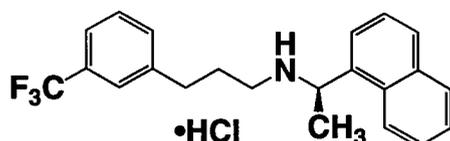


NAME OF THE MEDICINE

Sensipar® (cinacalcet hydrochloride) is presented in tablets as the hydrochloride salt. Cinacalcet hydrochloride is described chemically as N-[1-(R)-(1-naphthyl)ethyl]-3-[3-(trifluoromethyl)phenyl]-1-aminopropane hydrochloride and has the following structural formula:



DESCRIPTION

Cinacalcet is a calcimimetic agent that increases the sensitivity of the calcium sensing receptor to extracellular calcium. The empirical formula of cinacalcet hydrochloride is C₂₂H₂₂F₃N·HCl and it has a molecular weight of 393.9 g/mol (hydrochloride salt) and 357.4 g/mol (free base). It has one chiral centre having an R-absolute configuration. The R-enantiomer is the more potent enantiomer and has been shown to be responsible for pharmacodynamic activity.

Cinacalcet hydrochloride is a white to off-white, crystalline solid that is soluble in methanol or 95% ethanol and poorly soluble in water.

Sensipar® is a solid oral dosage form 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 (corresponding to 33 mg, 66 mg and 99 mg as the hydrochloride salt, respectively).

Sensipar® tablets are comprised of the active ingredient, and the following inactive ingredients: pre-gelatinised starch, microcrystalline cellulose, povidone, crospovidone, colloidal silicon dioxide, magnesium stearate, and water. Tablets are coated with colour (Opadry® II green), a clear film-coat (Opadry® clear) and carnauba wax.

PHARMACOLOGY

Mechanism of action

Cinacalcet reduces PTH while simultaneously lowering Ca x P, calcium and phosphorus levels in chronic kidney disease in patients receiving dialysis.

Secondary hyperparathyroidism (HPT) is a progressive disease, which occurs in patients with chronic kidney disease (CKD) and manifests as 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 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.

In CKD patients with uncontrolled secondary HPT, reductions in PTH were associated with a favourable impact on bone specific alkaline phosphatase (BALP), N-telopeptide (N-Tx), bone turnover, bone fibrosis, and incidence of bone fracture.

Studies in a rat model of chronic renal insufficiency (CRI) (5/6 nephrectomy) assessed the effects of cinacalcet treatment on parathyroid gland hyperplasia. Cinacalcet treatment reduced PTH and parathyroid cell proliferation to levels comparable to vehicle-treated, non-nephrectomised animals, demonstrating that cinacalcet prevented the development of secondary HPT.

Pharmacodynamics

Reductions in PTH levels correlate with cinacalcet concentrations. Nadir PTH occurs approximately 2 to 6 hours post dose, corresponding with cinacalcet C_{max}. After steady state is reached, serum calcium concentrations remain constant over the dosing interval.

Pharmacokinetics

Absorption and Distribution

After oral administration of cinacalcet, maximum plasma concentration is achieved in approximately 2 to 6 hours. The absolute bioavailability of cinacalcet is approximately 25%. Administration of cinacalcet with food results in an approximate 50 to 80% increase in bioavailability. Increases in plasma concentrations are similar, regardless of the fat content of the meal.

After absorption, cinacalcet concentrations decline in a biphasic fashion with an initial half-life of approximately 6 hours and a terminal half-life of 30 to 40 hours. Steady state drug levels are achieved within 7 days with minimal accumulation. The AUC and C_{max} of cinacalcet increase linearly over the once daily dose range of 30 to 180 mg. The pharmacokinetics of cinacalcet do not change over time. The volume of distribution is high (approximately 1000 L), indicating extensive distribution. Cinacalcet in plasma is

approximately 97% bound to plasma proteins and in whole blood, cinacalcet distributes minimally into red blood cells.

Metabolism and Excretion

Cinacalcet is metabolised by multiple enzymes, primarily CYP3A4, CYP1A2 and CYP2D6. The major circulating metabolites are inactive. After administration of a 75 mg radiolabeled dose to healthy volunteers, cinacalcet was rapidly and extensively metabolised by oxidation followed by conjugation. Renal excretion of metabolites was the prevalent route of elimination of radioactivity. Approximately 80% of the dose was recovered in the urine and 15% in the faeces.

Special Populations

Hepatic Insufficiency

Mild hepatic impairment did not alter the pharmacokinetics of cinacalcet. Compared to subjects with normal liver function, average AUC of cinacalcet was approximately 2 times higher in subjects with moderate impairment and approximately 4 times higher in subjects with severe impairment (see PRECAUTIONS). Because doses are titrated for each subject based on safety and efficacy parameters, no additional dose adjustment is necessary for subjects with hepatic impairment.

Renal Insufficiency

The pharmacokinetic profile of cinacalcet in patients with mild, moderate, and severe renal insufficiency, and those on haemodialysis or peritoneal dialysis is comparable to that in healthy volunteers. No dosage adjustment based on the degree of renal function is necessary.

Geriatric Patients

There are no clinically relevant differences due to age in the pharmacokinetics of cinacalcet. No dosage adjustment based on age is necessary.

