**Title:** Denosumab (Prolia and Xgeva)

- BCBSKS will review Prior Authorization requests

Prior Authorization Form:

Link to Drug List (Formulary):
https://www.bcbsks.com/CustomerService/PrescriptionDrugs/drug_list/

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**DESCRIPTION**
Denosumab, under the name of Xgeva, is indicated for prevention of skeletal-related events in patients with bone metastases from solid tumors, treatment of adults and skeletally mature adolescents with giant cell tumor of bone that is unresectable or where surgical resection is likely to result in severe morbidity, and treatment of hypercalcemia of malignancy refractory to bisphosphonate therapy.²
The intent of the denosumab medical drug criteria is to ensure appropriate selection of patients for treatment according to product labeling and/or clinical studies and/or guidelines and according to dosing recommended in product labeling. Patients considered candidates for therapy with these agents are appropriate patients with osteoporosis at high risk for fracture, appropriate patients at high risk for fracture receiving androgen deprivation therapy for prostate cancer, appropriate patients at high risk for fracture receiving adjuvant aromatase inhibitor therapy for breast cancer, and patients with bone metastases from solid tumors.

These agents will not be approved for patients in whom it would be contraindicated. Because use of these agents in combination with other osteoporosis agents including bisphosphonates, SERMs (selective estrogen receptor modulator), and Forteo (teriparatide) has not been studied, the criteria will not approve combination therapy.

**Target Drugs**
- Prolia (denosumab)
- Xgeva (denosumab)

**FDA Approved Indications and Dosages**

<table>
<thead>
<tr>
<th>Agent</th>
<th>Indication</th>
<th>Dosing and Administration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prolia®</td>
<td>The treatment of postmenopausal women with osteoporosis at high risk for fracture, defined as a history of osteoporotic fracture, or multiple risk factors for fracture; or patients who have failed or are intolerant to other available osteoporosis therapy.</td>
<td>The recommended dose is 60 mg via subcutaneous injection once every 6 months. Denosumab should be administered by a healthcare professional. All patients should receive calcium 1000 mg daily and at least 400 IU of vitamin D daily.</td>
</tr>
<tr>
<td>(denosumab)</td>
<td>Treatment to increase bone mass in men with osteoporosis at high risk for fracture, defined as a history of osteoporotic fracture, or multiple risk factors for fracture; or patients who have failed or are intolerant to other available osteoporosis therapy.</td>
<td></td>
</tr>
<tr>
<td>subcutaneous injection</td>
<td>Treatment of glucocorticoid-induced osteoporosis in men and women at high risk for fracture who are either initiating or continuing systemic glucocorticoids in a daily dosage equivalent to 7.5 mg or greater of prednisone and expected to remain on glucocorticoids for at least 6 months.</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Treatment to increase bone mass in men at high risk for fracture receiving androgen deprivation therapy for nonmetastatic prostate cancer.</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Treatment to increase bone mass in women at high risk for fracture receiving adjuvant aromatase inhibitor therapy for breast cancer.</td>
<td></td>
</tr>
<tr>
<td>Agent</td>
<td>Indication</td>
<td>Dosing and Administration</td>
</tr>
<tr>
<td>-----------------------------</td>
<td>-----------------------------------------------------------------------------</td>
<td>--------------------------------------------------------------------------------------------</td>
</tr>
</tbody>
</table>
| Xgeva® (denosumab) injection for subcutaneous use | • Prevention of skeletal related events in patients with multiple myeloma and in patients with bone metastases from solid tumors  
• Treatment of adults and skeletally mature adolescents with giant cell tumor of bone that is unresectable or resection likely to result in severe morbidity  
• Treatment of hypercalcemia of malignancy refractory to bisphosphonate therapy | **Skeletal related events in multiple myeloma:** 120 mg subcutaneously every 4 weeks  
**Giant cell tumor of bone:** 120 mg subcutaneously every 4 weeks with additional doses of 120 mg on Day 8 and 15 in first month of therapy  
**Hypercalcemia of malignancy:** 120 mg subcutaneously every 4 weeks with additional 120 mg doses on Days 8 and 15 of the first month of therapy |

**POLICY**

**Prolia**

**Prolia** will be approved when ALL of the following are met:
1. **ONE** of the following:
   a. The patient has a diagnosis of osteoporosis AND BOTH of the following:
      i. **ONE** of the following:
         1. The patient is a male  
         **OR**  
         2. The patient is postmenopausal  
         **OR**  
         3. The prescriber has provided information that the requested agent is medically appropriate for the patient’s gender  
   AND  
   ii. **TONE** of the following:
      1. The patient has a history of vertebral fracture(s), or low trauma or fragility fracture(s) [e.g, prior fracture from minor trauma such as falling from standing height or less] within the past 5 years  
      **OR**
2. BOTH of the following:
   a. The patient has a T-score that is –2.5 or lower
   **AND**
   b. ONE of the following:
      i. The patient has tried and had an inadequate response to a bisphosphonate
      **OR**
      ii. The patient has a documented intolerance, FDA labeled contraindication, or hypersensitivity to ALL bisphosphonates
   **OR**
   b. The patient is requesting the agent for osteopenia (osteoporosis prophylaxis) **AND** ALL of the following:
      i. ONE of the following:
         1. The patient is a male age 50 years of age or over
         **OR**
         2. The patient is postmenopausal
         **OR**
         3. The patient is age 50 years of age or over and the prescriber has provided information that the requested agent is medically appropriate for the patient’s gender
      **AND**
      ii. BOTH of the following:
         1. The patient has osteopenia, defined as a T-score between -1.0 to -2.50
         **AND**
         2. ONE of the following:
            a. 10-year probability of a hip fracture ≥ 3% per FRAX
            **OR**
            b. 10-year probability of a major osteoporosis-related fracture ≥ 20% per FRAX
      **AND**
      iii. ONE of the following:
         1. The patient has tried and had an inadequate response to a bisphosphonate
         **OR**
         2. The patient has a documented intolerance, FDA labeled contraindication, or hypersensitivity to ALL bisphosphonates
   **OR**
c. The patient has a diagnosis of breast cancer AND BOTH of the following:
   i. The patient is currently receiving aromatase inhibitor therapy AND
   ii. ONE of the following:
      1. The patient has a history of vertebral fracture(s), or low trauma or fragility fracture(s) [e.g., prior fracture from minor trauma such as falling from standing height or less] within the past 5 years
         OR
      2. The patient has a T-score of -1 or lower AND ONE of the following:
         a. The patient has tried and had an inadequate response to a bisphosphonate
         OR
         b. The patient has a documented intolerance, FDA labeled contraindication, or hypersensitivity to ALL bisphosphonates

