



UTILIZATION MANAGEMENT MEDICAL POLICY

POLICY: Bone Modifiers – Prolia Utilization Management Medical Policy

- Prolia® (denosumab subcutaneous injection – Amgen)

REVIEW DATE: 09/27/2023

OVERVIEW

Prolia, a receptor activator of nuclear factor kappa-B 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.
- **Bone loss (treatment to increase bone mass), in women with breast cancer** at high risk for fracture receiving adjuvant aromatase inhibitor 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 guidelines for breast cancer (version 4.2023 – March 23, 2023)⁶ and prostate cancer (version 4.2023 – September 7, 2023)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 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 intravenous infusion [Reclast]).
- **Postmenopausal Osteoporosis:** Prolia is prominently featured in guidelines for postmenopausal osteoporosis by the Endocrine Society (2019)³ and the American Association of Clinical Endocrinologists and the American College of Endocrinology (2020).⁴ Prolia is one of several agents cited as an alternative for patients at high risk for fractures. The Bone Health and Osteoporosis Foundation clinician's guide for prevention and treatment of osteoporosis (2022) cites Prolia as robustly reducing vertebral and non-vertebral fractures in studies involving women with postmenopausal osteoporosis.⁸

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 indications. 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.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

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

FDA-Approved Indications

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 (A and B):

A) Patient has breast cancer that is not metastatic to bone; AND

B) Patient is receiving aromatase inhibitor therapy.

Note: Examples of aromatase inhibitor therapy are anastrozole, letrozole, or exemestane.

Dosing. Approve 60 mg subcutaneously once every 6 months.

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 if the patient meets the following (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; OR

Note: Examples of androgen deprivation therapy are Lupron Depot (leuprolide depot suspension injection), Eligard (leuprolide acetate suspension injectable), Trelstar (triptorelin pamoate suspension injection), and Zoladex (goserelin implant).

ii. Patient has undergone bilateral orchiectomy.

Dosing. Approve 60 mg subcutaneously once every 6 months.

3. Glucocorticoid-Induced Osteoporosis – Treatment. Approve for 1 year if the patient meets the following (A and B):

A) Patient is either initiating or continuing systemic glucocorticoids; AND

Note: An example of a systemic glucocorticoid is prednisone.

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

i. Patient has tried zoledronic acid intravenous infusion (Reclast); OR

ii. Patient has tried at least one oral bisphosphonate or oral bisphosphonate-containing product and meets one of the following (a or b):

Note: Examples of oral bisphosphonate products include Fosamax (alendronate tablets and oral solution), Fosamax Plus D (alendronate/cholecalciferol tablets), Actonel (risedronate tablets), Atelvia (risedronate delayed-release tablets), and Boniva (ibandronate tablets).

a) According to the prescriber, patient has experienced inadequate efficacy to oral bisphosphonate therapy after a trial duration of 12 months; OR

Note: Examples of inadequate efficacy are ongoing and significant loss of bone mineral density (BMD), lack of a BMD increase, and/or an osteoporotic fracture or a fragility fracture.

b) Patient has experienced significant intolerance to an oral bisphosphonate; OR

Note: Examples of significant intolerance include severe gastrointestinal related adverse events and/or severe musculoskeletal related adverse events.

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 medical condition; OR

Note: Examples of pre-existing gastrointestinal medical conditions include esophageal lesions, esophageal ulcers, or abnormalities of the esophagus that delay esophageal emptying (stricture, achalasia).

iv. Patient meets one of the following conditions (a, b, or c):

a) Severe renal impairment; OR

Note: An example of severe renal impairment is a creatinine clearance < 35 mL/min.

b) Chronic kidney disease; OR

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

Dosing. Approve 60 mg subcutaneously once every 6 months.

4. Osteoporosis Treatment for a Postmenopausal Patient. Approve for 1 year if the patient meets the following (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. The patient meets both of the following (a and b):

a) Patient has low bone mass; AND

Note: An example of low bone mass includes a 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).

b) According to the prescriber, 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 intravenous injection (Boniva) or zoledronic acid intravenous infusion (Reclast); OR

ii. Patient has tried at least one oral bisphosphonate or oral bisphosphonate-containing product and meets one of the following (a or b):

Note: Examples of oral bisphosphonate products include Fosamax (alendronate tablets and oral solution), Fosamax Plus D (alendronate/cholecalciferol tablets), Actonel (risedronate tablets), Atelvia (risedronate delayed-release tablets), and Boniva (ibandronate tablets).

a) According to the prescriber, patient has experienced inadequate efficacy to oral bisphosphonate therapy after a trial duration of 12 months; OR

Note: Examples of inadequate efficacy are ongoing and significant loss of bone mineral density (BMD), lack of a BMD increase, and/or an osteoporotic fracture or a fragility fracture.

- b) Patient has experienced significant intolerance to an oral bisphosphonate; OR
Note: Examples of significant intolerance include severe gastrointestinal related adverse events and/or severe musculoskeletal related adverse events.
- 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 medical condition; OR
Note: Examples of pre-existing gastrointestinal medical conditions include esophageal lesions, esophageal ulcers, or abnormalities of the esophagus that delay esophageal emptying (stricture, achalasia).
- iv. Patient meets one of the following conditions (a, b, or c):
 - a) Severe renal impairment; OR
Note: An example of severe renal impairment is a creatinine clearance < 35 mL/min.
 - b) Chronic kidney disease; OR
 - c) Patient has had an osteoporotic fracture or a fragility fracture.

