This program applies to FlexRx Open, FlexRx Closed, GenRx Open, GenRx Closed, Medicaid, Health Insurance Marketplace, FocusRx and KeyRx formularies.

This is a FlexRx standard and GenRx standard prior authorization program.

The BCBS MN Step Therapy Supplement also applies to this program for all Commercial/HIM lines of business.

**FDA APPROVED INDICATIONS AND DOSAGE**

<table>
<thead>
<tr>
<th>Agent</th>
<th>Indication</th>
<th>Dosing and Administration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sensipar®</td>
<td>• Secondary Hyperparathyroidism (HPT) in adult patients with chronic kidney disease (CKD) on dialysis*</td>
<td></td>
</tr>
<tr>
<td>(cinacalcet)</td>
<td>• Hypercalcemia in adult patients with Parathyroid Carcinoma</td>
<td>Secondary HPT: initial dose 30mg orally once daily; titrate no more frequently than every 2-4 weeks sequential doses if 30, 60, 90, 120, and 180 mg once daily to target iPTH level of 150 to 300 pg/mL</td>
</tr>
<tr>
<td>tablets</td>
<td>• 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</td>
<td>Hypercalcemia with parathyroid carcinoma or primary HPT: initial dose 30mg orally twice daily; titrate every 2-4 weeks with sequential doses of 30mg twice daily, 60 mg twice daily, and 90 mg twice daily, and 90mg 3 or 4 times as necessary to normalize serum calcium level</td>
</tr>
</tbody>
</table>

*Limitations of Use: Sensipar is not indicated for use in patients with CKD who are not on dialysis

**CLINICAL RATIONALE**

**Secondary Hyperparathyroidism (HPT) in patients with Chronic Kidney Disease (CKD)**

Chronic kidney disease (CKD) is commonly associated with disorders of mineral and bone metabolism, manifested by either one or a combination of the following three components:

- Abnormalities of calcium, phosphorus, parathyroid hormone (PTH), fibroblast growth factor 23 (FGF23), and vitamin D metabolism
- Abnormalities in bone turnover, mineralization, volume linear growth, or strength
- Extraskeletal calcification

Secondary hyperparathyroidism (HPT) is a frequent complication in patients with chronic kidney disease (CKD), and its prevalence increases as kidney function declines (particularly to estimated glomerular filtration rate <60 mL/min/1.73 m²). It is characterized by elevated phosphorus levels, decreased free ionized calcium concentration, increased fibroblast growth factor 23 (FGF23) concentration, and vitamin D deficiency. The implications of untreated secondary HPT include renal bone disease, weakness, fractures, bone and muscle pain, as well as avascular necrosis.²
Treatment goals for HPT in dialysis patients include serum phosphate maintained between 3.5 and 5.5 mg/dL, serum corrected total calcium maintained <9.5 mg/dL, and parathyroid hormone (PTH) maintained less than 2 to 9 times the upper limit for the PTH assay. Persistently high phosphate (i.e. >5.5 mg/dL) should be treated before treating high PTH. Specific therapies for high PTH may increase the serum phosphate. Management of hyperphosphatemia involves dietary phosphate restriction to 900 mg daily and use of a combination of phosphate binders to block absorption of ingested phosphates. Phosphate binders are categorized as calcium containing and non-calcium containing. Calcium-containing binders include calcium carbonate and calcium acetate. Major non-calcium-containing binders include sevelamer and lanthanum. All are effective in lowering phosphate. Treatment options for increased PTH include calcimimetics, calcitriol, or synthetic vitamin D analogs. Combination of calcimimetics with calcitriol or synthetic vitamin D analogs may also be used. Synthetic vitamin D analogs (paricalcitol, doxercalciferol) and calcitriol are not recommended unless serum phosphate concentration is <5.5 mg/dL (<1.78 mmol/L) and serum calcium is <9.5 mg/dL (<2.37 mmol/L). Synthetic vitamin D analogs may be associated with lower risk of hypercalcemia and hyperphosphatemia compared with calcitriol. However, all vitamin D derivatives have the potential of increasing serum calcium and phosphate when administered at high doses. Calcimimetics [Sensipar (cinacalcet), Parsabiv (etelcalcetide)] increase the sensitivity of the parathyroid calcium-sensing receptor (CaSR) to calcium. CaSR regulates the parathyroid gland hyperplasia and PTH secretion. Calcimimetics reduce the plasma PTH concentration and decrease calcium and phosphate levels.

Recommended treatment approach to lower PTH depends on patients’ phosphate and calcium levels. For patients with phosphate <5.5 mg/dL (<1.78 mmol/L) and calcium <9.5 mg/dL (<2.38 mmol/L), calcitriol or other vitamin D analogs are recommended. Cinacalcet should not be used if serum calcium level is <8.4 mg/dL (2.1 mmol/L) since it lowers calcium concentration. Calcitriol is recommended in these patients. If patient has inadequate reduction of PTH on calcitriol and calcium is >8.4 mg/dL, cinacalcet is added. For patients with serum phosphate ≥5.5 mg/dL or serum calcium level ≥9.5 mg/dL and persistently elevated PTH, despite maximal therapies to reduce phosphate, calcimimetics is recommended over calcitriol or synthetic vitamin D analogs. Calcitriol and synthetic vitamin D analogs raise serum calcium and phosphate levels. During treatment with cinacalcet, serum levels of corrected total calcium should be maintained between 8.4 and 9.5 mg/dL (2.10 to 2.37 mmol/L).

