

PRODUCT MONOGRAPH

PrSensipar[®]

(cinacalcet hydrochloride)

Tablets

30 mg, 60 mg, 90 mg

Calcimimetic agent

Manufactured by:
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Sensipar[®]
(cinacalcet hydrochloride)

PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

| Route of Administration | Dosage Form/Strength | Clinically Relevant Nonmedicinal Ingredients |
|--------------------------------|-----------------------------|--|
| Oral | Tablet/30 mg, 60 mg, 90 mg | <i>For a complete listing of the nonmedicinal ingredients see Dosage Forms, Composition and Packaging section.</i> |

INDICATIONS AND CLINICAL USE

SENSIPAR (cinacalcet hydrochloride) is indicated for the treatment of secondary hyperparathyroidism (HPT) in patients with Chronic Kidney Disease (CKD) receiving dialysis.

SENSIPAR controls parathyroid hormone levels, calcium and phosphorous levels, and the serum calcium-phosphorous product (Ca x P), in patients with CKD receiving dialysis.

SENSIPAR is indicated for the reduction of hypercalcemia in patients with parathyroid carcinoma.

SENSIPAR is indicated for the reduction of clinically significant hypercalcemia, as defined by relevant treatment guidelines, in patients with primary HPT for whom parathyroidectomy is not clinically appropriate or is contraindicated.

CONTRAINDICATIONS

SENSIPAR (cinacalcet hydrochloride) is contraindicated in patients with hypersensitivity to any of the components of this product.

For a complete listing of the nonmedicinal ingredients see DOSAGE FORMS, COMPOSITION AND PACKAGING section.

WARNINGS AND PRECAUTIONS

Seizures

In clinical studies, seizures (primarily generalized or tonic-clonic) were observed in 1.4% (43/4039) of SENSIPAR-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. Therefore, serum calcium levels

should be closely monitored in patients receiving SENSIPAR, particularly in patients with a history of a seizure disorder.

Cardiovascular

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 SENSIPAR could not be completely excluded and may be mediated by reductions in serum calcium levels. Clinical trial data showed hypotension occurred in 7% of SENSIPAR-treated patients, 12% of placebo-treated patients, and heart failure occurred in 2% of patients receiving SENSIPAR or placebo.

Hypocalcemia

SENSIPAR 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.

Serum Calcium

In clinical trials of CKD patients receiving dialysis, SENSIPAR treatment was not initiated in patients with a serum calcium (corrected for albumin) less than the lower limit of the normal range. Since SENSIPAR lowers serum calcium, patients should be monitored for the occurrence of hypocalcemia.

In CKD patients receiving dialysis who were administered SENSIPAR, 4% of serum calcium values were less than 1.875 mmol/L (see ADVERSE REACTIONS). In the event of hypocalcemia, calcium-containing phosphate binders and/or vitamin D sterols can be used to raise serum calcium. If hypocalcemia persists, reduce the dose or discontinue administration of SENSIPAR (see DOSAGE AND ADMINISTRATION). Potential manifestations of hypocalcemia may include paresthesias, myalgias, cramping, tetany, and convulsions.

Cinacalcet is not indicated for CKD patients not receiving dialysis. Investigational studies have shown that cinacalcet-treated CKD patients not receiving dialysis have an increased risk for hypocalcemia (serum calcium levels < 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.

General

Adynamic bone disease may develop if intact parathyroid hormone (iPTH) levels are suppressed below 11.0 pmol/L. If iPTH levels decrease below 11.0 pmol/L in patients receiving dialysis treated with SENSIPAR, the dose of SENSIPAR and/or vitamin D sterols should be reduced or therapy discontinued.

Hepatic Insufficiency

Due to the potential for 2- to 4-fold higher plasma levels of SENSIPAR, patients with moderate to severe hepatic impairment should be closely monitored when initiating treatment (see ACTION AND CLINICAL PHARMACOLOGY).

Testosterone Levels

Testosterone levels are often below the normal range in patients with end stage renal disease. In a clinical study of CKD patients receiving dialysis, free testosterone levels decreased by a median of 31.3% in the SENSIPAR-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 SENSIPAR-treated patients.

Impairment of Fertility

SENSIPAR had no effect on fertility in animal studies.

Special Populations

Geriatric Use

Of the 1136 patients enrolled in the SENSIPAR phase 3 clinical program, 26% were > 65 years old, while 9% were > 75 years old. No overall differences in safety and efficacy of SENSIPAR were observed in patients greater or less than 65 years of age (see DOSAGE AND ADMINISTRATION).