Dosing. Approve 60 mg subcutaneously once every 6 months.

5. Osteoporosis Treatment (to Increase Bone Mass) for Men*. Approve for 1 year of the patient meets the following (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. The patient meets both of the following (a and b):
 - a) Patient has low bone mass; AND
Note: An example of low bone mass includes a 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).
 - b) According to the prescriber, 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 intravenous infusion (Reclast); OR
 - ii. Patient has tried at least one oral bisphosphonate or oral bisphosphonate-containing product and has had one of the following (a or b):
Note: Examples of oral bisphosphonate products include Fosamax (alendronate tablets and oral solution), Fosamax Plus D (alendronate/cholecalciferol tablets), Actonel (risedronate tablets), Atelvia (risedronate delayed-release tablets), and Boniva (ibandronate tablets).
 - a) According to the prescriber, patient has experienced inadequate efficacy to oral bisphosphonate therapy after a trial duration of 12 months; OR
Note: Example of inadequate efficacy are ongoing and significant loss of bone mineral density (BMD), lack of a BMD increase, and/or an osteoporotic fracture or a fragility fracture.
 - b) Patient has experienced significant intolerance to an oral bisphosphonate; OR
Note: Examples of significant intolerance include severe gastrointestinal related adverse events and/or severe musculoskeletal related adverse events.

- 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 medical condition; OR

Note: Examples of pre-existing gastrointestinal medical conditions include esophageal lesions, esophageal ulcers, or abnormalities of the esophagus that delay esophageal emptying (stricture, achalasia).
- iv. Patient meets one of the following conditions (a, b, or c):
 - a) Severe renal impairment; OR

Note: An example of severe renal impairment is a creatinine clearance < 35 mL/min.

 - b) Chronic kidney disease; OR
 - c) Patient has had an osteoporotic fracture or a fragility fracture.

* Refer to the Policy Statement

Dosing. Approve 60 mg subcutaneously 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 of medications for osteoporosis that Prolia should not be given with include teriparatide subcutaneous injection (Forteo), Tymlos (abaloparatide subcutaneous injection), oral bisphosphonates (e.g., alendronate, risedronate, ibandronate), intravenous bisphosphonates (zoledronic acid intravenous infusion [Reclast], ibandronate intravenous infusion), calcitonin nasal spray (Miacalcin/Fortical), and Evenity (romosozumab-aqqg subcutaneous injection). However, this does NOT exclude use of calcium and/or vitamin D supplements in combination with Prolia.

2. **Giant Cell Tumor of Bone.**

Studies with denosumab in giant cell tumor of the bone used dosing for Xgeva[®] (denosumab subcutaneous injection), 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[®] subcutaneous injection [prescribing information]. Thousand Oaks, CA: Amgen; January 2023.
2. Xgeva[®] subcutaneous injection [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.
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.
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.

6. The NCCN Breast Cancer Clinical Practice Guidelines in Oncology (version 4.2023 – March 23, 2023). © 2023 National Comprehensive Cancer Network. Available at: <http://www.nccn.org>. Accessed on September 19, 2023.
7. The NCCN Prostate Cancer Clinical Practice Guidelines in Oncology (version 4.2023 – September 7, 2023). © 2023 National Comprehensive Cancer Network. Available at: <http://www.nccn.org>. Accessed on September, 19, 2023.
8. LeBoff MS, Greenspan SL, Insogna KL, et al. The clinician’s guide to prevention and treatment of osteoporosis. *Osteoporosis Int.* 2022;33(10):2049-2102.

HISTORY

Type of Revision	Summary of Changes	Review Date
Annual Revision	Concurrent Use with Other Medications for Osteoporosis: To the Note which lists the medications that should not be used with Prolia, it was clarified that this does NOT exclude use of calcium and/or vitamin D supplements in combination with Prolia.	09/07/2022
Annual Revision	<p>To comply with standard wording, the phrase “as determined by the prescriber” was replaced with “according to the prescriber. In addition, the following changes were made:</p> <p>Glucocorticoid-Induced Osteoporosis – Treatment: The exception that the patient has had an osteoporotic fracture or a fragility fracture while receiving oral bisphosphonate therapy was removed. Instead, this exception was incorporated into a Note that lists osteoporotic fracture or a fragility fracture as an example of inadequate efficacy or significant intolerance to a trial of an oral bisphosphonate or an oral bisphosphonate-containing product. Femoral fracture was removed as an example of significant intolerance to an oral bisphosphonate.</p> <p>Osteoporosis Treatment for Men: The exception that the patient has had an osteoporotic fracture or a fragility fracture while receiving oral bisphosphonate therapy was removed. Instead, this exception was incorporated into a Note that lists osteoporotic fracture or a fragility fracture as an example of inadequate efficacy or significant intolerance to a trial of an oral bisphosphonate or an oral bisphosphonate-containing product. Femoral fracture was removed as an example of significant intolerance to an oral bisphosphonate.</p> <p>Osteoporosis Treatment for a Postmenopausal Patient: The exception that the patient has had an osteoporotic fracture or a fragility fracture while receiving oral bisphosphonate therapy was removed. Instead, this exception was incorporated into a Note that lists osteoporotic fracture or a fragility fracture as an example of inadequate efficacy or significant intolerance to a trial of an oral bisphosphonate or an oral bisphosphonate-containing product. Femoral fracture was removed as an example of significant intolerance to an oral bisphosphonate.</p>	09/27/2023