Department:	Pharmacy Management	**Original Approval:**	01/20/2016
Policy #:	PM134	**Last Approval:**	09/19/2018
Title:	Denosumab (Prolia®)		
Approved By:	UM Committee		

REQUIRED CLINICAL DOCUMENTATION FOR REVIEW.

Documentation required to determine medical necessity for Denosumab (Prolia): History and/or physical examination notes and relevant specialty consultation notes that address the problem and need for the service: -Diagnosis -T score -Medication list (current and past) to include start and end dates of previous trial for all osteoporosis regimens -Labs -Initial/Extended Approval -Height -Weight -Age.

BACKGROUND

Prolia, a RANK (receptor activator of nuclear factor kappa-B ligand [RANKL] inhibitor, is indicated for the treatment of postmenopausal women with osteoporosis at high risk of fracture, defined as a history of osteoporotic fracture, or multiple risk factors for fracture; or patients who have failed or are intolerant of other available therapy.[1] In postmenopausal women with osteoporosis, Prolia reduces the incidence of vertebral, nonvertebral, and hip fractures. Prolia is indicated for treatment to increase bone mass in men with osteoporosis at high risk for fracture, defined as a history of osteoporotic fracture, or multiple risk factors for fracture; or patients who have failed or are intolerant to other available osteoporosis therapy. Prolia is also indicated for the treatment of bone loss (to increase bone mass) in men at high risk for fracture receiving androgen deprivation therapy (ADT) for nonmetastatic prostate cancer. In such patients, Prolia reduced the incidence of vertebral fractures. Prolia is also indicated for the treatment of bone mass in women at high risk for fracture receiving adjuvant aromatase inhibitor (AI) therapy. The recommended dose of Prolia for all indications is 60 mg given as a single subcutaneous (SC) injection once every 6 months into the upper arm, the upper thigh, or the abdomen. Prolia should be given by a healthcare professional. All patients should receive calcium 1,000 mg daily and at least 400 IU vitamin D daily. The most common adverse events (AEs) with Prolia are back pain, pain in extremity, hypercholesterolemia, musculoskeletal pain, and cystitis. Pancreatitis has been reported in clinical trials, as well as osteonecrosis of the jaw (ONJ). Use of Prolia is contraindicated in those with pre-existing hypocalcemia; woman who are pregnant; and in those with a history of systemic hypersensitivity to any component of the product. Of note, denosumab injection is also available under the brand name Xgeva®, and is indicated for bone metastasis from solid tumors, giant cell tumor of bone, and hypercalcemia of malignancy.[2] The recommended dose for this indication is 120 mg SC every 4 weeks, with additional doses recommended for initial treatment for some of the indications.

DEFINITIONS

None.

INDICATIONS/CRITERIA

Medicaid Members	***Continue to criteria for approval below.***
Medicare Members	***Step-utilization of Part D drugs not required.***

Coverage of Prolia therapy is recommended in those who meet one of the following criteria:

FDA-Approved Indications

1. Osteoporosis Treatment for a Postmenopausal Patient.

Criteria. *Patient must meet the following criteria (A AND B)*:

- **A)** The patient meets ONE of the following conditions (i, ii, or iii):
  - **i.** The patient has had a T-score (current or at any time in the past) at or below -2.5 at the lumbar spine, femoral neck, total hip and/or 33% (one-third) radius (wrist);OR
  - **ii.** The patient has had an osteoporotic fracture or a fragility fracture; OR
  - **iii.** The patient has low bone mass or osteopenia (T-score [current or at any time in the past] between -1.0 and -2.5 at the lumbar spine, femoral neck, total hip and/or 33% [one-third] radius [wrist]) and the physician determines the patient is at high risk for fracture; AND
- **B)** The patient meets ONE of the following (i, ii, iii or iv):
  - **i.** The patient has tried one oral bisphosphonate or oral bisphosphonate-containing product and meets one of the following (a, b, or c):
    - **a)** The patient has had an inadequate response to oral bisphosphonate therapy after a trial duration of 12 months as determined by the prescribing physician (e.g., ongoing and significant loss of bone mineral density [BMD], lack of BMD increase); OR
    - **b)** The patient has had an osteoporotic fracture or fragility fracture while receiving oral bisphosphonate therapy; OR
    - **c)** The patient has experienced intolerability to an oral bisphosphonate (e.g., severe gastrointestinal [GI]-related adverse effects, severe musculoskeletal-related side effects, a femoral fracture); OR
  - **ii.** The patient cannot take an oral bisphosphonate due to one of the following circumstances (a, b or c):
    - **a)** The patient cannot swallow or has difficulty swallowing; OR
    - **b)** The patient cannot remain in an upright position post oral bisphosphonate administration; OR
    - **c)** The patient has a pre-existing GI medical condition (e.g., patient with esophageal lesions, esophageal ulcers, or abnormalities of the esophagus that delay esophageal emptying [stricture, achalasia]); OR
  - **iii.** The patient has tried intravenous Boniva or Reclast; OR
  - **iv.** The patient meets one of the following conditions (a, b, or c):
    - **a)** Severe renal impairment (creatinine clearance < 35 mL/min); OR
    - **b)** Chronic kidney disease (CKD); OR
    - **c)** The patient has had an osteoporotic fracture or a fragility fracture.

Prolia is indicated for the treatment of postmenopausal women with osteoporosis at high risk of fracture, defined as a history of osteoporotic fracture or multiple risk factors for fracture; or in patients who have failed or are intolerant of other available therapy.[1] Various guidelines support use of bisphosphonate therapy as first-line agents in many clinical scenarios.[3-5] In the AACE guidelines for PMO, osteoporosis is defined as a T-score of -2.5 or below in the lumbar spine, femoral neck or total hip and/or 33% (one-third radius). Other scenarios also are indicators for a diagnosis of osteoporosis (e.g., low trauma spine or hip fracture [regardless of BMD]). Bisphosphonates should not be used in patients with renal impairment. Oral bisphosphonates have caused severe GI adverse effects and severe musculoskeletal pain has been reported. Albeit rare, bisphosphonates have been associated with femoral fractures. In the professional opinion of specialist physicians reviewing the data, we have adopted these criteria.

Dosing in Osteoporosis Treatment for a Postmenopausal Patient. *Dosing must meet the following:* 60 mg SC once every 6 months.

Initial Approval/Extended Approval.

- **A)** Initial Approval. Initial approval is for 12 months.
- **B)** Extended Approval. Extended approval is at 12-month intervals.

Duration of Therapy in Osteoporosis Treatment for a Postmenopausal Patient. The duration of therapy is indefinite.

Labs/Diagnostics. In those without an osteoporotic fracture or a fragility fracture, patients must have had a T-score (current or at any time in the past) at or below -2.5, or low bone mass or osteopenia (T-score [current or at any time in the past] between -1.0 and -2.5]) and the physician determines the patient is at high risk of fracture.

2. Treatment of Bone Loss (to Increase Bone Mass) in Patients at High Risk for Fracture Receiving Androgen Deprivation Therapy (ADT) for Nonmetastatic Prostate Cancer.

Criteria. *Patient must meet the following criteria (A AND B)*:

- **A)** The patient has prostate cancer that is not metastatic to bone; AND
- **B)** The patient meets ONE of the following conditions (i or ii):
  - **i.** The patient is receiving ADT (e.g., Lupron Depot® [leuprolide for depot suspension], Eligard® [leuprolide acetate for injectable suspension], Trelstar® [triptorelin pamoate for injectable suspension], or Zoladex® [goserelin implant]); OR
  - **ii.** The patient has undergone bilateral orchiectomy.

