I. Medication Description

Denosumab is a fully human monoclonal antibody against receptor activator of nuclear factor kappa-beta ligand (RANKL). RANKL is expressed on the surface of osteoclasts, on activated T and B lymphocytes, and in lymph nodes. The inhibition of RANKL results in a down regulation of osteoclast activity and bone resorption.

II. Position Statement

Coverage is determined through a prior authorization process with supporting clinical documentation for every request.

III. Policy

Coverage of Prolia is provided for the following:

- Treatment of osteoporosis in men and postmenopausal women at high risk for fracture when:
  - Member is taking calcium and vitamin D AND
  - Member must have failed therapy with a plan-preferred medication (an oral or IV bisphosphonate) defined by a fracture while on therapy or worsening bone density, unless such a trial of an oral or IV bisphosphonate is shown to be inappropriate or contraindicated (i.e., presence of severe osteoporosis [T-scores -3.0 or worse in lumbar spine, femoral neck, or total hip region], history of major osteoporotic fracture, presence of renal insufficiency, etc) OR the following criteria must be met:
    - When requesting coverage of a brand medication for which an A/B rated generic is available, there is sufficient evidence that the use of the A/B rated generic equivalent has resulted in inadequate results AND
    - At least one of the following is met:
      - The plan-preferred medications are contraindicated or will likely cause an adverse reaction by or physical or mental harm to the member.
      - The plan-preferred medications are expected to be ineffective based on the known clinical history and conditions of the member and the member’s prescription drug regimen.
      - The member has tried the plan-preferred medications or another prescription drug in the same pharmacologic class or with the same mechanism of action and such prescription drug was discontinued due to lack of efficacy or effectiveness, diminished effect, or an adverse event.
      - The member is stable on the medication selected by their healthcare professional for the medical condition under consideration (where “stable” is defined as receiving the medication for an adequate period of time, have
achieved optimal response, and continued favorable outcomes are expected UNLESS the medication was initially selected due to the availability of a drug sample or a coupon card).

- The plan-preferred medication is not in the best interest of the member because it will likely cause a significant barrier to the member’s adherence or to compliance with the member’s plan of care, will likely worsen a comorbid condition of the member, or will likely decrease the member’s ability to achieve or maintain reasonable functional ability in performing daily activities AND

  o Member has at least one of the following:
    ▪ T-score equal to or worse than -2.5 in the lumbar spine, femoral neck, or total hip region OR
    ▪ A FRAX calculator based 10-year risk of at least 20% for a major osteoporotic fracture (spine, shoulder, hip, or wrist), or a 10-year risk of at least 3% for a hip fracture OR
    ▪ Presence or history of osteoporotic fracture

- Prevention of osteoporosis in postmenopausal women when:
  o Osteopenia is confirmed AND
  o Member is taking calcium and vitamin D AND
  o Member has previously failed therapy with or has a contraindication to the use of at least one plan-preferred medication (an oral or IV bisphosphonate) OR the following criteria are met:
    ▪ When requesting coverage of a brand medication for which an A/B rated generic is available, there is sufficient evidence that the use of the A/B rated generic equivalent has resulted in inadequate results AND
    ▪ At least one of the following is met:
      • The plan-preferred medications are contraindicated or will likely cause an adverse reaction by or physical or mental harm to the member.
      • The plan-preferred medications are expected to be ineffective based on the known clinical history and conditions of the member and the member’s prescription drug regimen.
      • The member has tried the plan-preferred medications or another prescription drug in the same pharmacologic class or with the same mechanism of action and such prescription drug was discontinued due to lack of efficacy or effectiveness, diminished effect, or an adverse event.
      • The member is stable on the medication selected by their healthcare professional for the medical condition under consideration (where “stable” is defined as receiving the medication for an adequate period of time, have achieved optimal response, and continued favorable outcomes are expected UNLESS the medication was initially selected due to the availability of a drug sample or a coupon card).
      • The plan-preferred medication is not in the best interest of the member because it will likely cause a significant barrier to the member’s adherence or to compliance with the member’s plan of care, will likely worsen a comorbid condition of the member, or will likely decrease the member’s ability to achieve or maintain reasonable functional ability in performing daily activities.

