POLICY: Bone Modifiers – Prolia® (denosumab injection for subcutaneous use)

APPROVAL DATE: 07/03/2019

OVERVIEW
Prolia, a receptor activator of nuclear factor kappa-B (RANK) ligand inhibitor, is indicated for the treatment of postmenopausal women with osteoporosis at high risk of fracture, defined as a history of osteoporotic fracture, or multiple risk factors for fracture; or patients who have failed or are intolerant of other available therapy. In postmenopausal women with osteoporosis, Prolia reduces the incidence of vertebral, nonvertebral, and hip fractures. Prolia is indicated for treatment to increase bone mass in men with osteoporosis at high risk for fracture, defined as a history of osteoporotic fracture, or multiple risk factors for fracture; or patients who have failed or are intolerant of other available osteoporosis therapy. Prolia is indicated for the treatment of glucocorticoid-induced osteoporosis in men and women at high risk of fracture who are either initiating or continuing systemic glucocorticoids in a daily equivalent to 7.5 mg or greater of prednisone and expected to remain on glucocorticoids for at least 6 months. 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. Prolia is also indicated for the treatment of bone loss (to increase bone mass) in men at high risk for fracture receiving androgen deprivation therapy (ADT) for nonmetastatic prostate cancer. In such patients, Prolia reduced the incidence of vertebral fractures. Prolia is indicated for the treatment of bone loss (to increase bone mass) in women at high risk for fracture receiving adjuvant aromatase inhibitor (AI) therapy. The recommended dose of Prolia for all indications is 60 mg given as a single subcutaneous (SC) injection once every 6 months into the upper arm, the upper thigh, or the abdomen. Prolia should be given by a healthcare professional. All patients should receive calcium 1,000 mg daily and at least 400 IU vitamin D daily. Of note, denosumab 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. The recommended dose for this indication is 120 mg SC every 4 weeks, with additional doses recommended for initial treatment for some of the indications.

Guidelines
Osteoporosis in Postmenopausal Women
In 2019 the Endocrine Society updated their clinical practice guidelines for osteoporosis in postmenopausal women. It is recommended to treat postmenopausal women with high risk of fractures as the benefits of pharmacological therapies outweigh the risks. In women at high risk of fractures, it is recommended that initial treatment include bisphosphonates (e.g., alendronate, risedronate, zoledronic acid injection [Reclast]) to reduce the risk of fractures. Concerns are present with oral bisphosphonates regarding gastrointestinal irritation. Also, there are concerns about renal toxicity, therefore, bisphosphonates should not be used in patients with a low estimated glomerular filtration rate (< 35 mL/min). An alternative initial therapy is Prolia in postmenopausal women with osteoporosis who are at high risk of osteoporotic fractures. In such patients fracture risk should be reassessed after 5 to 10 years to determine if therapy should continue or if patients should be treated with another osteoporosis therapy. Longer-term follow-up data support continuing low rates of fractures with 10 year of use. Forteo® (teriparatide injection for subcutaneous use) or Tymlos® (abaloparatide injection for subcutaneous use) are recommended in postmenopausal women with osteoporosis at very high risk of fracture such as patients with severe or multiple vertebral fractures. The treatment duration should be for up to 2 years to reduce vertebral and nonvertebral fractures. Comparatively, the evidence base for those two agents and fracture reduction is more limited regarding the numbers of trials and patients involved. The finding of
osteosarcoma in rats led to the Boxed Warning with both agents which limits therapy for a maximum of 24 months in a lifetime.

