Policy Number	**RX501.140**
Policy Effective Date	**01/01/2026**
Policy End Date	**12/31/2026**

Denosumab and Biosimilars for Non-Oncologic Indications

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Disclaimer

Medical policies are a set of written guidelines that support current standards of practice. They are based on current generally accepted standards of and developed by nonprofit professional association(s) for the relevant clinical specialty, third-party entities that develop treatment criteria, or other federal or state governmental agencies. A requested therapy must be proven effective for the relevant diagnosis or procedure. For drug therapy, the proposed dose, frequency and duration of therapy must be consistent with recommendations in at least one authoritative source. This medical policy is supported by FDA-approved labeling and/or nationally recognized authoritative references to major drug compendia, peer reviewed scientific literature and generally accepted standards of medical care. These references include, but are not limited to: MCG care guidelines, DrugDex (IIa level of evidence or higher), NCCN Guidelines (IIb level of evidence or higher), NCCN Compendia (IIb level of evidence or higher), professional society guidelines, and CMS coverage policy.

Carefully check state regulations and/or the member contract.

Each benefit plan, summary plan description or contract defines which services are covered, which services are excluded, and which services are subject to dollar caps or other limitations, conditions or exclusions. Members and their providers have the responsibility for consulting the member's benefit plan, summary plan description or contract to determine if there are any exclusions or other benefit limitations applicable to this service or supply. **If there is a discrepancy between a Medical Policy and a member's benefit plan, summary plan description or contract, the benefit plan, summary plan description or contract will govern.**

Legislative Mandates

EXCEPTION: For members residing in the state of Ohio, § 3923.60 requires any group or individual policy (Small, Mid-Market, Large Groups, Municipalities/Counties/Schools, State Employees, Fully-Insured, PPO, HMO, POS, EPO) that covers prescription drugs to provide for the coverage of any drug approved by the U. S. Food and Drug Administration (FDA) when it is prescribed for a use recognized as safe and effective for the treatment of a given indication in one or more of the standard medical reference compendia adopted by the United States Department of Health and Human Services or in medical literature even if the FDA has not approved the drug for that indication. Medical literature support is only satisfied when safety and efficacy has been confirmed in two articles from major peer-reviewed professional medical journals that present data supporting the proposed off-label use or uses as

generally safe and effective. Examples of accepted journals include, but are not limited to, Journal of American Medical Association (JAMA), New England Journal of Medicine (NEJM), and Lancet. Accepted study designs may include, but are not limited to, randomized, double blind, placebo controlled clinical trials. Evidence limited to case studies or case series is not sufficient to meet the standard of this criterion. Coverage is never required where the FDA has recognized a use to be contraindicated, and coverage is not required for non-formulary drugs.

Coverage

NOTE 1: Refer to RX502.061 Oncology Medications for oncologic indications of denosumab and associated biosimilars.

Denosumab (Prolia®) and its biosimilars **may be considered medically necessary** for any one of the following indications:

- Postmenopausal osteoporosis when the individual meets **ANY** of the following criteria:
  - A history of fragility fracture(s); **OR**
  - A pre-treatment T-score less than or equal to -2.5 AND at high risk for fracture.
- Osteoporosis in men when **ANY** of the following criteria are met:
  - History of fragility fracture(s); **OR**
  - A pre-treatment T-score less than or equal to -2.5 AND at high risk for a fracture.
- Glucocorticoid-induced osteoporosis when **ALL** the following criteria are met:
  - A pre-treatment T-score less than or equal to -2.5 OR history of a fragility fracture; **AND**
  - Currently receiving or will be initiating glucocorticoid therapy at an equivalent prednisone dose of greater than or equal to 5 mg/day with plans to continue prednisone for at least 6 months or more.

Denosumab (Prolia®) and its biosimilars **are considered experimental, investigational and/or unproven** for all non-Food and Drug Administration approved indications.

