Description
Denosumab (Prolia®, Xgeva®) is a receptor activator of nuclear factor kappa-B ligand inhibitor.

FDA Approved Indication
Prolia is indicated:
• For the treatment of postmenopausal women with osteoporosis at high risk for fracture*, or patients who have failed or are intolerant to other available osteoporosis therapy. In postmenopausal women with osteoporosis, Prolia reduces the incidence of vertebral, nonvertebral, and hip fractures
• For treatment to increase bone mass in men with osteoporosis at high risk for fracture*, or patients who have failed or are intolerant to other available osteoporosis therapy
• For treatment to increase bone mass in men at high risk for fracture* receiving androgen deprivation therapy for nonmetastatic prostate cancer. In these patients Prolia also reduced the incidence of vertebral fractures
• For treatment to increase bone mass in women at high risk for fracture* receiving adjuvant aromatase inhibitor therapy for breast cancer

*High risk of fracture is defined as a history of osteoporotic fracture, or multiple risk factors for fracture.

Xgeva is indicated:
• For the prevention of skeletal-related events in patients with multiple myeloma and in patients with bone metastases from solid tumors
• For the 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
• For the treatment of hypercalcemia of malignancy refractory to bisphosphonate therapy

Policy/Criteria
Provider must submit documentation (such as office chart notes, lab results or other clinical information) supporting that member has met all approval criteria.

It is the policy of health plans affiliated with Envolve Pharmacy Solutions™ that Prolia and Xgeva are medically necessary when the following criteria are met:

I. Initial Approval Criteria
A. Osteoporosis (must meet all):
   1. Request is for Prolia;
   2. Diagnosis of osteoporosis;
   3. If female, member is postmenopausal;
   4. Age ≥ 18 years or documentation of closed epiphyses;
   5. Member meets one of the following (a or b):
      a. Prescribed by or in consultation with one of the following specialists: a gynecologist, endocrinologist, rheumatologist, orthopedist, or physiatrist;
      b. Failure of a 12-month trial of an oral bisphosphonate (e.g., alendronate, risedronate) at up to maximally indicated doses, unless contraindicated or clinically significant adverse effects are experienced;
   6. Failure of a 12-month trial of injectable ibandronate (Boniva)* or zoledronic acid (Reclast)*; unless contraindicated or clinically significant adverse effects are experienced;
      *Requires prior authorization
   7. Member is not using Xgeva concomitantly;
8. Dose does not exceed 60 mg every 6 months.

Approval duration: 12 months

B. Prostate or Breast Cancer Treatment – Induced Bone Loss (must meet all):
1. Request is for Prolia;
2. Diagnosis of one of the following (a or b):
   a. Female with breast cancer receiving adjuvant aromatase inhibitor therapy [i.e. anastrozole (Arimidex®), exemestane (Aromasin®) or letrozole (Femara®)];
   b. Male with nonmetastatic prostate cancer receiving androgen deprivation therapy [i.e. leuprolide (Lupron®), bicalutamide (Casodex®) or Nilandron®];
3. Age ≥ 18 years or documentation of closed epiphyses;
4. Prior to therapy, member meets one of the following (a, b, or c):
   a. T-score ≤ -2.5 (DXA) at the femoral neck, spine, or total hip;
   b. History of osteoporotic fracture confirmed by radiographic imaging;
   c. T-score < -1.0 (DXA) at the femoral neck or spine, and one additional risk factor:
      i. 10-year probability of hip fracture ≥ 3% per the World Health Organization (WHO) Fracture Risk Assessment Tool (FRAX);
      ii. 10-year probability of a major osteoporosis-related fracture ≥ 20% per the WHO FRAX;
      iii. Age > 65 years;
      iv. Glucocorticoid therapy at daily dosage equivalent to ≥ 7.5 mg of prednisone for at least 3 months;
      v. Parental history of hip fracture;
      vi. Low body mass index (BMI < 20 kg/m²);
      vii. Current cigarette smoking;
      viii. Excessive alcohol consumption (≥ 3 drinks/day);
      ix. Rheumatoid arthritis;
5. Member is not using Xgeva concomitantly;
6. Dose does not exceed 60 mg every 6 months.

