Clinical Policy Title:	denosumab
Policy Number:	RxA.313
Drug(s) Applied:	Prolia®, Xgeva®
Original Policy Date:	02/07/2020
Last Review Date:	03/09/2021
Line of Business Policy Applies to:	All lines of Business

Background

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

- For the treatment of postmenopausal women with osteoporosis (OP) at high risk for fracture*, or patients who have failed or are intolerant to other available OP therapy. In postmenopausal women with OP, Prolia reduces the incidence of vertebral, nonvertebral, and hip fractures.
- For the treatment to increase bone mass in men with OP at high risk for fracture*, or patients who have failed or are intolerant to other available OP 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.
- For the treatment of glucocorticoid-induced osteoporosis in men and women at high risk of fracture* who are either initiating or continuing systemic glucocorticoids in a daily dosage equivalent to ≥ 7.5 mg of prednisone and expected to remain on glucocorticoids for ≥ 6 months.

**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 OP therapy.*

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.

Dosing Information

Drug Name	Indication	Dosing Regimen	Maximum Dose
denosumab (Prolia®)	Postmenopausal women with osteoporosis (PMO)	60 mg SC once every 6 months	60 mg/dose
	Men with osteoporosis		
	Men at high risk for fracture receiving androgen deprivation		

Drug Name	Indication	Dosing Regimen	Maximum Dose
	therapy for nonmetastatic prostate cancer		
	Women at high risk for fracture receiving adjuvant aromatase inhibitor therapy for breast cancer		
	Glucocorticoid-induced osteoporosis (GIO)		
denosumab (Xgeva®)	Multiple myeloma and bone metastasis from solid tumors	120 mg SC once every 4 weeks	20 mg/dose
	Giant cell tumor of bone	120 mg SC every 4 weeks with additional 120 mg doses on Days 8 and 15 of the first month of therapy only	120 mg/dose
	Hypercalcemia of malignancy		

Dosage Forms

- Denosumab (Prolia®): Injection (single-use prefilled syringe): 60 mg/mL
- Denosumab (Xgeva®): Injection (single-use vial): 120 mg/1.7 mL (70 mg/mL)

Clinical Policy

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

I. Initial Approval Criteria

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

1. Request is for Prolia®;
2. Diagnosis of PMO, GIO, or male osteoporosis and (a or b):
   a. Member is at very high risk for fracture (i or ii):
      i. BMD T-score at hip or spine ≤ -3.5;
      ii. BMD T-score at hip or spine ≤ -2.5 and major osteoporotic fracture (i.e., hip, spine, forearm, wrist, humerus);
   b. Failure of a 12-month trial of an oral bisphosphonate (alendronate is preferred) at up to maximally indicated doses, unless contraindicated or clinically significant adverse effects are experienced;
   **Prior authorization may be required for bisphosphonates*
3. Age 18 years or older or documentation of closed epiphyses;
4. Prolia® is prescribed by or in consultation with one of the following specialists: a gynecologist, endocrinologist, rheumatologist, geriatrician, orthopedist, or physiatrist;
5. Member is not using Xgeva® concomitantly;
6. Dose does not exceed 60 mg every 6 months.

Approval duration
Commercial: 12 months
Medicaid: 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. Prescribed by or in consultation with an oncologist;
4. Age 18 years of age or older or documentation of closed epiphyses;
5. Member is not using Xgeva® concomitantly;
6. Dose does not exceed 60 mg every 6 months.

Approval duration
Commercial: 12 months
Medicaid: 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 of age or older 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 of age or older;
         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 of age or older 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
Commercial: 12 months
Medicaid: 12 months

D. Systemic Mastocytosis (off-label) (must meet all)**:**

1. Request is for Xgeva®;
2. Diagnosis of systemic mastocytosis;
3. Member has osteopenia or osteoporosis with bone pain;
4. Prescribed by or in consultation with an oncologist;
5. Age 18 years of age or older or documentation of closed epiphyses;

6. Member is not using Prolia® concomitantly;
7. Dose is supported by peer-reviewed literature (prescriber must submit supporting evidence).