Paediatric Patients

The safety and efficacy of cinacalcet has not been studied in children and are not established. A single dose pharmacokinetic study has been completed in paediatric patients 6-17 years of age (N = 12). The pharmacokinetic parameters following a 15 mg dose are summarized in Table 1:

Table 1. Paediatric Single Dose PK results

| Parameter | 15 mg in Paediatric Subjects | | | | 30 mg in Adult ^a N = 13 |
|--------------------------------|------------------------------|-------------------|--------------------|--------------------|---------------------------------------|
| | 6-8 years N=3 | 9-11 years N=3 | 12-14 years N=3 | 15-17 years N=3 | |
| AUC _{0-t} hr*ng/mL | 29.5 (15.6) | 35.9 (35.8) | 11.3 (4.4) | 17.5 (5.9) | 40.4 (15.9) |
| C _{max} ng/mL | 11.0 (3.22) | 9.19 (7.28) | 3.87 (1.82) | 5.01 (2.15) | 5.97 (3.06) |

^aData are from a separate study in healthy adults
Data represent mean (standard deviation)

Whilst a 15 mg dose of cinacalcet was used in the paediatric PK study, this dose strength is not registered.

Six of the twelve subjects experienced decreases in serum calcium below the lower limit of normal (2.23 mmol/L). In these six subjects, baseline values were in the range of 2.20 to 2.52 mmol/L and the decreased values were in the range of 2.00 to 2.22 mmol/L. In the same study, QT interval prolongation, assessed as unrelated to cinacalcet, was reported in one of the twelve subjects.

The use of multiple doses in paediatric subjects has not been studied. On the basis of these limited data, there is a potential for higher exposures and greater pharmacodynamic effects in the lighter/younger relative to the heavier/old paediatric subjects when treated with identical doses of cinacalcet. (see PRECAUTIONS section: SERUM CALCIUM).

CLINICAL TRIALS

Secondary Hyperparathyroidism in Patients with Chronic Kidney Disease

Three, 6-month, multicentre, randomised, double-blind, placebo-controlled clinical studies were conducted in CKD patients receiving dialysis with uncontrolled secondary HPT (n = 665 on cinacalcet, 471 on placebo). The patient population consisted of both recently established and long-standing dialysis patients, with a range of 1 to 359 months. Cinacalcet was administered either alone or in combination with vitamin D sterols; 34% of patients were not receiving vitamin D sterols at study entry. The majority (more than 90%) of patients were receiving phosphate binders. Dose adjustments in phosphate binder therapy were permitted throughout the study. Vitamin D doses remained constant unless the patient developed hypercalcaemia, hypocalcaemia, or hyperphosphataemia. Patients continued on their previously prescribed drugs including: calcium channel blockers, ACE inhibitors, beta-blockers, hypoglycaemics, and lipid lowering agents. Cinacalcet (or placebo) was initiated at a dose of 30 mg and titrated every 3 or 4 weeks

to a maximum dose of 180 mg once daily to achieve an iPTH of 10.6 to 26.5 pmol/L (1.5 to 4 times the upper limit of normal). The severity of secondary HPT ranged from mild to severe (iPTH values of 28.8 to 969.5 pmol/L), with mean (SE) baseline iPTH concentrations across the 3 studies of 77.8 (2.2) and 72.5 (2.0) pmol/L for the cinacalcet and placebo groups, respectively. Significant reductions in iPTH, serum calcium-phosphorus product (Ca x P), calcium, and phosphorus were observed in the cinacalcet-treated patients compared with placebo-treated patients receiving standard of care, and the results were consistent across the 3 studies (Table 2).

Table 2. Effects of Cinacalcet on iPTH, Ca x P, Serum Calcium, and Serum Phosphorus in 6-month Phase 3 Studies (Patients Receiving Dialysis)

| | Study 1 | | Study 2 | | Study 3 | |
|---|----------------------|-------------------------|----------------------|-------------------------|----------------------|-------------------------|
| | Placebo (N = 205) | Cinacalcet (N = 205) | Placebo (N = 165) | Cinacalcet (N = 166) | Placebo (N = 101) | Cinacalcet (N = 294) |
| iPTH | | | | | | |
| Baseline (pmol/L) | 69.1 (2.9) | 67.5 (2.5) | 66.8 (2.6) | 69.2 (3.1) | 88.3 (5.1) | 90.0 (4.3) |
| Evaluation Phase (pmol/L) | 74.0 (3.5) | 40.8 (2.6) | 72.9 (3.4) | 38.3 (3.1) | 90.4 (5.8) | 55.8 (3.2) |
| Percent Change | 9.5 (2.8) | -38.4 (2.9) | 8.7 (2.8) | -47.5 (2.8) | 4.1 (3.4) | -40.3 (2.1) |
| Patients Achieving Primary Endpoint (iPTH ≤26.5 pmol/L) (%) | 4% | 41%** | 7% | 46%** | 6% | 35%** |
| Patients Achieving ≥ 30% Reduction in iPTH (%) | 11% | 61%** | 12% | 68%** | 10% | 59%** |
| Patients Achieving iPTH ≤ 31.8 pmol/L (%) | 9% | 55%** | 11% | 56%** | 9% | 45%** |
| Ca x P | | | | | | |
| Baseline (mmol ² /L ²) | 4.93 (0.09) | 5.00 (0.09) | 4.92 (0.09) | 4.92 (0.10) | 4.91 (0.11) | 4.80 (0.08) |
| Evaluation Phase (mmol ² /L ²) | 4.82 (0.08) | 4.21 (0.08) | 4.79 (0.09) | 4.02 (0.10) | 4.68 (0.11) | 4.03 (0.07) |
| Percent Change | 1.5 (1.8) | -13.0 (1.7)** | -0.7 (1.9) | -16.7 (2.1)** | -1.4 (2.4) | -12.8 (1.7)** |
| Calcium | | | | | | |
| Baseline (mmol/L) | 2.48 (0.01) | 2.46 (0.01) | 2.48 (0.01) | 2.51 (0.01) | 2.50 (0.02) | 2.45 (0.01) |
| Evaluation Phase (mmol/L) | 2.48 (0.01) | 2.30 (0.02) | 2.48 (0.01) | 2.31 (0.02) | 2.52 (0.02) | 2.28 (0.01) |
| Percent Change | 0.5 (0.4) | -6.3 (0.6)** | 0.3 (0.4) | -7.5 (0.6)** | 0.9 (0.5) | -6.5 (0.6)** |
| Phosphorus | | | | | | |
| Baseline (mmol/L) | 2.00 (0.04) | 2.04 (0.04) | 2.00 (0.04) | 1.96 (0.04) | 1.97 (0.05) | 1.97 (0.03) |
| Evaluation Phase (mmol/L) | 1.95 (0.03) | 1.84 (0.04) | 1.94 (0.04) | 1.74 (0.04) | 1.87 (0.04) | 1.77 (0.03) |
| Percent Change | 1.1 (1.8) | -7.1 (1.7)** | -0.9 (1.9) | -9.9 (2.0)** | -2.2 (2.5) | -7.2 (1.6)* |