Approval duration: 12 months

C. Bone Metastases, Multiple Myeloma, Giant Cell Tumor of Bone, Hypercalcemia of Malignancy (must meet all):
1. Request is for Xgeva for one of the following purposes (a, b, or c):
   a. Prevention of skeletal-related events in member with multiple myeloma or in member with bone metastases from solid tumors and both (i and ii):
      i. Age ≥ 18 years or documentation of closed epiphyses;
      ii. Dose does not exceed 120 mg every 4 weeks;
   b. 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 both (i and ii):
      i. Meets one of the following age requirements (a or b):
         a) Age ≥ 18 years;
         b) Age 13 through 17 years with skeletal maturity (defined by at least 1 mature long bone, e.g., closed epiphyseal growth plate of the humerus) and a history of body weight ≥ 45 kg;
      ii. Dose does not exceed 120 mg every 4 weeks with additional 120 mg doses on days 8 and 15 of the first month of therapy;
   c. Treatment of hypercalcemia of malignancy refractory to bisphosphonate therapy, and all of the following (i, ii, and iii):
      i. Age ≥ 18 years or documentation of closed epiphyses;
      ii. Albumin-corrected calcium > 12.5 mg/dL despite treatment with intravenous bisphosphonate therapy in the 30 days prior to initiation of Xgeva therapy;
      iii. Dose does not exceed 120 mg every 4 weeks with additional 120 mg doses on days 8 and 15 of the first month of therapy;
2. Member is not using Prolia concomitantly.

**Approval duration: 6 months**

D. Other diagnoses/indications

1. Refer to ERX.PA.01 if diagnosis is NOT specifically listed under section III
   (Diagnoses/Indications for which coverage is NOT authorized).

II. Continued Therapy

A. All Indications in Section I (must meet all):

1. Member meets one of the following (a or b):
   a. Currently receiving medication via a health plan affiliated with Envolve Pharmacy Solutions or member has previously met initial approval criteria;
   b. Documentation supports that member is currently receiving Prolia for induced bone loss associated with prostate or breast cancer treatment, or Xgeva for bone metastases, multiple myeloma, giant cell tumor of bone, or hypercalcemia of malignancy, and has received this medication for at least 30 days;

2. Member is responding positively to therapy (if hypercalcemia of malignancy, has not achieved complete response as indicated by corrected serum calcium < 10.8 mg/dL);

3. If request is for a dose increase, new dose does not exceed:
   a. Prolia: 60 mg every 6 months;
   b. Xgeva: 120 mg every 4 weeks.

**Approval duration: 12 months**

B. Other diagnoses/indications (must meet 1 or 2):

1. Currently receiving medication via a health plan affiliated with Envolve Pharmacy Solutions and documentation supports positive response to therapy.

**Approval duration: Duration of request or 6 months (whichever is less);** or

2. Refer to ERX.PA.01 if diagnosis is NOT specifically listed under section III (Diagnoses/Indications for which coverage is NOT authorized).

III. Diagnoses/Indications for which coverage is NOT authorized:

A. Non-FDA approved indications, which are not addressed in this policy, unless there is sufficient documentation of efficacy and safety according to the off-label use policy – ERX.PA.01 or evidence of coverage documents.

IV. Appendices/General Information

**Appendix A: Abbreviation/Acronym Key**

<table>
<thead>
<tr>
<th>Abbreviation/Acronym</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>BMI</td>
<td>body mass index</td>
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<tr>
<td>BMD</td>
<td>bone mineral density</td>
</tr>
<tr>
<td>DXA</td>
<td>dual energy X-ray absorptiometry</td>
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<tr>
<td>FDA</td>
<td>Food and Drug Administration</td>
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<tr>
<td>FRAX</td>
<td>Fracture Risk Assessment Tool</td>
</tr>
<tr>
<td>WHO</td>
<td>World Health Organization</td>
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</tbody>
</table>

**Appendix B: Therapeutic Alternatives**

*This table provides a listing of preferred alternative therapy recommended in the approval criteria. The drugs listed here may not be a formulary agent and may require prior authorization.*

<table>
<thead>
<tr>
<th>Drug Name</th>
<th>Dosing Regimen</th>
<th>Dose Limit/Maximum Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>alendronate</td>
<td>Osteoporosis 10 mg PO QD or 70 mg PO q week</td>
<td>Osteoporosis 10 mg/day or 70 mg/week</td>
</tr>
<tr>
<td></td>
<td>Osteoporosis Prophylaxis 5 mg PO QD</td>
<td>Glucocorticoid-induced Osteoporosis 5 mg/day</td>
</tr>
<tr>
<td></td>
<td>Osteoporosis Prophylaxis 5 mg PO QD or 35 mg PO q week</td>
<td>Osteoporosis Prophylaxis 5 mg/day or 35 mg/week</td>
</tr>
</tbody>
</table>
V. Dosage and Administration

