Clinical Policy: Denosumab (~~Prolia,~~ Xgeva)

Reference Number: LA.PHAR.58
Effective Date: 04.21
Last Review Date: 0~~4~~1.2~~1~~2 **Coding Implications**
Line of Business: Medicaid **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
Prior authorization is required. 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 Louisiana Healthcare Connections that ~~Prolia and~~ Xgeva is~~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* at up to maximally indicated doses unless all are contraindicated or clinically significant adverse effects are experienced to both IV and PO formulations (*see Appendices B, D*);~~
~~**Prior authorization may be required.*~~
~~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** - 12 months~~

~~**B. Prostate/Breast Cancer - Fracture Prevention** (must meet all):~~
~~1. Request is for Prolia;~~
~~2. Diagnosis of one of the following (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 ≥ 18 years or documentation of closed epiphyses on x-ray;~~
~~5. Failure of zoledronic acid* (Zometa® – prostate or breast cancer) or pamidronate* (breast cancer) at up to maximally indicated doses unless both are contraindicated or clinically significant adverse effects are experienced *(Appendices B, D)*;~~
~~**Prior authorization may be required.*~~
~~6. Prolia is not prescribed concurrently with Xgeva;~~
~~7. Dose does not exceed 60 mg every 6 months.~~
~~**Approval duration:**~~
~~**Medicaid** – 12 months~~

~~C.~~**A. 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, and member is receiving or initiating therapy (e.g., chemotherapy, transplant) for symptomatic disease;
   b. Bone metastasis secondary to solid tumor (e.g., breast, kidney, lung, prostate, thyroid);
3. Prescribed by or in consultation with an oncologist;
4. Age ≥ 18 years or documentation of closed epiphyses on x-ray;
5. For indications other than prostate or breast cancer, member meets one of the following (a or b):
   ~~5.~~a. F~~f~~ailure of zoledronic acid* (Zometa) or pamidronate* at up to maximally indicated doses, unless clinically significant adverse effects are experienced or both are contraindicated (*Appendices B, D*);
   **Prior authorization may be required.*
   b. Request is for Stage IV or metastatic cancer or associated conditions. Exception if "clinically equivalent therapy, contains identical active ingredient(s), and proven to have same efficacy.;
6. Xgeva is not prescribed concurrently with Prolia;
7. Dose does not exceed 120 mg every 4 weeks.

Approval duration:
Medicaid– 6 months

~~D.~~**B. 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;

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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 ≥ 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– 6 months

~~E.~~C. **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 ≥ 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 (*Appendix B*);
   **Prior authorization may be required.*
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– 6 months

~~F.~~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 or documentation of closed epiphyses on x-ray;
5. Member meets one of the following (a or b):
6.

~~6.~~a. Failure of zoledronic acid* (Zometa) or pamidronate* at up to maximally indicated doses unless clinically significant adverse effects are experienced or both are contraindicated *(Appendices B, D)*;
**Prior authorization may be required.*

b. Request is for Stage IV or metastatic cancer or associated conditions. Exception if "clinically equivalent therapy, contains identical active ingredient(s), and proven to have same efficacy.;

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.*

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Approval duration:
Medicaid – 6 months

~~G.~~E. **Other diagnoses/indications**
1. Refer to the off-label use policy if diagnosis is NOT specifically listed under section III (Diagnoses/Indications for which coverage is NOT authorized LA.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 Lousiana Healthcare Connections 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 – 12 months

B. Other diagnoses/indications (must meet 1 or 2):
1. Currently receiving medication via Louisiana Healthcare Connections 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 if diagnosis is NOT specifically listed under section III (Diagnoses/Indications for which coverage is NOT authorized): LA.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 policy – LA.PMN.53 for Medicaid or evidence of coverage documents.

IV. Appendices/General Information

Appendix A: Abbreviation/Acronym Key

ADT: androgen deprivation therapy	GIO: glucocorticoid-induced osteoporosis
BMD: bone mineral density	MM: multiple myeloma
FDA: Food and Drug Administration	PMO: postmenopausal osteoporosis

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Appendix B: Therapeutic Alternatives
This table provides a listing of preferred alternative therapy recommended in the approval criteria. The drugs listed here may require prior authorization.

Drug Name	Dosing Regimen	Dose Limit/ Maximum Dose
IV bisphosphonates		
ibandronate (Boniva)	Treatment: PMO Hypercalcemia of malignancy	Varies *See prescribing information and compendia for dosing.*
zoledronic acid (Reclast®; Zometa)	Reclast: Treatment/prevention: PMO, GIO Treatment: male osteoporosis Treatment: Paget disease Zometa: MM Bone metastasis from solid tumors Hypercalcemia of malignancy Systemic mastocytosis *(off-label)* Fracture prevention - breast/prostate cancer (*off-label*)	
pamidronate	MM Bone metastasis from breast cancer Hypercalcemia of malignancy Systemic mastocytosis *(off-label)* Fracture prevention – breast/prostate cancer (*off-label*)	
~~***Oral bisphosphonates***~~		
~~alendronate (Fosamax®)~~	~~Treatment/prevention: PMO~~ ~~Treatment: GIO, male osteoporosis~~ ~~Treatment: Paget disease~~	~~Varies~~ ~~*See prescribing information and compendia for dosing.*~~
~~Fosamax® Plus D (alendronate / cholecalciferol)~~	~~Treatment: PMO, male osteoporosis~~	
~~risedronate (Actonel®, Atelvia®)~~	~~Actonel:~~ ~~Treatment/prevention: PMO, GIO~~ ~~Treatment: male osteoporosis~~ ~~Treatment: Paget disease~~ ~~Atelvia:~~ ~~Treatment: PMO~~	
~~ibandronate (Boniva®)~~	~~Treatment/prevention: PMO~~	

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
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
	~~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	120 mg/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.; March 2020. Available at: http://www.prolia.com. Accessed October 26, 2020.~~

~~2.~~1. Xgeva Prescribing Information. Thousand Oaks, CA: Amgen Inc.; June 2020. Available at: http://www.xgeva.com. Accessed October 26, 2020.

~~3.~~2. Clinical Pharmacology [database online]. Tampa, FL: Gold Standard, Inc.; 2020. URL: http://www.clinicalpharmacology.com.

~~*Osteoporosis Diagnosis, Fracture Risk, and Treatment*~~

~~4. Shoback D, Rosen CJ, Black DM, et al. Pharmacological management of osteoporosis in postmenopausal women: an endocrine society guideline update. J Clin Endocrinol Metab; March 2020, 105(3): 587-594.~~

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~~*Male Osteoporosis*~~

~~10. 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*~~

~~11. 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

~~12.~~3. National Comprehensive Cancer Network Drugs and Biologics Compendium. Available at www.nccn.org. Accessed October 26, 2020.

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~~18.~~9. National Comprehensive Cancer Network. Systemic Mastocytosis Version 1.2020. Available at: https://www.nccn.org/professionals/physician_gls/pdf/mastocytosis.pdf. Accessed October 26, 2020.
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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	LDH Approval Date
Converted corporate policy to local policy	01.21	04.21
Removed Prolia criteria. LDH Prolia criteria utilized for Physician Administered Medication Prior Authorizations. For multiple myeloma or solid tumor, and systemic mastocytosis: allowed bypassing of redirection of step therapy in Stage IV or metastatic cancer settings.	04.22	

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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. LHCC 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.

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 LHCC administrative policies and procedures.

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