Clinical Policy: Denosumab (Prolia, Xgeva)

Reference Number: ERX.SPA.65
Effective Date: 10.01.16
Last Review Date: 02.21
Line of Business: Commercial, 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

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

Health plan approved formularies should be reviewed for all coverage determinations. Requirements to use preferred alternative agents apply only when such requirements align with the health plan approved formulary.

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It is the policy of health plans affiliated with Envolve Pharmacy Solutions™ 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 all are contraindicated or clinically significant adverse effects are experienced to both IV and PO formulations (*see Appendices B and 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: 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. Member meets one of the following (a or b):
   a. Failure of zoledronic acid* (Zometa® - prostate or breast cancer) or pamidronate* (breast cancer) at up to maximally indicated doses, unless clinically significant adverse effects are experienced or both are contraindicated (see *Appendices B and D*);
      **Prior authorization may be required.*
   b. Request is for the treatment associated with Stage IV or metastatic cancer for a State with regulations against step therapy in advanced oncology settings (*see Appendix E*);
6. Prolia is not prescribed concurrently with Xgeva;
7. Dose does not exceed 60 mg every 6 months.

Approval duration: 12 months

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, 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):
   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 *(see Appendices B and D)*;
      **Prior authorization may be required.*
   b. Request is for the treatment associated with Stage IV or metastatic cancer for a State with regulations against step therapy in advanced oncology settings (*see Appendix E*);
6. Xgeva is not prescribed concurrently with Prolia;
7. Dose does not exceed 120 mg every 4 weeks.

Approval duration: 6 months

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 ≥ 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: 6 months

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 ≥ 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: 6 months

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 ≥ 18 years or documentation of closed epiphyses on x-ray;
6. Member meets one of the following (a or b):
   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 *(see Appendices B and D)*;
      **Prior authorization may be required.*
   b. Request is for the treatment associated with Stage IV or metastatic cancer for a State with regulations against step therapy in advanced oncology settings (*see Appendix E*);

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: 6 months

G. Other diagnoses/indications
1. Refer to ERX.PA.01 if diagnosis is NOT specifically listed under section III (Diagnoses/Indications for which coverage is NOT authorized).

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 a health plan affiliated with Envolve Pharmacy Solutions 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: 12 months

B. Other diagnoses/indications (must meet 1 or 2)**:**
1. Currently receiving medication via a health plan affiliated with Envolve Pharmacy Solutions and documentation supports positive response to therapy.
   Approval duration: Duration of request or 6 months (whichever is less); or
2. Refer to ERX.PA.01 if diagnosis is NOT specifically listed under section III (Diagnoses/Indications for which coverage is NOT authorized).

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 – ERX.PA.01 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 and 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	

Drug Name	Dosing Regimen	Dose Limit Maximum Dose
	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

Bisphosphonates	Oral Formulations	IV Formulations
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

Appendix E: States with Regulations against Redirections in Stage IV or Metastatic Cancer

State	Step Therapy Prohibited?	Notes
FL	Yes	For stage 4 metastatic cancer and associated conditions.
GA	Yes	For stage 4 metastatic cancer. Redirection does not refer to review of medical necessity or clinical appropriateness.
IA	Yes	For standard of care stage 4 cancer drug use, supported by peer-reviewed, evidence-based literature, and approved by FDA.
LA	Yes	For stage 4 advanced, metastatic cancer or associated conditions. Exception if "clinically equivalent therapy, contains identical active ingredient(s), and proven to have same efficacy.
OH	Yes	**Applies to Commercial requests only** For stage 4 metastatic cancer and associated conditions
PA	Yes	For stage 4 advanced, metastatic cancer
TN	Yes	For advanced metastatic cancer and associated conditions
TX	Yes	For stage 4 advanced, metastatic cancer and associated conditions

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	120 mg/dose

VI. Product Availability

Drug Name	Availability
Denosumab (Prolia)	Injection (single-use prefilled syringe): 60 mg/1 mL
Denosumab (Xgeva)	Injection (single-use vial): 120 mg/1.7 mL

VII. References

1. Prolia Prescribing Information. Thousand Oaks, CA: Amgen Inc.; March 2020. Available at: http://www.prolia.com. Accessed October 26, 2020.
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19. National Comprehensive Cancer Network. Thyroid Carcinoma Version 2.2020. Available at: https://www.nccn.org/professionals/physician_gls/pdf/thyroid.pdf. Accessed October 26, 2020.

Reviews, Revisions, and Approvals	Date	P&T Approval Date
Converted to new template. All indications: Modified age requirement to apply to pediatric members with open epiphyses. Removed requirement for administration of calcium/vitamin D. Osteoporosis: aligned diagnosis criteria with FDA approved indication (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: Added requirement for no concomitant use of Prolia. Modified initial/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.	06.17	08.17
2Q 2018 annual review: Osteoporosis: Modified diagnosis criterion by removing requirement for evidence of diagnosis; added specialist requirement as an option in lieu of bisphosphonate trial; removed requirement related to pregnancy. Prostate and breast cancer treatments: removed requirement related pregnancy. Allowed COC for oncology related indications on re-auth. 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	11.18
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: 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
The MM/solid tumor common criteria line item, at risk for skeletal related event, is removed for solid tumor and for MM is replaced with receiving or initiating therapy for symptomatic disease per pivotal trials/NCCN; IV bisphosphonate trials are added per labels/NCCN to prostate/breast fracture prevention, MM/solid tumor (exception prostate/breast cancer), and systemic mastocytosis.	08.25.20	11.20
1Q 2021 annual review: Xgeva initial approval durations shortened to 6 months to reconcile with other lines of business and standard duration; references reviewed and updated.	10.26.20	02.21
For prostate/breast cancer - fracture prevention, multiple myeloma or solid tumor, and systemic mastocytosis: allowed bypassing of redirection if state regulations do not allow step therapy in Stage IV or metastatic cancer settings.	06.15.21	

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.