   OR

d. The patient has a diagnosis of nonmetastatic prostate cancer AND BOTH of the following:
   i. The patient is currently receiving androgen deprivation therapy (ADT) AND
   ii. ONE of the following:
      The patient has a history of vertebral fracture(s), or low trauma or fragility fracture(s) [e.g., prior fracture from minor trauma such as falling from standing height or less] within the past 5 years
      OR
      ONE of the following:
      a. ONE of the following:
         i. The patient has a T-score of -1 or lower
         OR
         ii. The patient has a history of an osteoporotic fracture
         AND
      b. ONE of the following:
         i. The patient has tried and had an inadequate response to a bisphosphonate
         OR
         ii. The patient has a documented intolerance, FDA labeled contraindication, or hypersensitivity to ALL bisphosphonates

OR
e. The patient has a diagnosis of glucocorticoid-induced osteoporosis **AND** ALL of the following:
   i. The patient is either initiating or currently taking glucocorticoids in a daily dosage equivalent to 7.5 mg or higher of prednisone **AND**
   ii. The patient’s expected current course of therapy of glucocorticoids is for a period of at least 6 months **AND**
   iii. **ONE** of the following:
      1. The patient has a history of vertebral fracture(s), or low trauma or fragility fracture(s) [e.g., prior fracture from minor trauma such as falling from standing height or less] within the past 5 years **OR**
      2. The patient has a BMD T-score of -2.5 or lower **OR**
      3. The patient has osteopenia, defined as a T-score between -1.0 to -2.50 **AND**
         a. 10-year probability of a hip fracture ≥ 3% per FRAX **OR**
         b. 10-year probability of a major osteoporosis-related fracture ≥ 20% per FRAX **AND**
   iv. **ONE** of the following:
      1. The patient has tried and had an inadequate response to a bisphosphonate **OR**
      2. The patient has a documented intolerance, FDA labeled contraindication, or hypersensitivity to ALL bisphosphonates **AND**
   2. **ONE** of the following:
      a. The patient is not receiving concomitant Xgeva (denosumab), bisphosphonate, SERM, parathyroid hormone analog (Forteo [teriparatide], Tymlos [abaloparatide]), or Evenity (romosozumab-aqqg) therapy **OR**
      b. The prescriber indicates that the patient will discontinue the current Xgeva (denosumab), bisphosphonate, SERM, parathyroid hormone analog (Forteo [teriparatide], Tymlos [abaloparatide]), or Evenity (romosozumab-aqqg) therapy before initiating the requested agent **AND**
   3. The patient does not have any FDA labeled contraindication(s) to the requested agent

**Length of approval:** 12 months
**Xgeva**

*Xgeva* will be approved when ALL the following are met:

1. **ONE of the following:**
   
a. There is information that the patient is currently being treated with the requested agent  
   **OR**
   
b. The prescriber states the patient is being treated with the requested agent AND is at risk if therapy is changed  
   **OR**
   
c. The patient has a diagnosis of multiple myeloma and **BOTH** of the following:
      
a. The request agent will be used for the prevention of skeletal-related events  
      **AND**
      
b. **ONE** of the following:
         
         1. The patient has tried and had an inadequate response to pamidronate OR zoledronic acid  
            **OR**
            
         2. The patient has a documented intolerance, FDA labeled contraindication or hypersensitivity to BOTH pamidronate AND zoledronic acid  
            **OR**
            
         3. The patient has renal insufficiency  
            **OR**
            
         4. The requested agent is a category 1, preferred agent in NCCN Guidelines for the requested diagnosis  
            **OR**
            
   d. The patient has a diagnosis of prostate cancer AND has documented bone metastases  
   **OR**
   
e. The patient has a diagnosis of breast cancer with documented bone metastases and **ONE** of the following:
      
a. The patient has tried and had an inadequate response to pamidronate OR zoledronic acid  
      **OR**
      
      b. The patient has a documented intolerance, FDA labeled contraindication or hypersensitivity to BOTH pamidronate AND zoledronic acid  
      **OR**
      
      c. The requested agent is a category 1, preferred agent in NCCN Guidelines for the requested diagnosis  
      **OR**
f. The patient has another solid tumor cancer diagnosis (e.g., thyroid, non-small cell lung, kidney cancer) with documented bone metastases and ONE of the following:
   a. The patient has tried and had an inadequate response to zoledronic acid OR
   b. The patient has a documented intolerance, FDA labeled contraindication, or hypersensitivity to zoledronic acid OR
c. The requested agent is a category 1, preferred agent in NCCN Guidelines for the requested diagnosis OR

g. The patient has a diagnosis of systemic mastocytosis and ONE of the following:
   a. BOTH of the following:
      1. The patient has tried zoledronic acid AND
      2. The patient has persistent bone pain OR
   b. The patient has a documented intolerance, FDA labeled contraindication, or hypersensitivity to zoledronic acid OR
c. The patient has renal insufficiency OR
d. The requested agent is a category 1, preferred agent in NCCN Guidelines for the requested diagnosis OR

h. The patient has a diagnosis of giant cell tumor of bone and BOTH of the following:
   a. The patient is an adult or skeletally mature adolescent (must be ≥ 13 years of age) AND
   b. ONE of the following:
      1. The tumor is recurrent OR
      2. The tumor is unresectable OR
      3. Resection is likely to result in severe morbidity OR
i. The patient has a diagnosis of hypercalcemia of malignancy and ONE of the following:
   a. BOTH of the following:
      1. The patient has had at least 2 doses of intravenous bisphosphonate therapy (e.g., pamidronate, zoledronic acid) AND
      2. The patient has failed or is refractory to intravenous bisphosphonate therapy (i.e., albumin-corrected calcium of ≥ 12.5 mg/dL [3.1 mmol/L])
   OR
   b. The patient has a documented intolerance, FDA labeled contraindication, or hypersensitivity to intravenous bisphosphonate therapy