* p < 0.05; ** p < 0.001 compared to placebo

Data represent mean (standard error) or percent

Mean iPTH and Ca x P by treatment group for the overall study population during the 6-month treatment period are presented in Figure 1 and Figure 2.

Figure 1. Mean (SE) Percent Change from Baseline in iPTH (Pooled Phase 3 Studies)

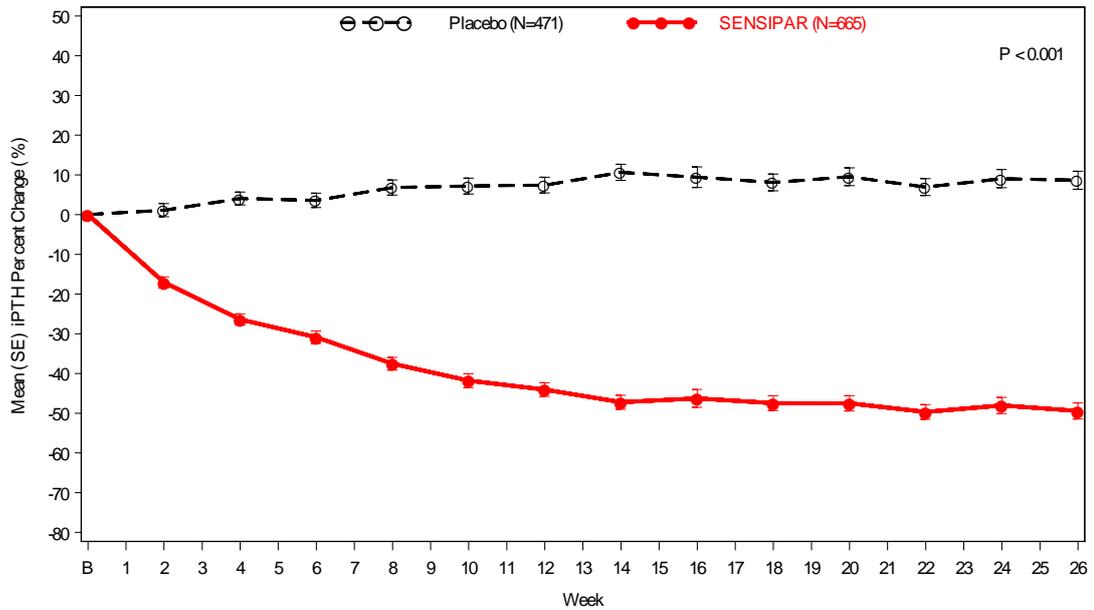
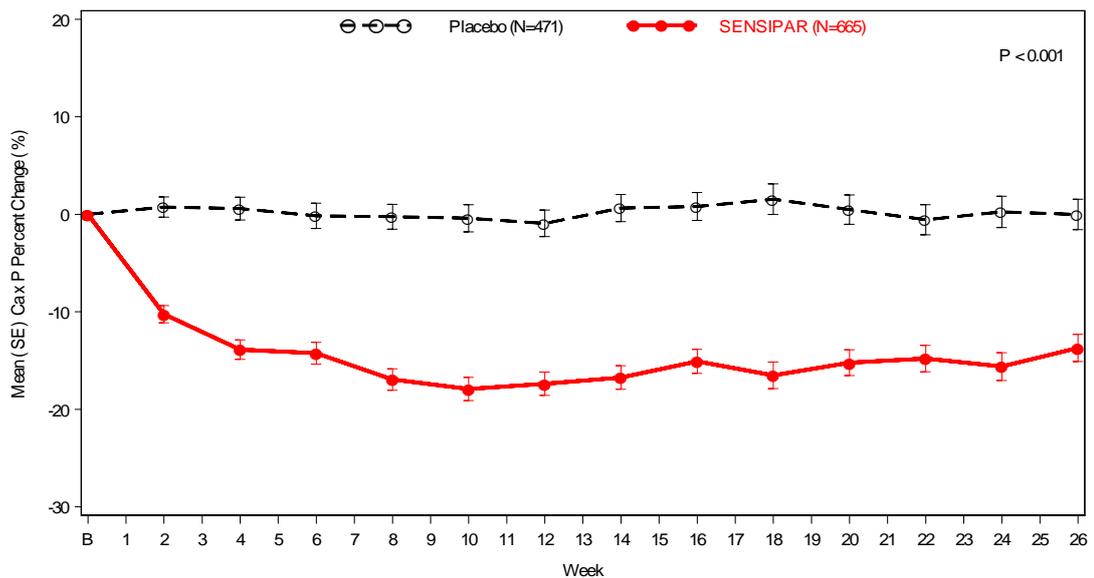


Figure 2. Mean (SE) Percent Change from Baseline in Ca x P (Pooled Phase 3 Studies)



In patients receiving cinacalcet, reductions in iPTH and Ca x P occurred within 2 weeks and were maintained for at least 12 months of treatment (n = 99 on cinacalcet, 111 on placebo).

