Effective Date **2/1/2022**
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Coverage Policy Number **IP0331**

Denosumab (Prolia®)

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Related Coverage Resources

INSTRUCTIONS FOR USE
The following Coverage Policy applies to health benefit plans administered by Cigna Companies. Certain Cigna Companies and/or lines of business only provide utilization review services to clients and do not make coverage determinations. References to standard benefit plan language and coverage determinations do not apply to those clients. Coverage Policies are intended to provide guidance in interpreting certain standard benefit plans administered by Cigna Companies. Please note, the terms of a customer's particular benefit plan document [Group Service Agreement, Evidence of Coverage, Certificate of Coverage, Summary Plan Description (SPD) or similar plan document] may differ significantly from the standard benefit plans upon which these Coverage Policies are based. For example, a customer's benefit plan document may contain a specific exclusion related to a topic addressed in a Coverage Policy. In the event of a conflict, a customer's benefit plan document always supersedes the information in the Coverage Policies. In the absence of a controlling federal or state coverage mandate, benefits are ultimately determined by the terms of the applicable benefit plan document. Coverage determinations in each specific instance require consideration of 1) the terms of the applicable benefit plan document in effect on the date of service; 2) any applicable laws/regulations; 3) any relevant collateral source materials including Coverage Policies and; 4) the specific facts of the particular situation. Coverage Policies relate exclusively to the administration of health benefit plans. Coverage Policies are not recommendations for treatment and should never be used as treatment guidelines. In certain markets, delegated vendor guidelines may be used to support medical necessity and other coverage determinations.

Overview

This policy supports medical necessity review for denosumab (Prolia®).

Medical Necessity Criteria

Denosumab (Prolia) is considered medically necessary when ONE of the following is met (1, 2, 3, 4 or 5):

1. **Bone Loss (Treatment to Increase Bone Mass) in Individuals with Breast Cancer at High Risk for Fracture Receiving Adjuvant Aromatase Inhibitor Therapy.** Individual meets **BOTH** of the following criteria (A and B):
    A. Individual has breast cancer that is not metastatic to bone
    B. Individual is receiving aromatase inhibitor therapy (for example, anastrozole, letrozole, or exemestane)

2. **Bone Loss (Treatment to Increase Bone Mass) in Individuals with Nonmetastatic Prostate Cancer at High Risk for Fracture Receiving Androgen Deprivation Therapy.** Individual meets **BOTH** of the following criteria (A and B):
    A. Individual has prostate cancer that is not metastatic to bone
    B. Individual meets **ONE** of the following conditions (i or ii):
        i. Individual is receiving androgen deprivation therapy [for example, Lupron Depot (leuprolide depot suspension injection), Eligard (leuprolide acetate suspension injectable), Trelstar (triptorelin pamoate suspension injection), and Zoladex (goserelin implant)]
        ii. Individual has undergone bilateral orchiectomy

3. **Glucocorticoid-Induced Osteoporosis – Treatment.** Individual meets **BOTH** of the following criteria (A and B):
    A. Individual is either initiating or continuing chronic systemic glucocorticoids
    B. Documentation of **ONE** of the following (i, ii, iii or iv):
        i. Individual has had failure or inadequate response to at least **ONE** of the following oral **OR** intravenous bisphosphonate products (a, b, c, or d):
        Note: Examples of failure/inadequate response include, osteoporotic or fragility fracture while receiving bisphosphonate therapy, ongoing and significant loss of BMD, or lack of a BMD increase.
            a. alendronate tablets or oral solution (Fosamax)
            b. ibandronate intravenous injection or tablets (Boniva)
            c. risedronate tablets/delayed release tablets (Actonel/Atelvia)
            d. zoledronic acid intravenous infusion (Reclast)
        ii. Individual has a contraindication per FDA label, significant intolerance, or is not a candidate* for oral **AND** intravenous bisphosphonate therapy

        **Note: Not a candidate due to being subject to a warning per the prescribing information (labeling), having a disease characteristic, individual clinical factor[s], or other attributes/conditions or is unable to administer and requires this dosage formulation*

        iii. Individual is at very high risk for fracture
        Note: Examples include, recent fracture within past 12 months, fractures while on approved osteoporosis therapy, multiple fractures, fractures while on drugs causing skeletal harm (e.g., long-term glucocorticoids), very low T-score (e.g., less than − 3.0), high risk for falls or history of injurious falls, and very high fracture probability by FRAX® (fracture risk assessment tool) (e.g., major osteoporosis fracture > 30%, hip fracture > 4.5%)
        iv. Individual has a history of beneficial clinical response with denosumab (Prolia)

4. **Osteoporosis Treatment for a Postmenopausal Woman.** Individual meets **BOTH** of the following criteria (A and B):
    A. Individual meets **ONE** of the following conditions (i, ii, or iii):
        i. Individual has had a bone mineral density (BMD) 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)
        ii. Individual has had an osteoporotic fracture or a fragility fracture
        iii. Individual meets **BOTH** of the following (a and b):
            a. Individual has low bone mass [for example, 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. Prescriber determines that the individual is at high risk for fracture [for example, the FRAX® (fracture risk assessment tool) 10-year probability for major osteoporotic fracture is at least 20% or the 10-year probability of hip fracture is at least 3%]
    B. Documentation of **ONE** of the following (i, ii, iii, or iv):

i. Individual has had failure or inadequate response to at least **ONE** of the following oral **OR** intravenous bisphosphonate products (a, b, c, or d):
Note: Examples of failure/inadequate response include, osteoporotic or fragility fracture while receiving bisphosphonate therapy, ongoing and significant loss of BMD, or lack of a BMD increase.
    a. alendronate tablets or oral solution (Fosamax)
    b. ibandronate intravenous injection or tablets (Boniva)
    c. risedronate tablets/delayed release tablets (Actonel/Atelvia)
    d. zoledronic acid intravenous infusion (Reclast)
ii. Individual has a contraindication per FDA label, significant intolerance, or is not a candidate* for oral **AND** intravenous bisphosphonate therapy