Approval duration
Commercial: 6 months
Medicaid: 6 months

E. Other Off-label Indications (must meet all)**:**

1. Request is for Xgeva®;
2. Diagnosis is for one of the following (a, b, c, d):
   a. Kidney cancer (used as a component of best supportive care for bony metastases);
   b. Non-small cell lung cancer (consider for supportive therapy in patients with bone metastases)
   c. Invasive breast cancer (used with calcium and Vitamin D supplementation in addition to chemotherapy or endocrine therapy for bone metastasis in patients with expected survival of ≥ 3 months and adequate renal function;
   d. Thyroid carcinoma (medullary, follicular, papillary, anaplastic & hurthle cell carcinoma) – consider as palliative care for bone metastases;
3. Prescribed by or in consultation with an oncologist;
4. Age 18 years of age or older;
5. Member is not using Prolia® concomitantly;
6. Dose is within FDA maximum limit for any FDA-approved indication or is supported by peer-reviewed literature for the relevant off-label use (prescriber must submit supporting evidence.

Approval duration
Commercial: 6 months
Medicaid: 6 months

II. Continued Therapy Approval

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

1. Member meets one of the following (a or b):
   a. Member is currently receiving medication that has been authorized by RxAdvance or member has previously met initial approval criteria listed in this policy;
   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
Commercial: 12 months
Medicaid: 12 months

III. Appendices

APPENDIX A: Abbreviation/Acronym Key

FDA: Food and Drug Administration
MM: multiple myeloma
OP: osteoporosis
PMO: postmenopausal women with osteoporosis
GIO: glucocorticoid-induced osteoporosis

BMD: bone mineral density

APPENDIX B: Therapeutic Alternatives

Below are suggested therapeutic alternatives based on clinical guidance. Please check drug formulary for preferred agents and utilization management requirements.

Drug Name	Dosing Regimen	Dose Limit/ Maximum Dose
alendronate (Fosamax®)	**Osteoporosis** :10 mg PO once daily or 70 mg PO every week **Glucocorticoid-induced osteoporosis** 5 mg PO once daily or 10 mg PO once daily (in postmenopausal women not receiving estrogen) **Osteoporosis prophylaxis** 5 mg PO once daily or 35 mg PO every week	Osteoporosis 10 mg/day or 70 mg/week Glucocorticoid-induced osteoporosis 5 mg/day or 10 mg/day (in postmenopausal women not receiving estrogen) Osteoporosis prophylaxis 5 mg/day or 35 mg/week
Fosamax® Plus D (alendronate/ cholecalciferol)	**Osteoporosis** 70 mg alendronate/2,800 units cholecalciferol or 70 mg alendronate/5,600 units cholecalciferol PO every week	70 mg alendronate/5,600 units cholecalciferol/week
Risedronate (Actonel®, Atelvia®)	**Osteoporosis (including prophylaxis)** 5 mg PO once daily or 35 mg PO every week or 75 mg PO once daily for 2 consecutive days for 2 doses/month or 150 mg PO every month **Glucocorticoid-induced osteoporosis** 5 mg PO once daily	Osteoporosis (including prophylaxis) 5 mg/day or 35 mg/week or 75 mg/day for 2 days per month or 150 mg/month Glucocorticoid-induced osteoporosis 5 mg/day
ibandronate (Boniva®)	**Osteoporosis (including prophylaxis)** 150 mg PO every month	150 mg/month

Drug Name	Dosing Regimen	Dose Limit/ Maximum Dose
zoledronic acid (Reclast®)	**Postmenopausal Osteoporosis, Men with Osteoporosis, Glucocorticoid induced Osteoporosis:** 5 mg IV every year	Postmenopausal Osteoporosis, Men with Osteoporosis, Glucocorticoid-induced Osteoporosis 5 mg/year
	Postmenopausal Osteoporosis prophylaxis 5 mg IV every 2 years	Postmenopausal Osteoporosis Prophylaxis 5 mg/2 years
	Paget's Disease of Bone 5 mg IV once; may re-treat in patients who have relapsed or who have symptoms	Paget's Disease of Bone 5 mg

Therapeutic alternatives are listed as Brand name® (generic) when the drug is available by brand name only and generic (Brand name®) when the drug is available by both brand and generic.