   AND
   2. ONE of the following:
      a. The patient is not receiving concomitant Prolia therapy
      OR
      b. The patient will discontinue Prolia before treatment with the requested agent

   AND
   3. The patient does not have any FDA labeled contraindications to the requested agent

Length of approval: 12 months

RATIONALE

PROLIA
Diagnosis of Osteoporosis
The National Osteoporosis Foundation states that the diagnosis of osteoporosis (OP) can be established by either measurement of bone mineral density (BMD) or by the occurrence of adulthood hip or vertebral fracture in the absence of major trauma (such as a motor vehicle accident or multiple story fall). For evaluation, BMD measurement should be taken by central dual-energy X-ray absorptiometry at the lumbar spine and femoral neck (hip). A BMD taken at the one-third (33%) radius site can be used for diagnosing osteoporosis when the hip and lumbar spine cannot be measured or are unusable or uninterpretable. In postmenopausal women and men age 50 and older, WHO diagnostic T-score criteria is applied to the BMD measurement. For those patients that are not postmenopausal women and not men age 50 and older, WHO BMD classification should not be applied and the diagnosis of osteoporosis should not be made on densitometric criteria alone. T-score between -1 and -2.5 with a fragility fracture of the proximal humerus, pelvis, or possibly distal forearm.
### WHO Definitions of bone density

<table>
<thead>
<tr>
<th>Condition</th>
<th>T-score Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>T-score ≥ -1.0</td>
</tr>
<tr>
<td>Low bone mass (osteopenia)</td>
<td>T-score between -1.0 and -2.5</td>
</tr>
<tr>
<td>Osteoporosis</td>
<td>T-score ≤ -2.5</td>
</tr>
</tbody>
</table>

The WHO absolute fracture risk model (Fracture Risk Algorithm, FRAX) was developed to calculate the 10-year probability of a hip fracture and the 10-year probability of a major osteoporotic fracture, taking into account femoral neck BMD and clinical risk factors.

### Treatment

According to the National Osteoporosis Foundation, postmenopausal women and men age 50 and older presenting with the following should be considered for treatment:

- A hip or vertebral fracture
- T-score of -2.5 or lower at the femoral neck, total hip, or lumbar spine (or at the 33% radius site if necessary)
- Low bone mass (T-score between -1 and -2.5) and a 10-year probability of a hip fracture ≥ 3% or a 10-year probability of a major osteoporosis-related fracture ≥ 20% based on the US-adapted WHO algorithm

The American Association of Clinical Endocrinologists (AACE), the Endocrine Society, and the North American Menopause Society all agree with these treatment thresholds for postmenopausal women. The Endocrine Society also agrees with these treatment thresholds for men with increased fracture risk.

### Postmenopausal women

The AACE recommends alendronate, risedronate, zoledronic acid, or denosumab as first-line agents. For patients unable to use oral therapy, teriparatide, denosumab, or zoledronic acid should be considered as initial therapy. Teriparatide, denosumab, or zoledronic acid can be considered as initial therapy for those who have the highest fracture risk (e.g., older women who have had multiple vertebral fractures or hip fractures, or who have very low T-scores). For patients at high risk of spine fracture but not at risk for hip or nonvertebral fractures, ibandronate and raloxifene may be appropriate, and raloxifene has a “side benefit” of reducing breast cancer risk. Raloxifene or ibandronate may be appropriate initial therapy in some cases where patients require drugs with spine-specific efficacy. Denosumab is the agent of choice for patients with renal insufficiency, but this agent is not recommended for dialysis patients or those with stage 5 kidney disease due to the high risk of hypocalcemia.

The American College of Physicians (ACP) recommends that clinicians offer alendronate, risedronate, zoledronic acid, or denosumab to reduce the risk for hip and vertebral fractures in women who have known osteoporosis. The ACP also recommends against using menopausal estrogen therapy or menopausal estrogen plus progestogen therapy or raloxifene for the treatment of osteoporosis in women. In their guidelines, they state that “Although raloxifene has some benefit in reducing vertebral fractures, it does not reduce hip fracture or nonvertebral fractures and is associated with serious harms, including thromboembolism.”

The Endocrine Society recommends initial treatment with bisphosphonates (alendronate, risedronate, zoledronic acid, and ibandronate) to reduce fracture risk. The Society recommends
denosumab as an alternative initial treatment, with teriparatide and abaloparatide reserved for those with very high risk of fracture, and raloxifene or bazadoxifene for patients with a low risk of deep vein thrombosis and for whom bisphosphonates or denosumab are not appropriate, or with a high risk of breast cancer.5

The Endocrine Society 2012 Clinical Practice Guideline: Osteoporosis in Men recommends the following: men at high risk of fracture be treated with medication approved by regulatory agencies such as the U.S. FDA or the European Medicines Agency (EMA) (at the time of this writing, alendronate, risedronate, zoledronic acid, and teriparatide; also denosumab for men receiving ADT [androgen deprivation therapy] for prostate cancer) and that the selection of therapeutic agent be individualized based on factors including fracture history, severity of osteoporosis (T-scores), and the risk for hip fracture.7

The ACP recommends bisphosphonates to reduce the risk for vertebral fracture in men who have clinically recognized osteoporosis.11

**Glucocorticoid-Induced Osteoporosis**
The efficacy and safety of denosumab in the treatment of patients with glucocorticoid-induced osteoporosis was assessed in the 12-month primary analysis of a 2-year, randomized, multicenter, double-blind, parallel-group, active-controlled study of 795 patients (70% women and 30% men) aged 20 to 94 years (mean age of 63 years) treated with greater or equal to 7.5mg/day oral prednisone (or equivalent) for less than 3 months prior to study enrollment and planning to continue treatment for a total of at least 6 months (glucocorticoid-initiating subpopulation; n=290), or 3 or more months prior to study enrollment and planning to continue treatment for a total of at least 6 months (glucocorticoid-continuing subpopulation; n=505). Enrolled patients less than 50 years of age were required to have a history of osteoporotic fracture. Enrolled patients at or greater than 50 years of age who were in the glucocorticoid-continuing subpopulation were required to have a baseline BMD T-score of ≤ -2.0 at the lumbar spine, total hip, or femoral neck; or a BMD T-score of ≤ -1.0 at the lumbar spine, total hip, or femoral neck and a history of osteoporotic fracture.

