

# Cinacalcet hydrochloride (Sensipar)

GRACE POON, PHARMD

Currently, >300,000 patients with end-stage renal disease require dialysis. Secondary hyperparathyroidism is a serious complication of end-stage renal disease and can lead to renal osteodystrophy and other organ failure. Vitamin D sterols and phosphate binders are used to treat hyperparathyroidism, but they can cause hypercalcemia, which contributes to vascular and soft-tissue calcification. Cinacalcet (Sensipar) is the first agent in its class that treats secondary hyperparathyroidism by increasing the sensitivity of calcium-sensing receptors. It is also indicated for the treatment of hypercalcemia in patients with parathyroid carcinoma. All clinical trials concluded that cinacalcet is effective for the reduction of parathyroid hormone, serum calcium, phosphorus, and calcium-phosphate product levels. Cinacalcet is available as a once-daily oral therapy. Adverse effects are generally mild.

According to the 2004 US Renal Data System Annual Data Report, >300,000 patients with end-stage renal disease (ESRD) require dialysis. The number of these patients is estimated to double by 2010. Despite dramatic advances in medicine, the mortality rate for patients with ESRD remains >20% per year (1).

Secondary hyperparathyroidism is a serious complication of dialysis and can lead to renal osteodystrophy and other organ dysfunctions (2, 3). Renal osteodystrophy is associated with bone pain and reduced bone mass. The incidence of hip fracture is 85 times higher among dialysis patients compared with healthy individuals of the same age (4). With failing kidneys, the body has difficulty maintaining phosphorus levels within normal limits. Hyperphosphatemia promotes the development of parathyroid gland hyperplasia. 1,25-Dihydroxyvitamin D synthesis, which is essential for the absorption of calcium, is decreased in patients with ESRD, which leads to hypocalcemia (5). Calcium-sensing receptors on the parathyroid cells are the key regulators of parathyroid hormone (PTH) secretion. Patients with ESRD tend to have less sensitive calcium-sensing receptors. Hypocalcemia triggers the body to increase PTH secretion and promotes parathyroid gland hyperplasia. Elevated PTH increases serum calcium by increasing gastrointestinal calcium absorption, decreasing calcium clearance, and increasing bone calcium release (5–7). Elevated serum calcium and phosphorus levels increase the formation of calcium-phosphorus product, which is associated with calcification of soft tissue, joints, blood vessels, myocardium, lungs, liver, and kidneys (8). According to Taal et al, the mortality rate is tripled in patients with calcium-phosphorus product levels >64 mg<sup>2</sup>/dL<sup>2</sup> (6).

**Table 1. Laboratory target ranges for patients with secondary hyperparathyroidism\***

Test	Goals
Parathyroid hormone	150–300 pg/mL
Serum phosphate	3.5–5.5 mg/dL
Serum calcium	8.4–9.5 mg/dL
Calcium-phosphorus product	<55 mg <sup>2</sup> /dL <sup>2</sup>

\*Data from reference 9.

The goals of treatment are to prevent hyperphosphatemia, maintain normal serum calcium, and restore calcitriol. *Table 1* shows the laboratory target ranges for patients with secondary hyperparathyroidism according to the National Kidney Foundation Kidney Disease Outcomes Quality Initiative Clinical Practice Guidelines on Bone Metabolism and Disease in Chronic Kidney Disease (9).

Vitamin D sterols and phosphate binders are used to treat hyperparathyroidism (10). One common adverse effect of those medications is hypercalcemia, which contributes to vascular and soft-tissue calcification (5). Also, days of treatment may be required before vitamin D sterols have their maximum effect (6). Cinacalcet, which was approved by the Food and Drug Administration in March 2004, is the first agent in its class that treats secondary hyperparathyroidism by increasing the sensitivity of calcium-sensing receptors.

## INDICATION

Cinacalcet is indicated for the treatment of hypercalcemia in patients with parathyroid carcinoma or for secondary hyperparathyroidism in patients with chronic kidney disease who require dialysis (11).

## PHARMACOLOGY

Cinacalcet is a type II calcimimetic agent with a novel mechanism of action (7, 11). It binds to the transmembrane region of

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the calcium-sensing receptor, which leads to a different structural configuration that is more sensitive to serum calcium. Unlike vitamin D sterols, cinacalcet does not increase serum calcium levels; therefore, adverse effects associated with hypercalcemia can be avoided.

## PHARMACOKINETICS

**Absorption:** The maximum plasma concentration ( $C_{max}$ ) is reached in approximately 2 to 6 hours after oral administration. Food affects both  $C_{max}$  and area under the curve ( $AUC_{(0 \rightarrow \infty)}$ ). A food effect study in healthy individuals showed an 82% increase in  $C_{max}$  and a 68% increase in AUC (11).

