PRIOR AUTHORIZATION POLICY

POLICY: Sensipar® (cinacalcet tablets – Amgen, Inc.)

APPROVAL DATE: 02/06/2019

OVERVIEW

Sensipar is a calcium-sensing receptor agonist (calcimimetic) indicated for the treatment of secondary hyperparathyroidism (HPT) in adult patients with chronic kidney disease (CKD) on dialysis.[1] It is also indicated for the treatment of hypercalcemia in adult patients with parathyroid carcinoma and 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.

Secondary HPT is a frequent complication of CKD caused by a reduction in circulating calcitriol levels and disturbances in calcium and phosphorous metabolism.[2] This leads to increases in the parathyroid hormone (PTH) levels, which then leads to osteoclastic activity resulting in bone resorption and marrow fibrosis.

Parathyroid carcinoma is a rare malignant cancer and an uncommon cause of primary HPT.[3] It is associated with higher serum calcium and PTH levels than primary HPT due to benign adenoma. The primary cause of morbidity in patients with parathyroid carcinoma is due to complications of hypercalcemia (e.g., cardiac arrhythmias, renal failure). Surgical resection of the malignancy may relieve symptoms and reduce serum calcium levels. Medical therapy with Sensipar and intravenous bisphosphonates are useful adjunct therapies to control hypercalcemia.

Guidelines

The Kidney Disease: Improving Global Outcomes (KDIGO) clinical practice guidelines (2017) for the treatment of CKD-mineral bone disorder (MBD) recommends the use of Sensipar, calcitriol, vitamin D analogues, or a combination of these agents in CKD stage 5D (dialysis) patients with elevated or rising PTH.[4] The guidelines recognize that there are no randomized controlled trials showing that treatment to achieve a specific PTH level results in improved outcomes. There is no established "cause and effect" relationship between the measured biochemical variables and observed outcomes. Therefore, the guidelines recommend interpreting changes in PTH in conjunction with calcium and phosphorous levels to guide therapeutic decisions. Overall, in patients with CKD stage 5D, the KDIGO guidelines suggest maintaining intact PTH (iPTH) levels in the range of approximately two to nine times the upper limit of normal (ULN) for the assay. Any marked changes in PTH levels in either direction within this range should prompt an initiation or change in therapy to avoid progression to iPTH levels outside of this range.

POLICY STATEMENT
Prior authorization is recommended for prescription benefit coverage of Sensipar. Because of the specialized skills required for evaluation and diagnosis of patients treated with Sensipar, as well as the monitoring required for adverse events and long-term efficacy, approval requires Sensipar to be prescribed by, or in consultation with, a physician who specializes in the condition being treated. All approvals are provided for 1 year in duration unless otherwise noted below.

Automation: When available, the ICD-9/ICD-10 codes for Malignant Neoplasm of Parathyroid Gland (ICD-9: 194.1* and ICD-10: C75.0*) AND "oncologist or endocrinologist" will be used as part of automation to allow approval of the requested medication.

RECOMMENDED AUTHORIZATION CRITERIA
Coverage of Sensipar is recommended in those who meet the following criteria:

FDA-Approved Indications

1. **Secondary Hyperparathyroidism.** Approve for 1 year if the patient meets the following criteria (A, B, and C):
   A) Patient has chronic kidney disease (CKD) and is on dialysis; AND
   B) The intact parathyroid hormone (iPTH) level is at least two times the upper limit of normal (ULN) as defined by the laboratory reference value measured on two separate occasions; AND
   C) Sensipar is prescribed by, or in consultation with, a nephrologist or endocrinologist.

   Sensipar is indicated for the treatment of secondary hyperparathyroidism in patients with CKD on dialysis.[1] The KDIGO guidelines recommend that if the iPTH levels fall below two times the ULN for the assay, the use of calcimimetics, calcitriol, or vitamin D analogues should be reduced or discontinued.[4] The guidelines also suggest maintaining iPTH levels in the two to nine times ULN range; initiation or change in therapy is suggested if there are marked changes in either direction of this range.

2. **Hypercalcemia due to Parathyroid Carcinoma.** Approve for 1 year if prescribed by, or in consultation with, an oncologist or endocrinologist.

