Clinical Policy: Denosumab (Prolia, Xgeva)

Reference Number: CP.PHAR.58
Effective Date: 03.01.11
Last Review Date: 02.19
Line of Business: Commercial, HIM, Medicaid

Coding Implications
Revision Log

See Important Reminder at the end of this policy for important regulatory and legal information.

Description

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

FDA Approved Indication(s)

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

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 Centene Corporation® 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. Age ≥ 18 years or documentation of closed epiphyses;
4. 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 (*alendronate is preferred*) at up to maximally indicated doses, unless contraindicated or clinically significant adverse effects are experienced;
5. Failure of a 12-month trial of zoledronic acid (Reclast®) unless contraindicated or clinically significant adverse effects are experienced;
   **Prior authorization is required for zoledronic acid*
6. Member is not using Xgeva concomitantly;
7. Dose does not exceed 60 mg every 6 months.

Approval duration:
Medicaid/HIM – 12 months
Commercial – 6 months or to the member's renewal date, whichever is longer

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. Member is not using Xgeva concomitantly;
5. Dose does not exceed 60 mg every 6 months.

Approval duration:
Medicaid/HIM – 12 months
Commercial – 6 months or to the member's renewal date, whichever is longer

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:
Medicaid/HIM – 6 months
Commercial – 6 months or to the member's renewal date, whichever is longer

D. Other diagnoses/indications

1. Refer to the off-label use policy for the relevant line of business if diagnosis is NOT specifically listed under section III (Diagnoses/Indications for which coverage is NOT authorized): CP.CPA.09 for commercial, HIM.PHAR.21 for health insurance marketplace, and CP.PMN.53 for Medicaid.

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 Centene benefit 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:
Medicaid/HIM – 12 months
Commercial – 6 months or to the member's renewal date, whichever is longer

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

1. Currently receiving medication via Centene benefit and documentation supports positive response to therapy.
   Approval duration: Duration of request or 6 months (whichever is less); or

2. Refer to the off-label use policy for the relevant line of business if diagnosis is NOT specifically listed under section III (Diagnoses/Indications for which coverage is NOT authorized): CP.CPA.09 for commercial, HIM.PHAR.21 for health insurance marketplace, and CP.PMN.53 for Medicaid.

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 policies – CP.CPA.09 for commercial, HIM.PHAR.21 for health insurance marketplace, and CP.PMN.53 for Medicaid or evidence of coverage documents.

IV. Appendices/General Information

Appendix A: Abbreviation/Acronym Key

FDA: Food and Drug Administration OP: osteoporosis

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 for all relevant lines of business and may require prior authorization.

Drug Name	Dosing Regimen	Dose Limit/ Maximum Dose
alendronate (Fosamax®)	**Osteoporosis** 10 mg PO QD or 70 mg PO q week **Glucocorticoid-induced osteoporosis** 5 mg PO QD or 10 mg PO QD (in postmenopausal women not receiving estrogen) **Osteoporosis prophylaxis** 5 mg PO QD or 35 mg PO q 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 q week	70 mg alendronate/5,600 units cholecalciferol/week
risedronate (Actonel®, Atelvia®)	**Osteoporosis (including prophylaxis)** 5 mg PO QD or 35 mg PO q week or 75 mg PO QD for 2 consecutive days for 2 doses/month or 150 mg PO q month **Glucocorticoid-induced osteoporosis** 5 mg PO QD	Osteoporosis (including prophylaxis) 5 mg/day or 35 mg/week or 75 mg/day for 2 days per month or 150 mg/month

Drug Name	Dosing Regimen	Dose Limit/ Maximum Dose
		Glucocorticoid-induced osteoporosis 5 mg/day
ibandronate (Boniva®)	**Osteoporosis (including prophylaxis)** 150 mg PO q month	150 mg/month
zoledronic acid (Reclast®)	**Postmenopausal Osteoporosis, Men with Osteoporosis, Glucocorticoid-induced Osteoporosis** 5 mg IV q year **Postmenopausal Osteoporosis prophylaxis** 5 mg IV q 2 years **Paget's Disease of Bone** 5 mg IV once; may re-treat in patients who have relapsed or who have symptoms	Postmenopausal Osteoporosis, Men with Osteoporosis, Glucocorticoid-induced Osteoporosis 5 mg/year Postmenopausal Osteoporosis Prophylaxis 5 mg/2 years 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