**Distribution:** Distribution of cinacalcet is consistent with the two-compartment pharmacokinetic model. The half-life is 30 to 40 hours, and therefore, steady-state can be achieved in approximately 7 days. Cinacalcet is highly protein bound. The volume of distribution is 1000 L (11).

**Metabolism:** Cinacalcet is metabolized by CYP3A4, CYP2D6, and CYP1A2 (11).

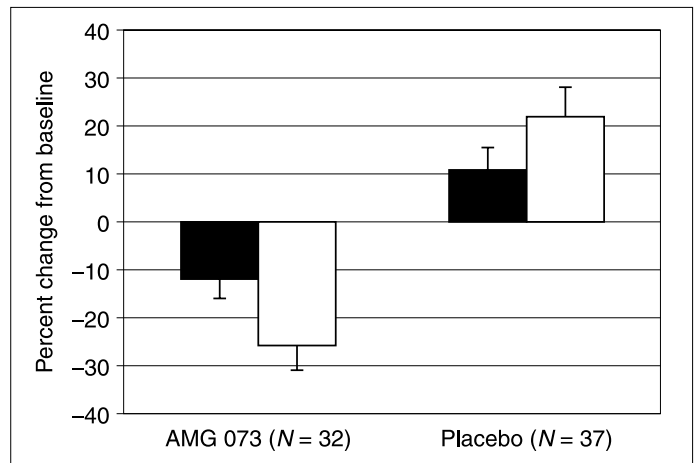
**Excretion:** 80% of the metabolites are excreted renally (11).

## CLINICAL TRIALS

Several clinical trials have been conducted to assess the effectiveness of cinacalcet in suppressing PTH secretion and reducing serum calcium, phosphorus, and calcium-phosphorus product levels. Three are discussed in this article. Their study designs were similar, but the dosage of cinacalcet used and the duration of the study varied significantly (Table 2). Short-term studies were excluded. One open-label study evaluated the effectiveness of cinacalcet for the treatment of parathyroid carcinoma.

### Treatment of secondary hyperparathyroidism in patients receiving hemodialysis (phase III trials)

Block et al presented the findings of two identical randomized, double-blind, placebo-controlled, multicenter trials conducted between December 20, 2001, and January 16, 2003. Eligible subjects were at least 18 years of age, received thrice-weekly hemodialysis, and had secondary hyperparathyroidism. In the treatment arm, patients initially received cinacalcet 30 mg orally once daily. The dose was increased every 3 weeks in 30-mg increments, up to a daily maximum dose of 180 mg/day. The goal was to maintain PTH levels <250 pg/mL. Phosphate binders and vitamin D sterols were used concurrently with the study drug. Dosage-adjustment guidelines for vitamin D sterols were specified prior to the study. A total of 741 subjects were eligible for the study. Demographic characteristics were similar between the two groups. By the end of the 26-week treatment, 43% of the patients who received cinacalcet reached the goal compared with 5% in the placebo



**Figure 1.** Concurrent mean percent change from baseline in parathyroid hormone (□) and calcium-phosphorus product (■) during the maintenance phase. Values are mean ± standard error of the mean. AMG 073 is cinacalcet. Reprinted from Lindberg et al, 2003 (13) with permission from Blackwell Publishing.

group ( $P < 0.001$ ). Mean PTH levels decreased by 43% from baseline in the cinacalcet group compared with a 9% increase in the placebo group. Stratified analysis showed that the efficacy of cinacalcet was not influenced by sex, race, age, duration of dialysis, baseline biochemical variables, the presence of diabetes, or the use of vitamin D sterols (12). This study was conducted in 63 sites in the USA and 62 sites in Europe and Australia; hence, the results may be generalizable to a large population.

Lindberg et al conducted a placebo-controlled, double-blind, randomized, multicenter study in 78 patients for 18 weeks. Those who were randomized to the cinacalcet group received an initial dose of 20 mg orally once daily. The dose was titrated every 3 weeks up to 30, 40, or 50 mg/day. The objective of the study was to assess the reduction of PTH, serum calcium, phosphorus, and calcium-phosphorus product levels. The researchers allowed concurrent use of vitamin D sterols and phosphate binders. Guidelines for the use of vitamin D sterols were predefined in the study protocol. The results of the study showed an average PTH decrease of 26% among patients in the cinacalcet group compared with an average 22% increase in the placebo group ( $P < 0.001$ ) (Figure 1). Cinacalcet reduced PTH regardless of baseline vitamin D use. Serum calcium decreased by 4.7% in the cinacalcet group compared with no change in the placebo group ( $P < 0.001$ ). Calcium-phosphorus product levels decreased by 11.9% in the cinacalcet group compared with a 10.9% increase in the placebo group ( $P < 0.001$ ) (Figure 1) (13). The maximum dose of 50 mg/day used in this study was significantly lower than the dose recommended by the manufacturer.

