

Clinical Policy: Denosumab (Prolia, Xgeva)

Reference Number: CP.PHAR.58

Effective Date: 03.01.11

Last Review Date: 02.20

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:

- **Postmenopausal osteoporosis (PMO):** 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.
- **Male osteoporosis:** For the 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.
- **Male osteoporosis - oncology:** For treatment to increase bone mass in men at high risk for fracture* receiving androgen deprivation therapy (ADT) for nonmetastatic prostate cancer. In these patients Prolia also reduced the incidence of vertebral fractures.
- **Female osteoporosis - oncology:** For treatment to increase bone mass in women at high risk for fracture* receiving adjuvant aromatase inhibitor therapy for breast cancer.
- **Glucocorticoid-induced osteoporosis (GIO):** For the treatment of GIO 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 osteoporosis therapy.*

Xgeva is indicated:

- **Multiple myeloma (MM) and solid tumors:** For the prevention of skeletal-related events in patients with MM and in patients with bone metastases from solid tumors.
- **Giant cell tumor of the bone:** 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.
- **Hypercalcemia of malignancy:** 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.

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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 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. Member has completed a 3-year trial of bisphosphonate therapy (*alendronate is preferred*) at up to maximally indicated doses unless contraindicated or clinically significant adverse effects are experienced to both IV and PO formulations (*see Appendix D*);
**Prior authorization may be required for bisphosphonates*
3. Age ≥ 18 years or documentation of closed epiphyses on x-ray;
4. *Prolia* is not prescribed concurrently with *Xgeva*;
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

B. Prostate/Breast Cancer - Fracture Prevention (must meet all):

1. Request is for *Prolia*;
2. One of the following diagnoses (a or b):

- a. Prostate cancer and member is receiving ADT (e.g., leuprolide (Lupron[®]), bicalutamide (Casodex[®]) or Nilandron[®]);
- b. Breast cancer and member is receiving adjuvant endocrine therapy (e.g., tamoxifen or aromatase inhibitors such as anastrozole (Arimidex[®]), exemestane (Aromasin[®]) or letrozole (Femara[®]));
3. Prescribed by or in consultation with an oncologist;
4. Age \geq 18 years or documentation of closed epiphyses on x-ray;
5. Prolia is not prescribed concurrently with Xgeva;
6. 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. Multiple Myeloma or Solid Tumor (must meet all):

1. Request is for Xgeva;
2. Diagnosis of one of the following (a or b):
 - a. MM;
 - b. Bony metastasis from solid tumor (e.g., breast, kidney, lung, prostate, thyroid);
3. Member is at risk for a skeletal-related event (e.g., pathologic fracture, radiation therapy or surgery to bone, spinal cord compression);
4. Prescribed by or in consultation with an oncologist;
5. Age \geq 18 years or documentation of closed epiphyses on x-ray;
6. Xgeva is not prescribed concurrently with Prolia;
7. Dose does not exceed 120 mg every 4 weeks.

Approval duration:

Medicaid/HIM – 6 months

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

D. Giant Cell Tumor of Bone (must meet all):

1. Request is for Xgeva;
2. Diagnosis of giant cell tumor of bone (a or b):
 - a. Metastatic or unresectable disease;
 - b. Localized disease and Xgeva is prescribed as a single agent or in combination with interfereon alfa or radiation therapy;
3. Prescribed by or in consultation with an oncologist;
4. Age \geq 18 years or documentation of closed epiphyses on x-ray;
5. Xgeva is not prescribed concurrently with Prolia;
6. Dose does not exceed 120 mg every 4 weeks plus 120 mg on days 8 and 15 of first month of therapy.

Approval duration:

Medicaid/HIM – 6 months

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

E. Hypercalcemia of Malignancy (must meet all):

1. Request is for Xgeva;
2. Diagnosis of hypercalcemia of malignancy:

3. Prescribed by or in consultation with an oncologist;
4. Age \geq 18 years or documentation of closed epiphyses on x-ray;
5. Albumin-corrected calcium $>$ 12.5 mg/dL despite IV bisphosphonate therapy in the last 30 days;
6. Xgeva is not prescribed concurrently with Prolia;
7. Dose does not exceed 120 mg every 4 weeks plus 120 mg on days 8 and 15 of first month of therapy.

