

- POLICY:** Bone Modifiers – Denosumab Products (Prolia) Utilization Management Medical Policy
- Bıldıyos® (denosumab-nxxp subcutaneous injection – Shanghai Henlius Biotech/Organon)
 - Conexxence® (denosumab-bnht subcutaneous injection – Fresenius)
 - Ospomyv™ (denosumab-dssb subcutaneous injection – Samsung Bioepis)

EFFECTIVE DATE: 1/1/2026

LAST REVISIONS DATE: 09/15/2025

COVERAGE CRITERIA FOR: UCare Medical Assistance and Exchange Plans Only (PMAP, Connect, MSC+, MnCare, all Individual and Family Plans)

OVERVIEW

Denosumab products (Prolia, biosimilars) are receptor activator of nuclear factor kappa-B ligand inhibitors indicated for the following uses:¹⁻³

- **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.¹⁻³ Of note, denosumab subcutaneous injection is also available under the brand name Xgeva® (and biosimilars) 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.⁴

Dosing Information

For all indications, the dose is 60 mg once every 6 months as a subcutaneous injection.¹⁻³

Guidelines

Several guidelines address denosumab products (Prolia, biosimilars).

- **Breast Cancer/Prostate Cancer:** The National Comprehensive Cancer Network guidelines for breast cancer (version 4.2024 – July 3, 2024)⁵ and prostate cancer (version 4.2024 – May 17, 2024)⁶ note that if patients are receiving agents that impact bone mineral density (BMD), bisphosphonates (oral/intravenous), as well as denosumab (Prolia, biosimilars), should be considered to maintain or improve BMD and/or reduce the risk of fractures.
- **Glucocorticoid-Induced Osteoporosis (GIO):** In 2022, the American College of Rheumatology published guidelines for the prevention and treatment of GIO.⁷ In various clinical scenarios, oral bisphosphonates are preferred, followed by intravenous bisphosphonates (e.g., zoledronic acid intravenous infusion [Reclast]). Denosumab products (Prolia, biosimilars) have a role in higher-risk patients.

- **Postmenopausal Osteoporosis:** Denosumab products (Prolia, biosimilars) are prominently featured in guidelines for postmenopausal osteoporosis by the Endocrine Society (2019)⁸ and the American Association of Clinical Endocrinologists and the American College of Endocrinology (2020).⁹ Denosumab products (Prolia, biosimilars) are 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 denosumab products (Prolia, biosimilars) as robustly reducing vertebral and non-vertebral fractures in studies involving women with postmenopausal osteoporosis.¹⁰

Safety

There is a Boxed Warning for denosumab products (Prolia, biosimilars) regarding hypocalcemia in patients with advanced kidney disease.¹⁻³ Patients with advanced chronic kidney disease are at greater risk of severe hypocalcemia following denosumab (Prolia, biosimilar) administration. Severe hypocalcemia resulting in hospitalization, life-threatening events, and fatal cases have been reported. The presence of chronic kidney disease mineral and bone disorder (CKD-MBD) greatly increases the risk of hypocalcemia. Before starting denosumab products (Prolia, biosimilars) in patients with advanced chronic kidney disease, evaluate for the presence of CKD-MBD. Treatment with denosumab products (Prolia, biosimilars) in these patients should be supervised by a healthcare provider with expertise in the diagnosis and management of CKD-MBD.

POLICY STATEMENT

Prior Authorization is recommended for medical benefit coverage of denosumab products (Prolia, biosimilars). 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 1 year in duration. 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 denosumab products (Prolia, biosimilars) is recommended for requests meeting both the preferred product step therapy requirements and indication requirements.

Preferred Product(s): Prolia Jubbonti and Stoboclo

Non-Preferred Products(s): Bıldıyos, Conexence and Ospomyv

Step Therapy Requirements:

Authorization for a non-preferred biologic product or biosimilar will be granted if the patient has had any one of the listed issues below (A, B, C, or D) with all preferred product(s). Chart notes documenting the issue must be provided at time of request:

- A. Allergic reaction to a specific inactive ingredient in all preferred biologic products or biosimilars OR

- B. Adverse reaction to a specific inactive ingredient in all preferred biologic products or biosimilars OR
- C. Therapeutic success while taking a non-preferred biologic product or biosimilar and therapeutic failure during an adequate trial of all preferred biologic products or biosimilars which allowed sufficient time for a positive treatment outcome documented by medical chart notes OR
- D. The patient has a diagnosis not included in the FDA-approved indications of all preferred products, but is included in the FDA-approved indications of the non-preferred product

Please note:

- Factors such as patient or prescriber preference or healthcare facility's or pharmacy's inability or unwillingness to order or stock the preferred product(s) will not be considered
- Common side effects to all products and infusion-related reactions are not considered documented allergic reactions to a preferred product as they would be expected with the innovator and biosimilar products
- Continuation of therapy overrides are not available to bypass required trial(s) of preferred biosimilar or biologic reference product
- Generally, an adequate trial of a drug is considered to be three months or longer in order to allow time for efficacy to be established

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 BOTH of the following (A and B): [\[EviCore\]](#)
- 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.