Use in Pregnancy

There are no studies on the use of SENSIPAR in pregnant women. SENSIPAR was not teratogenic in rabbits when given a dose of 0.4 times, on an area under the curve (AUC) basis, the maximum human dose for secondary HPT (180 mg once daily). There were no effects on fertility in males or females at exposures up to 4 times a human dose of 180 mg/day. In pregnant rats, there were slight decreases in body weight and food consumption at the highest dose. The non-teratogenic dose in rats was 4.4 times, on an AUC basis, the maximum dose for patients with secondary HPT (180 mg once daily). Decreased fetal weights were seen in rats at doses where dams had severe hypocalcemia. SENSIPAR has been shown to cross the placental barrier in rabbits. Although animal studies have shown no evidence of teratogenicity, SENSIPAR should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Women who become pregnant during SENSIPAR treatment are encouraged to enroll in Amgen's Pregnancy Surveillance Program. Patients or their physicians should call 1-866-512-6436 to enroll.

Nursing Mothers

It is not known whether SENSIPAR is excreted in human milk. Studies in rats have shown that SENSIPAR is excreted in the milk with a high milk to plasma ratio. A decision should be made whether to discontinue nursing or discontinue SENSIPAR, taking into account the importance of SENSIPAR to the mother.

Women who choose to continue SENSIPAR while nursing are encouraged to enroll in Amgen's Lactation Surveillance Program. Patients or their physicians should call 1-866-512-6436 to enroll.

Use in Children

The safety and efficacy of SENSIPAR in pediatric patients have not been established.

Carcinogenicity

SENSIPAR, administered orally for 104 weeks, showed no evidence of carcinogenic potential in mice and rats. Doses administered to mice and rats resulted in total systemic exposure (AUCs) 2 times the exposures observed in humans. The nature, incidence, and distribution of tumours in rats and mice of both sexes did not indicate any SENSIPAR-induced carcinogenesis. A decreased incidence of thyroid C-cell adenomas was observed in rats treated with SENSIPAR.

Mutagenicity

SENSIPAR was negative in the Ames assay, chromosomal aberration assay, Chinese Hamster Ovary HGPRT forward mutation assay, and in the mouse micronucleus assay. These tests indicate that SENSIPAR has no genetic toxicity either with respect to DNA damage, including gene mutations, large scale chromosomal damage, recombinations or numerical changes.

Effect on the Ability to Drive and Use Machines

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

Laboratory Monitoring

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 SENSIPAR. Once the maintenance dose levels have been established, serum calcium and serum phosphorus should be measured approximately monthly, and PTH (iPTH) every 1 to 3 months (see DOSAGE AND ADMINISTRATION). Either the intact PTH (iPTH) or bio-active PTH (biPTH) may be used to measure plasma PTH levels. Treatment with SENSIPAR does not alter the relationship between iPTH and biPTH.

ADVERSE REACTIONS

Adverse Drug Reaction Overview

Studies were conducted in patients with CKD receiving dialysis. SENSIPAR (cinacalcet hydrochloride) was safe and generally well tolerated.

Hypocalcemia

SENSIPAR 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 (see WARNINGS AND PRECAUTIONS).

Clinical Trial Adverse Drug Reactions

Because clinical trials are conducted under very specific conditions the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse drug reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates.

Secondary Hyperparathyroidism in Patients with Chronic Kidney Disease Receiving Dialysis

In three double-blind placebo-controlled clinical trials, 1126 CKD patients receiving dialysis received study drug (656 SENSIPAR, 470 placebo) for up to six 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 SENSIPAR-treated group) are provided in Table 1. The most frequently reported events in the SENSIPAR group were nausea and vomiting which were generally mild to moderate in severity, brief in duration, and infrequently led to discontinuation of study drug.

Table 1. Adverse Event Incidence (≥ 5%) in Patients Receiving Dialysis

| Preferred Term | Placebo (n = 470) % | Cinacalcet (n = 656) % |
|-----------------------------|---------------------------|------------------------------|
| Nausea | 19 | 31 |
| Vomiting | 15 | 27 |
| Diarrhea | 20 | 21 |
| Headache | 17 | 16 |
| Myalgia | 14 | 15 |
| Pain Abdominal | 14 | 12 |
| Infection Upper Respiratory | 13 | 12 |
| Dizziness | 8 | 10 |
| Dyspnea | 9 | 9 |
| Pain Limb | 10 | 9 |
| Dyspepsia | 8 | 8 |
| Arthralgia | 9 | 7 |
| Fever | 10 | 7 |
| Fatigue | 7 | 7 |
| Hypertension | 5 | 7 |
| Hypotension | 12 | 7 |
| Edema Peripheral | 7 | 7 |
| Asthenia | 4 | 7 |
| Cough | 7 | 6 |
| Pruritus | 7 | 6 |
| Anorexia | 4 | 6 |
| Thrombosis Vascular Access | 7 | 6 |
| Pain Chest, Non-Cardiac | 4 | 6 |
| Access Infection | 4 | 5 |

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

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

12-Month Experience with SENSIPAR in Secondary Hyperparathyroidism

Two hundred sixty-six patients from the two pivotal phase 3 studies continued to receive SENSIPAR 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 two treatment groups, and comparable to those observed in the pivotal phase 3 studies.

