

## Clinical Policy: Denosumab (Prolia, Xgeva)

Reference Number: ERX.SPMN.107

Effective Date: 10/16

Last Review Date: 09/16

[Coding Implications](#)

[Revision Log](#)

See [Important Reminder](#) at the end of this policy for important regulatory and legal information.

### Policy/Criteria

It is the policy of health plans affiliated with Envolve Pharmacy Solutions® that denosumab (Prolia®, Xgeva®) is **medically necessary** when the following criteria are met:

#### I. Initial Approval Criteria

##### A. Osteoporosis (must meet all):

1. Age  $\geq$  18 years;
2. Request is for Prolia;
3. Diagnosis of one of the following:
  - a. Postmenopausal osteoporosis;
  - b. Male with primary osteoporosis;
  - c. Male with hypogonadal osteoporosis who is receiving testosterone but remains at high risk for fracture or who has a contraindication to testosterone;
4. Member meets one of the following:
  - a. T-score  $\leq$  -2.5 (DXA) at the femoral neck or spine;
  - b. History of osteoporotic fracture;
  - c. T-score  $<$  -1.0 (DXA) at the femoral neck or spine with a 10-year probability of hip fracture  $\geq$  3% or a 10-year probability of a major osteoporosis-related fracture  $\geq$  20% per the WHO Fracture Risk Assessment Tool (FRAX)<sup>6</sup>;
5. Member had inadequate response (decline in BMD of  $\geq$  5% or continued fractures after one year of therapy) to oral bisphosphonate therapy and injectable ibandronate (Boniva) or zoledronic acid (Reclast) therapy, unless contraindicated or intolerant;
6. If member has received Reclast (zoledronic acid), one year has passed since use of Reclast;
7. Member has been counseled on and is receiving adequate vitamin D and/or calcium supplementation, if appropriate;
8. The prescribed dose of Prolia 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. Age  $\geq$  18 years;
2. Request is for Prolia;
3. Diagnosis of one of the following:
  - a. Female with breast cancer receiving adjuvant aromatase inhibitor therapy;

- b. Male with non-metastatic prostate cancer receiving androgen deprivation therapy;
- 4. Prior to therapy, meets one of the following:
  - a. T-score  $\leq$  -2.5 (DXA) at the femoral neck or spine;
  - b. History of osteoporotic fracture;
  - c. T-score  $<$  -1.0 (DXA) at the femoral neck or spine and one additional risk factor:
    - i. 10-year probability of hip fracture  $\geq$  3% per the WHO Fracture Risk Assessment Tool (FRAX);
    - ii. 10-year probability of a major osteoporosis-related fracture  $\geq$  20% per the WHO FRAX;
    - iii. Age  $>$  65 years;
    - iv. Glucocorticoid therapy at daily dosage equivalent to  $\geq$  7.5 mg of prednisone for at least 3 months;
    - v. Parental history of hip fracture;
    - vi. Low body mass index (BMI  $<$  20 kg/m<sup>2</sup>);
    - vii. Current cigarette smoking;
    - viii. Excessive alcohol consumption ( $\geq$  3 drinks/day);
    - ix. Rheumatoid arthritis;
- 3. Member has been counseled on and is receiving adequate vitamin D and/or calcium supplementation, if appropriate;
- 4. The prescribed dose of Prolia does not exceed 60 mg every 6 months.

**Approval duration: 12 months**

**C. Bone Metastases, Giant Cell Tumor of Bone, Hypercalcemia of Malignancy (must meet all):**

- 1. Request is for Xgeva for one of the following purposes:
  - b. Prevention of skeletal-related events in the presence of bone metastases from solid tumors (this does not include multiple myeloma);
    - i. Age  $\geq$  18 years;
    - ii. Prescribed dose of Xgeva does not exceed 120 mg every 4 weeks;
    - iii. Receiving calcium and vitamin D, if necessary, to treat or prevent hypocalcemia;
  - c. 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;
    - i. Meets one of the following age requirements:
      - a. Age  $\geq$  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  $\geq$  45 kg;
    - ii. Prescribed dose of Xgeva does not exceed 120 mg every 4 weeks with additional 120 mg doses on days 8 and 15 of the first month of therapy;

- iii. Receiving calcium and vitamin D, if necessary, to treat or prevent hypocalcemia;
- d. Treatment of hypercalcemia of malignancy refractory to bisphosphonate therapy;
  - i. Age  $\geq$  18 years;
  - ii. Albumin-corrected calcium of  $> 12.5$  mg/dL despite treatment with intravenous bisphosphonate therapy in the 30 days prior to initiation of Xgeva therapy;
  - iii. Prescribed dose of Xgeva does not exceed 120 mg every 4 weeks with additional 120 mg doses on days 8 and 15 of the first month of therapy.

**Approval duration: 3 months**

**D. Other diagnoses/indications:** Refer to ERX.SPMN.16 - Global Biopharm Policy.

**II. Continued Approval**

**A. Prolia (must meet all):**

- 1. Currently receiving medication via health plan benefit or member has previously met all initial approval criteria.

**Approval duration: 12 months**

**B. Xgeva (must meet all):**

- 1. Currently receiving medication via health plan benefit or member has previously met all initial approval criteria;
- 2. If hypercalcemia of malignancy, has not achieved complete response as indicated by corrected serum calcium  $< 10.8$  mg/dL.

