

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use SENSIPAR safely and effectively. See full prescribing information for SENSIPAR.

SENSIPAR® (cinacalcet) tablets, for oral use
Initial US Approval: 2004

RECENT MAJOR CHANGES

Indications and Usage, Primary Hyperparathyroidism (1.3) 11/2014
Warnings and Precautions, Hypocalcemia (5.1) 11/2014

INDICATIONS AND USAGE

Sensipar is a calcium-sensing receptor agonist indicated for:

- Secondary Hyperparathyroidism (HPT) in adult patients with chronic kidney disease (CKD) on dialysis. (1.1)
- Hypercalcemia in adult patients with Parathyroid Carcinoma (PC). (1.2)
- Hypercalcemia in adult patients with primary HPT for whom parathyroidectomy would be indicated on the basis of serum calcium levels, but who are unable to undergo parathyroidectomy. (1.3)

DOSAGE AND ADMINISTRATION

For all indications, Sensipar should be taken with food or shortly after a meal and should always be taken whole and not divided.

- Secondary HPT in patients with CKD on dialysis (2.1):
 - Starting dose is 30 mg once daily.
 - Titrate dose no more frequently than every 2 to 4 weeks through sequential doses of 30, 60, 90, 120, and 180 mg once daily as necessary to achieve targeted intact parathyroid hormone (iPTH) levels.
 - iPTH levels should be measured no earlier than 12 hours after most recent dose.
- Hypercalcemia in patients with PC or hypercalcemia in patients with primary HPT (2.2):
 - Starting dose is 30 mg twice daily.
 - Titrate dose every 2 to 4 weeks through sequential doses of 30 mg twice daily, 60 mg twice daily, 90 mg twice daily, and 90 mg three or four times daily as necessary to normalize serum calcium levels.

DOSAGE FORMS AND STRENGTHS

Tablets: 30, 60, and 90 mg tablets (3)

CONTRAINDICATIONS

Sensipar treatment initiation is contraindicated if serum calcium is less than the lower limit of the normal range. (4, 5.1)

WARNINGS AND PRECAUTIONS

- *Hypocalcemia*: Life threatening events and fatal outcomes were reported. Hypocalcemia can prolong QT interval, lower the threshold for seizures, and cause hypotension, worsening heart failure, and/or arrhythmia. Monitor serum calcium carefully for the occurrence of hypocalcemia during treatment (2.3, 5.1)
- *Adynamic Bone Disease*: May develop if iPTH levels are suppressed below 100 pg/mL. (5.2)
- *Hepatic Impairment*: Cinacalcet exposure (i.e. area under the plasma concentration time curve) is increased in patients with moderate and severe hepatic impairment. Patients should be closely monitored for serum calcium, serum phosphorus, and iPTH levels throughout treatment. (5.3, 8.7)

ADVERSE REACTIONS

The most common adverse reactions (i.e., ≥ 25%) associated with Sensipar were nausea and vomiting. (6.1, 6.2)

To report SUSPECTED ADVERSE REACTIONS, contact Amgen Medical Information at 1-800-77-AMGEN (1-800-772-6436) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DRUG INTERACTIONS

- Co-administration with a strong CYP3A4 inhibitor may increase serum levels of cinacalcet. Dose adjustment and monitoring of iPTH serum phosphorous and serum calcium may be required. (7.1)
- Cinacalcet is a strong inhibitor of CYP2D6. Dose adjustments may be required for concomitant medications that are predominantly metabolized by CYP2D6. (7.2)

USE IN SPECIFIC POPULATIONS

- *Pregnancy*: Sensipar should only be used if the potential benefit justifies the potential risk to the fetus. Pregnancy registry available. (8.1)
- *Pediatric Use*: A fatal outcome was reported in a pediatric clinical trial patient with severe hypocalcemia. Sensipar is not indicated for use in pediatric patients (8.4).

See 17 for PATIENT COUNSELING INFORMATION

Revised: 11/2014

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FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

1.1 Secondary Hyperparathyroidism

Sensipar is indicated for the treatment of secondary hyperparathyroidism (HPT) in adult patients with chronic kidney disease (CKD) on dialysis [see *Clinical Studies (14.1)*].

Limitations of Use:

Sensipar is not indicated for use in adult patients with CKD who are not on dialysis because of an increased risk of hypocalcemia [see *Warnings and Precautions (5.1)*].

1.2 Parathyroid Carcinoma

Sensipar is indicated for the treatment of hypercalcemia in adult patients with Parathyroid Carcinoma [see *Clinical Studies (14.2)*].