APPENDIX C: Contraindications/Boxed Warnings

- Contraindication(s):
  - Prolia®: hypocalcemia, pregnancy, and known hypersensitivity to Prolia®.
  - Xgeva®: hypocalcemia and known clinically significant hypersensitivity to Xgeva®.

- Boxed warning(s):
  - none reported

APPENDIX D: General Information

The World Health Organization uses the following classifications for osteoporosis and osteopenia:

Category	T-Score
Normal	-1.0 or above
Low bone mass (osteopenia)	Between -1.0 and -2.5
Osteoporosis	-2.5 or below

References

1. Prolia Prescribing Information. Thousand Oaks, CA: Amgen Inc.; March 2020. Available at: http://www.prolia.com. Accessed January 19, 2021.
2. FRAX: WHO Fracture Risk Assessment Tool. Available at http://www.shef.ac.uk/FRAX/. Accessed January 19, 2021.
3. Xgeva Prescribing Information. Thousand Oaks, CA: Amgen Inc.; June 2020. Available at: http://www.xgeva.com. Accessed January 19, 2021.
4. National Comprehensive Cancer Network Drugs and Biologics Compendium. Available at www.nccn.org. Accessed February 18, 2021.
5. National Comprehensive Cancer Network. Prostate Cancer Version 2.2021. Available at: https://www.nccn.org/professionals/physician_gls/pdf/prostate.pdf . Accessed January 19, 2021.

6. National Comprehensive Cancer Network. Breast Cancer Version 1.2021. Available at: https://www.nccn.org/professionals/physician_gls/pdf/breast.pdf . Accessed January 19, 2021.
7. Gralow JR, Biermann JS, Farooki A, et al. NCCN task force report: bone health in cancer care. Journal of the NCCN. 2013; 11(S3): S1-S50. Accessed on January 19, 2021.
8. Cosman F, de Beur SJ, LeBoff MS, et al. Position paper: clinician's guide to prevention and treatment of osteoporosis. Osteoporosis Int. 2014; 25(10): 2359-2381. Accessed on January 19, 2021
9. Camacho PM, Petak SM, Binkley N, et al. American Association of Clinical Endocrinologists and American College of Endocrinology practice guidelines for the diagnosis and treatment of postmenopausal osteoporosis – 2016. Endocrin Pract. 2016; 22(Suppl 4). Accessed on January 19, 2021.
10. Watts NB, Adler RA, Bilezikian JP, et al. Osteoporosis in men: an Endocrine Society clinical practice guideline. J Clin Endocrinol Metab. 2012; 97(6): 1802-1822. Accessed on January 19, 2021.
11. Denosumab. In: National Comprehensive Cancer Network Drugs and Biologics Compendium. Available at NCCN.org. Accessed January 19, 2021.
12. Buckley L, Guyatt G, Fink HA, et al. American College of Rheumatologist guideline for the prevention and treatment of glucocorticoid-induced osteoporosis. 2017; Arthritis & Rheumatology: 69(8):1521-1537 DOI 10.1002/art.40137
13. Exams and test for osteoporosis. Available at https://www.spineuniverse.com/conditions/osteoporosis/exams-tests-osteoporosis . Accessed January 19, 2021.

Review/Revision History	Review/Revision Date	P&T Approval Date
Policy established.	01/2020	02/07/2020
Policy was reviewed: 1. Policy title table was updated. 2. Line of Business Policy Applies to was update to "All lines of business". 3. Initial approval duration for all indications was updated to 6 months, and continued approval duration was updated to 12 months. 4. Continued Therapy criteria II.A.1 was rephrased to "Currently receiving medication that has been authorized by RxAdvance..." 5. APPENDIX D: General Information added. 6. References were updated.	07/31/2020	09/14/2020
Policy was reviewed: 1. Osteoporosis: Initial criteria I.A.4 was updated. 2. Initial approval duration was updated to 12 months. 3. Approval criteria for systemic mastocytosis and other NCCN recommended off-label indications were added. 4. References were reviewed and updated	01/19/2021	03/09/2021