VENTURA COUNTY
HEALTH CARE PLAN

UTILIZATION REVIEW MEDICAL POLICY

POLICY: Bone Modifiers – Prolia Utilization Review Medical Policy
- Prolia® (denosumab injection for subcutaneous use – Amgen)

REVIEW DATE: 07/29/2020

OVERVIEW

Prolia, a receptor activator of nuclear factor kappa-B (RANK) ligand inhibitor, is indicated for the following uses:[1]

- **Bone loss (treatment to increase bone mass), in men with nonmetastatic prostate cancer** at high risk for fracture receiving androgen deprivation therapy (ADT).
- **Bone loss (treatment to increase bone mass), in women with breast cancer** at high risk for fracture receiving adjuvant aromatase inhibitor (AI) therapy.
- **Glucocorticoid-induced osteoporosis** (treatment), 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 expected to remain on glucocorticoids for at least 6 months.
- **Osteoporosis,** treatment of **postmenopausal women** at high risk of fracture.
- **Osteoporosis,** treatment to **increase bone mass in men** at high risk for fracture.

In general, high risk of fractures 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] Of note, denosumab subcutaneous injection is also available under the brand name Xgeva®, and is indicated for the prevention of skeletal-related events in patients with multiple myeloma, as well as in patients with bone metastases from solid tumors, giant cell tumor of bone, and hypercalcemia of malignancy.[2]

Dosing Information

For all indications, the dose is 60 mg once every 6 months as a subcutaneous injection.[1]

Guidelines

Several guidelines address Prolia.

- **Breast Cancer/Prostate Cancer:** The National Comprehensive Cancer Network (NCCN) guidelines for breast cancer (version 5.2020 – July 15, 2020)[6] and prostate cancer (version 2.2020 – May 21, 2020)[7] note that if patients are receiving agents that impact bone mineral density (BMD), bisphosphonates (oral/intravenous), as well as Prolia, should be considered to maintain or improve BMD and/or reduce the risk of fractures.
- **Glucocorticoid-Induced Osteoporosis (GIO):** In 2017, the American College of Rheumatology (ACR) updated guidelines for the prevention and treatment of GIO.[5] In various clinical scenarios, oral bisphosphonates are preferred, followed by intravenous bisphosphonates (e.g., zoledronic acid injection).
- **Postmenopausal Osteoporosis:** Prolia is prominently featured in guidelines for postmenopausal osteoporosis by the Endocrine Society (2019)[3] and the American Association of Clinical Endocrinologists (AACE) and the American College of Endocrinology (ACE) [2020][4]. Prolia is one of among several agents cited as an alternative for patients at high risk for fractures.

POLICY STATEMENT

Prior authorization is recommended for medical benefit coverage of Prolia. Approval is recommended for those who meet the **Criteria** and **Dosing** for the listed indication(s). Extended approvals are allowed if the patient continues to meet the Criteria and Dosing. Requests for doses outside of the established dosing documented in this policy will be considered on a case-by-case basis by a clinician (i.e., Medical Director or Pharmacist). All approvals are provided for the duration noted below. In the approval indication, as appropriate, an asterisk (*) is noted next to the specified gender. In this context, the specified gender is defined as follows: men are defined as individuals with the biological traits of a man, regardless of the individual's gender identity or gender expression.

RECOMMENDED AUTHORIZATION CRITERIA

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

FDA-Approved Indications

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1. **Bone Loss (Treatment to Increase Bone Mass) in Patients with Breast Cancer at High Risk for Fracture Receiving Adjuvant Aromatase Inhibitor Therapy.** Approve for 1 year if the patient meets the following criteria (A and B):
   - **A)** Patient has breast cancer that is not metastatic to bone; AND
   - **B)** Patient is receiving aromatase inhibitor therapy (e.g., anastrozole, letrozole, or exemestane).

   Dosing. Approve 60 mg SC once every 6 months.

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2. **Bone Loss (Treatment to Increase Bone Mass) in Patients with Nonmetastatic Prostate Cancer at High Risk for Fracture Receiving Androgen Deprivation Therapy.** Approve for 1 year of the patient meets the following criteria (A and B):
   - **A)** Patient has prostate cancer that is not metastatic to bone; AND
   - **B)** Patient meets ONE of the following conditions (i or ii):
     - **i.** Patient is receiving androgen deprivation therapy (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.** Patient has undergone bilateral orchiectomy.

   Dosing. Approve 60 mg SC once every 6 months.

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3. **Glucocorticoid-Induced Osteoporosis – Treatment.** Approve for 1 year of the patient meets the following criteria (A and B):
   - **A)** Patient is either initiating or continuing systemic glucocorticoids (e.g., prednisone); AND
   - **B)** Patient meets ONE of the following (i, ii, iii, or iv):
     - **i.** Patient has tried zoledronic acid injection (Reclast); OR
     - **ii.** Patient has tried at least one oral bisphosphonate or oral bisphosphonate-containing product and meets one of the following (a, b, or c):
       - **a)** Patient has had an inadequate response to oral bisphosphonate therapy after a trial duration of 12 months as determined by the prescriber (e.g., ongoing and significant loss of bone mineral density [BMD], lack of BMD increase); OR

b) Patient has had an osteoporotic fracture or fragility fracture while receiving oral bisphosphonate therapy; OR
c) 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

iii. Patient cannot take an oral bisphosphonate due to one of the following circumstances (a, b, or c):
a) Patient cannot swallow or has difficulty swallowing; OR
b) Patient cannot remain in an upright position post oral bisphosphonate administration; OR
c) 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

iv. 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) Patient has had an osteoporotic fracture or a fragility fracture.

Dosing. Approve 60 mg SC once every 6 months.