Prolia is the only agent indicated for the treatment of bone loss (to increase bone mass) in men at high risk for fracture receiving ADT for nonmetastatic prostate cancer.[1] Clinical practice guidelines from the Endocrine Society regarding osteoporosis in men (2012)[5] recommend Prolia for selected men receiving ADT for prostate cancer. In the professional opinion of specialist physicians reviewing the data, we have adopted these criteria.

Dosing in the Treatment of Bone Loss (to Increase Bone Mass) in Patients Receiving Androgen Deprivation Therapy (ADT) for Nonmetastatic Prostate Cancer. *Dosing must meet the following:* 60 mg SC once every 6 months.

Initial Approval/Extended Approval.

A) Initial Approval. Initial approval is for 12 months.
B) Extended Approval. Extended approval is at 12-month intervals.

Duration of Therapy in the Treatment of Bone Loss (to Increase Bone Mass) in Patients Receiving Androgen Deprivation Therapy (ADT) for Nonmetastatic Prostate Cancer. Therapy is indefinite as long as the patient is currently receiving ADT.

Labs/Diagnostics. None required.

3. Treatment of Bone Loss (to Increase Bone Mass) in Patients Receiving Adjuvant Aromatase Inhibitor (AI) Therapy for Breast Cancer.

Criteria. *Patient must meet the following criteria (A AND B)*:

A) The patient has breast cancer that is not metastatic to bone; AND
B) The patient is receiving AI therapy (e.g., anastrozole, letrozole, or exemestane).

Prolia is the only agent indicated as a treatment to increase bone mass in women at high risk for fracture receiving AI therapy for breast cancer.[1] Prolia is only indicated for this use in women.[1] However, men may also receive AI therapy for breast cancer.[6] In the professional opinion of specialist physicians reviewing the data, we have adopted these criteria.

Dosing in the Treatment of Bone Loss (to Increase Bone Mass) in Patients Receiving Adjuvant Aromatase Inhibitor (AI) Therapy for Breast Cancer: *Dosing must meet the following:* 60 mg SC once every 6 months.

Initial Approval/Extended Approval.

A) *Initial Approval*. Initial approval is for 12 months.
B) *Extended Approval*. Extended approval is at 12-month intervals.

Duration of Therapy in the Treatment of Bone Loss (to Increase Bone Mass) in Patients Receiving Adjuvant Aromatase Inhibitor (AI) Therapy for Breast Cancer. Therapy is indefinite as long as the patient is currently receiving AI therapy.

Labs/Diagnostics. None required.

4. Osteoporosis Treatment (to Increase Bone Mass) for Men*.

Criteria. *Patient must meet the following criteria (A AND B)*:

A) The patient meets ONE of the following conditions (i, ii, or iii):
- **i.** The patient has had a T-score (current or at any time in the past) at or below -2.5 at the lumbar spine, femoral neck, or total hip, and/or 33% (one-third) radius (wrist); OR
- **ii.** The patient has had an osteoporotic fracture or a fragility fracture; OR
- **iii.** The patient has low bone mass or osteopenia (T-score [current or at any time in the past] between -1.0 and -2.5 at the lumbar spine, femoral neck, total hip and/or 33% [one-third] radius [wrist]) and the physician determines the patient is at high risk for fracture; AND