1.3 Primary Hyperparathyroidism

Sensipar is indicated for the treatment of hypercalcemia in adult patients with primary HPT for whom parathyroidectomy would be indicated on the basis of serum calcium levels, but who are unable to undergo parathyroidectomy [see *Clinical Studies (14.3)*].

2 DOSAGE AND ADMINISTRATION

Sensipar tablets should be taken whole and should not be divided. Sensipar should be taken with food or shortly after a meal.

Dosage must be individualized.

2.1 Secondary Hyperparathyroidism in Adult Patients with Chronic Kidney Disease on Dialysis

The recommended starting oral dose of Sensipar is 30 mg once daily. Serum calcium and serum phosphorus should be measured within 1 week and intact parathyroid hormone (iPTH) should be measured 1 to 4 weeks after initiation or dose adjustment of Sensipar [see *Dosage and Administration (2.3)*]. Sensipar should be titrated no more frequently than every 2 to 4 weeks through sequential doses of 30, 60, 90, 120, and 180 mg once daily to target iPTH levels of 150 to 300 pg/mL. Serum iPTH levels should be assessed no earlier than 12 hours after dosing with Sensipar.

Sensipar can be used alone or in combination with vitamin D sterols and/or phosphate binders.

During dose titration, serum calcium levels should be monitored frequently and if levels decrease below the normal range, appropriate steps should be taken to increase serum calcium levels, such as by providing supplemental calcium, initiating or increasing the dose of calcium-based phosphate binder, initiating or increasing the dose of vitamin D sterols, or temporarily withholding treatment with Sensipar [see *Dosage and Administration (2.3)* and *Warnings and Precautions (5.1)*].

2.2 Parathyroid Carcinoma and Primary Hyperparathyroidism

The recommended starting oral dose of Sensipar is 30 mg twice daily.

The dose of Sensipar should be titrated every 2 to 4 weeks through sequential doses of 30 mg twice daily, 60 mg twice daily, and 90 mg twice daily, and 90 mg 3 or 4 times daily as necessary to normalize serum calcium levels. Serum calcium should be measured within 1 week after initiation or dose adjustment of Sensipar [see *Dosage and Administration (2.3)* and *Warnings and Precautions (5.1)*].

2.3 Monitoring for Hypocalcemia

Once the maintenance dose has been established, serum calcium should be measured approximately monthly for patients with secondary hyperparathyroidism with CKD on dialysis, and every 2 months for patients with parathyroid carcinoma or primary hyperparathyroidism [see *Dosage and Administration (2.1, 2.2)*].

For secondary hyperparathyroidism patients with CKD on dialysis, if serum calcium falls below 8.4 mg/dL but remains above 7.5 mg/dL, or if symptoms of hypocalcemia occur, calcium-containing phosphate binders and/or vitamin D sterols can be used to raise serum calcium. If serum calcium falls below 7.5 mg/dL, or if symptoms of hypocalcemia persist and the dose of vitamin D cannot be increased, withhold administration of Sensipar until serum calcium levels reach 8.0 mg/dL and/or symptoms of hypocalcemia have resolved. Treatment should be reinitiated using the next lowest dose of Sensipar [see *Dosage and Administration (2.1)*].

3 DOSAGE FORMS AND STRENGTHS

Sensipar tablets are formulated as light-green, film-coated, oval-shaped tablets marked with “AMG” on one side and “30” or “60” or “90” on the opposite side of the 30 mg, 60 mg, or 90 mg strengths, respectively.

4 CONTRAINDICATIONS

Sensipar treatment initiation is contraindicated if serum calcium is less than the lower limit of the normal range [see *Warnings and Precautions (5.1)*].

5 WARNINGS AND PRECAUTIONS

5.1 Hypocalcemia

Sensipar lowers serum calcium and, therefore, patients should be carefully monitored for the occurrence of hypocalcemia during treatment [see *Dosage and Administration (2.1, 2.2, 2.3)* and *Adverse Reactions (6.1)*]. Life threatening events and fatal outcomes associated with hypocalcemia have been reported in patients treated with Sensipar, including pediatric patients [see *Pediatric Use (8.4)*]. Potential manifestations of hypocalcemia include paresthesias, myalgias, muscle cramping, tetany, and convulsions.

Sensipar is not indicated for patients with CKD not on dialysis [see *Indications and Usage (1)*]. In patients with secondary HPT and CKD not on dialysis, the long term safety and efficacy of Sensipar have not been established. Clinical studies indicate that Sensipar-treated patients with CKD not on dialysis have an increased risk for hypocalcemia compared with Sensipar-treated patients with CKD on dialysis, which may be due to lower baseline calcium levels. In a phase 3 study of 32 weeks duration and including 404 patients with CKD not on dialysis (302 cinacalcet, 102 placebo), in which the median dose for cinacalcet was 60 mg per day at the completion of the study, 80% of Sensipar-treated patients experienced at least one serum calcium value < 8.4 mg/dL compared with 5% of patients receiving placebo.