Quarles et al conducted a randomized, double-blind, placebo-controlled study to assess the efficacy of cinacalcet for the treatment of secondary hyperparathyroidism in patients with ESRD. Seventy-one eligible patients were enrolled in the study. The researchers assessed the decrease of PTH, serum calcium, serum phosphorus, and calcium-phosphorus product levels. Patients were allowed to take phosphate binders and vitamin D sterols during the trial. The dose of cinacalcet used in this study was 25 mg, 50 mg, 75 mg, or 100 mg, which differed from the doses used

**Table 2. Comparison of study designs of three randomized, double-blind, placebo-controlled multicenter trials of cinacalcet**

	Number of patients	Duration of the study	Cinacalcet dose/day
Block et al (12)	741	26 weeks	30–180 mg
Lindberg et al (13)	78	18 weeks	10–50 mg
Quarles et al (14)	71	18 weeks	25–100 mg

by Block et al. The mean dose was  $74 \pm 5.3$  mg. In the treatment arm, the maximum reduction of PTH from baseline was approximately 60%. Serum calcium decreased by 4.6% compared with a 2.6% increase in the placebo group ( $P < 0.001$ ). Serum phosphorus was similar between both groups. Vomiting was the most common adverse effect among patients who received cinacalcet (14).

### Pharmacokinetics of cinacalcet in patients receiving hemodialysis

Ohashi et al conducted a pharmacokinetics study to assess whether hemodialysis would affect cinacalcet plasma concentration. Eight patients with ESRD were enrolled in the study. Patients received 25 mg, 50 mg, 75 mg, or 100 mg of cinacalcet on a day without hemodialysis and on a day with hemodialysis 1 week after. Hemodialysis did not affect the pharmacokinetics of cinacalcet (15). This is the only published clinical trial that evaluated the effects of hemodialysis on the pharmacokinetics of cinacalcet. Of note, all patients enrolled in this study were Japanese, and the study population was very small. Larger trials composed of subjects with different ethnicities are needed.

### Treatment of parathyroid carcinoma

Ten patients participated in an open-label study to evaluate the effectiveness of cinacalcet in treating parathyroid carcinoma. The dosages were individualized based on patients' needs. Maintenance doses ranged from 70 mg twice daily to 90 mg 4 times daily. The baseline mean serum calcium was 14.7 mg/dL. During treatment, the change of serum calcium ranged from  $-7.4$  to  $0.9$  mg/dL (11).

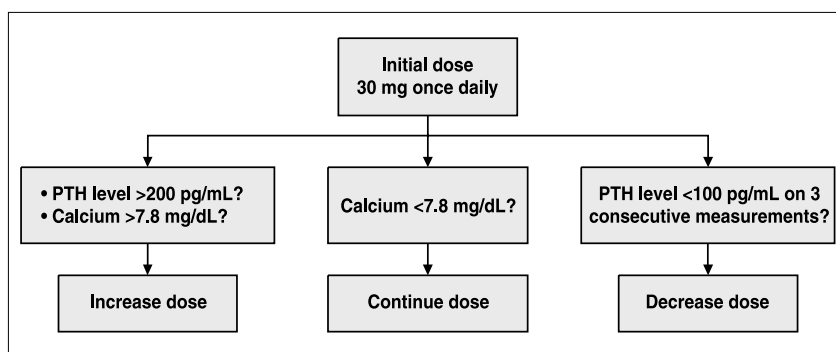
### ADVERSE EFFECTS

Table 3 summarizes the adverse events reported in three double-blind, placebo-controlled clinical trials. The trials included 1126 patients with chronic kidney disease requiring dialysis who

**Table 3. Adverse event incidence ( $\geq 5\%$ ) in patients on dialysis\***

	Placebo (n = 470)	Sensipar (cinacalcet) (n = 656)
Nausea	19%	31%
Vomiting	15%	27%
Diarrhea	20%	21%
Myalgia	14%	15%
Dizziness	8%	10%
Hypertension	5%	7%
Asthenia	4%	7%
Anorexia	4%	6%
Chest pain, noncardiac	4%	6%
Access infection	4%	5%

\*Included are events that were reported at a greater incidence in the Sensipar group than in the placebo group. Reprinted from package insert (11) with permission from Amgen, Inc.