<table>
<thead>
<tr>
<th>Drug Name</th>
<th>Indication</th>
<th>Dosing Regimen</th>
<th>Maximum Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Denosumab (Prolia)</td>
<td>Osteoporosis, men receiving androgen deprivation therapy for nonmetastatic prostate cancer, women receiving adjuvant aromatase inhibitor therapy for breast cancer</td>
<td>60 mg SC q6 months</td>
<td>60 mg/dose</td>
</tr>
<tr>
<td>Denosumab (Xgeva)</td>
<td>Multiple myeloma and bone metastases from solid tumors</td>
<td>120 mg SC q4 weeks</td>
<td>120 mg/dose</td>
</tr>
<tr>
<td></td>
<td>Giant cell tumor of bone, hypercalcemia of malignancy</td>
<td>120 mg SC q4 weeks with additional 120 mg doses on Days 8 and 15 of the first month of therapy</td>
<td>120 mg/dose</td>
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</table>

VI. Product Availability

<table>
<thead>
<tr>
<th>Drug Name</th>
<th>Availability</th>
</tr>
</thead>
<tbody>
<tr>
<td>Denosumab (Prolia)</td>
<td>Injection (single-use prefilled syringe): 60 mg/1 mL</td>
</tr>
</tbody>
</table>
### VII. References


### Reviews, Revisions, and Approvals

<table>
<thead>
<tr>
<th>Reviews, Revisions, and Approvals</th>
<th>Date</th>
<th>P&amp;T Approval Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>Policy split from USS.CP.PHAR.20 Osteoporosis Injectable Therapy, combined with Xgeva, and converted to new template.</td>
<td>08.16</td>
<td>09.16</td>
</tr>
<tr>
<td>Xgeva: Added FDA indication for hypercalcemia of malignancy. Changed approval periods to initial 3 months and continuation 6 months. Removed Zometa and pamidronate trial as prerequisite for Xgeva. In reauthorization criteria, removed question on ONJ and for giant cell tumor, removed question about 3 months of treatment and MRI/CT indication to continue treatment and added point that there is no indication of disease progression. Removed safety criteria. Added definition of skeletal maturity per PI. Added max dosing. Under Section B, “Prostate or Breast Cancer Treatment – Induced Bone Loss”, removed requirement that member fail prior bisphosphonate therapy, particularly Reclast therapy, as Reclast does not have an analogous FDA approved indication.</td>
<td></td>
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<tr>
<td>Prolia: Added max dosing, definition of bisphosphonate trial failure, and preferencing for injectable ibandronate and zoledronic acid therapy. Removed safety criteria. Calcium/vitamin D requirement language edited to be less specific. For men with osteoporosis- criteria distinguished between primary osteoporosis and hypogonadal osteoporosis; added testosterone requirement for hypogonadal osteoporosis.</td>
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</table>
**Reviews, Revisions, and Approvals**

<table>
<thead>
<tr>
<th>Date</th>
<th>P&amp;T Approval Date</th>
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<tbody>
<tr>
<td>06.17</td>
<td>08.17</td>
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</table>

Added “at femoral neck or spine” to T score. Removed requirement that patient must be over 50 in cases where the osteoporosis diagnosis relies on history of an osteoporotic fracture. Added FRAX criteria for fracture risk. For cancer treatment induced bone loss criteria- amended to allow coverage of osteopenic members (T score < -1.0) with one additional risk factor for fracture since aromatase inhibitors/androgen deprivation therapy are already major risk factors.

Converted to new template.

All indications: Modified age requirement to apply to pediatric members with open epiphyses. Removed requirement for administration of calcium/vitamin D.

Osteoporosis: aligned diagnosis criteria with FDA approved indication (removed criteria related to males with primary osteoporosis or hypogonadal osteoporosis, and removed coverage of osteopenic members [T score < -1.0]).

Osteoporosis, prostate or breast cancer treatment-induced bone loss: Added “at total hip” to T score. Added that osteoporotic fracture should be confirmed by radiographic imaging.

Bone metastases, giant cell tumor of bone, hypercalcemia of malignancy: Added requirement for no concomitant use of Prolia. Modified initial/re-auth approval durations from 3/6 months to 6/12 months.

Re-auth: Combined Prolia and Xgeva criteria sets. Added requirement for documentation of positive response and max dosing.


**Important Reminder**

This clinical policy has been developed by appropriately experienced and licensed health care professionals based on a review and consideration of currently available generally accepted standards of medical practice; peer-reviewed medical literature; government agency/program approval status; evidence-based guidelines and positions of leading national health professional organizations; views of physicians practicing in relevant clinical areas affected by this clinical policy; and other available clinical information.

This Clinical Policy is not intended to dictate to providers how to practice medicine, nor does it constitute a contract or guarantee regarding payment or results. Providers are expected to exercise professional medical judgment in providing the most appropriate care, and are solely responsible for the medical advice and treatment of members.

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