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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 if the patient meets BOTH of the following (A and B): [\[EviCore\]](#)
- A) Patient has prostate cancer that is not metastatic to bone; AND
 - B) Patient meets ONE of the following (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 BOTH of 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 (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 (a or b):

a) Patient meets BOTH of the following [(1) and (2)]:

(1) According to the prescriber, the patient has severe renal impairment or chronic kidney disease; AND

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

(2) Patient has been evaluated for the presence of chronic kidney disease mineral and bone disorder to reduce the risk of denosumab (Prolia, biosimilars)-induced hypocalcemia; OR

b) 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 BOTH of the following (A and B):

A) Patient meets ONE of the following (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 (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 (a or b):
 - a)** Patient meets BOTH of the following [(1) and (2)]:
 - (1)** According to the prescriber, the patient has severe renal impairment or chronic kidney disease; AND

Note: An example of severe renal impairment is a creatinine clearance < 35 mL/minute.
 - (2)** Patient has been evaluated for the presence of chronic kidney disease mineral and bone disorder to reduce the risk of denosumab (Prolia, biosimilars)-induced hypocalcemia; OR
 - b)** Patient has had an osteoporotic fracture or a fragility fracture.

Dosing. Approve 60 mg subcutaneously once every 6 months.

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- 5. Osteoporosis Treatment (to Increase Bone Mass) for Men*.** Approve for 1 year if the patient meets BOTH of the following (A and B):
- A)** Patient meets ONE of the following (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
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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 (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 (a or):
 - a) Patient meets BOTH of the following [(1) and (2)]:
 - (1) According to the prescriber, the patient has severe renal impairment or chronic kidney disease; AND

Note: An example of severe renal impairment is a creatinine clearance < 35 mL/minute.
 - (2) Patient has been evaluated for the presence of chronic kidney disease mineral and bone disorder to reduce the risk of denosumab (Prolia, biosimilars)-induced hypocalcemia; OR
 - b) Patient has had an osteoporotic fracture or a fragility fracture.

Dosing. Approve 60 mg subcutaneously once every 6 months.

Other Uses with Supportive Evidence

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6. **Treatment of Bone Loss in Patients with Prostate Cancer Receiving Androgen Deprivation Therapy.** Approve for 1 year if the patient is receiving androgen deprivation therapy. [\[EviCore\]](#)
Note: Examples of androgen deprivation therapy are Lupron Depot (leuprolide depot suspension injection), Eligard (leuprolide acetate suspension injectable), Trelstar (triptorelin pamoate suspension injection), Zoladex (goserelin implant), and Orgovyx (relugolix tablets).

Dosing. Approve 60 mg subcutaneously once every 6 months.

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- 7. Increase Bone Mineral Density in Patients with Breast Cancer.** Approve for 1 year if the patient meets ONE of the following (i or ii): [\[EviCore\]](#)
- i.** Patient meets BOTH of the following (a and b):
 - a)** Patient is postmenopausal; AND
 - b)** Patient is receiving aromatase inhibitor therapy; OR
Note: Examples of aromatase inhibitor therapy are anastrozole, letrozole, or exemestane.
 - ii.** Patient meets BOTH of the following (a and b):
 - a)** Patient is premenopausal; AND
 - b)** Patient is receiving estrogen deprivation therapy
Note: Examples of estrogen deprivation therapy are leuprolide acetate, Lupron Depot (leuprolide acetate intramuscular injection), Trelstar (triptorelin pamoate intramuscular injection), Zoladex (goserelin acetate subcutaneous injection), anastrozole, letrozole, and exemestane.

Dosing. Approve 60 mg subcutaneously once every 6 months.

* Refer to the Policy Statement.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of denosumab products (Prolia, biosimilars) are not recommended in the following situations:

1. Concurrent Use with Other Medications for Osteoporosis.

Note: Examples of medications for osteoporosis that denosumab products (Prolia, biosimilars) 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). Denosumab products (Prolia, biosimilars) are not indicated for use as combination therapy.¹ However, this does NOT exclude use of calcium and/or vitamin D supplements in combination with denosumab products (Prolia, biosimilars).

2. Giant Cell Tumor of Bone. [\[EviCore\]](#)

Studies in giant cell tumor of the bone used dosing of denosumab subcutaneous injection (Xgeva, biosimilars), 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.^{3,4}

3. Osteoporosis Prevention. Denosumab products (Prolia, biosimilars) are not indicated for the prevention of osteoporosis.^{1,2}

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

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6. Xgeva® subcutaneous injection [prescribing information]. Thousand Oaks, CA: Amgen; June 2020.

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8. The NCCN Prostate Cancer Clinical Practice Guidelines in Oncology (version 4.2024 – May 17, 2024). © 2024 National Comprehensive Cancer Network. Available at: <http://www.nccn.org>. Accessed on September 4, 2024.

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HISTORY

Type of Revision	Summary of Changes	Review Date
New UCare Policy	Policy reviewed and approved by UCare P&T committee as a new policy for 1/1/2026.	09/15/2025