Parathyroid Carcinoma
Parathyroid carcinoma has been estimated to cause hyperparathyroidism (HPT). Parathyroid carcinoma is suspected in patients with primary hyperparathyroidism who present with parathyroid crisis (or marked hypercalcemia and very high parathyroid hormone (PTH) concentrations. Two criteria with more definitive diagnosis are local invasion of contiguous structures or lymph node or distant metastases. Clinical manifestations of parathyroid carcinoma could include hypercalcemia [14.6-15.9 mg/dL (3.7-4.0 mmol/L)], hyperparathyroidism (5-10 fold higher than the upper limit of normal), parathyroid crisis, neck mass, bone disease, renal disease, and pancreatitis. Up to one-third of patients have lymph node metastases at initial presentation, and one-third have distant metastases, usually to liver and bone. Hypercalcemia is the principal cause of morbidity and mortality from parathyroid carcinoma. Initial treatment of hypercalcemia in patients with parathyroid carcinoma is similar to management in patients with hypercalcemia due to other causes and includes hydration with infusion of saline to restore fluid volume and intravenous bisphosphonates.

Treatment of hypercalcemia should be aimed both at lowering the serum calcium concentration and, if possible, treating the underlying disease. Effective treatments reduce serum calcium by inhibiting bone resorption, increasing urinary calcium excretion, or decreasing intestinal
calcium absorption. Patients with asymptomatic or mildly symptomatic (e.g. constipation) hypercalcemia (calcium <12 mg/dL [3 mmol/L]) do not require immediate treatment. Similarly, a serum calcium of 12 to 14 mg/dL (3 to 3.5 mmol/L) may be well tolerated chronically and may not require immediate treatment. However, an acute rise to these concentrations may cause marked changes in sensorium, which requires more aggressive measures. In addition, patients with severe hypercalcemia [serum calcium concentration [14 mg/dL (3.5 mmol/L)] require treatment, regardless of symptoms. Treatment of severe hypercalcemia consists of three-pronged approach:

- Volume expansion with isotonic saline. In the absence of renal or heart failure, loop diuretic therapy to directly increase calcium excretion is not recommended
- Administration of calcitonin, Typically, calcitonin is administered along with a bisphosphonate in patients with calcium > 14 mg/dL who are also symptomatic
- Concurrent administration of zoledronic acid or pamidronate; zoledronic acid is superior to pamidronate in reversing hypercalcemia related to malignancy

For patients with hypercalcemia that is refractory to bisphosphonates, the addition or substitution of a calcimimetic drug maybe beneficial.

**Primary Hyperparathyroidism**

Primary hyperparathyroidism (HPT) is a common disorder that arises from autonomous overproduction of PTH by abnormal parathyroid glands. It is characterized by the persistent elevation of total serum calcium levels with corresponding elevated or inappropriately normal PTH levels. Primary HPT is often recognized as a result of biochemical screening or as part of an evaluation for decreased bone mass. Patients with symptomatic primary HPT (nephrolithiasis, symptomatic hypercalcemia) should have parathyroid surgery. Surgery may not be mandatory in patients with symptomatic primary HPT. Most asymptomatic patients do not have progression of disease, as defined by worsening hypercalcemia, hypercalciuria, bone disease, and/or nephrolithiasis. The primary goal is to identify the asymptomatic patients at risk for disease progression, as well as those who have features of the disease that may improve following parathyroidectomy.

Parathyroidectomy is the definitive treatment for primary HPT and is the preferred treatment for all patients with symptomatic primary HPT. Asymptomatic patients need to meet one of the following to be considered parathyroidectomy candidates:

- Serum calcium concentration of 1.0 mg/dL (0.25 mmol/L) or more above the upper limit of normal
- Skeletal indications – bone density at the hip, lumbar spine, or distal radius that is more than 2.5 standard deviations below the peak bone mass or previous asymptomatic fracture (by radiograph, computed tomography (CT), magnetic resonance imaging (MRI), or vertebral fracture assessment)
- Renal indications – estimated glomerular filtration rate (eGFR) <60 mL/min; 24-hour urinary calcium >400 mg/day (>10 mmol/day); nephrolithiasis or nephrocalcinosis by radiograph, ultrasound or CT
- Age less than 50 years

If surgery is not recommended, then long-term monitoring for worsening hypercalcemia, renal impairment, and bone loss is recommended. The development of any of these findings indicates disease progression and the need for surgical intervention. For patients who are not surgical candidates, the following is recommended:

- For patients whose primary indication for surgery is symptomatic and/or severe hypercalcemia, cinacalcet is recommended over bisphosphonates, particularly for those patients whose bone density is not in osteoporotic range
• For patients whose primary indication for surgery is osteoporosis and risk for fracture, bisphosphonates are recommended. Alendronate has been most extensively evaluated in patients with primary HPT
• If there is no need to improve bone density or to lower serum calcium, pharmacologic therapy is not recommended\textsuperscript{10,11}

For additional clinical information see the Prime Therapeutics Formulary Chapter 4.9L: Endocrine and Metabolic Drugs, Miscellaneous (Calcimimetic Agents) and Formulary Chapter 7.7D: Phosphate Binders.