Cinacalcet decreased iPTH and Ca x P levels regardless of disease severity (ie, baseline iPTH value), dialysis modality (PD versus HD), duration of dialysis, and whether or not vitamin D sterols were administered. Approximately 60% of patients with mild (iPTH from 31.8 to 53.0 pmol/L), moderate (iPTH between 53.0 and 84.8 pmol/L), or severe (iPTH above 84.8 pmol/L) secondary HPT achieved at least a 30% reduction in iPTH levels. Cinacalcet treatment also reduced iPTH and Ca x P in patients with elevated Ca x P levels.

The impact of cinacalcet on bone disease, including the risk of adynamic bone disease, has not been conclusively evaluated.

The pivotal clinical studies were designed to evaluate the effect of cinacalcet on biochemical parameters, including PTH, serum calcium and phosphorus. Clinical outcomes such as quality of life, rate of parathyroidectomy, symptomatic bone disease, hospitalisation, or mortality were not pre-specified endpoints and were not evaluated within individual studies. The pivotal efficacy and safety studies in patients with secondary hyperparathyroidism of chronic kidney disease, requiring dialysis, did not examine quality of life benefits. There were no differences between cinacalcet and placebo treated patients in terms of statistically significant differences in self-reported cognitive functioning scale scores during the efficacy assessment phase.

EVOLVE (EValuation Of Cinacalcet HCl Therapy to Lower CardioVascular Events) was a randomised, double-blind clinical study evaluating cinacalcet HCl vs. placebo for the reduction of the risk of all-cause mortality and cardiovascular events in 3,883 patients with secondary HPT and CKD receiving dialysis. The study did not meet its primary objective of demonstrating a reduction in risk of all-cause mortality or cardiovascular events including myocardial infarction, hospitalisation for unstable angina, heart failure or peripheral vascular event (HR 0.93; 95% CI: 0.85, 1.02; p = 0.112). Because the primary composite endpoint did not reach statistical significance, secondary endpoints were not tested for statistical significance. Primary and secondary endpoints are shown in Table 3.

Table 3. Primary and Secondary Endpoints

| Endpoints | Cinacalcet N=1948 n (%) | Placebo N=1935 n(%) | Hazard Ratio (95% CI) |
|---|--|------------------------------------|----------------------------------|
| Primary composite endpoint | 938 (48) | 952 (49) | 0.93 (0.85, 1.02) |
| Components of primary composite endpoint | | | |
| <i>All-cause mortality</i> | 703 (36) | 718 (37) | 0.94 (0.85, 1.04) |
| <i>Myocardial infarction</i> | 187 (10) | 183 (9) | 0.97 (0.79, 1.19) |
| <i>Hospitalisation for unstable angina</i> | 56 (3) | 66 (3) | 0.82 (0.58, 1.18) |
| <i>Heart failure</i> | 206 (11) | 236 (12) | 0.82 (0.68, 0.99) |
| <i>Peripheral vascular event</i> | 184 (9) | 200 (10) | 0.87 (0.72, 1.07) |
| Secondary endpoints | | | |
| <i>CV Mortality</i> | 377 (19) | 391 (20) | 0.92 (0.80, 1.07) |
| <i>Stroke</i> | 115 (6) | 102 (5) | 1.07 (0.82, 1.40) |
| <i>Bone fracture</i> | 238 (12) | 255 (13) | 0.89 (0.75, 1.07) |
| <i>Parathyroidectomy</i> | 140 (7) | 278 (14) | 0.44 (0.36, 0.54) |

Parathyroid Carcinoma

Twenty-nine patients with parathyroid carcinoma were enrolled in an open-label study. Parathyroid carcinoma and severe hypercalcaemia in these patients was persistent despite previous parathyroidectomy and bisphosphonate therapy. The study consisted of two phases, a dose-titration phase and a maintenance phase. Cinacalcet was administered at doses ranging from 30 mg twice daily to 90 mg four times daily, and mean serum calcium declined from 3.53 to 3.10 mmol/L across the titration phase (up to 16 weeks). Sixty-two percent of patients (18 of 29) achieved a reduction in serum calcium of at least 0.25 mmol/L.

Primary HPT for Whom Parathyroidectomy is Not a Treatment Option

Seventeen patients with primary HPT for whom parathyroidectomy was not a treatment option were enrolled in an open-label study. The study consisted of two phases, a dose-titration phase and a maintenance phase. Cinacalcet was administered at doses ranging from 30 mg twice daily to 90 mg four times daily, and mean serum calcium declined from 3.18 to 2.60 mmol/L across the titration phase (up to 16 weeks). Eighty-eight percent of patients (15 of 17) achieved a reduction in serum calcium of at least 0.25 mmol/L.

An additional 114 patients with primary HPT and hypercalcaemia, including 25 patients with recurrent primary HPT after parathyroidectomy, were enrolled in 3 controlled studies and one open label study. In one study of 45 patients with primary HPT, including 12 patients with recurrent primary HPT after parathyroidectomy, cinacalcet normalised

serum calcium in approximately 80% of patients, and this was sustained for up to 3 years.