B) The patient meets ONE of the following (i, ii, iii or iv):
- **i.** The patient has tried one oral bisphosphonate or oral bisphosphonate-containing product and has had one of the following (a, b, or c):
  - **a)** The patient has had an inadequate response to oral bisphosphonate therapy after a trial duration of 12 months as determined by the prescribing physician (e.g., ongoing and significant loss of BMD, lack of BMD increase); OR
  - **b)** The patient has had an osteoporotic fracture or fragility fracture while receiving oral bisphosphonate therapy; OR
  - **c)** The patient has experienced intolerability to an oral bisphosphonate (e.g., severe GI-related adverse effects, severe musculoskeletal-related side effects, a femoral fracture); OR
- **ii.** The patient cannot take an oral bisphosphonate due to one of the following circumstances (a, b or c):
  - **a)** The patient cannot swallow or has difficulty swallowing; OR
  - **b)** The patient cannot remain in an upright position post oral bisphosphonate administration; OR
  - **c)** The patient has a pre-existing GI medical condition (e.g., patient with esophageal lesions, esophageal ulcers, or abnormalities of the esophagus that delay esophageal emptying [stricture, achalasia]); OR
- **iii.** The patient has tried Reclast; OR
- **iv.** The patient meets one of the following conditions (a, b, or c):
  - **a)** Severe renal impairment (creatinine clearance < 35 mL/min); OR
  - **b)** Chronic kidney disease (CKD); OR
  - **c)** The patient has had an osteoporotic fracture or a fragility fracture.

***** Refer to the Policy Statement

Prolia is indicated for treatment to increase bone mass in men with osteoporosis at high risk for fracture, defined as a history of osteoporotic fracture, or multiple risk factors for fracture; or patients who have failed or are intolerant to other available osteoporosis therapies.[1] The 2012 clinical practice guidelines from the Endocrine Society (2012) regarding osteoporosis in men recommend that men at high risk of fracture receive treatment and that other agents are indicated for the treatment of osteoporosis in men (e.g., alendronate, Actonel® [risedronate tablets], Reclast® [zoledronic acid injection], Forteo® [teriparatide injection]).[6] Guidelines from the Endocrine Society recommend pharmacologic therapy for men aged ≥ 50 years who have had spine or hip fractures, those with T-scores of -2.5 or below, and men at high risk of fracture based on low bone mineral density and/or

clinical risk factors. In the professional opinion of specialist physicians reviewing the data, we have adopted these criteria.

Dosing in Osteoporosis Treatment (to Increase Bone Mass) in Men. *Dosing must meet the following:* 60 mg SC once every 6 months.

Initial Approval/Extended Approval.

A) *Initial Approval*. Initial approval is for 12 months.

B) *Extended Approval*. Extended approval is at 12-month intervals.

Duration of Therapy in Osteoporosis Treatment (to Increase Bone Mass) in Men. Therapy is indefinite.

Labs/Diagnostics. In those without an osteoporotic fractures or a fragility fracture patients must have had a T-score (current or at any time in the past) at or below -2.5, or low bone mass or osteopenia (T-score [current or at any time in the past] between -1.0 and -2.5] and the physician determines the patient is at high risk of fracture.

5. Glucocorticoid-Induced Osteoporosis (GIO) Treatment.

Criteria. *Patient must meet the following criteria (A AND B)*:

A) The patient is either initiating or continuing systemic glucocorticoids (e.g., prednisone); AND

B) The patient meets ONE of the following (i, ii, iii, or iv):

- **i.** The patient has tried one oral bisphosphonate or oral bisphosphonate-containing product and meets one of the following (a, b, or c):
  - **a)** The patient has had an inadequate response to oral bisphosphonate therapy after a trial duration of 12 months as determined by the prescribing physician (e.g., ongoing and significant loss of BMD, lack of BMD increase); OR
  - **b)** The patient has had an osteoporotic fracture or fragility fracture while receiving oral bisphosphonate therapy; OR
  - **c)** The patient has experienced intolerability to an oral bisphosphonate (e.g., severe gastrointestinal [GI]-related adverse effects, severe musculoskeletal-related side effects, a femoral fracture); OR
- **ii.** The patient cannot take an oral bisphosphonate due to one of the following circumstances (a, b, or c):
  - **a)** The patient cannot swallow or has difficulty swallowing; OR
  - **b)** The patient cannot remain in an upright position post oral bisphosphonate administration; OR
  - **c)** The patient has a pre-existing gastrointestinal (GI) medical condition (e.g., patient with esophageal lesions, esophageal ulcers, or abnormalities of the esophagus that delay esophageal emptying [stricture, achalasia]); OR
- **iii.** The patient has tried zoledronic acid injection (Reclast); OR
- **iv.** The patient meets one of the following conditions (a, b, or c):
  - **a)** Severe renal impairment (creatinine clearance < 35 mL/min); OR
  - **b)** Chronic kidney disease (CKD); OR

c) The patient has had an osteoporotic fracture or a fragility fracture.

