Medicare Advantage Medical Utilization Review Policy

Policy:	**Bone Modifiers – Prolia Utilization Management Medical Policy** • Prolia® (denosumab subcutaneous injection – Amgen)
Date:	10/13/2023
Applicable Lines of Business:	Medicare Advantage - Medical
Applicable States:	NGS, J6: Wisconsin, Minnesota, Illinois NGS, JK: New York, Connecticut, Massachusetts, Maine, New Hampshire, Rhode Island, Vermont

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 indication(s). Extended approvals are allowed if the patient continues to meet the Criteria and Dosing. 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.

This policy incorporates Medicare coverage guidance as set forth in National Coverage Determinations (NCDs) and Local Coverage Determinations (LCDs), as well as in companion policy articles and other guidance applicable to the relevant service areas. These documents are cited in the References section of this policy. In some cases, this guidance includes specific lists of HCPCS and ICD-10 codes to help inform the coverage determination process. The Articles that include specific lists for billing and coding purposes will be included in the Reference section of this policy. However, to the extent that this policy cites such lists of HCPCS and ICD-10 codes, they should be used for reference purposes only. The presence of a specific HCPCS or ICD-10 code in a chart or companion article to an LCD is not by itself sufficient to approve coverage. Similarly, the absence of such a code does not necessarily mean that the applicable condition or diagnosis is excluded from coverage.

Note: Conditions for coverage outlined in this Medicare Advantage Medical Policy may be less restrictive than those found in applicable National Coverage Determinations, Local Coverage Determinations and/or Local Coverage Articles. Examples of situations where this clinical policy may be less restrictive include, but are not limited to, coverage of additional indications supported by CMS-approved compendia and the exclusion from this policy of additional coverage criteria requirements outlined in applicable National Coverage Determinations, Local Coverage Determinations and/or Local Coverage Articles.

RECOMMENDED AUTHORIZATION CRITERIA

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

FDA-APPROVED INDICATIONS

1. Osteoporosis Treatment for a Postmenopausal Patient.

Criteria. 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.** 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, the patient is at high risk for fracture; AND

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

i. The patient has osteoporosis with a high risk for fracture, defined as either having a history of osteoporotic fracture OR having multiple risk factors for fractures;[10] OR

ii. The 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, the 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), a lack of a BMD increase, and/or an osteoporotic fracture or a fragility fracture.
- **b.** The 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. 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; 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. The patient has tried ibandronate intravenous injection (Boniva) or zoledronic acid intravenous infusion (Reclast) or at least one other available osteoporosis therapy;[10] OR

v. The 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 (CKD); OR
- **c.** The patient has had an osteoporotic fracture or a fragility fracture.

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.

Criteria. Approve for 1 year if the patient meets 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. 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 SC once every 6 months.

3. Bone Loss (Treatment to Increase Bone Mass) in Patients with Breast Cancer at High Risk for Fracture Receiving Adjuvant Aromatase Inhibitor Therapy.

Criteria. Approve for 1 year if the patient meets the following criteria (A and B):
A) The patient has breast cancer; AND
B) Patient is receiving aromatase inhibitor therapy.
Note: Examples of aromatase inhibitor therapy are anastrozole, letrozole, or exemestane.

Dosing. Approve 60 mg SC once every 6 months.

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

Criteria. 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, 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, the patient is at high risk for fracture; AND

B) The patient meets ONE of the following condition (i, ii, iii, iv, or v):
- **i.** The patient has osteoporosis with a high risk for fracture, defined as either having a history of osteoporotic fracture OR having multiple risk factors for fractures;[10] OR
- **ii.** The 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, the 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), a lack of a BMD increase, and/or an osteoporotic fracture or a fragility fracture.
  - **b.** The 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.** 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; 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.** The patient has tried zoledronic acid intravenous infusion (Reclast) or at least one other available osteoporosis therapy;[10] OR

v. The 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 (CKD); OR
- **c.** The patient has had an osteoporotic fracture or a fragility fracture.

***** Refer to the Policy Statement

Dosing. Approve 60 mg SC once every 6 months.