- Prolia: hypocalcemia, pregnancy
- Xgeva: hypocalcemia

V. Dosage and Administration

Drug Name	Indication	Dosing Regimen	Maximum Dose
Denosumab (Prolia)	Postmenopausal women with osteoporosis	60 mg SC once every 6 months	60 mg/dose
	Men with osteoporosis		
	Men at high risk for fracture receiving androgen deprivation therapy for nonmetastatic prostate cancer		
	Women at high risk for fracture receiving adjuvant aromatase inhibitor therapy for breast cancer		
	Glucocorticoid-induced osteoporosis		
Denosumab (Xgeva)	Multiple myeloma and bone metastasis from solid tumors	120 mg SC once every 4 weeks	120 mg/dose

Drug Name	Indication	Dosing Regimen	Maximum 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		

VI. Product Availability

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

VII. References

1. Prolia Prescribing Information. Thousand Oaks, CA: Amgen Inc.; May 2018. Available at http://www.prolia.com. Accessed June 1, 2018.
2. FRAX: WHO Fracture Risk Assessment Tool. Available at http://www.shef.ac.uk/FRAX/. Accessed June 19, 2017.
3. Xgeva Prescribing Information. Thousand Oaks, CA: Amgen Inc.; January 2018. Available at http://www.xgeva.com. Accessed February 8, 2018.
4. Prostate cancer (Version 2.2017). In: National Comprehensive Cancer Network Guidelines. Available at NCCN.org. Accessed February 8, 2018.
5. Breast cancer (Version 4.2017). In: National Comprehensive Cancer Network Guidelines. Available at NCCN.org. Accessed February 8, 2018.
6. 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.
7. 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.
8. 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).
9. 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.
10. Denosumab. In: National Comprehensive Cancer Network Drugs and Biologics Compendium. Available at NCCN.org. Accessed February 8, 2018.
11. 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

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	P&T Approval Date
Added FDA indication for giant cell tumors	03.14	03.14
Added FDA indication for hypercalcemia of malignancy. Updated background and safety information.	02.15	03.15
Changed approval periods to initial 3 months and continuation 6 months Converted algorithms into bullet points and adopted new template Removed Zometa and pamidronate trial as prerequisite for Xgeva In Reauthorization algorithm, 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 Table 1 safety concerns	08.15	10.15
Prolia split from CP.PHAR.20.Osteoporosis Injection Therapy, converted to new template and combined with Xgeva into denosumab policy. Criteria updated as follows: added max dosing, definition of bisphosphonate trial failure and, if contraindication/intolerance, that it be to one of the two oral drugs listed and to Reclast. Calcium/vitamin D requirement language edited to be less specific. Osteoporosis criteria: for men with osteoporosis, criteria added to require testosterone for hypogonadal osteoporosis. Added "at femoral neck or spine" to T score. Added FRAX criteria for fracture risk. Removed requirement that patient must be over 50 in cases where the osteoporosis diagnosis relies on history of an osteoporotic fracture. Cancer treatment induced bone loss criteria: risk of fracture criteria in these populations is informed by FRAX calculations/recommendations. Criteria changes to Xgeva: For members under 18 with giant cell tumor of the bone, added definition of skeletal maturity per PI. Added max dosing.	02.16	03.16
Edited I.A.4. to acknowledge option "c" – "T-score <-1.0..." by stating "one of the following" rather than "a or b". 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.	06.16	08.16