Approval duration:

Medicaid/HIM – 6 months

Commercial – 6 months or to the member’s renewal date, whichever is longer

F. 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 \geq 18 years or documentation of closed epiphyses on x-ray;
6. Failure of zoledronic acid (Zometa[®]) at up to maximally indicated doses unless contraindicated or clinically significant adverse effects are experienced (*Appendix D*);
**Prior authorization may be required.*
7. Xgeva is not prescribed concurrently with Prolia;
8. Dose is within FDA maximum limit for any FDA-approved indication or is supported by practice guidelines or peer-reviewed literature for the relevant off-label use (prescriber must submit supporting evidence).*

**Prescribed regimen must be FDA-approved or recommended by NCCN.*

Approval duration:

Medicaid/HIM – 6 months

Commercial – 6 months or to the member’s renewal date, whichever is longer

G. 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 or Xgeva for a covered cancer-related indication and has received this medication for at least 30 days;
2. Member is responding positively to therapy;
3. If request is for a dose increase, new dose does not exceed (a or b):
 - a. Prolia: 60 mg every 6 months;

- b. Xgeva: 120 mg every 4 weeks or is supported by practice guidelines or peer-reviewed literature for the relevant off-label use (prescriber must submit supporting evidence).*

*Prescribed regimen must be FDA-approved or recommended by NCCN.

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

ADT: androgen deprivation therapy

BMD: bone mineral density

FDA: Food and Drug Administration

GIO: glucocorticoid-induced osteoporosis

MM: multiple myeloma

PMO: postmenopausal 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
<i>IV bisphosphonates</i>		
ibandronate (Boniva)	Treatment: PMO <i>See prescribing information for dose.</i>	Varies
zoledronic acid (Reclast [®] ; Zometa)	Reclast: Treatment/prevention: PMO, GIO Treatment: male osteoporosis Treatment: Paget disease Zometa: Oncology-related indications including <ul style="list-style-type: none"> • hypercalcemia of malignancy, and • systemic mastocytosis (<i>off-label</i>) 	

Drug Name	Dosing Regimen	Dose Limit/ Maximum Dose
	<i>See prescribing information for dose.</i>	
Oral bisphosphonates		
alendronate (Fosamax [®])	Treatment/prevention: PMO Treatment: GIO, male osteoporosis Treatment: Paget disease <i>See prescribing information for dose.</i>	Varies
Fosamax [®] Plus D (alendronate / cholecalciferol)	Treatment: PMO, male osteoporosis <i>See prescribing information for dose.</i>	
risedronate (Actonel [®] , Atelvia [®])	Actonel: Treatment/prevention: PMO, GIO Treatment: male osteoporosis Treatment: Paget disease Atelvia: Treatment: PMO <i>See prescribing information for dose.</i>	
ibandronate (Boniva [®])	Treatment/prevention: PMO <i>See prescribing information for dose.</i>	

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, known hypersensitivity to Prolia
 - Xgeva: hypocalcemia, known clinically significant hypersensitivity to Xgeva
- Boxed warning(s): none reported

Appendix D: IV/PO Bisphosphonates: Examples of Contraindications and Adverse Effects

Bisphosphonates	Oral Formulations	IV Formulations
Contraindications		
Hypocalcemia	X	X
Increased risk of aspiration	X	-
Hypersensitivity to product component	X	X
Inability to stand/sit upright for at least 30 minutes	X	-
Creatinine clearance < 35 mL/min or evidence of acute renal impairment	-	X
Esophagus abnormalities which delay emptying such as stricture or achalasia	X	-
Clinically significant warnings or adverse side effects		
Pregnancy	X	X

Bisphosphonates	Oral Formulations	IV Formulations
Eye inflammation	X	X
Acute renal failure	X	X
Osteonecrosis of the jaw	X	X
Atypical femoral shaft fracture	X	X
Drug interactions (product-specific)	X	X
Severe or incapacitating musculoskeletal pain	X	X

V. Dosage and Administration

Drug Name	Indication	Dosing Regimen	Maximum Dose
Denosumab (Prolia)	Treatment: PMO, GIO, male osteoporosis	60 mg SC once every 6 months	60 mg/dose
	Oncology: fracture prevention - Men at high risk for fracture receiving ADT for nonmetastatic prostate cancer - Women at high risk for fracture receiving adjuvant aromatase inhibitor therapy for breast cancer		
Denosumab (Xgeva)	MM Solid tumor - bone metastasis	120 mg SC once every 4 weeks	20 mg/dose
	Giant cell tumor of bone Hypercalcemia of malignancy	120 mg SC every 4 weeks plus 120 mg on Days 8 and 15 of first month of therapy	120mg/dose

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.; July 2019. Available at: <http://www.prolia.com>. Accessed October 14, 2019.
 2. Xgeva Prescribing Information. Thousand Oaks, CA: Amgen Inc.; May 2019. Available at: <http://www.xgeva.com>. Accessed October 14, 2019.
 3. Clinical Pharmacology [database online]. Tampa, FL: Gold Standard, Inc.; 2019. URL: <http://www.clinicalpharmacology.com>.
- Osteoporosis Diagnosis, Fracture Risk, and Treatment*
4. Eastell R, Rosen CJ, Black DM, et al. Pharmacological management of osteoporosis in postmenopausal women: An Endocrine Society Clinical Practice Guideline. *J Clin Endocrinol Metab*; 2019, 104: 1595–1622.
 5. Camacho PM, Petak SM, Brinkley N et al. AACE/ACE Guidelines- American Association of Clinical Endocrinologists and American College of Endocrinology Clinical Practice

Guidelines for Diagnosis and Treatment of Postmenopausal Osteoporosis. Endocrine Practice Vol 22 (suppl 4) September 2016.