QT Prolongation

Decreases in serum calcium can also prolong the QT interval, potentially resulting in ventricular arrhythmia. Cases of QT prolongation and ventricular arrhythmia secondary to hypocalcemia have been reported in patients treated with Sensipar.

Seizures

In clinical studies, seizures (primarily generalized or tonic-clonic) were observed in 1.4% (43/3049) 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.

Hypotension and/or Worsening Heart Failure

In postmarketing safety surveillance, isolated, idiosyncratic cases of hypotension, worsening heart failure, and/or arrhythmia have been reported in patients with impaired cardiac function, in which a causal relationship to Sensipar could not be completely excluded and which may be mediated by reductions in serum calcium levels [see *Adverse Reactions (6.2)*].

5.2 Adynamic Bone Disease

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

5.3 Hepatic Impairment

Cinacalcet exposure, as defined by the Area Under the Plasma Drug Concentration Time Curve ($AUC_{0-\infty}$), is increased by 2.4 and 4.2 fold in patients with moderate and severe hepatic impairment, respectively. These patients should be monitored throughout treatment with Sensipar [see *Use in Specific Populations (8.7)* and *Clinical Pharmacology (12.3)*].

6 ADVERSE REACTIONS

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared with rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.

Secondary Hyperparathyroidism in Patients with Chronic Kidney Disease on Dialysis

In three double-blind, placebo-controlled clinical trials, 1126 patients with CKD on dialysis received study drug (656 Sensipar, 470 placebo) for up to 6 months. The most frequently reported adverse reactions are listed in Table 1.

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.

Table 1. Adverse Reactions with Frequency \geq 5% in Patients on Dialysis in Short-Term Studies for up to 6 Months

	Placebo (n = 470)	Sensipar (n = 656)
Event*:	(%)	(%)
Nausea	19	31
Vomiting	15	27
Diarrhea	20	21
Myalgia	14	15
Dizziness	8	10
Hypertension	5	7
Asthenia	4	7

Anorexia	4	6
Pain Chest, Non-Cardiac	4	6
Dialysis Access Site Infection	4	5

*Included are events that were reported at a greater incidence in the Sensipar group than in the placebo group.

In a randomized, 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 (mean duration of treatment was 21 months in the Sensipar group), the most frequently reported adverse reactions (incidence of $\geq 5\%$ in the Sensipar group and a difference $\geq 1\%$ compared to placebo) are listed in Table 2.

Table 2. Frequency of Adverse Reactions in Dialysis Patients Treated for up to 64 Months in a Long-Term Study¹

	Placebo (N=1923)	Sensipar (N=1938)
	3699 subject-years	4044 subject-years
Percent of subjects reporting Adverse Reactions (%)	90.9	93.2
Nausea	15.5	29.1
Vomiting	13.7	25.6
Diarrhea	18.7	20.5
Dyspnea	11.5	13.4
Cough	9.8	11.7
Hypotension	10.5	11.6
Headache	9.6	11.5
Hypocalcaemia	1.4	11.2
Muscle spasms	9.2	11.1
Abdominal pain	9.6	10.9
Abdominal pain upper	6.3	8.2
Hyperkalemia	6.1	8.1
Upper respiratory tract infection	6.3	7.6
Dyspepsia	4.6	7.4
Dizziness	4.7	7.3
Decreased appetite	3.5	5.9
Asthenia	3.8	5.4
Constipation	3.8	5.0

¹ Adverse reactions that occurred in $\geq 5\%$ Frequency in the Sensipar group and a difference $\geq 1\%$ compared to the placebo group (Safety Analysis Set)

Crude incidence rate = $100 * \text{Total number of subjects with event} / N$

N=Number of subjects receiving at least one dose of study drug

Additional adverse reaction rates from the long-term, randomized, double-blind placebo controlled study for Sensipar versus placebo are as follows: seizure (2.5%, 1.6%), rash (2.2%, 1.9%), hypersensitivity reactions (9.4%, 8.3%).

Parathyroid Carcinoma and Primary Hyperparathyroidism

The safety profile of Sensipar in these patient populations is generally consistent with that seen in patients with CKD on dialysis. Forty six patients were treated with Sensipar in a single arm study, 29 with Parathyroid Carcinoma and 17 with intractable pHPT. Nine (20%) of the patients withdrew from the study due to adverse events. The most frequent adverse reactions and the most frequent cause of withdrawal in these patient populations were nausea and vomiting. Severe or prolonged cases of nausea and vomiting can lead to

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