**Note: Not a candidate due to being subject to a warning per the prescribing information (labeling), having a disease characteristic, individual clinical factor[s], or other attributes/conditions or is unable to administer and requires this dosage formulation*

iii. Individual is at very high risk for fracture
Note: Examples include, recent fracture within past 12 months, fractures while on approved osteoporosis therapy, multiple fractures, fractures while on drugs causing skeletal harm (e.g., long-term glucocorticoids), very low T-score (e.g., less than − 3.0), high risk for falls or history of injurious falls, and very high fracture probability by FRAX® (fracture risk assessment tool) (e.g., major osteoporosis fracture > 30%, hip fracture > 4.5%)
iv. Individual has a history of beneficial clinical response with denosumab (Prolia)

5. **Osteoporosis - Treatment to Increase Bone Mass in Men.** Individual meets **BOTH** of the following criteria (A and B):
    A. Individual meets **ONE** of the following conditions (i, ii, or iii):
        i. Individual has had a bone mineral density (BMD) 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)
        ii. Individual has had an osteoporotic fracture or a fragility fracture
        iii. Individual meets **BOTH** of the following (a and b):
            a. Individual has low bone mass [for example, 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. Prescriber determines that the individual is at high risk for fracture [for example, the FRAX® (fracture risk assessment tool) 10-year probability for major osteoporotic fracture is at least 20% or the 10-year probability of hip fracture is at least 3%]
    B. Documentation of **ONE** of the following (i, ii, iii, or iv):
        i. Individual has had failure or inadequate response to at least **ONE** of the following oral **OR** intravenous bisphosphonate products (a, b, c, or d):
        Note: Examples of failure/inadequate response include, osteoporotic or fragility fracture while receiving bisphosphonate therapy, ongoing and significant loss of BMD, or lack of a BMD increase.
            a. alendronate tablets or oral solution (Fosamax)
            b. ibandronate intravenous injection or tablets (Boniva)
            c. risedronate tablets/delayed release tablets (Actonel/Atelvia)
            d. zoledronic acid intravenous infusion (Reclast)
        ii. Individual has a contraindication per FDA label, significant intolerance, or is not a candidate* for oral **AND** intravenous bisphosphonate therapy

Note: Not a candidate due to being subject to a warning per the prescribing information (labeling), having a disease characteristic, individual clinical factor[s], or other attributes/conditions or is unable to administer and requires this dosage formulation

iii. Individual is at very high risk for fracture
Note: Examples include, recent fracture within past 12 months, fractures while on approved osteoporosis therapy, multiple fractures, fractures while on drugs causing skeletal harm (e.g., long-term glucocorticoids), very low T-score (e.g., less than − 3.0), high risk for falls or history of injurious falls, and very high fracture probability by FRAX® (fracture risk assessment tool) (e.g., major osteoporosis fracture > 30%, hip fracture > 4.5%)

iv. Individual has a history of beneficial clinical response with denosumab (Prolia)

When coverage is available and medically necessary, the dosage, frequency, duration of therapy, and site of care should be reasonable, clinically appropriate, and supported by evidence-based literature and adjusted based upon severity, alternative available treatments, and previous response to therapy.

Note: Receipt of sample product does not satisfy any criteria requirements for coverage.

Reauthorization Criteria

Denosumab (Prolia) is considered medically necessary for continued use when initial criteria are met AND there is documentation of beneficial response.

Authorization Duration

Initial approval duration: up to 12 months

Reauthorization approval duration: up to 12 months

Conditions Not Covered

Denosumab (Prolia) is considered experimental, investigational or unproven for **ANY** other use including the following (this list may not be all inclusive):

1. **Concurrent Use with Other Medications for Osteoporosis.**
   Note: Examples 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). Prolia is not indicated for use as combination therapy.[1]

2. **Giant Cell Tumor of Bone.**
   Studies with denosumab in giant cell tumor of the bone used dosing for Xgeva, 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]

Coding / Billing Information

Note: 1) This list of codes may not be all-inclusive.

2) Deleted codes and codes which are not effective at the time the service is rendered may not be eligible for reimbursement.

Considered Medically Necessary when criteria in the applicable policy statements listed above are met:

HCPCS Codes	Description
J0897	Injection, denosumab, 1 mg

Background

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

Prolia is available as a 60mg/1ml single-dose prefilled syringe.

Guidelines
Several guidelines address Prolia.

- Breast Cancer/Prostate Cancer: The National Comprehensive Cancer Network guidelines for breast cancer (version 5.2021 – June 28, 2021)[6] and prostate cancer (version 2.2021 – February 17, 2021)[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.

References

1. Prolia® subcutaneous injection [prescribing information]. Thousand Oaks, CA: Amgen; May 2021.
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. Available at: https://www.endocrine.org/guidelines-and-clinical-practice/clinical-practice-guidelines/osteoporosis-in-postmenopausal-women. Accessed on August 12, 2021.
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. Available at: https://www.rheumatology.org/Portals/0/Files/Guideline-for-the-Prevention-and-Treatment-of-GIOP.pdf. Accessed on August 12, 2021.
6. The NCCN Breast Cancer Clinical Practice Guidelines in Oncology (Version 5.2021 – June 28, 2021). © 2021 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed on August 10, 2021.
7. The NCCN Prostate Cancer Clinical Practice Guidelines in Oncology (Version 2.2021 – February 17, 2021). © 2021 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed on August 12, 2021.