6. National Osteoporosis Foundation Clinician’s Guide to Prevention and Treatment of Osteoporosis. Osteoporosis International 2014. Available at: <http://nof.org/files/nof/public/content/file/2791/upload/919.pdf>. Accessed October 31, 2018.
7. Siris ES, Adler R, Bilezikian J, et al. The clinical diagnosis of osteoporosis: a position statement from the National Bone Health Alliance Working Group. Osteoporos Int (2014) 25:1439–1443. DOI 10.1007/s00198-014-2655-z.
8. Hodsman AB, Bauder DC, Dempster DW, et al. Parathyroid hormone and teriparatide for the treatment of osteoporosis: a review of the evidence and suggested guidelines for its use. Endocr Rev. 2005 Aug;26(5):688-703. Epub 2005 Mar 15.

Male Osteoporosis

9. Watts NB, Adler RA, Bilezikian JP, et al. Osteoporosis in men: an Endocrine Society clinical practice guidelines. J Clin Endocrinol Metab 2012;97(6):1802-1822.

Glucocorticoid-Induced Osteoporosis

10. Buckley L, Guyatt G, Fink HA, et al. 2017 American College of Rheumatology guideline for the prevention and treatment of glucocorticoid-induced osteoporosis. Arthritis Rheumatol. 2017; 69(8): 1521-1537.

Oncology

11. National Comprehensive Cancer Network Drugs and Biologics Compendium. Available at www.nccn.org. Accessed October 14, 2019.
12. National Comprehensive Cancer Network. Breast Cancer Version 3.2019. Available at: https://www.nccn.org/professionals/physician_gls/pdf/breast.pdf. Accessed October 14, 2019.
13. National Comprehensive Cancer Network. Prostate Cancer Version 4.2019. Available at: https://www.nccn.org/professionals/physician_gls/pdf/prostate.pdf. Accessed October 14, 2019.

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
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	02.16	03.16

Reviews, Revisions, and Approvals	Date	P&T Approval Date
<p>be to one of the two oral drugs listed and to Reclast. Calcium/vitamin D requirement language edited to be less specific.</p> <p>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.</p> <p>Removed requirement that patient must be over 50 in cases where the osteoporosis diagnosis relies on history of an osteoporotic fracture.</p> <p>Cancer treatment induced bone loss criteria: risk of fracture criteria in these populations is informed by FRAX calculations/recommendations.</p> <p>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.</p>		
<p>Edited I.A.4. to acknowledge option “c” – “T-score <-1.0...” by stating “one of the following” rather than “a or b”.</p> <p>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>	06.16	08.16
<p>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.</p>	08.16	08.16
<p>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.</p> <p>Osteoporosis: 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: Modified initial/re-auth approval durations from 3/6 months to 6/12 months.</p> <p>Re-auth: Combined Prolia and Xgeva criteria sets; added requirement for documentation of positive response and max dosing; removed reasons to discontinue.</p>	06.17	08.17
<p>2Q2018 annual review: policies combined for commercial and Medicaid lines of business; added HIM line of business to the policy.</p> <p>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</p>	02.20.18	05.18

Reviews, Revisions, and Approvals	Date	P&T Approval Date
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.		
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
2Q 2019 annual review: no significant changes; added geriatrician as a prescriber specialist option for osteoporosis; references reviewed and updated.	02.26.19	05.19
1Q 2020 annual review: removed HIM disclaimer for HIM NF drugs; Prolia: very high fracture risk or 3-year bisphosphonate trial added with required contraindication to both PO/IV formulations; specialists removed; age 18 or closed epiphyses added per PI; nonmetastatic limitation removed from prostate cancer per NCCN; breast cancer expanded to include men; Xgeva: examples of skeletal related event and solid tumor added; oncologist added; lower age limit and weight restriction removed from giant cell tumor to include NCCN recommended localized disease; NCCN recommended use for systemic mastocytosis added with Zometa trial; hypercalcemia continuation of therapy criteria removed given response fluidity; references reviewed and updated.	11.19.19	02.20

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.

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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.

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