Parathyroid Carcinoma and Primary Hyperparathyroidism

One hundred sixty patients with primary HPT or parathyroid carcinoma participated in SENSIPAR clinical trials with exposure for up to 5.5 years.

The safety profile of SENSIPAR in these patient populations is generally consistent with that seen in patients with CKD receiving dialysis. The most frequent adverse drug reactions in these patient populations were nausea and vomiting.

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

Laboratory values

Serum calcium levels should be monitored in patients receiving SENSIPAR (see WARNINGS AND PRECAUTIONS and DOSAGE AND ADMINISTRATION). In the three phase 3 studies in patients with CKD receiving dialysis, 4% of all serum calcium values in patients receiving SENSIPAR were < 1.875 mmol/L, compared with < 1% in the placebo group.

Post-Market Adverse Drug Reactions

There have been reports of diarrhea, myalgia, rash, and hypersensitivity reactions, including angioedema and urticaria, associated with SENSIPAR therapy.

Isolated cases of severe hypersensitivity reactions have been reported.

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

DRUG INTERACTIONS

Drug-Drug Interactions

Effect of SENSIPAR on other drugs

Drugs metabolized by CYP450 2D6: SENSIPAR (cinacalcet hydrochloride) is an inhibitor of CYP2D6. Therefore, dose adjustments of concomitant medications that are predominantly metabolized by CYP2D6 (eg, metoprolol) and particularly those with a narrow therapeutic index (eg, flecainide, vinblastine, thioridazine and most tricyclic antidepressants) may be required.

Desipramine: Concurrent administration of 90 mg SENSIPAR with 50 mg desipramine, a tricyclic antidepressant metabolized primarily by CYP2D6, increased desipramine exposure by approximately 3.6-fold in CYP2D6 extensive metabolizers.

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

Drugs metabolized by other CYP enzymes

Based on *in vitro* data, SENSIPAR is not an inhibitor of other CYP enzymes at concentrations achieved clinically, including CYP1A2, CYP2C9, CYP2C19, and CYP3A4. *In vitro* studies indicate that SENSIPAR is not an inducer of CYP1A2, CYP2C19 and CYP3A4.

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

Warfarin: SENSIPAR does not affect the pharmacokinetics or pharmacodynamics (as measured by prothrombin time and 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.

Effect of other drugs on SENSIPAR

SENSIPAR is metabolized by multiple cytochrome P450 enzymes, primarily CYP3A4 and CYP1A2, which limits the potential for other drugs to increase cinacalcet concentrations.

Ketoconazole: SENSIPAR is metabolized in part by the enzyme CYP3A4. Co-administration of 200 mg bid of ketoconazole, a strong inhibitor of CYP3A4, caused an approximate 2-fold increase in cinacalcet exposure. Dose adjustment of SENSIPAR may be required if a patient initiates or discontinues therapy with a strong CYP3A4 inhibitor (eg, ketoconazole, erythromycin, itraconazole) or inducer (eg, rifampin, phenytoin) of this enzyme.

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

Pantoprazole: Co-administration of pantoprazole (80 mg qd) did not alter the pharmacokinetics of SENSIPAR.

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

Drug-Food Interactions

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

Drug-Herb Interactions

Interactions with herbal products have not been established.

Drug-Laboratory Test Interactions

Interactions with laboratory tests have not been established.

DOSAGE AND ADMINISTRATION

SENSIPAR (cinacalcet hydrochloride) is administered orally. Tablets should be taken whole and should not be divided. Take SENSIPAR with food or shortly after a meal (see DRUG INTERACTIONS).

Secondary Hyperparathyroidism in Patients with Chronic Kidney Disease Receiving Dialysis

The recommended starting oral dose of SENSIPAR is 30 mg once daily. 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 WARNINGS AND PRECAUTIONS). Calcium levels should be corrected for albumin or ionized calcium levels should be measured.