INDICATIONS

Sensipar® may be used to treat the biochemical manifestations of secondary hyperparathyroidism in patients with end stage renal disease, receiving dialysis (see CLINICAL TRIALS). Sensipar® should be used as adjunctive therapy.

Sensipar® is indicated for the treatment of hypercalcaemia in patients with parathyroid carcinoma.

Sensipar® may be used to treat the biochemical manifestations of primary hyperparathyroidism in patients for whom parathyroidectomy is not a treatment option.

CONTRAINDICATIONS

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

Hypocalcaemia: Sensipar® treatment should not be initiated if serum calcium is less than the lower limit of the normal range (see PRECAUTIONS).

PRECAUTIONS

Serum Calcium

Cinacalcet treatment should not be initiated in patients with CKD receiving dialysis if serum calcium is less than 8.4 mg/dL [2.1 mmol/L]. Since cinacalcet lowers serum calcium, patients should be monitored for the occurrence of hypocalcaemia.

Life threatening events and fatal outcomes associated with hypocalcaemia have been reported in patients treated with cinacalcet including in paediatric patients. Decreases in serum calcium can prolong the QT interval, potentially resulting in ventricular arrhythmia. Cases of QT prolongation and ventricular arrhythmia secondary to hypocalcaemia have been reported in patients treated with cinacalcet. Manifestations of hypocalcaemia may also include paresthesias, myalgias, cramping, tetany, and seizures.

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 [2.1 mmol/L] but remains above 7.5 mg/dL [1.88 mmol/L], or if symptoms of hypocalcaemia occur, calcium-containing phosphate binders and/or vitamin D sterols can be used to raise

serum calcium. If hypocalcaemia persists, reduce the dose or discontinue administration of cinacalcet. If serum calcium falls below 7.5 mg/dL [1.88 mmol/L], or if symptoms of hypocalcaemia persist and the dose of vitamin D cannot be increased, withhold administration of cinacalcet until serum calcium levels reach 8.0 mg/dL [2.0 mmol/L] and/or symptoms of hypocalcaemia have resolved. Treatment should be reinitiated using the next lowest dose of cinacalcet (see DOSAGE AND ADMINISTRATION).

In the 6-month registrational trials of patients with CKD on dialysis, 66% of patients receiving cinacalcet compared with 25% of patients receiving placebo developed at least one serum calcium value < 8.4 mg/dL [2.1 mmol/L]. In CKD patients receiving dialysis who were administered cinacalcet, 29% of patients in the 6-month registrational trials and 21% and 33% of patients (within the first 6 months and overall, respectively) in the EVOLVE clinical trial, had at least one serum calcium value less than 7.5 mg/dL [1.88 mmol/L]. In the EVOLVE clinical trial, 1.1% of patients in the cinacalcet group and 0.1% in the placebo group permanently discontinued study drug due to hypocalcaemia.

Cinacalcet is not indicated for CKD patients not receiving dialysis. Investigational studies have shown that CKD patients not receiving dialysis treated with cinacalcet have an increased risk of hypocalcaemia (serum calcium levels less than 8.4 mg/dL [2.1 mmol/L]) compared with cinacalcet-treated CKD patients receiving dialysis, which may be due to lower baseline calcium levels and/or the presence of residual kidney function.

Seizures

In clinical studies, seizures (primarily generalized or tonic-clonic) were observed in 1.4% (43/3049) of cinacalcet-treated patients and 0.7% (5/687) of placebo-treated patients. 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.

Hypotension and/or Worsening Heart Failure

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

Upper Gastrointestinal Bleeding

Cases of gastrointestinal bleeding, mostly upper gastrointestinal bleeding, have occurred in patients using calcimimetics, including Sensipar, from postmarketing and clinical trial sources. The exact cause of GI bleeding in these patients is unknown.

Patients with risk factors for upper GI bleeding (such as known gastritis, esophagitis, ulcers or severe vomiting) may be at increased risk for GI bleeding when receiving Sensipar treatment. Monitor patients for worsening of common GI adverse reactions of nausea and vomiting associated with Sensipar (see Adverse Effects) and for signs and symptoms of GI bleeding and ulcerations during Sensipar therapy. Promptly evaluate and treat any suspected GI bleeding.

Adynamic Bone

In CKD patients receiving dialysis adynamic bone may develop if PTH levels are suppressed below 100 pg/mL (10.6 pmol/L). If PTH levels decrease below the recommended target range in patients treated with cinacalcet, the dose of vitamin D sterols and/or cinacalcet should be reduced or therapy discontinued.

Hepatic Insufficiency

Due to the potential for 2 to 4 times higher plasma levels of cinacalcet in patients with moderate to severe hepatic impairment, physicians should closely monitor these patients when initiating cinacalcet (see PHARMACOKINETICS).

Testosterone Levels

Testosterone levels are often below the normal range in patients with end-stage renal disease. In a clinical study of CKD patients on dialysis, free testosterone levels decreased by a median of 31.3% in the cinacalcet treated patients and by 16.3% in the placebo-treated patients after 6 months of treatment. The clinical significance of these reductions in serum testosterone is unknown. An open label extension of this study showed no further reductions in free and total testosterone concentrations over a period of 3 years in cinacalcet-treated patients.

Neoplastic Events

In EVOLVE, a randomised, double-blind, placebo-controlled clinical study of 3,883 dialysis patients, neoplastic events were reported in 2.9 and 2.5 patients per 100 patient-years in cinacalcet and placebo-treatment groups, respectively. A causal relationship to cinacalcet has not been established.