Prolia is indicated 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 or greater of prednisone and excepted to remain on glucocorticoids for at least 6 months.[1,9] 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.[1] Several bisphosphonates are indicated for the treatment of GIO (e.g., alendronate, risedronate and Reclast) and are recommended in ACR 2017 guidelines for the prevention and treatment of GIO.[8] Bisphosphonates should not be used in patients with renal impairment. Oral bisphosphonates have caused severe GI adverse effects and severe musculoskeletal pain has been reported. Oral bisphosphonates are contraindicated if patients have abnormalities of the esophagus which delay emptying (stricture or achalasia). Patients must also not lie down for at least 30 minutes post oral bisphosphonate administration. In the professional opinion of specialized physicians reviewing the data, we have adopted these criteria.

Dosing in Glucocorticoid-Induced Osteoporosis Treatment. *Dosing must meet the following:* 60 mg SC once every 6 months.

Initial Approval/Extended Approval.

A) *Initial Approval.* Initial approval is for 12 months.

B) *Extended Approval.* Extended approval is at 12-month intervals if the patient is continuing systemic glucocorticoids.

Duration of Therapy in Glucocorticoid-Induced Osteoporosis Treatment. The duration of therapy is indefinite.

Labs/Diagnostics. None required.

Waste Management for All:

Prolia is supplied in a single-use prefilled syringe that contains 60 mg of denosumab in 1 mL and as a single-use vial that contains 60 mg of denosumab in 1 mL. Only one vial should be needed per dose.

Conditions Not Recommended for Approval

Prolia has not been shown to be effective, or there are limited or preliminary data or potential safety concerns that are not supportive of general approval for the following conditions. Rationale for non-coverage for these specific conditions is provided below. (Note: This is not an exhaustive list of Conditions Not Recommended for Approval.)

1. **Osteoporosis Prevention.** Prolia is not indicated for the prevention of osteoporosis.[1]

2. **Concurrent Use of Prolia with Other Medications for Osteoporosis** (e.g., Forteo, Tymlos™ [abaloparatide SC injection], bisphosphonates [alendronate, risedronate, ibandronate, zoledronic acid {Reclast}], calcitonin nasal spray, except calcium and Vitamin D). Prolia is not indicated for use

as combination therapy.[1] It is recommended that patients on Prolia should also receive calcium and vitamin D therapy.

3. **Giant Cell Tumor of Bone.** Studies with denosumab in giant cell tumor of the bone used dosing for Xgeva® (denosumab injection for SC use), which is indicated 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.[2]

Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

SPECIAL CONSIDERATIONS

None.

LIMITATIONS/EXCLUSIONS

Please refer to a product line's certificate of coverage for benefit limitations and exclusions for these services:

PRODUCT LINE	LINK TO CERTIFICATE OF COVERAGE
MEDICARE ADVANTAGE	http://healthfirst.chpw.org/for-members/resource-library/handbooks-and-guides
WASHINGTON APPLE HEALTH	http://chpw.org/our-plans/apple-health/
INTEGRATED MANAGED CARE	http://chpw.org/our-plans/apple-health/

Citations & References

References	1. Prolia® injection for subcutaneous use [prescribing information]. Thousand Oaks, CA: Amgen; June 2018. 2. Xgeva® injection for subcutaneous use [prescribing information]. Thousand Oaks, CA: Amgen; June 2018. 3. Camacho PM, Petak SM, Binkley N, et al. American Association of Clinical Endocrinologists and American College of Endocrinology clinical practice guidelines for the diagnosis and treatment of postmenopausal osteoporosis. *Endocrin Pract*. 2016;22(Suppl 4):1-42. Available at: http://journals.aace.com/doi/pdf/10.4158/EP161435.GL. Accessed on June 26, 2018.