**Approval duration: 6 months**

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

- 1. Currently receiving medication via health plan benefit and documentation supports positive response to therapy; or
- 2. Refer to ERX.SPMN.16 - Global Biopharm Policy.

**Background**

*Description/Mechanism of Action:*

Denosumab is a human IgG2 monoclonal antibody with affinity and specificity for human RANKL (receptor activator of nuclear factor kappa-B ligand). Denosumab binds to RANKL, a transmembrane or soluble protein essential for the formation, function, and survival of osteoclasts, the cells responsible for bone resorption. 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 and their precursors. Prevention of the RANKL/RANK interaction inhibits osteoclast formation, function, and survival, thereby decreasing bone resorption and increasing bone mass and strength in both cortical and trabecular bone.

*FDA Approved Indications:*

Prolia (denosumab) is a RANK ligand (RANKL) inhibitor/subcutaneous injectable solution indicated for:

- Treatment of postmenopausal women with osteoporosis at high risk for fracture\*. In postmenopausal women with osteoporosis, Prolia reduces the incidence of vertebral, nonvertebral, and hip fractures.
- 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.
- 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.
- 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, multiple risk factors for fracture, or patients who have failed or are intolerant to other available osteoporosis therapy.*

Xgeva (denosumab) is a RANK ligand (RANKL) inhibitor/subcutaneous injection indicated for:

- Xgeva is indicated for the prevention of skeletal-related events in patients with bone metastases from solid tumors.  
Limitation of use: Xgeva is not indicated for the prevention of skeletal-related events in patients with multiple myeloma.
- 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.
- Treatment of hypercalcemia of malignancy refractory to bisphosphonate therapy.

**Appendices**

**Appendix A: Abbreviation Key**

BMD: bone mineral density

DXA: dual energy X-ray absorptiometry

FRAX: WHO Fracture Risk Assessment Tool

**Coding Implications**

Codes referenced in this clinical policy are for informational purposes only. Inclusion or exclusion of any codes does not guarantee coverage. Providers should reference the most up-to-date sources of professional coding guidance prior to the submission of claims for reimbursement of covered services.

HCPCS Codes	Description
J0897	Injection, denosumab, 1 mg

Reviews, Revisions, and Approvals	Date	Approval Date
<p>Policy split from USS.CP.PHAR.20 Osteoporosis Injectable Therapy, combined with Xgeva, and converted to new template.</p> <p><u>Xgeva:</u>                      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.</p> <p><u>Prolia:</u>                      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. 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 &lt; -1.0) with one additional risk factor for fracture since</p>		09/16

Reviews, Revisions, and Approvals	Date	Approval Date
aromatase inhibitors/androgen deprivation therapy are already major risk factors.		

**References**

1. Prolia Prescribing Information. Irvine, CA: Spectrum Pharmaceuticals, Inc.; February 2015. Available at <http://www.prolia.com>. Accessed February 3, 2016.
2. Rosen HN, Drezner MK. Clinical manifestations, diagnosis, and evaluation of osteoporosis in postmenopausal women. In: UpToDate, Waltham, MA: Walters Kluwer Health; 2016. Available at UpToDate.com. Accessed February 12, 2016.
3. Rosen HN, Drezner MK. Overview of the management of osteoporosis in postmenopausal women. In: UpToDate, Waltham, MA: Walters Kluwer Health; 2016. Available at UpToDate.com. Accessed February 9, 2016.
4. Rosen HN. The use of bisphosphonates in postmenopausal women with osteoporosis. In: UpToDate, Waltham, MA: Walters Kluwer Health; 2016. Available at UpToDate.com. Accessed February 12, 2016.
5. Finkelstein JS. Treatment of osteoporosis in men. In: UpToDate, Waltham, MA: Walters Kluwer Health; 2016. Available at UpToDate.com. Accessed February 12, 2016.
6. FRAX: WHO Fracture Risk Assessment Tool. Available at <http://www.shef.ac.uk/FRAX/>. Accessed February 16, 2016.
7. Xgeva Prescribing Information. Thousand Oaks, CA: Amgen Inc.; June 2015.
8. Prostate cancer (Version 2.2016). In: National Comprehensive Cancer Network Guidelines. Available at NCCN.org. Accessed February 16, 2016.
9. Breast cancer (Version 1.2016). In: National Comprehensive Cancer Network Guidelines. Available at NCCN.org. Accessed February 16, 2016.

**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.

This policy is the property of Envolve Pharmacy Solutions. Unauthorized copying, use, and distribution of this Policy or any information contained herein is strictly prohibited. By accessing this policy, you agree to be bound by the foregoing terms and conditions, in addition to the Site Use Agreement for Health Plans associated with Envolve Pharmacy Solutions.

©2016 Envolve Pharmacy Solutions. All rights reserved. All materials are exclusively owned by Envolve Pharmacy Solutions and are protected by United States copyright law and international copyright law. No part of this publication may be reproduced, copied, modified, distributed, displayed, stored in a retrieval system, transmitted in any form or by any means, or otherwise published without the prior written permission of Envolve Pharmacy Solutions. You may not alter or remove any trademark, copyright or other notice contained herein.