Parathyroid Carcinoma and Primary Hyperparathyroidism

The recommended starting dose of SENSIPAR for adults is 30 mg twice per day.

The dosage of SENSIPAR should be titrated sequentially every 2 to 4 weeks through dosages of 30 mg twice daily, 60 mg twice daily, and 90 mg twice daily to reduce serum calcium levels. For further information on higher dosages (90 mg 3 or 4 times daily) see CLINICAL TRIALS: Parathyroid Carcinoma and Primary HPT for Whom Parathyroidectomy is not a Treatment Option.

Special Populations

Geriatric patients

Age does not alter the pharmacokinetics of SENSIPAR; no dose adjustment is required for geriatric patients.

Patients with renal impairment

Renal impairment does not alter the pharmacokinetics of SENSIPAR; no dosage adjustment is necessary for renal impairment.

Patients with hepatic impairment

Moderate to severe hepatic impairment (Child-Pugh classification) increases SENSIPAR 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 SENSIPAR.

OVERDOSAGE

Doses titrated up to 300 mg once daily have been safely administered to patients receiving dialysis. Overdosage of SENSIPAR (cinacalcet hydrochloride) 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 levels (see WARNINGS AND PRECAUTIONS).

Since SENSIPAR is highly protein bound, hemodialysis is not an effective treatment for overdosage of SENSIPAR.

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|---|
| For management of a suspected drug overdose, contact your regional Poison Control Centre. |
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ACTION AND CLINICAL PHARMACOLOGY

Mechanism of Action

Secondary hyperparathyroidism is a progressive disease, which occurs in patients with chronic kidney disease and manifests as increases in parathyroid hormone levels and derangements in calcium and phosphorous 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. SENSIPAR (cinacalcet hydrochloride) 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.

Pharmacodynamics

Reduction in iPTH levels is correlated with cinacalcet concentration. 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.

Pharmacokinetics

Absorption and Distribution

After oral administration of SENSIPAR, maximum plasma concentration is achieved in approximately 2 to 6 hours. The absolute bioavailability of cinacalcet is approximately 25%. Administration of SENSIPAR 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 dose range of 30 to 180 mg once daily. The pharmacokinetics of cinacalcet does not change over time. The volume of distribution is high (approximately 1000 L), indicating extensive distribution. Cinacalcet is approximately 97% bound to plasma proteins and distributes minimally into red blood cells.

Metabolism and Excretion

Cinacalcet is metabolized by multiple enzymes, primarily CYP3A4 and CYP1A2. The major circulating metabolites are inactive. After administration of a 75 mg radio-labeled dose to healthy volunteers, cinacalcet was rapidly and extensively metabolized 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 feces.

Special Populations and Conditions

Geriatric Patients

The pharmacokinetics of SENSIPAR are similar in patients greater than, or less than, 65 years of age. No dosage adjustment based on age is necessary.

Pediatric Patients

The pharmacokinetics of SENSIPAR have not been studied in patients < 18 years of age (see WARNINGS AND PRECAUTIONS).

Hepatic Insufficiency

Mild hepatic impairment did not notably affect the pharmacokinetics of SENSIPAR. Compared to subjects with normal liver function, average AUC of cinacalcet was approximately 2-fold higher in subjects with moderate impairment and approximately 4-fold higher in subjects with severe impairment (see WARNINGS AND 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 SENSIPAR in patients with mild, moderate, and severe renal insufficiency, and those on hemodialysis or peritoneal dialysis is comparable to that in healthy volunteers. No dosage adjustment based on renal function is necessary.

STORAGE AND STABILITY

Store at 15°C to 30°C

Shelf-life:

- Tablets stored in bottles: 48 months

DOSAGE FORMS, COMPOSITION AND PACKAGING

SENSIPAR (cinacalcet hydrochloride) tablets are composed of cinacalcet hydrochloride, pre-gelatinized starch, microcrystalline cellulose, povidone, crospovidone, colloidal silicon dioxide, magnesium stearate, and water. Tablets are coated with colour (Opadry® II green), clear film-coat (Opadry® clear), and carnauba wax.

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 bottles of 30 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 bottles of 30 tablets.

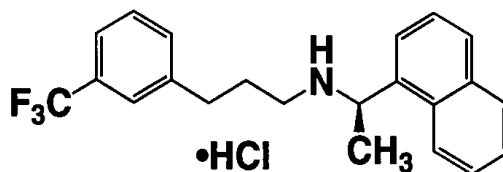
SENSIPAR 90 mg tablets are formulated as light green, film-coated, oval-shaped tablets marked with “AMG” on one side and “90” on the opposite side, packaged in bottles of 30 tablets.