Laboratory Tests

Patients with CKD and Secondary Hyperparathyroidism

Serum calcium 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 should be measured approximately monthly, and PTH every 1 to 3 months (see DOSAGE AND ADMINISTRATION). Either the intact PTH (iPTH) or bio-intact PTH (biPTH) may be used to measure PTH levels; treatment with cinacalcet does not alter the relationship between iPTH and biPTH.

Patients with Parathyroid Carcinoma and Patients with Primary Hyperparathyroidism for Whom Parathyroidectomy is Not a Treatment Option

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 to 3 months (see DOSAGE AND ADMINISTRATION).

Interference with Laboratory and Diagnostic Tests

None known.

Effects on Fertility

Cinacalcet did not impair mating or fertility in rats at oral doses up to 75 mg/kg/day, with systemic exposures up to 2 times human exposure at the maximum recommended clinical dose (MRCD), based on AUC.

Studies in monkeys showed that cinacalcet depressed serum testosterone concentrations by 70-90% at oral doses 5-100 mg/kg/day, corresponding to systemic exposures 0.1-1 times the clinical exposure, on an AUC basis, at the MRCD of 360 mg/day. The highest dose also resulted in a 42% reduction in testicular weights.

Use in Pregnancy

Pregnancy Category: B3*

Cinacalcet crossed the placental barrier in rabbits; foetal plasma cinacalcet concentrations were about 10 –13 % of the maternal plasma concentrations. There was no evidence of teratogenicity in rats or rabbits. Foetal body weights were decreased in rats at 50 mg/kg/day PO (approximately 2 times the clinical exposure at the MRCD, based on AUC) and increased incidences of unossified sternebrae occurred in rats at exposures 0.1 – 2 times the clinical exposure, with maternal toxicity.

There are no adequate and well-controlled studies of cinacalcet in pregnant women. Because animal reproduction studies are not always predictive of human response,

cinacalcet should be used during pregnancy only if the potential benefit justifies the potential risk to the foetus.

*Drugs which have been taken by only a limited number of pregnant women and women of childbearing age, without an increase in the frequency of malformation or other direct or indirect harmful effects on the human fetus having been observed. Studies in animals have shown evidence of an increased occurrence of fetal damage, the significance of which is considered uncertain in humans.

Use in lactation

It is not known whether cinacalcet is excreted in human milk. Cinacalcet is excreted in the milk of lactating rats with a high milk to plasma ratio. Oral administration of cinacalcet to female rats during gestation and lactation at doses of 25 mg/kg/day and above (exposures at and above 1.5 times the clinical exposure at the MRCD, based on AUC) was associated with increases in neonatal loss and reduced body weight gain of suckling rats.

Considering the rat study findings and because many drugs are excreted in breast milk, a decision should be made to discontinue nursing or discontinue cinacalcet, taking into account the importance of cinacalcet to the mother.

Paediatric Use

The safety and efficacy of cinacalcet in paediatric patients have not been established. Cinacalcet is not indicated for use in paediatric patients. A fatal outcome was reported in a paediatric clinical trial patient with severe hypocalcaemia (see PHARMACOLOGY: Paediatric Patients and PRECAUTIONS: Serum Calcium).

Use in the Elderly

Of the 1136 patients enrolled in the cinacalcet phase 3 clinical programme, 26% were over 65 years old, and 9% were over 75 years old. No differences in the safety and efficacy of cinacalcet were observed in patients greater or less than 65 years of age (see DOSAGE AND ADMINISTRATION: Geriatric Patients).

Effects on Ability to Drive and Use Machines

No effects on the ability to drive or operate machinery have been observed.

Carcinogenicity

Cinacalcet, administered orally at dietary doses up to 200 mg/kg to mice and 35 mg/kg/day to rats for 104 weeks, showed no evidence of carcinogenic potential. These doses resulted in total systemic exposure (AUCs) approximately equivalent to the

exposures observed in humans given the maximum dose of 360 mg/day. A decreased incidence of thyroid C-cell adenomas was observed in rats treated with cinacalcet.

Genotoxicity

Cinacalcet was negative in the Ames assay, Chinese Hamster Ovary HGPT forward mutation assay, in vitro chromosome aberration assay and the mouse micronucleus assay. These tests indicate that cinacalcet is unlikely to pose a genotoxic risk to humans.

Coadministration with Other Products

Administer cinacalcet with caution in patients receiving any other medications known to lower serum calcium. Closely monitor serum calcium levels in patients receiving other medications known to lower serum calcium.

INTERACTIONS WITH OTHER MEDICINES

Effect of Cinacalcet on Other Drugs

Drugs metabolised by the enzyme cytochrome P450 2D6 (CYP2D6) – cinacalcet is an inhibitor of CYP2D6. Therefore, dose adjustments of concomitant medications may be required when cinacalcet is administered with medications that are predominantly metabolised by this enzyme (eg, metoprolol) and particularly those with a narrow therapeutic index (eg, flecainide, vinblastine, thioridazine and most tricyclic antidepressants).

Desipramine: Concurrent administration of 90 mg cinacalcet with 50 mg desipramine, a tricyclic antidepressant metabolised primarily by CYP2D6, increased desipramine exposure approximately 3.6 times in CYP2D6 extensive metabolisers.

Amitriptyline: Co-administration of 25 mg or 100 mg cinacalcet with 50 mg amitriptyline, a tricyclic antidepressant metabolised in part by CYP2D6, increased exposure to amitriptyline and its active metabolite nortriptyline by approximately 20% in extensive metabolisers of CYP2D6 enzymes. Dose reductions of amitriptyline may be required in some subjects receiving cinacalcet concurrently.

