PRIOR AUTHORIZATION POLICY

POLICY: Bone Modifiers – Denosumab Products (Prolia) Prior Authorization Policy
- Jubbonti® (denosumab-bbdz subcutaneous injection – Sandoz)
- Prolia® (denosumab subcutaneous injection – Amgen)

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OVERVIEW

Denosumab products (Prolia, biosimilar) are receptor activator of nuclear factor kappa-B ligand inhibitors indicated for the following uses:[1,2]

- **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 i**ncrease 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.[1,2] Of note, denosumab subcutaneous injection is also available under the brand name Xgeva® (and biosimilar) 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.[3,4]

Dosing Information

For all indications, the dose is 60 mg once every 6 months as a subcutaneous injection.[1,2]

Guidelines

Several guidelines address denosumab products (Prolia, biosimilar).

- **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, biosimilar), 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, biosimilar) have a role in higher-risk patients.
- **Postmenopausal Osteoporosis:** Denosumab products (Prolia, biosimilar) 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, biosimilar) 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, biosimilar) 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, biosimilar) regarding hypocalcemia in patients with advanced kidney disease.[1,2] 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, biosimilar) in patients with advanced chronic kidney disease, evaluate for the presence of CKD-MBD. Treatment with denosumab products (Prolia, biosimilar) 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 prescription benefit coverage of denosumab products (Prolia, biosimilar). 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: Smart Coverage Review uses patient claims history to answer Prior Authorization questions regarding medication history of Boniva® (ibandronate intravenous infusion) or Reclast® (zoledronic acid intravenous infusion). A 2-year look back period will be used to check claims history and automate for use of either agent (Boniva intravenous or Reclast). If not in claims, medication can be obtained through Prior Authorization criteria. For all reviews, other Prior Authorization criteria listed below will also be applied.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of denosumab products (Prolia, biosimilar) are 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 BOTH of 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.

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):
   - **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.

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, biosimilar)-induced hypocalcemia; OR

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

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. 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, biosimilar)-induced hypocalcemia; OR

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

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, total hip, and/or 33% (one-third) radius (wrist); OR

ii. Patient has had an osteoporotic fracture or a fragility fracture; OR

iii. 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 of 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 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: 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 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, biosimilar)-induced hypocalcemia; OR
b) Patient has had an osteoporotic fracture or a fragility fracture.

Other Uses with Supportive Evidence

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.
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).

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):
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.

* Refer to the Policy Statement.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of denosumab products (Prolia, biosimilar) 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, biosimilar) 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, biosimilar) 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, biosimilar).

2. **Giant Cell Tumor of Bone.** Studies in giant cell tumor of the bone used dosing of denosumab subcutaneous injection (Xgeva, biosimilar), 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, biosimilar) are 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

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