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

Drug Substance

| | |
|---------------------|--|
| Proper name: | cinacalcet hydrochloride |
| Chemical name: | N-[1-(R)-(1-naphthyl)ethyl]-3-[3-(trifluoromethyl)phenyl]-1-aminopropane hydrochloride |
| Molecular weight: | 393.9 g/mol (hydrochloride salt), 357.4 g/mol (free base) |
| Structural formula: | |



Physicochemical properties:

| | |
|--|---|
| Physical Form: | White to off white crystalline powder |
| Solubility: | Slightly soluble in water and in acetonitrile; freely soluble in methanol, ethanol, methylene chloride, and chloroform; very slightly soluble in hexane; sparingly soluble in isopropyl alcohol |
| pH: | 5.1 |
| pKa: | 8.72 |
| Partition coefficient (octanol:water): | 4.79:log P |
| Melting Point: | 178°C to 184°C |

CLINICAL TRIALS

Secondary Hyperparathyroidism in Patients with Chronic Kidney Disease Receiving Dialysis

Three, 6-month, multicenter, randomized, double-blind, placebo-controlled clinical studies were conducted in CKD patients receiving dialysis with uncontrolled secondary HPT (n=1136). The patient population consisted of both recently established and long-standing dialysis patients, with a range of 1 to 359 months. SENSIPAR (cinacalcet hydrochloride) 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 (> 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 hypercalcemia, hypocalcemia, or hyperphosphatemia. Patients continued on their previously prescribed drugs including: calcium channel blockers, ACE inhibitors, beta-blockers, hypoglycemics, and lipid lowering agents. SENSIPAR (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 11 to 27.5 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 29.8 to 1005.2 pmol/L), with mean (SE) baseline iPTH concentrations across the three studies of 78 (2.2) and 72 (2.0) pmol/L for the SENSIPAR and placebo groups, respectively. Significant reductions in iPTH, serum calcium-phosphorus product (Ca x P), calcium, and phosphorus were observed in the SENSIPAR-treated patients compared with placebo-treated patients receiving standard of care, and the results were consistent across the three studies (Table 2). Mean iPTH and Ca x P by treatment group for the overall study population during the 6-month treatment period are presented in Figures 1 and 2.

Table 2. Effects of SENSIPAR 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) | SENSIPAR (n = 205) | Placebo (n = 165) | SENSIPAR (n = 166) | Placebo (n = 101) | SENSIPAR (n = 294) |
| iPTH | | | | | | |
| Baseline (pmol/L) | 69 (2.9) | 67 (2.5) | 67 (2.5) | 69 (3.1) | 88 (5.1) | 90 (4.3) |
| Evaluation Phase (pmol/L) | 74 (3.5) | 41 (2.6) | 73 (3.4) | 38 (3.1) | 90 (5.8) | 56 (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 ≤ 250 pg/mL; 27.5 pmol/L) (%) | 4% | 41%** | 7% | 46%** | 6% | 35%** |
| Patients Achieving ≥ 30% Reduction in iPTH (%) | 11% | 61%** | 12% | 68%** | 10% | 59%** |
| Patients Achieving iPTH ≤ 300 pg/mL; (33 pmol/L) (%) | 9% | 55%** | 11% | 56%** | 9% | 45%** |
| Ca x P | | | | | | |
| Baseline (mmol ² /L ²) | 4.9 (0.09) | 5 (0.09) | 4.9 (0.01) | 4.9 (0.01) | 4.9 (0.11) | 4.8 (0.08) |
| Evaluation Phase (mmol ² /L ²) | 4.8 (0.08) | 4.2 (1.0) | 4.8 (0.01) | 4.0 (0.10) | 4.7 (0.10) | 4.0 (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 (0.025) | 2.45 (0.025) | 2.48 (0.025) | 2.5 (0.025) | 2.5 (0.025) | 2.45 (0.0125) |
| Evaluation Phase (mmol/L) | 2.48 (0.025) | 2.3 (0.025) | 2.48 (0.025) | 2.3 (0.025) | 2.5 (0.025) | 2.28 (0.025) |
| Percent Change | 0.5 (0.3) | -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 (0.032) | 2.03 (0.032) | 2 (0.032) | 1.97 (0.1) | 1.97 (0.032) | 1.97 (0.032) |
| Evaluation Phase (mmol/L) | 1.94 (0.032) | 1.84 (0.032) | 1.94 (0.1) | 1.74 (0.032) | 1.87 (0.032) | 1.78 (0.032) |
| 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