   Sensipar is indicated for the treatment of hypercalcemia in patients with parathyroid carcinoma.[1]

3. **Hypercalcemia in Patients with Primary Hyperparathyroidism.** Approve for 1 year if the patient meets both of the following criteria (A and B):
   A) Patient has failed or is unable to undergo parathyroidectomy due to a contraindication; AND
   B) Sensipar is prescribed by, or in consultation with, a nephrologist or endocrinologist.

   Sensipar is indicated for the treatment of hypercalcemia in patients with primary hyperparathyroidism who are unable to undergo parathyroidectomy.[1]

Other Uses with Supportive Evidence

4. **Hyperparathyroidism in Post-Renal Transplant Patients.** Approve Sensipar for the duration noted if the patient meets ONE of the following conditions (A or B):

A) Initial Therapy. Approve for 1 year if the patient meets ALL of the following criteria (i, ii, iii, and iv)
- **i.** Patient is post-renal transplant for > 3 months and has hypercalcemia (serum calcium above the normal range as defined by the laboratory reference value); AND
- **ii.** Patient has tried vitamin D analogues to treat secondary hyperparathyroidism and has failed or is limited by hypercalcemia; AND
- **iii.** The intact parathyroid hormone (iPTH) level is above the normal range as defined by the laboratory reference value; AND
- **iv.** Sensipar is prescribed by, or in consultation with, a transplant physician, nephrologist, or endocrinologist.

B) Patient is Currently Receiving Sensipar Approve for 1 year if the patient meets ALL of the following criteria (i, ii, and iii):
- **i.** Patient has hypercalcemia (serum calcium above the normal range as defined by the laboratory reference value); AND
- **ii.** The intact parathyroid hormone (iPTH) level is above the normal range as defined by the laboratory reference value; AND
- **iii.** Sensipar is prescribed by, or in consultation with, a transplant physician, nephrologist, or endocrinologist.

The KDIGO clinical practice guidelines (2017) for the treatment of CKD-mineral bone disorder (MBD) note that although Sensipar is not approved for the treatment of hyperparathyroidism in kidney transplant recipients, it is used in these patients, especially those with significant hypercalcemia.[4]

In one study with 14 renal transplant patients with persistent HPT, Sensipar 30 mg once daily (QD) for 3 months significantly reduced serum calcium concentration.[5] The serum PTH level and phosphate level did not change in response to Sensipar. In another small, prospective study, 11 post-renal transplant patients (transplant > 2 years) with persistent HPT received Sensipar (30 mg QD mostly) to maintain serum calcium levels within a pre-defined range for 10 weeks.[6] Patients had normal serum levels of 1,25-dihydroxyvitamin D and 25-hydroxyvitamin D. After Week 2, total serum calcium and ionized calcium remained within normal limits until Week 10. Serum iPTH levels decreased by about 18% during the study and serum phosphate levels increased.

A 2012 meta-analysis reviewed 21 studies with 411 kidney transplant patients treated with Sensipar for HPT.[7] The treatment duration varied from 3 to 24 months, with a wide range of doses. None of the trials included in the analysis were randomized controlled trials. The meta-analysis concluded that Sensipar was an effective treatment option for post-renal transplant patients with HPT. Sensipar decreased calcium levels by 1.14 mg/dL, increased phosphorous levels by 0.46 mg/dL and decreased iPTH levels by 102 pg/mL. All of these results were statistically significant. Another retrospective observational study evaluated Sensipar use for persistent HPT in 23 kidney transplant patients after long-term follow-up (median 53 months).[8] Patients had been persistently hypercalcemic for > 12 months after transplant and before starting Sensipar treatment. Three months after Sensipar initiation, there was a significant reduction in calcium and an increase in phosphorus levels toward normal levels that were maintained throughout the follow-up period. There were no changes in renal function. A review article also outlined a treatment algorithm for the management of hypercalcemia with Sensipar in post-renal transplant patients based on the available published data and clinical experience.[9]

A 2014 randomized, double-blind, placebo-controlled, multicenter, Phase III study (n = 114) compared Sensipar with placebo for the treatment of hypercalcemia in patients with persistent HPT following

renal transplant.[10] Eligible patients were between 9 weeks and 24 months post-transplant, had stable renal function, a corrected serum Ca > 10.5 mg/dL and an iPTH > 100 pg/mL. Between 22 and 26 weeks of Sensipar therapy (dosing within current labeling guidelines), 78.9% of patients in the Sensipar group achieved the primary endpoint, a mean corrected total serum Ca level of < 10.2 mg/dL, compared with only 3.5% of patients receiving placebo (P < 0.001). Therapy with Sensipar did not significantly improve bone mineral density at the femoral neck when measured at Week 52 (Sensipar vs. placebo, P = 0.266). However, Sensipar significantly increased phosphorous levels and decreased iPTH levels at Week 26.

