EXPRESS SCRIPTS®

PRIOR AUTHORIZATION POLICY

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

TAC APPROVAL DATE: 01/07/2015

LAY CRITERIA EFFECTIVE DATE: 01/12/2015

OVERVIEW

Sensipar is a calcium-sensing receptor agonist (calcimimetic) indicated for the treatment of secondary hyperparathyroidism (HPT) in patients with chronic kidney disease (CKD) on dialysis.[1] It is also indicated for the treatment of hypercalcemia in patients with parathyroid carcinoma and for the treatment of severe hypercalcemia in 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 (2009) for the treatment of CKD-mineral bone disorder (MBD) recommends the use of Sensipar, calcitriol, vitamin D analogs, 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 levels results in improved outcomes. There is no established "cause and effect" relationship between the measured biochemical variables and observed outcomes. So the guidelines recommend interpreting changes in PTH together 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 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: None.

RECOMMENDED AUTHORIZATION CRITERIA

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

Food and Drug Administration (FDA)-Approved Indications

1. **Secondary Hyperparathyroidism.** Approve if 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 values 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 the two times the ULN for the assay, calcimimetics, calcitriol, or vitamin D analogs be reduced or stopped.[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 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. **Severe Hypercalcemia in Patients with Primary Hyperparathyroidism.** Approve if 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 severe 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 if patient meets all of the following criteria (a, b, c, and d):
   - **a)** Patient is post renal transplant for > 3 months and has hypercalcemia (serum calcium above the normal range as defined by the laboratory reference values); AND
   - **b)** Patient has tried vitamin D analogues to treat secondary hyperparathyroidism and has failed or is limited by hypercalcemia; AND
   - **c)** The intact parathyroid hormone (iPTH) level is above the normal range as defined by the laboratory reference values; AND

d) Sensipar is prescribed by or in consultation with a transplant physician, nephrologist or endocrinologist.

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. Another small, prospective study in 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 since it 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 reported on 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 use there was a significant reduction in calcium and 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 outlines 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 of a mean corrected total serum Ca value of < 10.2 mg/dL, compared with only 3.5% of patients receiving placebo ($P < 0.001$). Therapy with Senspiar 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.

An additional 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 found to be maintained for up to 3 years and there were no changes in renal function observed.

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

1. Sensipar® [prescribing information]. Thousand Oaks, CA: Amgen Inc.; November 2014.
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7. Cohen JB, Gordon CE, Balk EM, et al. Cinacalcet for the treatment of hyperparathyroidism in kidney transplant recipients: A systematic review and meta-analysis. *Transplantation.* 2012;94:1041-1048.
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10. Evenepoel P, Cooper K, Holdaas H, et al. A randomized study evaluating cinaclcet to treat hypercalcemia in renal transplant recipients with persistent hyperparathyroidism. *Am J Transplant*. 2014;14:2545-2555.
11. Torregrosa JV, Morales E, Diaz JM, et al. Cinacalcet for hypercalcaemic secondary hyperparathyroidism after renal transplantation: a multicentre, retrospective, 3-year study. *Nephrology*. 2014;19:84-93.

OTHER REFERENCES UTILIZED

- Behets GJ, Spasovski G, Sterline LR, et al. Bone histomorphometry before and after long-term treatment with cinacalcet in dialysis patients with secondary hyperparathyroidism. *Kidney Int.* 2014 October 22. [Epub ahead of print].

HISTORY

Type of Revision	Summary of Changes*	TAC Approval Date	Lay Criteria Effective Date
Annual revision	Reviewed and approved by the Express Scripts TAC.	12/12/2012	---
Annual revision	Reviewed and approved by the Express Scripts TAC.	12/11/2013	---
Annual revision	Requirement for intact parathyroid hormone level to be below nine times the upper limit of normal removed from policy.	01/07/2015	01/12/2015

TAC – Therapeutic Assessment Committee; * For a further summary of criteria changes, refer to respective TAC minutes available at: http://esidepartments/sites/Dep043/Committees/TAC/Forms/AllItems.aspx.