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

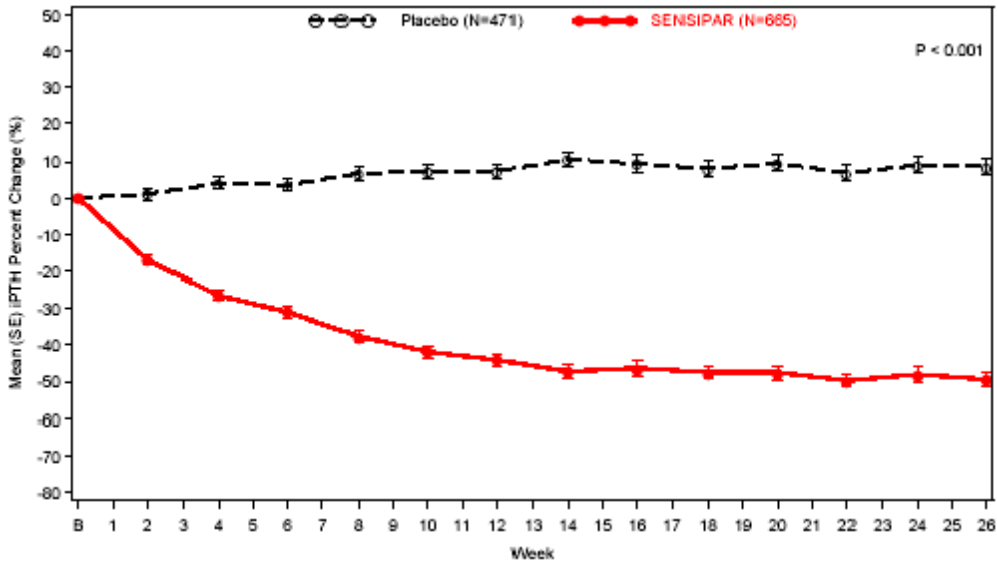
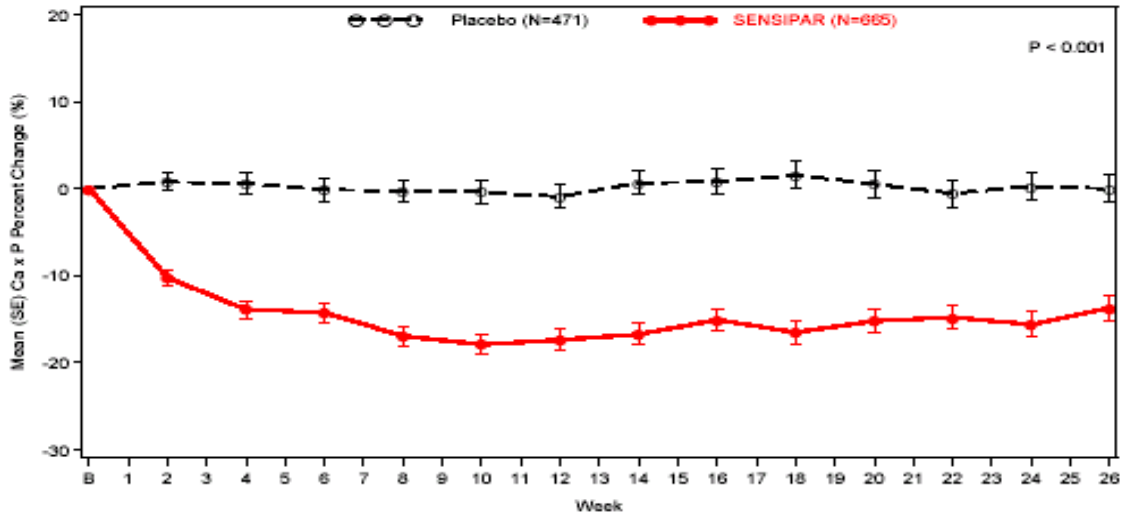


Figure 2. Mean (SE) Percent Change from Baseline in Ca x P (Pooled Phase 3 Studies)



Reductions in iPTH and Ca x P occurred within 2 weeks and were maintained for up to 12 months of treatment. SENSIPAR 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 ≥ 33 to ≤ 55 pmol/L), moderate (iPTH > 55 to 88 pmol/L), or severe (iPTH > 88 pmol/L) secondary HPT achieved a $\geq 30\%$ reduction in iPTH levels. SENSIPAR treatment reduced iPTH and Ca x P regardless of pre-treatment Ca x P levels.

Bone Health

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.