Patients were randomized (1:1) to receive either an oral daily bisphosphonate (risedronate 5 mg daily) or denosumab 60 mg subcutaneously once every 6 months for one year. Patients also received at least 1000 mg of calcium and 800 IU of vitamin D daily.

Denosumab was both non-inferior and superior to risedronate at 12 months for effect on bone mineral density at the lumbar spine in both glucocorticoid-continuing (4.4% [95% CI 3.8–5.0] vs 2.3% [1.7–2.9]; p<0.0001) and glucocorticoid-initiating (3.8% [3.1–4.5] vs 0.8% [0.2–1.5]; p<0.0001) subpopulations. Incidence of adverse events, serious adverse events (including infections), and fractures was similar between treatment groups.8

Due to the lack of evidence on the effect on fracture risk, concomitant use of osteoporosis agents is not recommended. There are no head-to-head trials with a preplanned endpoint of reduced fractures comparing one drug with another for osteoporosis.4
Breast Cancer
The National Comprehensive Cancer Network (NCCN) Guidelines in Oncology-Breast Cancer state that:
- Denosumab, zoledronic acid, or pamidronate (all with calcium and vitamin D supplementation) should be given in addition to chemotherapy or endocrine therapy if bone metastasis is present, expected survival ≥ 3 months, and renal function is adequate. The optimal schedule for zoledronic acid is monthly for 12 doses, then quarterly. The optimal schedule and duration of denosumab or pamidronate is unknown (NCCN category 1).
- Women on an aromatase inhibitor should have monitoring of bone health with a bone mineral density determination at baseline and periodically thereafter. The use of estrogen, progesterone, or selective estrogen receptor modulators to treat osteoporosis or osteopenia in women with breast cancer is discouraged. The use of a bisphosphonate (oral/IV) or denosumab is acceptable to maintain or to improve bone mineral density and reduce risk of fractures in postmenopausal (natural or induced) patients receiving adjuvant endocrine therapy.9

The efficacy and safety of Prolia in the treatment of bone loss in women receiving adjuvant aromatase inhibitor (AI) therapy for breast cancer was assessed in a 2-year, randomized (1:1), double-blind, placebo-controlled, multinational study. Women had baseline BMD T-scores between -1.0 to -2.5 at the lumbar spine, total hip, or femoral neck, and had not experienced fracture after age 25. The primary efficacy variable was percent change in lumbar spine BMD from baseline to month 12. Lumbar spine BMD was higher at 12 months in Prolia-treated patients as compared to placebo-treated patients [-0.7% placebo, +4.8% Prolia; treatment difference 5.5% (95% CI: 4.8, 6.3); p<0.0001].

Prostate Cancer
The NCCN Guidelines in Oncology-Prostate Cancer state that:
NOF. Androgen depravation therapy (ADT) should be considered “secondary osteoporosis” using the FRAX algorithm. Zoledronic acid and alendronate increased bone mineral density, a surrogate for fracture risk, during ADT for prostate cancer. Treatment with either denosumab, zoledronic acid or alendronate is recommended when the absolute fracture risk warrants drug therapy10.

• The efficacy and safety of Prolia in the treatment of bone loss in men with nonmetastatic prostate cancer receiving androgen deprivation therapy (ADT) were demonstrated in a 3-year, randomized (1:1), double blind, placebo controlled multinational study. Men had either a BMD T-score at the lumbar spine, total hip, or femoral neck between -1.0 and -4.0, or a history of an osteoporotic fracture. With approximately 62% of patients followed for 3 years, treatment differences in BMD at 3 years were 7.9% (-1.2% placebo, +6.8% Prolia) at the lumbar spine, 5.7% (-2.6% placebo, +3.2% Prolia) at the total hip, and 4.9% (-1.8% placebo, +3.0% Prolia) at the femoral neck. Consistent effects on BMD were observed at the lumbar spine in relevant subgroups defined by baseline age, BMD, and baseline history of vertebral fracture.1

Safety
Prolia carries the following contraindications:
- Hypocalcemia
- Pregnancy
- Known hypersensitivity to Prolia
Hypocalcemia must be corrected before initiating Prolia therapy.1

**XGEVA**

**Giant cell tumor of bone**

Giant cell tumor of bone (GCTB) is the most common benign bone tumor predominant in young adults.2 In the United States, GCTB accounts for approximately 3 to 5 percent of all primary bone tumors and 15 to 20 percent of all benign bone tumors.3 GCTB usually occurs after skeletal maturity, with a peak incidence in patients between 20 and 39 years old. The disease is extremely rare before the age of 20.3

Intralesional excision with or without an effective adjuvant is an adequate primary treatment for resectable tumors. Serial embolizations, denosumab, and interferon are included as primary treatment in the National Comprehensive Cancer Network (NCCN) guidelines as options for patients with lesions that are resectable with acceptable morbidity or unresectable axial lesions.2

**Multiple myeloma**4

The National Comprehensive Cancer Network (NCCN) Guidelines in Oncology for Multiple Myeloma recommend bisphosphonates (zoledronic acid is preferred) or denosumab as preventative options for skeletal-related events for all patients receiving primary treatment. If the patient has renal insufficiency NCCN prefers denosumab over bisphosphonates.

**Prostate cancer**5

The National Comprehensive Cancer Network (NCCN) Guidelines in Oncology for (prostate cancer) prefer denosumab (category 1, preferred) to bisphosphonates (e.g., pamidronate or zoledronic acid) to treat bone metastases related skeletal events, maintain or improve bone mineral density and reduce risk of fractures.

**Solid tumor**6-9

The National Comprehensive Cancer Network (NCCN) Guidelines in Oncology for several solid tumor types (i.e., thyroid, non-small cell lung cancer, kidney cancer, breast cancer, prostate cancer) recommend IV bisphosphonates or denosumab as therapeutics options to treat bone metastases related skeletal events, maintain or improve bone mineral density and reduce risk of fractures.