Drugs metabolised by other cytochrome P450 (CYP) enzymes - based on in vitro data, cinacalcet is not an inhibitor of other CYP enzymes at concentrations achieved clinically, including CYP1A2, CYP2C9, CYP2C19, and CYP3A4.

Warfarin: Multiple oral doses of cinacalcet did not affect the pharmacokinetics or pharmacodynamics (as measured by prothrombin time and the clotting factor VII) of warfarin.

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 CYP3A4, CYP1A2 or CYP2C9 in humans.

Midazolam: Co-administration of cinacalcet (90 mg) with orally administered midazolam (2 mg), a CYP3A4 and CYP3A5 substrate, did not alter the pharmacokinetics of midazolam. These data suggest that cinacalcet would not affect the pharmacokinetics of those classes of drugs that are metabolised by CYP3A4 and CYP3A5, such as certain immunosuppressants, including cyclosporin and tacrolimus.

Effect of Other Drugs on Cinacalcet

Cinacalcet is metabolised by multiple cytochrome P450 enzymes, primarily CYP3A4, CYP1A2 and CYP2D6, which limit the potential for other drugs to increase cinacalcet concentrations.

Ketoconazole: Cinacalcet is metabolised in part by the enzyme CYP3A4. Co-administration of ketoconazole, a strong inhibitor of CYP3A4, caused an approximate 2-fold increase in cinacalcet exposure. Dose adjustment of cinacalcet may be required if a patient receiving cinacalcet initiates or discontinues therapy with a strong CYP3A4 inhibitor (eg, ketoconazole, erythromycin, itraconazole) or inducer (eg, rifampicin, phenytoin, St. John's Wort) of this enzyme.

Calcium carbonate: Co-administration of calcium carbonate (1500 mg) did not alter the pharmacokinetics of cinacalcet.

Sevelamer HCl: Co-administration of sevelamer HCl (2400 mg tid) did not alter the pharmacokinetics of cinacalcet.

Pantoprazole: Co-administration of pantoprazole (2400 mg) did not alter the pharmacokinetics of cinacalcet.

ADVERSE EFFECTS

Studies were conducted in patients with CKD receiving dialysis, and in patients with parathyroid carcinoma or primary HPT for whom parathyroidectomy is not a treatment option. Cinacalcet was safe and generally well tolerated. However, nausea and vomiting are very common adverse reactions.

Secondary Hyperparathyroidism in Patients with Chronic Kidney Disease

In 3 double-blind placebo-controlled clinical trials, 1126 CKD patients on dialysis received study drug (656 cinacalcet, 470 placebo) for up to 6 months. Adverse events reported during the studies were typical for the dialysis patient population. The most frequently reported adverse events (incidence of at least 5% in the cinacalcet group) are provided in Table 4. The most frequently reported events in the cinacalcet group were nausea and vomiting which were generally mild to moderate in severity, brief in duration, and infrequently led to discontinuation of study drug. Rash and hypocalcaemia have been observed.

Seizures were observed in 1.4% (13/910) of cinacalcet-treated patients and 0.7% (5/641) of placebo-treated patients across all completed placebo controlled trials.

Table 4. Adverse Events Reported (at least 5%) in Patients with Secondary Hyperparathyroidism (SHPT) Receiving Dialysis

| Body system and preferred terms | Percent of reports | |
|---------------------------------|-----------------------|--------------------|
| | Cinacalcet n = 656 | Placebo n = 470 |
| Body as a whole | | |
| Fever | 7 | 10 |
| Oedema peripheral | 7 | 7 |
| Fatigue | 7 | 7 |
| Asthenia | 7 | 4 |
| Pain chest (non-cardiac) | 6 | 4 |
| Access infection | 5 | 4 |
| Cardiovascular | | |
| Hypotension | 7 | 12 |
| Hypertension | 7 | 5 |
| Thrombosis vascular access | 6 | 7 |
| CNS / PNS | | |
| Headache | 16 | 17 |
| Dizziness | 10 | 8 |
| Gastrointestinal | | |
| Nausea | 31 | 19 |
| Vomiting | 27 | 15 |
| Diarrhoea | 21 | 20 |
| Pain abdominal | 12 | 14 |
| Dyspepsia | 8 | 8 |
| Anorexia | 6 | 4 |
| Musculo-skeletal | | |
| Myalgia | 15 | 14 |
| Pain limb | 9 | 10 |
| Arthralgia | 7 | 9 |
| Respiratory | | |
| Infection upper respiratory | 12 | 13 |
| Dyspnoea | 9 | 9 |
| Cough | 6 | 7 |
| Skin and appendages | | |
| Pruritus | 6 | 7 |

The incidence of serious adverse events (29 % vs 31%) and deaths (2% vs 3%) was similar in the cinacalcet and placebo groups, respectively.

12-Month Experience with Cinacalcet

Two hundred and sixty-six patients from the 2 pivotal phase 3 studies continued to receive cinacalcet or placebo treatment in a 6-month double-blind extension study (12-month total treatment duration). The incidence and nature of adverse events in this study were similar in the 2 treatment groups, and comparable to those observed in the pivotal phase 3 studies.

Other Clinical Experience with Sensipar in Secondary Hyperparathyroidism

In EVOLVE, a randomised, double-blind placebo controlled study of 3,883 patients with secondary HPT and CKD receiving dialysis in which patients were treated for up to 64 months, the most frequently reported adverse reactions (incidence of $\geq 5\%$ in the Sensipar group and $\geq 1\%$ compared to placebo) were nausea, vomiting, diarrhoea, dyspnoea, cough, hypotension, headache, hypocalcaemia, muscle spasms, abdominal pain, abdominal pain-upper, hyperkalaemia, upper respiratory tract infection, dyspepsia, dizziness, decreased appetite, asthenia and constipation.