REFERENCES
Sensipar (cinacalcet) Prior Authorization

OBJECTIVE
The intent of the Sensipar (cinacalcet) Prior Authorization (PA) program is to ensure appropriate selection of patients for treatment according to product labeling and/or clinical studies and/or guidelines. The PA defines appropriate use as a diagnosis consistent with FDA approved labeling. For patients with CKD on dialysis with HPT (intact parathyroid hormone > 300 pg/mL), the PA considers the requested agent to be second-line after use of prerequisite agents, unless the patient has a documented intolerance, FDA labeled contraindication, or hypersensitivity to these prerequisites. Requests for the requested agent will be reviewed when patient-specific documentation has been provided.

TARGET AGENT
Sensipar® (cinacalcet)

PRIOR AUTHORIZATION CRITERIA FOR APPROVAL
Sensipar (cinacalcet) will be approved when ALL of the following are met:
1. ONE of the following:
   a. The patient has a diagnosis of hypercalcemia due to parathyroid carcinoma
      OR
   b. The patient has a diagnosis of primary hyperparathyroidism (HPT) and BOTH of the following:
      i. The patient has a pretreatment serum calcium level that is above the testing laboratory’s upper limit of normal
      AND
      ii. The patient is unable to undergo parathyroidectomy
      OR
   c. The patient has a diagnosis of secondary hyperparathyroidism (HPT) due to chronic kidney disease (CKD) AND ALL of the following:
      i. The patient is on dialysis
      AND
      ii. The patient has a pretreatment or current intact PTH (iPTH) level that is >300 pg/mL
      AND
      iii. The patient has tried and had an inadequate response to BOTH a phosphate binder [e.g. calcium acetate, calcium carbonate, sevelamer carbonate, Fosrenostar (lanthanum carbonate), Renagel* (sevelamer hydrochloride)] AND a vitamin D analog [e.g. calcitriol, Hectorol (doxercalciferol), Rayaldee (calcifediol), Zemplar (paricalcitol)] OR the patient has a documented intolerance, FDA labeled contraindication, or hypersensitivity to ALL prerequisite agents
      OR
   d. The patient has an indication that is supported by compendia (DrugDex with 1 or 2a level of evidence) for the requested agent
      AND
2. ONE of the following:
   a. The patient is NOT currently being treated with another calcium sensing receptor agonist [e.g. Parsabiv (etelcalcetide)]
      OR
   b. The patient is currently being treated with another calcium sensing receptor agonist AND will discontinue prior to initiating the requested agent
      AND
3. The patient does NOT have any FDA labeled contraindications to the requested agent

Length of approval: 12 months
*prerequisite agent maybe subject to Step Therapy (ST) program
Step Therapy Supplement

This program applies to FlexRx Closed, FlexRx Open, GenRx Closed, GenRx Open, Health Insurance Marketplace, FocusRx and KeyRx formularies.

Please note, this does not include or apply to quantity limit questions.

STEP THERAPY SUPPLEMENT

OBJECTIVE
The intent of the Step Therapy Supplement is to provide additional questions, to ensure compliance to MN Statute 62Q.184. These questions will apply if the step therapy component within a Prior Authorization or Step Therapy program is not able to be approved.

CONDITIONS FOR APPROVAL
The requested agent will be approved when ONE of the following are met:

1. The patient is currently being treated with the requested agent as indicated by ALL of the following:
   a. A statement by the prescriber that the patient is currently taking the requested agent
   AND
   b. A statement by the prescriber that the patient is currently receiving a positive therapeutic outcome on requested agent
   AND
   c. The prescriber states that a change in therapy is expected to be ineffective or cause harm

OR

2. The patient’s medication history include the required prerequisite/preferred agent(s) as indicated by:
   a. Evidence of a paid claim(s) within the past 999 days
   OR
   b. The prescriber has stated that the patient has tried the required prerequisite/preferred agent(s) in the past 999 days AND the required prerequisite/preferred agent(s) was discontinued due to lack of effectiveness or an adverse event

OR

3. The prescriber has provided documentation that the required prerequisite/preferred agent(s) cannot be used due to a documented medical condition or comorbid condition that is likely to cause an adverse reaction, decrease ability of the patient to achieve or maintain reasonable functional ability in performing daily activities or cause physical or mental harm

Length of Approval: As per program specific criteria