**Hypercalcemia of malignancy**

Hypercalcemia is relatively common in patients with cancer, occurring in approximately 20 to 30 percent of cases. There are three major mechanisms by which hypercalcemia of malignancy can occur: tumor secretion of parathyroid hormone-related protein, osteolytic metastases with local release of cytokines, and tumor production of 1,25-dihydroxyvitamin D (calcitriol).10,11

Mild hypercalcemia is defined as calcium between 10.5 and 11.9 mg/dL. Moderate hypercalcemia is defined as calcium between 12 and 13.9 mg/dL. Severe hypercalcemia is defined as calcium ≥ 14 mg/dL. Calcium in serum is bound to proteins, principally albumin. As a result, total serum calcium concentrations in patients with low or high serum albumin levels may not accurately reflect the physiologically important ionized (or free) calcium concentration. In patients with hypoalbuminemia or hyperalbuminemia, the measured serum calcium concentration should be corrected for the abnormality in albumin or for standard units.10,11
Treatment of the underlying malignancy is always the primary goal of therapy. However, additional therapies, especially for moderate to severe hypercalcemia are essential when simultaneously treating the underlying malignancy. Bisphosphonates are first-line therapy and the mainstay for long-term therapy. Through direct mechanisms they induce osteoclast apoptosis, and indirectly by acting on the osteoblasts they can reduce osteoclastic bone resorption. Bisphosphonates affect proliferation and differentiation of osteoblasts and prevent their apoptosis, and they can also neutralize the RANKL-mediated stimulation of osteoclasts. After receiving the first dose of pamidronate or zoledronic acid patients can be retreated if serum calcium does not return to normal or remain normal. It is recommended that a minimum of 7 days elapse before retreatment, to allow for full response to the initial dose.

**Efficacy**

Xgeva (denosumab) is a human IgG2 monoclonal antibody that binds to human RANKL, a transmembrane or soluble protein essential for the formation, function, and survival of osteoclasts, the cells responsible for bone resorption, thereby modulating calcium release from bone. Increased osteoclast activity, stimulated by RANKL, is a mediator of bone pathology in solid tumors with osseous metastases. Similarly, giant cell tumors of bone consist of stromal cells expressing RANKL and osteoclast-like giant cells expressing RANK receptor, and signaling through the RANK receptor contributes to osteolysis and tumor growth. Denosumab prevents RANKL from activating its receptor, RANK, on the surface of osteoclasts, their precursors, and osteoclast-like giant cells.

**Bone metastasis from solid tumors**

The safety and efficacy of Xgeva for the prevention of skeletal-related events in patients with bone metastases from solid tumors was demonstrated in three international, randomized, double-blind, active-controlled, non-inferiority trials (Study 20050136, Study 20050244, and Study 20050103) comparing Xgeva with zoledronic acid. In each trial, the main outcome measure was demonstration of noninferiority of time to first skeletal-related event (SRE) as compared to zoledronic acid. Supportive outcome measures were superiority of time to first SRE and superiority of time to first and subsequent SRE. An SRE was defined as any of the following: pathologic fracture, radiation therapy to bone, surgery to bone, or spinal cord compression. The results of these studies are summarized in the table below.

<table>
<thead>
<tr>
<th>Study 20050136 Metastatic Breast Cancer</th>
<th>Study 20050244 Metastatic Solid Tumors or Multiple Myeloma</th>
<th>Study 20050103 Metastatic CRPCa</th>
</tr>
</thead>
<tbody>
<tr>
<td>Xgeva N=1026</td>
<td>Zoledronic Acid N=1020</td>
<td>Xgeva N=950</td>
</tr>
<tr>
<td>315 (30.7)</td>
<td>372 (36.5)</td>
<td>341 (35.9)</td>
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<tr>
<td>Number of Patients with SREs (%)</td>
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<td>386 (40.6)</td>
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<tr>
<td>Radiation to Bone</td>
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<tr>
<td>82 (8.0)</td>
<td>119 (11.7)</td>
<td>177 (18.6)</td>
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<tr>
<td>Pathological Fracture</td>
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<td>203 (21.3)</td>
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<td>212 (20.7)</td>
<td>238 (23.3)</td>
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<tr>
<td>Surgery to Bone</td>
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<tr>
<td>12 (1.2)</td>
<td>8 (0.8)</td>
<td>1 (0.1)</td>
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<td>Spinal Cord Compression</td>
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<td>9 (0.9)</td>
<td>7 (0.7)</td>
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<tr>
<td>Median Time to SRE (months)</td>
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<tr>
<td>NR</td>
<td>26.4</td>
<td>20.7</td>
</tr>
<tr>
<td>Components of First SRE</td>
<td></td>
<td>17.1</td>
</tr>
</tbody>
</table>
### Multiple myeloma

The efficacy of Xgeva for the prevention of skeletal-related events (SRE) in newly diagnosed multiple myeloma patients was evaluated in an international, randomized, double-blind, active-controlled, non-inferiority trial (Study 20090482) comparing Xgeva with zoledronic acid. The main efficacy outcome measure was non-inferiority of time to first SRE. Additional efficacy outcome measures were superiority of time to first SRE, time to first and subsequent SRE, and overall survival. An SRE was defined as any of the following: pathologic fracture, radiation therapy to bone, surgery to bone, or spinal cord compression. The results of this study are summarized in the table below.