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4. Osteoporosis Treatment for a Postmenopausal Patient. Approve for 1 year if the patient meets the following criteria (A and B):

A) Patient meets ONE of the following conditions (i, ii, or iii):
i. 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. Patient has had an osteoporotic fracture or a fragility fracture; OR
iii. Patient has low bone mass (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 prescriber determines the patient is at high risk for fracture; AND

B) Patient meets ONE of the following (i, ii, iii or iv):
i. Patient has tried ibandronate injection (Boniva) or zoledronic acid injection (Reclast); OR
ii. Patient has tried at least one oral bisphosphonate or oral bisphosphonate-containing product and meets one of the following (a, b, or c):
a) Patient has had an inadequate response to oral bisphosphonate therapy after a trial duration of 12 months as determined by the prescriber (e.g., ongoing and significant loss of bone mineral density [BMD], lack of BMD increase); OR
b) Patient has had an osteoporotic fracture or fragility fracture while receiving oral bisphosphonate therapy; OR
c) 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

iii. Patient cannot take an oral bisphosphonate due to one of the following circumstances (a, b, or c):
a) Patient cannot swallow or has difficulty swallowing; OR
b) Patient cannot remain in an upright position post oral bisphosphonate administration; OR
c) 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

iv. 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) Patient has had an osteoporotic fracture or a fragility fracture.

Dosing. Approve 60 mg SC once every 6 months.

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5. Osteoporosis Treatment (to Increase Bone Mass) for Men*. Approve for 1 year of the patient meets the following criteria (A and B):

A) Patient meets ONE of the following conditions (i, ii, or iii):
- **i.** 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.** Patient has had an osteoporotic fracture or a fragility fracture; OR
- **iii.** Patient has low bone mass (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 prescriber determines the patient is at high risk for fracture; AND

B) Patient meets ONE of the following (i, ii, iii or iv):
- **i.** Patient has tried zoledronic acid injection (Reclast); OR
- **ii.** Patient has tried at least one oral bisphosphonate or oral bisphosphonate-containing product and has had one of the following (a, b, or c):
  - **a)** Patient has had an inadequate response to oral bisphosphonate therapy after a trial duration of 12 months as determined by the prescriber (e.g., ongoing and significant loss of bone mineral density [BMD], lack of BMD increase); OR
  - **b)** Patient has had an osteoporotic fracture or fragility fracture while receiving oral bisphosphonate therapy; OR
  - **c)** 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
- **iii.** Patient cannot take an oral bisphosphonate due to one of the following circumstances (a, b or c):
  - **a)** Patient cannot swallow or has difficulty swallowing; OR
  - **b)** Patient cannot remain in an upright position post oral bisphosphonate administration; OR
  - **c)** 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
- **iv.** 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)** Patient has had an osteoporotic fracture or a fragility fracture.

***** Refer to the Policy Statement

Dosing. Approve 60 mg SC once every 6 months.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Prolia is not recommended in the following situations:

1. Concurrent Use with Other Medications for Osteoporosis.
Note: Examples include teriparatide injection for subcutaneous use (Forteo®/Bonsity®), Tymlos® (abaloparatide injection for subcutaneous use), oral bisphosphonates (e.g., alendronate, risedronate,

ibandronate), intravenous bisphosphonates (zoledronic acid injection [Reclast], intravenous ibandronate), calcitonin nasal spray (Miacalcin®/Fortical®), and Evenity® (romosozumab-aqqg injection for subcutaneous use]). Prolia is not indicated for use as combination therapy.[1]

2. Giant Cell Tumor of Bone.
Studies with denosumab in giant cell tumor of the bone used dosing for Xgeva® (denosumab injection for subcutaneous 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]

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

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

REFERENCES

1. Prolia® injection for subcutaneous use [prescribing information]. Thousand Oaks, CA: Amgen; March 2020.
2. Xgeva® injection for subcutaneous use [prescribing information]. Thousand Oaks, CA: Amgen; June 2020.
3. 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(5):1595-1622. Available at: https://www.endocrine.org/guidelines-and-clinical-practice/clinical-practice-guidelines/osteoporosis-in-postmenopausal-women. Accessed on July 27, 2020.
4. 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-2020 update. *Endocrin Pract*. 2020;26(Suppl 1):1-46. Available at: https://journals.aace.com/doi/pdf/10.4158/GL-2020-0524SUPPL. Accessed on July 27, 2020.
5. 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 July 29, 2020.
6. The NCCN Breast Cancer Clinical Practice Guidelines in Oncology (Version 5.2020 – July 15, 2020). © 2020 National Comprehensive Cancer Network, Inc. Available at: http://www.nccn.org. Accessed on July 27, 2020.
7. The NCCN Prostate Cancer Clinical Practice Guidelines in Oncology (Version 2.2020 – May 21, 2020). © 2020 National Comprehensive Cancer Network, Inc. Available at: http://www.nccn.org. Accessed on July 27, 2020.

HISTORY

Type of Revision	Summary of Changes	Review Date
Annual revision	Criteria added for the treatment of glucocorticoid-induced osteoporosis.	06/27/2018
Annual revision	Removed the following sections from the document: Initial Approval/Extended Approval, Duration of Therapy, Labs/Diagnostics and Waste Management. The following criteria change were made: **Conditions Not Recommended for Approval:** Added Evenity to the list of medications that should not be used concomitantly with Prolia.	07/03/2019
Annual revision	In related criteria the word "prescriber" is replacing the word/phrase "physician" or "prescribing physician". Additionally, the following changes were made: **Conditions Not Recommended for Approval:** For the criteria regarding Concurrent Use of Other Medications for Osteoporosis, the examples of other medications used for osteoporosis in the note were revised. Reference to calcium and vitamin D was deleted.	07/29/2020

APPENDIX A.

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:

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

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.