A multicenter, observational, retrospective study (n = 193) found that treatment with Sensipar for 6 months reduced calcium and iPTH levels, as well as increased phosphorous levels, in patients with secondary HPT following renal transplant (median 20 months post-transplant).[11] The results were maintained for up to 3 years and no changes in renal function were observed.

A recent prospective, open-label, self-controlled study evaluated the long-term effects of Sensipar on calcium and phosphate homeostasis in kidney transplant recipients with hypercalcemic hyperparathyroidism (n = 44).[12] The study was a long-term follow-up to a previously reported study that evaluated the effect of six-week Sensipar treatment on calcium homeostasis. The biochemical parameters of mineral and bone metabolism were measured pre- and post-treatment; therefore, each patient served as his or her own control. Sensipar 30 mg QD was initiated after a median period of 1.8 (0.8 to 4.7) years after transplantation; one patient started on Sensipar 60 mg due to severe hypercalcemia for almost half a year. Eight patients received active vitamin D analogues in addition to Sensipar. The median treatment period with Sensipar was 6.2 (3.9 to 7.6) years. During the observation period, seven patients returned to dialysis because of graft loss due to chronic transplant failure. The study data showed that Sensipar effectively controlled hypercalcemia and significantly lowered the iPTH levels. The mean difference between pre- and post-treatment medians of total serum calcium was -0.30 mmol/L (-0.34 to -0.26 mmol/L; P < 0.001). The mean difference between pre- and post-treatment median values of intact PTH was -79 pg/mL (-103 to -55 pg/mL; P < 0.001); the difference between the pre- and post-treatment intact PTH values remained significant even after excluding the eight patients who received active vitamin D analogues. Levels of osteocalcin and bone alkaline phosphatase levels decreased over time (P < 0.05), whereas C-telopeptide levels remained stable.

A recent retrospective observational study evaluated the efficacy of Sensipar in patients post-kidney transplant with persistent hypercalcemia (n = 30).[13] Sensipar 30 mg/day was initiated at different time points after kidney transplant; the mean time was 43 ± 37 months (range, 4.7 to 157) after kidney transplant. The dose of Sensipar was adjusted based on serum calcium levels. The graft function in all of the patients was stable during the observation time. The mean treatment time was 17 ± 22 months. Treatment with Sensipar resulted in a significant decrease in serum calcium levels (mean 9.9 ± 0.7 mg/dL, range 8.7 to 11.7; P < 0.001), a decrease in intact PTH levels (308 ± 199 pg/dL, range 117 to 1,000; P < 0.001), and an increase in phosphate levels (mean 2.8 ± 0.6 mg/dL, range 1.7 to 4.0; P < 0.001).

A 2017 study involved 47 post-renal transplant patients who received Sensipar treatment for secondary HPT and hypercalcemia.[14] Sensipar treatment was initiated at a median of 25 months after renal transplant, with 12 patients initiating therapy during the early posttransplant period (up to 30 days after surgery). The dose of Sensipar was adjusted based on serum calcium and iPTH levels. The mean follow-up time was approximately 46 months (range of 12 to 60 months). Serum calcium levels were

reduced; Sensipar induced calcium reduction was sustained during the entire follow-up. Serum iPTH levels were also reduced during the study. The authors concluded that long-term treatment with Sensipar is effective in correcting hypercalcemia and maintaining serum calcium within normal levels. Sensipar was also effective in correcting hypophosphatemia. The effect of Sensipar on serum iPTH levels was modest. Treatment with Sensipar did not significantly affect graft function.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Sensipar has not been shown to be effective, or there are limited or preliminary data or potential safety concerns that are not supportive of general approval for the following conditions. Rationale for non-coverage for these specific conditions is provided below. (Note: This is not an exhaustive list of Conditions Not Recommended for Approval.)

1. **Patients with Primary Hyperparathyroidism eligible for Parathyroidectomy.** Parathyroidectomy is the primary treatment for primary hyperparathyroidism.

2. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

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