In 2016 the American Association of Clinical Endocrinologists (AACE) and the American College of Endocrinology (ACE) updated clinical practice guidelines for the diagnosis and treatment of postmenopausal osteoporosis. Osteoporosis in postmenopausal women can be defined as follows: 1) T-score -2.5 or below in the lumbar spine, femoral neck, total hip, and/or 33% (one-third) radius; 2) low trauma spine or hip fracture (regardless of bone mineral density [BMD]), osteopenia or low bone mass (T-score between -1.0 and -2.5) with a fragility fracture of proximal humerus, pelvis or possibly distal forearm; 3) osteopenia or low bone mass (T-score between -1.0 and -2.5) with fragility fracture or proximal humerus, pelvis, or possibly distal forearm; 4) low bone mass or osteopenia and high FRAX fracture probability based on country-specific thresholds. The ACCE/ACE guidelines state approved agents with efficacy to reduce hip, non-vertebral and spine fractures include alendronate, risedronate, zoledronic acid injection (Reclast), and Prolia which are appropriate as initial therapy for most patients at high-risk of fracture. Forteo, Prolia, or zoledronic acid injection (Reclast) should be considered for patients unable to use oral therapy and as initial therapy for patients who are at especially high-risk of fracture. Raloxifene or ibandronate may be appropriate initial therapies in some scenarios in which patients require medications with spine-specific efficacy. Concomitant use of agents for the prevention or treatment of postmenopausal osteoporosis is not recommended.

### Osteoporosis in Men

In 2012 the Endocrine Society issued a clinical practice guideline regarding osteoporosis in men. Men at high risk of fracture should receive medications indicated in men (e.g., alendronate, Actonel, zoledronic acid injection [Reclast]). Zoledronic acid (Reclast) has been shown to reduce the risk of hip fracture in women with postmenopausal osteoporosis. For most men who are candidates for medication therapy, an oral bisphosphonate (e.g., alendronate) may be preferred. For men with upper or lower gastrointestinal issues, a non-oral therapy (e.g., zoledronic acid injection [Reclast], Forteo) may be an alternative. Men receiving androgen deprivation therapy for prostate cancer should receive Prolia in certain circumstances (e.g., severe osteoporosis), as this agent is indicated for this condition.

### Glucocorticoid-Induced Osteoporosis (GIO)

In 2017, the American College of Rheumatology (ACR) updated guidelines for the prevention and treatment of GIO. In various clinical scenarios, oral bisphosphonates are preferred, followed by intravenous bisphosphonates (e.g., zoledronic acid injection).

### Other

The National Comprehensive Cancer Network (NCCN) guidelines for breast cancer (version 2.2019 – July 2, 2019) and prostate cancer (version 2.2019 – April 17, 2019) note that if patients are receiving agents that impact BMD bisphosphonates (oral/intravenous), as well as Prolia, should be considered to maintain or improve BMD and/or reduce the risk of 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. 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

1. Osteoporosis Treatment for a Postmenopausal Patient. Approve for 1 year of the patient meets the following criteria (A and B):
   A) The patient meets ONE of the following conditions (i, ii, or iii):
      i. The 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. The patient has had an osteoporotic fracture or a fragility fracture; OR
      iii. The 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 physician determines the patient is at high risk for fracture; AND
   B) The patient meets ONE of the following (i, ii, iii or iv):
      i. The patient has tried at least one oral bisphosphonate or oral bisphosphonate-containing product and meets one of the following (a, b, or c):
         a) The patient has had an inadequate response to oral bisphosphonate therapy after a trial duration of 12 months as determined by the prescribing physician (e.g., ongoing and significant loss of bone mineral density [BMD], lack of BMD increase); OR
         b) The patient has had an osteoporotic fracture or fragility fracture while receiving oral bisphosphonate therapy; OR
         c) The 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
      ii. 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 (e.g., patient with esophageal lesions, esophageal ulcers, or abnormalities of the esophagus that delay esophageal emptying [stricture, achalasia]); OR
      iii. The patient has tried intravenous Boniva or Reclast; OR
      iv. The 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) The patient has had an osteoporotic fracture or a fragility fracture.

Dosing. Approve 60 mg SC once every 6 months.

2. Treatment of Bone Loss (to Increase Bone Mass) in Patients at High Risk for Fracture Receiving Androgen Deprivation Therapy for Nonmetastatic Prostate Cancer. Approve for 1 year of 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. The patient is receiving ADT (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. The patient has undergone bilateral orchiectomy.
Dosing. Approve 60 mg SC once every 6 months.

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

Dosing. Approve 60 mg SC once every 6 months.