**Figure 2.** Titration guidelines used by Block et al (12). PTH indicates parathyroid hormone.

received cinacalcet or placebo for up to 6 months. Nausea and vomiting were the most common adverse effects associated with the use of cinacalcet. Hypocalcemia is a possible adverse effect of cinacalcet. Patients with a serum calcium level less than the lower limit of the normal range (8.4 mg/dL) should not receive cinacalcet, as stated in the package insert (8).

### DOSING AND ADMINISTRATION

#### Secondary hyperparathyroidism in patients receiving hemodialysis

The recommended starting dose is 30 mg orally once daily (8). The dose can then be titrated in 30-mg increments based on the patient's needs. The recommended maximum daily dose for the treatment of secondary hyperparathyroidism is 180 mg/day. Dosage adjustments should not be made more frequently than every 2 to 4 weeks. PTH levels need to be measured 1 to 4 weeks after dose initiation or dosage adjustment. Figure 2 summarizes the titration guidelines used by Block et al.

#### Parathyroid carcinoma

The recommended starting dose is 30 mg orally twice daily (8). The dose can then be titrated based on calcium levels. Dosage adjustment should not be made more frequently than every 2 to 4 weeks.

#### Special populations

*Renal impairment:* No dosage adjustment needed.

*Hepatic impairment:* Half-life is prolonged by 33% and 70% in patients with moderate and severe hepatic impairment, respectively. No dosage adjustment is needed, but patients should be closely monitored.

*Age:* No dosage adjustment is needed for patients who are  $\geq 65$  years of age. Clinical data support the drug's efficacy in children.

#### Pregnancy/lactation

Cinacalcet is classified as pregnancy category C by the manufacturer (8).

### DRUG INTERACTIONS

Since cinacalcet is metabolized by CYP3A4, CYP2D6, and CYP1A2, many drug interactions can potentially occur (8).

In cases of concurrent therapy with medications metabolized by CYP2D6 (e.g., flecainide, vinblastine, and most tricyclic antidepressants), the patient should be monitored closely. Dosage adjustment may be required.

**Table 4. Pharmacy acquisition cost of cinacalcet and vitamin D sterols**

	Cost/tablet	Cost/month
<b>Type II calcimimetics</b>		
Cinacalcet 30 mg	\$8.10	\$243*
Cinacalcet 60 mg	\$16.20	\$486*
Cinacalcet 90 mg	\$24.30	\$729*
<b>Vitamin D sterols</b>		
Calcitriol 0.25 µg	\$0.79	\$23.70*
Calcitriol 0.5 µg	\$1.25	\$37.50*
Doxercalciferol 2.5 µg	\$3.67	\$58.72†

\*Calculation is based on once-daily dosing.

†Calculation is based on dosing 4 times a week.

In cases of concurrent therapy with medications metabolized by CYP3A4 (e.g., ketoconazole, itraconazole, and erythromycin), the patient should be monitored closely. Dosage adjustment may be required. Strong inhibitors of CYP3A4 such as ketoconazole can increase the cinacalcet concentration by 2.3 times.

#### DOSAGE FORMS

Cinacalcet is commercially available as 30-mg, 60-mg, or 90-mg tablets. Each bottle contains 30 tablets (8).

#### ECONOMIC ISSUES

Table 4 lists Baylor University Medical Center's contract prices for cinacalcet and vitamin D sterols. Cinacalcet is a relatively new drug, so no analysis has been published on the cost-effectiveness of cinacalcet for the treatment of secondary hyperparathyroidism.

#### SUMMARY AND CRITICAL ISSUES

Secondary hyperparathyroidism is a serious sequela of ESRD. Traditional therapy, such as vitamin D sterols, remains suboptimal. It can cause hypercalcemia and creates a new set of problems, such as vascular and soft-tissue calcification. Cinacalcet is the first member of a new class of drugs called type II calcimimetics. It reduces PTH levels by increasing the sensitivity of calcium-sensing receptors to calcium. In Block et al, 43% of the cinacalcet-treated patients had a PTH level <250 pg/mL compared with 4% of the placebo group by the end of a 26-week study. All clinical trials concluded that cinacalcet is effective for the reduction of PTH, serum calcium, phosphorus, and calcium-phosphorus product levels. Hemodialysis does not affect the pharmacokinetics of the drug.

Cinacalcet is available as a once-daily oral therapy, which is appropriate for both inpatient and outpatient use. Adverse

effects of cinacalcet are mild. No dosage adjustment is required for patients with hepatic or renal dysfunction.

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