<table>
<thead>
<tr>
<th>Study 20090482 Multiple Myeloma</th>
<th>Xgeva N = 859</th>
<th>Zoledronic Acid N = 859</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>First On-study SRE</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number of Patients who had SREs (%)</td>
<td>376 (43.8)</td>
<td>383 (44.6)</td>
</tr>
<tr>
<td>Components of First SRE</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Radiation to Bone</td>
<td>47 (5.5)</td>
<td>62 (7.2)</td>
</tr>
<tr>
<td>Pathological Fracture</td>
<td>342 (39.8)</td>
<td>38 (39.3)</td>
</tr>
<tr>
<td>Surgery to Bone</td>
<td>37 (4.3)</td>
<td>48 (5.6)</td>
</tr>
<tr>
<td>Spinal Cord Compression</td>
<td>6 (0.7)</td>
<td>4 (0.5)</td>
</tr>
<tr>
<td>median time to SRE (months)</td>
<td>22.8 (14.7, NE)</td>
<td>24 (16.6, 33.3)</td>
</tr>
<tr>
<td>Hazard Ratio (95% CI)</td>
<td>0.98 (0.85, 1.14)</td>
<td></td>
</tr>
</tbody>
</table>

*CRPC = castrate-resistant prostate cancer
*NR = not reached
*Superiority testing performed only after denosumab demonstrated to be noninferior to zoledronic acid with trial
*All skeletal events postrandomization; new events defined by occurrence ≥ 21 days after preceding event
*Adjusted p-values are presented

### Giant cell tumor of bone

The safety and efficacy of Xgeva for the treatment of giant cell tumor of bone in adults or skeletally mature adolescents were demonstrated in two open-label trials (Study 20062004 and Study 20040215) that enrolled patients with histologically confirmed measurable giant cell tumor of bone that was either recurrent, unresectable, or for which planned surgery was likely to result in severe morbidity.

Study 20062004 was a single arm, pharmacodynamic, and proof concept trial conducted in 37 adult patients with unresectable or recurrent giant cell tumor of bone. Patients were required to have histologically confirmed giant cell tumor of bone and radiologic evidence of measurable disease from a computed tomography (CT) or magnetic imaging (MRI) obtained within 28 prior to study enrollment.
Study 20040215 was a parallel-cohort, proof of concept, and safety trial conducted in 282 adult or skeletally mature adolescent patients with histologically confirmed giant cell tumor of bone and evidence of measurable active disease. Patients enrolled into one of three cohorts: Cohort 1 enrolled 170 patients with surgically unsalvageable disease; Cohort 2 enrolled 101 patients with surgically salvageable disease where the investigator determined that the planned surgery was likely to result in severe morbidity; Cohort 3 enrolled 11 patients who previously participated in Study 20062004.

The primary endpoint in both Study 20062004 and Study 20040215 was objective response rate using modified Response Evaluation Criteria in Solid Tumors (RECIST 1.1). The RECIST 1.1 overall in both studies was 25% (95% CI; 19,32). All responses were partial responses.

**Hypercalcemia of malignancy**

The safety and efficacy of Xgeva was demonstrated in an open-label, single-arm trial (Study 20070315) that enrolled 33 patients with hypercalcemia of malignancy (with or without bone metastases) refractory to treatment with intravenous bisphosphonate therapy.

In this trial, refractory hypercalcemia of malignancy was defined as an albumin-corrected calcium of >12.5 mg/dL (3.1 mmol/L) despite treatment with intravenous bisphosphonate therapy in 7-30 days prior to initiation of Xgeva therapy. The primary outcome measure was the proportion of patients achieving a response, defined as corrected serum calcium ≤ 11.5 mg/dL. A complete response was defined as corrected serum calcium ≤ 10.8 mg/dL. By day ten 63.6% had a response (95% CI). The median time to response was 9 days (95% CI), and the median duration of response was 104 days (95% CI). By day ten 36.4% of patients had a complete response (95% CI). The median time to complete response was 23 days (95% CI) and the median duration of complete response was 34 days (95% CI).

**Safety**

Hypocalcemia is contraindicated when using denosumab. The patient’s calcium level should be corrected prior to use. This agent should not be used in pregnancy as it may cause fetal harm. Osteonecrosis of the jaw (ONJ) has been reported with the use of denosumab. A routine oral exam should be performed by the prescriber prior to therapy initiation and appropriate preventive dentistry should be considered prior to therapy in patients with risk factors for ONJ. Good oral hygiene should be maintained during therapy with denosumab.

Denosumab carries the following contraindications:

- Hypocalcemia
- Known hypersensitivity to denosumab
CODING
The following codes for treatment and procedures applicable to this policy are included below for informational purposes. Inclusion or exclusion of a procedure, diagnosis or device code(s) does not constitute or imply member coverage or provider reimbursement. Please refer to the member’s contract benefits in effect at the time of service to determine coverage or non-coverage of these services as it applies to an individual member.

CPT/HCPCS
J0897 Injection, denosumab, 1 mg

DIAGNOSES

**Prolia**

<table>
<thead>
<tr>
<th>ICD-10</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>C61</td>
<td>Malignant neoplasm of prostate</td>
</tr>
<tr>
<td>M81.0</td>
<td>Age-related osteoporosis without current pathological fracture</td>
</tr>
<tr>
<td>T50.905A</td>
<td>Adverse effect of unspecified drugs, medicaments and biological substances, initial encounter</td>
</tr>
<tr>
<td>T50.905D</td>
<td>Adverse effect of unspecified drugs, medicaments and biological substances, subsequent encounter</td>
</tr>
<tr>
<td>T50.905S</td>
<td>Adverse effect of unspecified drugs, medicaments and biological substances, sequela</td>
</tr>
<tr>
<td>Z79.811</td>
<td>Long term (current) use of aromatase inhibitors</td>
</tr>
<tr>
<td>Z87.311</td>
<td>Personal history of (healed) other pathological fracture</td>
</tr>
<tr>
<td>Z87.312</td>
<td>Personal history of (healed) stress fracture</td>
</tr>
<tr>
<td>Z87.81</td>
<td>Personal history of (healed) traumatic fracture</td>
</tr>
</tbody>
</table>