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

Forty-six patients participated in the clinical trial supporting the indications in patients with parathyroid carcinoma (29 patients) and primary HPT who had failed or had contraindications to surgery (17 patients), ie, for whom parathyroidectomy is not a treatment option. Patients were treated for as long as 3 years. The mean duration of follow-up was 328 days for patients with parathyroid carcinoma and 347 days for patients with primary HPT. SENSIPAR was administered at dosages ranging from 30 mg twice daily to 90 mg four times daily (13 patients received the 90 mg four times daily dosage). The primary endpoint of the study was a reduction of serum calcium of ≥ 1 mg/dL (0.25 mmol/L). Eighteen of 29 patients (62%) with parathyroid carcinoma and 15 of 17 patients (88%) with primary HPT achieved a reduction of serum calcium of ≥ 1 mg/dL (0.25 mmol/L). In patients with parathyroid carcinoma, mean serum calcium declined from 14.1 mg/dL at baseline to 12.4 mg/dL (3.5 mmol/L to 3.1 mmol/L) at the end of the titration phase (up to 16 weeks). In patients with primary HPT, serum calcium levels declined from 12.7 mg/dL at baseline to 10.4 mg/dL (3.2 mmol/L to 2.6 mmol/L) at the end of the titration phase (up to 16 weeks).

DETAILED PHARMACOLOGY

Preclinical Studies

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

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PART III: CONSUMER INFORMATION

Sensipar®
cinacalcet hydrochloride tablets

This leaflet is part III of a three-part "Product Monograph" published when SENSIPAR was approved for sale in Canada and is designed specifically for consumers. This leaflet is a summary and will not tell you everything about SENSIPAR. Contact your doctor or pharmacist if you have any questions about the drug.

ABOUT THIS MEDICATION**What the medication is used for:**

SENSIPAR is used:

- to treat secondary hyperparathyroidism (high-per-pear-uh-THIGH-royd-izm) in patients with chronic kidney disease (CKD) receiving dialysis;
- to reduce high levels of calcium in the blood (hypercalcemia) in patients with parathyroid cancer;
- to reduce high levels of calcium in the blood (hypercalcemia) in patients with primary hyperparathyroidism when removal of the gland(s) is not possible.

What it does:

Four small glands located behind the thyroid gland in your neck are called parathyroid glands. They make a hormone called parathyroid hormone (PTH). Normally, PTH makes sure you have just enough calcium and phosphorus in your blood to keep your bones, heart, muscles, nerves and blood vessels working well.

Secondary hyperparathyroidism

When your kidneys are working, PTH keeps your calcium and phosphorus levels normal by moving the right amounts of calcium and phosphorus in and out of your bones. Chronic Kidney Disease (CKD) can cause a condition called secondary hyperparathyroidism.

When your kidneys aren't working properly, the calcium and phosphorus balance in your body is upset, and your parathyroid glands send out too much PTH to your body. This can cause bone disease and also may be a risk factor for heart disease and abnormal calcification of blood vessels and other parts of the body. SENSIPAR treats secondary hyperparathyroidism by lowering PTH. This helps keep calcium and phosphorus within proper levels.

Parathyroid carcinoma/Primary hyperparathyroidism

Primary hyperparathyroidism is caused by an overactive, enlarged parathyroid gland (or glands), occasionally due to cancer of the parathyroid gland. In primary hyperparathyroidism, your

parathyroid glands send out too much PTH to your body and your blood level of calcium becomes high. SENSIPAR lowers PTH by telling your parathyroid glands to stop releasing too much PTH into your blood. This helps lower your blood calcium levels.

When it should not be used:

You should not take SENSIPAR if you are hypersensitive (allergic) to any of the ingredients in the tablet.

What the medicinal ingredient is:

Cinacalcet hydrochloride

What the important nonmedicinal ingredients are:

Pre-gelatinized starch, microcrystalline cellulose, povidone, crospovidone, colloidal silicon dioxide, magnesium stearate, Opadry® II green, clear film-coat (Opadry® clear), and carnauba wax.

What dosage forms it comes in:

SENSIPAR is available as small, green tablets packaged in bottles of 30 tablets. Each tablet contains 30 mg, 60 mg, or 90 mg of cinacalcet hydrochloride.

WARNINGS AND PRECAUTIONS**BEFORE you use SENSIPAR talk to your doctor or pharmacist if:**

1. You have or had seizures. The risk of having a seizure is greater if you have had seizures before.
2. You have or had heart problems (low blood pressure or worsening heart failure).
3. You have or had liver problems.
4. You have lower blood calcium levels.
5. You are pregnant, breastfeeding, or plan to do so.