- To increase bone mass in adult men at high risk for fracture receiving androgen deprivation therapy for prostate cancer.
- To increase bone mass in adult women at high risk for fracture receiving adjuvant aromatase inhibitor therapy for breast cancer.
Coverage of Xgeva is provided for the following:
- When used for the prevention of skeletal-related events in members with bone metastases from solid tumor cancers in adults. Coverage is NOT provided for prevention of skeletal-related events in members with multiple myeloma.
- When used for the treatment of adults and skeletally mature adolescents (defined as at least one mature long bone) with giant cell tumor of the bone that is unresectable or where surgical resection is likely to result in severe morbidity.
- For the treatment of hypercalcemia of malignancy refractory to bisphosphonate therapy.

IV. Quantity Limitations

- Prolia: 60mg every 6 months
- Xgeva: 120mg every 4 weeks for prevention of skeletal-related events in members with bone metastases from solid tumors and for maintenance therapy for giant cell tumor of the bone.
- Xgeva: 360mg in the first 4 weeks of treatment of giant cell tumor of the bone.
- Xgeva: 120mg every 4 weeks, with additional 120mg on days 8 and 15 for the first month of therapy for the treatment of hypercalcemia of malignancy.

V. Coverage Duration

Coverage is available for one year and may be renewed.

VI. Coverage Renewal Criteria

Coverage of Prolia can be renewed based on the following criteria:
- For the treatment or prevention of osteoporosis:
  - Documentation of condition stabilization or improvement as shown through repeat DXA scans and fracture history AND
  - Absence of unacceptable toxicity
- To increase bone mass in men with prostate cancer on androgen-deprivation therapy or in females with breast cancer on an aromatase inhibitor:
  - Member is still using either androgen-deprivation therapy or an aromatase inhibitor AND
  - Absence of unacceptable toxicity

Coverage of Xgeva can be renewed based on the following criteria:
- For prevention of skeletal-related events in members with bone metastases, giant cell tumor of the bone, or hypercalcemia of malignancy:
  - Absence of unacceptable toxicity

VII. Billing/Coding Information

- Pertinent diagnoses:
  - Secondary malignant neoplasm of bone- C79.51
### Drug Therapy Guidelines

<table>
<thead>
<tr>
<th>RANKL Inhibitors: Prolia®, Xgeva® (denosumab)</th>
<th>Last Review Date: 4/2017</th>
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- Osteoporosis - M80-M81
- Breast cancer - C50
- Malignant neoplasm of prostate –C61, C79.51
- Hypercalcemia –E83.52
- Giant Cell Tumor of Bone – D48.0
- Kidney cancer- C64.1, C64.2, C64.9, C65.1, C65.2, C65.9, Z85.528
- Non-Small Cell Lung Cancer – C33, C34.00-C34.02, C34.10-C34.12, C34.2, C34.30-C34.32, C34.80-C34.82, C34.90-C34.92, C79.51
- Thyroid Carcinoma- C73, C79.51

#### Prolia/Xgeva:
- J0897
- 1 billable unit = 1mg

### VIII. Summary of Policy Changes

- **1/2010:**
  - Addition of Xgeva® to Prolia® policy
  - Renamed to RANKL Inhibitors
- **1/1/12:** Addition of diagnostic criteria for osteoporosis
- **9/15/12:** Addition of FDA-approved indications to increase bone mass in members with prostate cancer or breast cancer being treated with certain medications
- **3/15/13:** Addition of FDA-approved indication to treat osteoporosis in men at high risk for fracture
- **6/2013:** Addition of new FDA-approved indication for Xgeva for the treatment of giant cell tumor of the bone
- **3/15/14:** Adult only indications specified in policy section
- **12/8/14:** Included coverage for the treatment of hypercalcemia of malignancy
- **3/15/15:** Inclusion of coverage criteria for general prevention of osteoporosis in postmenopausal females
- **7/1/15:** Formulary distinctions made
- **3/15/16:** No policy changes
- **1/1/17:** Differentiated indications for Prolia and Xgeva
- **5/1/17:** Step therapy criteria added

### IX. References


The Plan fully expects that only appropriate and medically necessary services will be rendered. The Plan reserves the right to conduct pre-payment and post-payment reviews to assess the medical appropriateness of the above-referenced therapies.

The preceding policy is a guideline to allow for coverage of the pertinent medication/product, and is not meant to serve as a clinical practice guideline.