**Xgeva**

<table>
<thead>
<tr>
<th>ICD-10</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>C33</td>
<td>Malignant neoplasm of trachea</td>
</tr>
<tr>
<td>C34.01</td>
<td>Malignant neoplasm of right main bronchus</td>
</tr>
<tr>
<td>C34.02</td>
<td>Malignant neoplasm of left main bronchus</td>
</tr>
<tr>
<td>C34.11</td>
<td>Malignant neoplasm of upper lobe, right bronchus or lung</td>
</tr>
<tr>
<td>C34.12</td>
<td>Malignant neoplasm of upper lobe, left bronchus or lung</td>
</tr>
<tr>
<td>C34.2</td>
<td>Malignant neoplasm of middle lobe, bronchus or lung</td>
</tr>
<tr>
<td>C34.31</td>
<td>Malignant neoplasm of lower lobe, right bronchus or lung</td>
</tr>
<tr>
<td>C34.32</td>
<td>Malignant neoplasm of lower lobe, left bronchus or lung</td>
</tr>
<tr>
<td>C34.81</td>
<td>Malignant neoplasm of overlapping sites of right bronchus and lung</td>
</tr>
<tr>
<td>C34.82</td>
<td>Malignant neoplasm of overlapping sites of left bronchus and lung</td>
</tr>
<tr>
<td>C40.01</td>
<td>Malignant neoplasm of scapula and long bones of right upper limb</td>
</tr>
<tr>
<td>C40.02</td>
<td>Malignant neoplasm of scapula and long bones of left upper limb</td>
</tr>
<tr>
<td>C40.11</td>
<td>Malignant neoplasm of short bones of right upper limb</td>
</tr>
<tr>
<td>C40.12</td>
<td>Malignant neoplasm of short bones of left upper limb</td>
</tr>
<tr>
<td>C40.21</td>
<td>Malignant neoplasm of long bones of right lower limb</td>
</tr>
<tr>
<td>C40.22</td>
<td>Malignant neoplasm of long bones of left lower limb</td>
</tr>
<tr>
<td>C40.31</td>
<td>Malignant neoplasm of short bones of right lower limb</td>
</tr>
<tr>
<td>C40.32</td>
<td>Malignant neoplasm of short bones of left lower limb</td>
</tr>
</tbody>
</table>
C40.81  Malignant neoplasm of overlapping sites of bone and articular cartilage of right limb
C40.82  Malignant neoplasm of overlapping sites of bone and articular cartilage of left limb
C40.91  Malignant neoplasm of unspecified bones and articular cartilage of right limb
C40.92  Malignant neoplasm of unspecified bones and articular cartilage of left limb
C41.0   Malignant neoplasm of bones of skull and face
C41.1   Malignant neoplasm of mandible
C41.2   Malignant neoplasm of vertebral column
C41.3   Malignant neoplasm of ribs, sternum and clavicle
C41.4   Malignant neoplasm of pelvic bones, sacrum and coccyx
C41.9   Malignant neoplasm of bone and articular cartilage, unspecified
C73     Malignant neoplasm of thyroid gland
C79.51  Secondary malignant neoplasm of bone
C79.52  Secondary malignant neoplasm of bone marrow
E83.52  Hypercalcemia

### REVISIONS

<table>
<thead>
<tr>
<th>Date</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>08-14-2012</td>
<td>Policy added to the bcbsks.com web site.</td>
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</table>
| 03-12-2013 | Policy published 07-01-2016. Policy effective 08-01-2016. In Description section:  
  - Added the Prolia FDA Indication, "4. Treatment to increase bone mass in men with osteoporosis at high risk of fracture."
  - Added in A. Prolia the medically necessary indication of:  "4. Treatment of osteoporosis (T-score below -2.5) in men who have failed or are unable to tolerate oral bisphosphonates [e.g. alendronate (Fosamax), risedronate (Actonel), ibandronate (Boniva)]."
  - In the Policy Guidelines removed from item 3, "... in men who are not receiving androgen deprivation therapy or..." to read, "In the absence of safety data, using denosumab for the treatment of osteoporosis in premenopausal women or children is not recommended."
  - Added guideline "8. Men seem to respond to available therapies in the same way that women respond. Bisphosphonates are considered the treatment of choice for most men with osteoporosis requiring pharmacologic therapy. Denosumab is an alternative option for men who cannot tolerate oral or intravenous bisphosphonates." |
| 08-01-2016 | Rationale section updated  
  References updated  
  Updated to current criteria and removed:  
  "Prolia is considered medically necessary for the following indications:  
  1. Treatment of osteoporosis (T-score below -2.5) in postmenopausal women who have failed or are unable to tolerate oral bisphosphonates [e.g. alendronate (Fosamax), risedronate (Actonel), ibandronate (Boniva)].  
  2. Treatment of bone loss in women receiving aromatase inhibitor (AI) therapy for breast cancer and have failed or are unable to tolerate oral bisphosphonates [e.g. alendronate (Fosamax), risedronate (Actonel), ibandronate (Boniva)]." |

Contains Public Information
REVISIONS

3. Treatment of bone loss in men receiving androgen deprivation therapy (ADT) for nonmetastatic prostate cancer.
4. Treatment of osteoporosis (T-score below -2.5) in men who have failed or are unable to tolerate oral bisphosphonates [e.g. alendronate (Fosamax), risedronate (Actonel), ibandronate (Boniva)].

Xgeva

"Xgeva is considered medically necessary for the prevention of skeletal-related events (e.g., fracture, spinal cord compression, bone pain requiring surgery / radiation therapy) in patients with bone metastases from solid tumors."

- Removed Policy Guidelines
  1. Given the absence of long-term safety data and availability of other agents, denosumab is not recommended for the prevention of osteoporosis.
  2. For postmenopausal women with uncomplicated osteoporosis (T-score below -2.5), denosumab is not recommended as initial therapy. Oral bisphosphonates are preferred as initial therapy because of their efficacy, favorable cost, and the availability of long-term safety data.
  3. In the absence of safety data, using denosumab for the treatment of osteoporosis in premenopausal women or children is not recommended.
  4. Patients who have hypocalcemia should not receive denosumab until hypocalcemia is corrected.
  5. Patients with chronic kidney disease (creatinine clearance <30 mL/min, including patients receiving dialysis) are at higher risk for hypocalcemia following denosumab administration than patients with normal renal function.
  6. Because serious infections and skin reactions were reported more frequently in the denosumab than in the placebo group, patients should be advised to seek medical attention if they develop signs of an infection or skin reaction.
  7. Additional recommendations include administration of calcium 1000 mg daily and at least 400 IU of vitamin D daily.
  8. Men seem to respond to available therapies in the same way that women respond. Bisphosphonates are considered the treatment of choice for most men with osteoporosis requiring pharmacologic therapy. Denosumab is an alternative option for men who cannot tolerate oral or intravenous bisphosphonates."