Reviews, Revisions, and Approvals	Date	P&T Approval Date
Under Section B, "Prostate or Breast Cancer Treatment – Induced Bone Loss", amended criteria 4 to allow coverage of osteopenic members (T score < -1.0) with one additional risk factor for fracture.	08.16	08.16
All indications: Modified age requirement to apply to pediatric members with open epiphyses. Removed requirement for administration of calcium/vitamin D. Removed hypersensitivity contraindication. Split hypocalcemia contraindication into its own criterion and specified time frame for which lab result is acceptable. Osteoporosis: removed criteria related to males with primary osteoporosis or hypogondal 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: Modified intial/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; removed reasons to discontinue.	06.17	08.17
2Q2018 annual review: policies combined for commercial and Medicaid lines of business; added HIM line of business to the policy. Commercial: combined CP.CPA.170 (Xgeva) and CP.CPA.202 (Prolia); added age and requirement for no concomitant use of Prolia/Xgeva; modified approval duration from length of benefit to 6 months or to the member's renewal date, whichever is longer; allowed COC for oncology related indications on re-auth; Osteoporosis: added specialist or failure of an on oral bisphosphonate requirement; added trial/failure of zoledronic acid (Reclast); Prostate/Breast Cancer treatment: added requirement related to risk assessment; Hypercalcemia: added lab requirement for albumin-corrected calcium > 12.5 mg/dL Medicaid: All indications: removed requirements related to pregnancy (for Prolia) and hypocalcemia monitoring; allowed COC for oncology related indications on re-auth; Osteoporosis: Modified diagnosis criterion by removing requirement for evidence of diagnosis; added specialist requirement as an option in lieu of bisphosphonate trial; Criteria added for new FDA indication: multiple myeloma; added Appendix C: Contraindications; references reviewed and updated.	02.20.18	05.18
Criteria added for new FDA indication for Prolia: glucocorticoid-induced osteoporosis; removed requirement for objective diagnosis of high fracture risk osteoporosis in prostate or breast cancer treatment with induced bone loss; references reviewed and updated.	06.26.18	02.19

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. The Health Plan makes no representations and accepts no liability with respect to the content of any external information used or relied upon in developing this clinical policy. This clinical policy is consistent with standards of medical practice current at the time that this clinical policy was approved. "Health Plan" means a health plan that has adopted this clinical policy and that is operated or administered, in whole or in part, by Centene Management Company, LLC, or any of such health plan's affiliates, as applicable.

The purpose of this clinical policy is to provide a guide to medical necessity, which is a component of the guidelines used to assist in making coverage decisions and administering benefits. It does not constitute a contract or guarantee regarding payment or results. Coverage decisions and the administration of benefits are subject to all terms, conditions, exclusions and limitations of the coverage documents (e.g., evidence of coverage, certificate of coverage, policy, contract of insurance, etc.), as well as to state and federal requirements and applicable Health Plan-level administrative policies and procedures.

This clinical policy is effective as of the date determined by the Health Plan. The date of posting may not be the effective date of this clinical policy. This clinical policy may be subject to applicable legal and regulatory requirements relating to provider notification. If there is a discrepancy between the effective date of this clinical policy and any applicable legal or regulatory requirement, the requirements of law and regulation shall govern. The Health Plan retains the right to change, amend or withdraw this clinical policy, and additional clinical policies may be developed and adopted as needed, at any time.

This clinical policy does not constitute medical advice, medical treatment or medical care. It is not intended to dictate to providers how to practice medicine. 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 clinical policy is not intended to recommend treatment for members. Members should consult with their treating physician in connection with diagnosis and treatment decisions.

Providers referred to in this clinical policy are independent contractors who exercise independent judgment and over whom the Health Plan has no control or right of control. Providers are not agents or employees of the Health Plan.

This clinical policy is the property of the Health Plan. Unauthorized copying, use, and distribution of this clinical policy or any information contained herein are strictly prohibited. Providers, members and their representatives are bound to the terms and conditions expressed herein through the terms of their contracts. Where no such contract exists, providers, members and their representatives agree to be bound by such terms and conditions by providing services to members and/or submitting claims for payment for such services.

Note:
For Medicaid members, when state Medicaid coverage provisions conflict with the coverage provisions in this clinical policy, state Medicaid coverage provisions take precedence. Please refer to the state Medicaid manual for any coverage provisions pertaining to this clinical policy.

For Health Insurance Marketplace members, when applicable, this policy applies only when the prescribed agent is on your health plan approved formulary. Request for non-formulary drugs must be reviewed using the formulary exception policy.