Additional adverse event rates for Sensipar versus placebo are as follows: seizure (2.5%, 1.6%), rash (2.2%, 1.9%), and hypersensitivity reactions (9.4%, 8.3%).

Parathyroid Carcinoma and Primary HPT for Whom Parathyroidectomy is not a Treatment Option

Overall, the safety profile in patients with parathyroid carcinoma or intractable (failed or contraindicated to surgery) primary HPT was similar to that seen in patients with CKD and secondary HPT; the most frequent adverse events in this patient group were nausea and vomiting.

Summary of the Safety of Cinacalcet in Subjects with Primary HPT

The safety profile of cinacalcet was similar across the 5 studies in primary HPT. Overall, common adverse events observed in these studies included gastrointestinal events (nausea, vomiting, abdominal pain), headache, paresthesia, anxiety, asthenia, dizziness, and arthralgia. Most adverse events were mild to moderate in severity. The most common event considered related to cinacalcet was nausea, which was also the most common adverse event leading to withdrawal. The safety profile of cinacalcet in this subject population was generally consistent with that in subjects with CKD and no unique safety concern was identified for cinacalcet in the treatment of primary HPT.

Seizures were observed in 0.7% (1/140) of cinacalcet-treated patients and 0.0% (0/46) of placebo-treated patients in all clinical studies.

Post Marketing Data

Spontaneous post marketing reports have been received describing diarrhoea, myalgia, rash, seizures, gastrointestinal bleeding and hypersensitivity reactions, including angioedema and urticaria, in association with cinacalcet HCl administration.

Isolated idiosyncratic cases of hypotension and/or worsening of heart failure have been reported in cinacalcet-treated patients with impaired cardiac function in post marketing safety surveillance.

Common: between 1% and 10%; uncommon: between 0.1% and 1%; rare: between 0.01% and 0.1%; very rare: between 0.001% and 0.01%).

Immune system disorders

Uncommon: hypersensitivity reactions

Skin and subcutaneous tissue disorders

Common: rash

Very rare: angioedema and urticaria

Gastrointestinal disorders

Rare: diarrhoea

Musculo-skeletal and connective tissue disorders

Rare: myalgia

Common: back pain

Laboratory Values

Low laboratory serum calcium levels were very common in clinical studies. Serum calcium levels should be monitored in patients receiving cinacalcet (see PRECAUTIONS and DOSAGE AND ADMINISTRATION).

DOSAGE AND ADMINISTRATION

Sensipar® is administered orally. It is recommended that Sensipar® be taken with food or shortly after a meal. Tablets should be taken whole and should not be divided.

Patients with End Stage Renal Disease Receiving Dialysis

Sensipar® reduces PTH while simultaneously lowering Ca x P, calcium and phosphorus levels in patients receiving dialysis.

The recommended starting dose for adults is 30 mg once per day.

Sensipar® should be titrated every 2 to 4 weeks to a maximum dose of 180 mg once daily to achieve a target PTH between 1.5 to 5 times the upper limit of normal.

In CKD patients, PTH levels should be assessed at least 12 hours after dosing with cinacalcet.

During dose titration, serum calcium levels should be monitored frequently and if serum calcium levels decrease below the normal range, appropriate steps should be taken to increase serum calcium levels (see PRECAUTIONS).

Parathyroid Carcinoma and Primary HPT for Whom Parathyroidectomy is not a Treatment Option

The recommended starting dose of Sensipar® for adults is 30 mg twice daily.

The dosage of Sensipar® 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 normalise serum calcium.

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

Moderate to severe hepatic impairment (Child-Pugh classification) increases cinacalcet drug concentrations by approximately 2 to 4 fold. In patients with moderate-severe hepatic impairment, PTH and serum calcium concentrations should be closely monitored during dose titration of cinacalcet.

OVERDOSAGE

Doses titrated up to 300 mg once daily have been safely administered to patients receiving dialysis. Overdosage of cinacalcet may lead to hypocalcaemia. In the event of overdosage, patients should be monitored for signs and symptoms of hypocalcaemia and appropriate measures taken to correct serum calcium levels (see PRECAUTIONS).

Since cinacalcet is highly protein bound, haemodialysis is not an effective treatment for overdosage of cinacalcet.

In case of overdose, immediately contact the Poisons Information Centre (in Australia, call 13 11 26) for advice.

PRESENTATION AND STORAGE CONDITIONS

Sensipar® 30 mg tablets are formulated as light green, film-coated, oval-shaped tablets marked with “AMG” on one side and “30” on the opposite side, packaged in blister packs of 28 tablets.

Sensipar® 60 mg tablets are formulated as light green, film-coated, oval-shaped tablets marked with “AMG” on one side and “60” on the opposite side, packaged in blister packs of 28 tablets.

Sensipar® 90 mg tablets are formulated as light green, film-coated, oval-shaped tablets marked with “AMG” on one side and “90” on the opposite side, packaged in blister packs of 28 tablets.

Store below 30°C.

NAME AND ADDRESS OF THE SPONSOR

Amgen Australia Pty Ltd
Level 7, 123 Epping Road
North Ryde, NSW 2113
ABN 31 051 057 428

POISON SCHEDULE OF THE MEDICINE

S4

DATE OF FIRST INCLUSION IN THE AUSTRALIAN REGISTER OF THERAPEUTIC GOODS

25 January 2005

DATE OF MOST RECENT AMENDMENT

12 December 2017

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