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5. Glucocorticoid-Induced Osteoporosis – Treatment.

Criteria. Approve for 1 year if the patient meets ALL of the following criteria (A and B):

A) The patient is either initiating or continuing systemic glucocorticoids; AND
Note: An example of a systemic glucocorticoid is prednisone.

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

i. The patient has a high risk for fracture, defined as either having a history of osteoporotic fracture OR having multiple risk factors for fractures;[10] OR

ii. The 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, the 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), a lack of a BMD increase, and/or an osteoporotic fracture or a fragility fracture.
- **b.** The 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. 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; 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. The patient has tried zoledronic acid intravenous infusion (Reclast) or at least one other available osteoporosis therapy;[10] OR

v. The 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 (CKD); OR
- **c.** The patient has had an osteoporotic fracture or a fragility fracture.

Dosing. Approve 60 mg SC once every 6 months.

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.

1. 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.
9. Centers for Medicare and Medicaid Services, National Government Services, Inc, Local Coverage Article: Billing and Coding: Denosumab (Prolia ™, Xgeva ™) - Related to LCD L33394 (A52399) (Original effective date 10/1/15; revision effective date 10/1/2023). Accessed on October 13, 2023.
10. Centers for Medicare and Medicaid Services, National Government Services, Inc, Local Coverage Determination (LCD): Drugs and Biologicals, Coverage of, for Label and Off-Label Uses (L33394) [original date 10/01/2015; revision effective date 11/1/2022]. Accessed on October 13, 2023.

HISTORY

Type of Revision	Summary of Changes	Date
Policy created	New Medicare Advantage Medical Policy	7/11/2018
Policy revision	Reviewed and revised original policy created 07/11/2018 in accordance with Local Coverage Article A52399.	08/28/2019
Policy revision	Completion of 2019 monthly monitoring process in accordance with Local Coverage Determination L33394, Local Coverage Article A52399.	11/22/2019
Policy revision	Non-clinical update to policy to add the statement "This policy incorporates Medicare coverage guidance as set forth in National Coverage Determinations (NCDs) and Local Coverage Determinations (LCDs), as well as in companion policy articles and other guidance applicable to the relevant service areas. These documents are cited in the References section of this policy. In some cases, this guidance includes specific lists of HCPCS and ICD-10 codes to help inform the coverage determination process. The Articles that include specific lists for billing and coding purposes will be included in the Reference section of this policy. However, to the extent that this policy cites such lists of HCPCS and ICD-10 codes, they should be used for reference purposes only. The presence of a specific HCPCS or ICD-10 code in a chart or companion article to an LCD is not by itself sufficient to approve coverage. Similarly, the absence of such a code does not	1/30/2020

	necessarily mean that the applicable condition or diagnosis is excluded from coverage."	
Policy revision	Removed criteria requiring Prolia be administered incident to a physician's service, which was determined to be administrative and not applicable to this clinical policy.	03/24/2020
Policy revision	*Added the following to the Policy Statement "Note: Conditions for coverage outlined in this Medicare Advantage Medical Policy may be less restrictive than those found in applicable National Coverage Determinations, Local Coverage Determinations and/or Local Coverage Articles. Examples of situations where this clinical policy may be less restrictive include, but are not limited to, coverage of additional indications supported by CMS-approved compendia and the exclusion from this policy of additional coverage criteria requirements outlined in applicable National Coverage Determinations, Local Coverage Determinations and/or Local Coverage Articles." *Updated references *Removed criteria for all indications requiring hypocalcemia be corrected prior to initiation with Prolia and requiring that patient take concomitant calcium and vitamin D supplementation *Added criteria defining osteoporosis (T-score, high risk, or previous history of fracture) to osteoporosis indications *Changed "prescribing physician" to "prescriber" throughout policy.	08/10/2020
Policy revision	For osteoporosis in postmenopausal patients, osteoporosis in men, and glucocorticoid-induced osteoporosis – changed wording of inadequate response to inadequate efficacy and intolerability to significant intolerance. Added examples of oral bisphosphonate products.	09/01/2021
Policy revision	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: **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. **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. **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.	10/13/2023