

Sensipar™ tablets are formulated as light-green, film-coated, oval-shaped tablets for oral administration in strengths of 30 mg, 60 mg, and 90 mg of cinacalcet as the free base equivalent (33 mg, 66 mg, and 99 mg as the hydrochloride salt, respectively).

Cinacalcet is described chemically as N-[1-(R)-(-)-(1-naphthyl)ethyl]-3-[3-(trifluoromethyl)phenyl]-1-aminopropane hydrochloride and has the following structural formula:



Inactive Ingredients: Sensipar™ tablets are comprised of the active ingredient, and the following inactive ingredients: pre-gelatinized starch, microcrystalline cellulose, povidone, crospovidone, colloidal silicon dioxide, and magnesium stearate. Tablets are coated with color (Opadry® II green) and clear film-coat (Opadry® clear), carnauba wax, and Opacode® black ink.

CLINICAL PHARMACOLOGY

Mechanism of Action

Secondary hyperparathyroidism (HPT) 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. Sensipar™ directly lowers PTH levels by

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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 ($AUC_{(0\text{-inf})}$) were increased 82% and 68%, respectively, when cinacalcet was administered with a high-fat meal compared to fasting. C_{max} and $AUC_{(0\text{-inf})}$ 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, $AUC_{(0\text{-inf})}$, 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

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the $AUC_{(0\text{-}inf)}$ 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. See PRECAUTIONS and DOSAGE AND ADMINISTRATION.

Renal Insufficiency: The pharmacokinetic profile of a 75 mg Sensipar™ 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 Sensipar™ in geriatric patients (age ≥ 65, n = 12) is similar to that for patients who are < 65 years of age (n = 268).

Pediatric Patients: The pharmacokinetics of Sensipar™ have not been studied in patients < 18 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 $AUC_{(0\text{-}inf)}$ and C_{max} 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 (see DOSAGE AND ADMINISTRATION).

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 (subjects subsequently received 2400 mg sevelamer HCl two more times on Day 1 and three more times on Day 2).

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.

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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.

Pharmacodynamics

Reduction in intact PTH (iPTH) levels correlated with cinacalcet concentrations in CKD patients. The nadir in iPTH level occurs approximately 2 to 6 hours post dose, corresponding with the C_{max} of cinacalcet. After steady state is reached, serum calcium concentrations remain constant over the dosing interval in CKD patients.

CLINICAL STUDIES

Secondary Hyperparathyroidism in Patients with Chronic Kidney Disease on Dialysis

Three 6-month, multicenter, randomized, double-blind, placebo-controlled clinical studies of similar design were conducted in CKD patients on dialysis. A total of 665 patients were randomized to Sensipar™ and 471 patients to placebo. The mean age of the patients was 54 years, 62% were male, and 52% Caucasian. The average baseline iPTH level by the Nichols intact immunoradiometric assay (IRMA) was 712 pg/mL, with 26% of the patients having a baseline iPTH level > 800 pg/mL. The mean baseline Ca x P ion product was 61 mg^2/dL^2. The average duration of dialysis prior to study enrollment was 67 months. Ninety-six percent of patients were on hemodialysis and 4% peritoneal dialysis. At study entry, 66% of the patients were receiving vitamin D sterols and 93% were receiving phosphate binders. Sensipar™ (or placebo) was initiated at a dose of 30 mg once daily and titrated every 3 or 4 weeks to a maximum dose of 180 mg once daily to achieve an iPTH of ≤ 250 pg/mL. The dose was not increased if a patient had any of the following: iPTH ≤ 200 pg/mL, serum calcium < 7.8 mg/dL, or any symptoms of hypocalcemia. If a patient experienced symptoms of hypocalcemia or had a serum calcium < 8.4 mg/dL, calcium supplements and/or calcium-based phosphate binders could be increased. If these measures were insufficient, the vitamin D dose could be increased. Approximately 70% of the Sensipar™ patients and 80% of the placebo patients completed the 6-month studies. In the primary efficacy analysis, 40% of Sensipar™ patients and 5% of placebo patients achieved an iPTH ≤ 250 pg/mL ($p<0.001$) (Table 1, Figure 1). Secondary efficacy parameters also improved in patients treated with Sensipar™. These studies showed that Sensipar™ reduced PTH while lowering Ca x P, calcium and phosphorus levels (Table 1, Figure 2). The median dose of Sensipar™ at the completion of the studies was 90 mg. Patients with milder disease typically required lower doses.

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Similar results were observed when either the iPTH or bio-intact PTH (biPTH) assay was used to measure PTH levels in CKD patients on dialysis; treatment with cinacalcet did not alter the relationship between iPTH and biPTH.

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