If you become pregnant while taking SENSIPAR, you are encouraged to enroll in Amgen's Pregnancy Surveillance Program. If you choose to breastfeed while taking SENSIPAR, you are encouraged to enroll in Amgen's Lactation Surveillance Program. You can enroll in these programs by calling 1-866-512-6436.

SENSIPAR is not recommended for patients with CKD not receiving dialysis.

SENSIPAR should not be used in children.

INTERACTIONS WITH THIS MEDICATION

Please tell your doctor or pharmacist if you are taking or have recently taken any other medicines, even those not prescribed.

Drugs that may interact with SENSIPAR include: ketoconazole, erythromycin, itraconazole, metoprolol, flecainide, vinblastine, thioridazine, rifampin, phenytoin, or medicines such as tricyclic antidepressants (desipramine, amitriptyline).

PROPER USE OF THIS MEDICATION

It is important to take SENSIPAR exactly as your doctor has instructed you. Your doctor will tell you how much SENSIPAR to take. Your doctor will order regular blood tests to measure how you are responding to SENSIPAR and may increase or decrease your dose based on your PTH, calcium, and phosphate levels.

Usual Adult Dose:

If you have secondary hyperparathyroidism the usual starting dose for SENSIPAR is one 30 mg tablet once daily.

If you have parathyroid cancer or primary hyperparathyroidism, the usual starting dose for SENSIPAR is one 30 mg tablet twice daily.

SENSIPAR is taken once a day with food or right after a meal. SENSIPAR tablets must be taken whole and are not to be divided. It's best to take SENSIPAR at the same time each day.

Overdose:

Tell your doctor or contact your regional Poison Control Centre immediately if you think you took more than the recommended dose of SENSIPAR.

In case of drug overdose, contact a health care practitioner, hospital emergency department or regional Poison Control Centre immediately, even if there are no symptoms.

Missed Dose:

Do not take a double dose to make up for forgotten daily doses. If you have forgotten a dose of SENSIPAR, you should take your next daily dose as normal.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

All medicines have side effects.

If you have any of the following side effects while taking SENSIPAR, you should tell your doctor right away.

- Nausea and vomiting. These are the most common side effects seen with SENSIPAR treatment. This may make it difficult to take your medicines.
- Diarrhea and muscle pain. These side effects also are commonly reported.
- Rash or hypersensitivity (allergic reactions). Cases of rash have been commonly reported, while cases of hypersensitivity (allergic reactions) have been uncommonly reported.
- Hives (urticaria) is very rarely reported.
- Swelling of the face, lips, mouth, tongue or throat which may cause difficulty in swallowing or breathing (angioedema) is also very rarely reported.

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM

| Symptom/effect | | Talk with your doctor or pharmacist | | Stop taking drug and call your doctor or pharmacist |
|----------------|--|-------------------------------------|--------------|---|
| | | Only if severe | In all cases | |
| Common | Diarrhea | √ | | |
| | Hypocalcemia/ low calcium level (symptoms include: numbness/ tingling around mouth, muscle aches/cramps, seizures) | | √ | |
| Uncommon | Seizures | | √ | √ |
| | Hypersensitivity (allergic reactions) | | √ | √ |
| Very Rare | Low blood pressure or worsening heart failure | | √ | √ |
| | Swelling of the face, lips, mouth, tongue or throat (angioedema) | | √ | √ |
| | Severe hypersensitivity (allergic reactions) | | √ | √ |

This is not a complete list of side effects. For any unexpected effects while taking SENSIPAR, contact your doctor or pharmacist.

HOW TO STORE IT

Store SENSIPAR tablets at room temperature (15°C to 30°C).

REPORTING SUSPECTED SIDE EFFECTS

You can report any suspected adverse reactions associated with the use of health products to the Canada Vigilance Program by one of the following 3 ways:

- Report online at www.healthcanada.gc.ca/medeffect
- Call toll-free at 1-866-234-2345
- Complete a Canada Vigilance Reporting Form and:
 - Fax toll-free to 1-866-678-6789, or
 - Mail to: Canada Vigilance Program
Health Canada
Postal Locator 0701D
Ottawa, Ontario K1A 0K9

Postage paid labels, Canada Vigilance Reporting Form and the adverse reaction reporting guidelines are available on the MedEffect® Canada Web site at www.healthcanada.gc.ca/medeffect.

Note: *Should you require information related to the management of side effects, contact your health professional. The Canada Vigilance Program does not provide medical advice.*

MORE INFORMATION

This document plus the full product monograph, prepared for health professionals can be obtained by contacting the sponsor, Amgen Canada Inc., at: 1-866-502-6436

This leaflet was prepared by Amgen Canada Inc.

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