	4. Qaseem A, Forciae MA, McLean RM, et al, for the Clinical Guidelines Committee of the American College of Physicians. Treatment of low bone density or osteoporosis to prevent fractures in men and women: a clinical practice guideline update from the American College of Physicians. *Ann Intern Med*. 2017;166(11):818-837. 5. Cosman F, de Beur SJ, LeBoff MS, et al. Clinician's guide to prevention and treatment of osteoporosis. *Osteoporos Int*. 2014;25:2359-2381. Available at: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4176573/pdf/198_2014_Article_2794.pdf. Accessed on June 26, 2018. 6. 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. 7. Harlan LC, Zujewski J, Goodman MT, Stevens JL. Breast cancer in men in the US: a population-based study of diagnosis, treatment and survival. *Cancer*. 2010;116(15):3558-3568. 8. 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. Available at: https://www.rheumatology.org/Portals/0/Files/Guideline-for-the-Prevention-and-Treatment-of-GIOP.pdf. Accessed on June 15, 2018. 9. Saag KG, Wagman RB, Geusens P, et al. Denosumab versus risedronate in glucocorticoid-induced osteoporosis: a multicenter, randomized, double-blind, active-controlled, double-dummy, non-inferiority study. *Lancet Diabetes Endocrinol*. 2018;6:445-454.
CFR	
WAC	WAC 284-43-2050
RCW	
Contract Citation	☐ WAH ☐ IMC ☐ MA
Other Requirements	
NCQA Elements	

Revision History

Revision Date	Revision Description	Revision Made By
01/13/2016	New	Kelly Force; Yusuf Rashid, RPh
01/20/2016	Approval	MMLT
01/12/2017	No revisions	Fran McGaugh
01/13/2017	Approval	MMLT

07/24/2017	Criteria completely updated and revised	Michael Sporck, Pharmacy Intern Sophia Yun, PharmD
07/25/2017	Approved	MMLT
03/09/2018	Reassigned from UM146 to PM134	Cindy Bush
05/03/2018	Transferred to new template	Cindy Bush
06/12/2018	No revisions	Jennifer Farley, PharmD
06/14/2018	Approval	UM Committee
08/06/2018	Revised	Jennifer Farley, PharmD
09/19/2018	Approval	UM Committee

Appendix A: Cockcroft-Gault Equation for Estimating Creatinine Clearance

There are many different methods that can be used to calculate an estimated creatinine clearance (CrCl). The Cockcroft-Gault is one formula that provides an estimate of CrCl using serum creatinine. It is only for adults. This formula tends to overestimate CrCl in obese persons and to underestimate it in those who are lean. The Cockcroft-Gault equation for calculating CrCl is as follows:

CrCl in adults **(men)** = $\frac{\text{(140 minus age [in years] X weight [in kg])}}{\text{(72 X serum creatinine [in mg/dL])}}$

For women, multiple the above results by 0.85. The steps, for clarity, are as follows:

1) Subtract the patient's age in years from 140.
2) Multiple by the patient's weight in kg (if weight is in pounds, divide by 2.2 to get kg).
3) Multiple the patient's serum creatinine (in mg/dL) by 72.
4) Divide the total from 2) by the total from 3).
5) If the patient is female, take the total from 4) and multiple by 0.85.

For example, a man who is 55 years of age, who weighs 160 pounds (72.7 kg), and with a serum creatinine 0.9 mg/dL, would have a calculated creatinine clearance of 95 mL/minute. For a woman with these same values, her CrCl would be 81 mL/minute.