- Removed Documentation recommendations:
  - Prolia - DEXA report and clinical records to include medication history
  - Xgeva - Clinical records documenting bone metastases

Rationale section added

In Coding section:
  - Added ICD-10 codes:
    - Prolia - C61, M81.0, T50.905A, T50.905D, T50.905S, Z79.811, Z87.311, Z87.312, Z87.81
    - Xgeva - C33, C34.01, C34.02, C34.11, C34.12, C34.2, C34.31, C34.32, C34.81, C34.82, C40.01, C40.02, C40.11, C40.12, C40.21, C40.22, C40.31, C40.32, C40.81, C40.82, C40.91, C40.92, C41.0, C41.1, C41.2, C41.3, C41.4, C41.9, C73, C79.51, C79.52, E83.52

References updated

05-10-2017

Description section updated

In Policy section:
  - Prolia
    - In Item 1 a i added "the prescriber has provided documentation that the requested agent is medically appropriate for the patient's gender" to read "The patient is a male, a postmenopausal female, OR the prescriber has provided documentation that the requested agent is medically appropriate for the patient's gender"
    - In Item 1 a ii added "The patient has" and removed "with" to read "The patient has a diagnosis of osteoporosis defined as ONE of the following:"
REVISIONS

- In Item 1 a ii 1 revised "a history of" to "experienced previous"
- In Item 1 a ii 2 i removed "is female and", "either", "or selective estrogen receptor (SERM)" to read "The patient has failed a bisphosphonate"
- In Item 1 a ii 2 added "The patient has a documented intolerance, FDA labeled contraindication, or hypersensitivity to a bisphosphonate OR"
- In Item 1 a ii 2 iii added "The patient has a documented intolerance, FDA labeled contraindication, or hypersensitivity to a bisphosphonate OR"
- In Item 1 a ii 2 removed "is female and", "or selective estrogen receptor (SERM)" to read "The patient has failed a bisphosphonate"
- In Item 1 a ii 2 added "iii. BOTH of the following:"
  a. The patient is female OR the prescriber has provided documentation that SERM (selective estrogen receptor modulator) is medically appropriate for the patient’s gender AND"
- In Item 1 a ii 2 iii b added "The patient has failed a SERM" and removed "The patient is male and has failed a bisphosphonate" to read "The patient has failed a SERM OR the patient has a documented intolerance, FDA labeled contraindication, or hypersensitivity to a SERM"
- In Item 1 b i added "OR the prescriber has provided documentation that the requested agent is medically appropriate for the patient’s gender" and removed "woman" to read "The patient is a male age 50 years of age and over, the patient is postmenopausal, OR the prescriber has provided documentation that the requested agent is medically appropriate for the patient’s gender"
- In Item 1 b iii 1 removed "is female and", "or SERM", "The patient is male and has failed a bisphosphonate OR", and "a SERM" to read "The patient has failed a bisphosphonate OR the patient has a documented intolerance, FDA labeled contraindication, or hypersensitivity to a bisphosphonate"
- In Item 1 b iii 1 added "BOTH of the following:"
  i. The patient is female OR the prescriber has provided documentation that SERM is medically appropriate for the patient’s gender AND
  ii. The patient has failed a SERM OR the patient has a documented intolerance, FDA labeled contraindication, or hypersensitivity to a SERM"
- In Item 1 c added "has" and removed "is a woman with" to read "The patient has a diagnosis of breast cancer who is receiving aromatase inhibitor therapy AND ONE of the following:
- In Item 1 d added "has" and "nonmetastatic" and removed "is a man with" to read "The patient has a diagnosis of nonmetastatic prostate cancer receiving androgen deprivation therapy (ADT) AND ONE of the following:"
- In Item 3 a removed "in the past 30 days" to read "The patient is not receiving concomitant Xgeva (denosumab), bisphosphonate, SERM, or Forteo (teriparatide) therapy"
- In Item 3 b added "prior to initiation of the requested agent" and removed "therapy" to read "The prescriber indicates that the patient will discontinue the current Xgeva (denosumab), bisphosphonate, SERM, or Forteo (teriparatide) prior to initiation of the requested agent"
- In Item 1 a iv added "measured within the last 4 weeks" and removed "tested" to read "The patient's calcium levels have been measured within the last 4 weeks"

Rationale section updated
References updated

12-26-2019
Description section updated

In Policy section:

<table>
<thead>
<tr>
<th>Prolia Summary of Changes</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Added study information on using Prolia for treatment of glucocorticoid-induced osteoporosis in men and women at high risk for fracture</td>
</tr>
</tbody>
</table>
REVISIONS

- Replaced ‘failed’ with standardized ‘tried and had an inadequate response to’

Xgeva Summary of Changes

- Multiple myeloma
  - Added renal insufficiency as way of approving (per NCCN denosumab is preferred in this situation for this diagnosis)
  - Updated to allow for use in prevention of skeletal-related events in patients with multiple myeloma per labeling update
  - Added in statement allowing for NCCN changes to preferred agents to be approved without need to update criteria

- Prostate cancer
  - Allowed for approval if the patient has bone metastases without trying zoledronic acid (NCCN lists denosumab as category 1, preferred)

- Other solid tumor cancer diagnoses
  - Added in statement allowing for NCCN changes to preferred agents to be approved without need to update criteria

- Hypercalcemia of malignancy
  - Require that the patient has had at least 2 doses of intravenous bisphosphonate therapy before determining that patient has failed or is refractory to IV bisphosphonate therapy (per zoledronic acid PI if serum calcium does not return to normal or remain normal the dose should be repeated after at least 7 days to allow for full response to the initial dose)
  - For all indications except hypercalcemia of malignancy – removed denial point if patient was hypocalcemic – this is a labeled contraindication and would be denied at this requirement
  - Updated failed wording to standard tried and had an inadequate response to
  - Added allowance for continuation of therapy

Rationale section updated
References updated

REFERENCES

Prolia

**Xgeva**

**Other References**
1. Blue Cross and Blue Shield of Kansas Urology Liaison Committee: June 2017, August 2018.