4. Osteoporosis Treatment (to Increase Bone Mass) for Men*. Approve for 1 year of the patient meets the following criteria (A and B):
   A) The patient meets ONE of the following conditions (i, ii, or iii):
      i. The 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. The patient has had an osteoporotic fracture or a fragility fracture; OR
      iii. The 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 physician determines the patient is at high risk for fracture; AND
   B) The patient meets ONE of the following (i, ii, iii or iv):
      i. The 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) The patient has had an inadequate response to oral bisphosphonate therapy after a trial duration of 12 months as determined by the prescribing physician (e.g., ongoing and significant loss of BMD, lack of BMD increase); OR
         b) The patient has had an osteoporotic fracture or fragility fracture while receiving oral bisphosphonate therapy; OR
         c) The patient has experienced intolerability to an oral bisphosphonate (e.g., severe GI-related adverse effects, severe musculoskeletal-related side effects, a femoral fracture); OR
      ii. 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 (e.g., patient with esophageal lesions, esophageal ulcers, or abnormalities of the esophagus that delay esophageal emptying [stricture, achalasia]); OR
      iii. The patient has tried Reclast; OR
      iv. The 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) 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.
5. **Glucocorticoid-Induced Osteoporosis (GIO) Treatment.** Approve for 1 year of the patient meets the following criteria (A and B):

   A) The patient is either initiating or continuing systemic glucocorticoids (e.g., prednisone); AND
   B) The patient meets ONE of the following (i, ii, iii, or iv):

   i. The patient has tried at least one oral bisphosphonate or oral bisphosphonate-containing product and meets one of the following (a, b, or c):

      a) The patient has had an inadequate response to oral bisphosphonate therapy after a trial duration of 12 months as determined by the prescribing physician (e.g., ongoing and significant loss of BMD, lack of BMD increase); OR
      b) The patient has had an osteoporotic fracture or fragility fracture while receiving oral bisphosphonate therapy; OR
      c) The 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

   ii. 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 (e.g., patient with esophageal lesions, esophageal ulcers, or abnormalities of the esophagus that delay esophageal emptying [strictures, achalasia]); OR

   iii. The patient has tried zoledronic acid injection (Reclast); OR

   iv. The 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) The patient has had an osteoporotic fracture or a fragility fracture.

**Dosing.** Approve 60 mg SC once every 6 months.

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**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. Rationale for non-coverage for these specific conditions is provided below. (Note: This is not an exhaustive list of Conditions Not Recommended for Approval.)

1. **Osteoporosis Prevention.** Prolia is not indicated for the prevention of osteoporosis.¹

2. **Concurrent Use with Other Medications for Osteoporosis.** Note: Examples of other therapies are Forteo® (teriparatide injection for subcutaneous use), Tymlos® (abaloparatide injection for subcutaneous use), bisphosphonates (alendronate, risedronate, ibandronate, zoledronic acid [Reclast]), calcitonin nasal spray, and Evenity® (romosozumab-aqqg injection for subcutaneous use). Prolia is not indicated for use as combination therapy.¹ Calcium and Vitamin D may be given concurrently. Prolia is not indicated for use as combination therapy.¹

3. **Giant Cell Tumor of Bone.**
Studies with denosumab in giant cell tumor of the bone used dosing for Xgeva® (denosumab injection for SC 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

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

HISTORY

<table>
<thead>
<tr>
<th>Type of Revision</th>
<th>Summary of Changes</th>
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<tbody>
<tr>
<td>Annual revision</td>
<td>Criteria added for the treatment of glucocorticoid-induced osteoporosis.</td>
<td>06/27/2018</td>
</tr>
<tr>
<td>Annual revision</td>
<td>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: 1. <strong>Conditions Not Recommended for Approval</strong>: Added Evenity to the list of medications that should not be used concomitantly with Prolia.</td>
<td>07/03/2019</td>
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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:

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

For women, multiply the above results by 0.85. The steps, for clarity, are as follows:
1) Subtract the patient’s age in years from 140.
2) Multiply by the patient’s weight in kg (if weight is in pounds, divide by 2.2 to get kg).
3) Multiply 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 multiply 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.