NOTE 2: Denosumab (Prolia®) biosimilars include**:**

- Denosumab-bbdz (Jubbonti®)
- Denosumab-dssb (Ospomyv™)
- Denosumab-bmwo (Stoboclo®)
- Denosumab-bnht (Conexxence®)
- Denosumab-kvqq (Bosaya™)
- Denosumab-nxxp (Bildyos®)
- Denosumab-qbde (Enoby™)
- Denosumab-desu (Osvyrti®)
- Denosumab-mobz (Boncresa®)

Policy Guidelines

None.

Description

Osteoporosis

Osteoporosis is a bone disease that develops when bone mineral density and bone mass decreases, or when the quality or structure of bone changes. This can lead to a decrease in bone strength that can increase the risk of fractures.

Osteoporosis can affect women and men of all races and ethnic groups; it can occur at any age, although the risk for development increases as one ages. For many women, the disease can begin to develop a year or two before menopause. It is most common in non-Hispanic White women and Asian women. African American and Hispanic women have a lower, but still significant, risk of developing osteoporosis. For men, it is more common in non-Hispanic whites. (7)

Postmenopausal Osteoporosis

Most postmenopausal women with osteoporosis have bone loss related to estrogen deficiency and/or age. A diagnosis can be made in the presence of a fragility fracture (occurring spontaneously or from minor trauma), particularly in the spine, hip, wrist, humerus, rib, and pelvis; or with a T-score of ≤-2.5 standard deviations (SDs) at any site based upon bone mineral density measurements by dual-energy x-ray absorptiometry (DXA). The National Bone Health Alliance suggests a clinical diagnosis may be made if there is a clear elevated risk for fracture, such as when the fracture risk assessment tool (FRAX) 10-year probability of major osteoporotic fracture is ≥20 percent or the 10-year probability of hip fracture is ≥3 percent. (8)

T-score

The World Health Organization (WHO) established a classification of bone mineral density by DXA according to the standard deviation difference between a patient's bone mineral density (BMD) and that of a young adult reference population; see Table 1.

Table 1. Diagnostic categories for osteoporosis and low bone mass based on BMD measurement by DXA

Category	Bone Mass
Normal	A value for BMD within 1.0 SD of the young adult female reference mean (T-score greater than or equal to -1.0 SD).
Low bone mass (osteopenia)	A value for BMD more than 1.0 but less than 2.5 SD below the young adult female reference mean (T-score less than -1 and greater than -2.5 SD).
Osteoporosis	A value for BMD 2.5 or more SD below the young adult female reference mean (T-score less than or equal to -2.5 SD).
Severe (established) osteoporosis	A value for BMD more than 2.5 SD below the young adult female reference mean in the presence of one or more fragility fractures.

BMD: bone mineral density; DXA: dual-energy x-ray absorptiometry; SD: standard deviation.
Data from: WHO scientific group on the assessment of osteoporosis at the primary health care level: Summary meeting report, 2004. Geneva: World Health Organization, 2007. (8)

The WHO thresholds were chosen based upon fracture risk in postmenopausal White women. Similar diagnostic threshold values for men are less well defined, although for any given BMD, the age-adjusted fracture risk is similar in men and women. The International Society for Clinical Densitometry (ISCD) recommends the application of the WHO classification for men aged 50 years and older. (8)

Fracture Risk Assessment Tool (FRAX)
The Fracture Risk Assessment Tool, or FRAX, is a computer-based calculator that estimates the 10-year probability of hip fracture and major osteoporotic fracture (hip, clinical spine, proximal humerus, or forearm) in untreated patients between ages 40 and 90 years using easily obtainable clinical risk factors for fractures, with or without femoral neck bone mineral density. The FRAX algorithm uses femoral neck BMD (g/cm^2) for calculation of fracture probability. (9)

Glucocorticoid-Induced Osteoporosis
Glucocorticoids increase the risk of fracture, particularly vertebral fractures, which occur early in treatment during the rapid phase of bone loss and at higher BMD levels than in postmenopausal osteoporosis. Fractures have been reported in as many as 30-50 percent of glucocorticoid users, with the incidence of fracture higher with advanced age, larger doses, and longer duration of therapy. Glucocorticoids increase bone resorption and reduce bone formation. Glucocorticoids stimulate osteoclast proliferation by suppressing synthesis of osteoprotegerin, an inhibitor of osteoclast differentiation from hematopoietic cells of the macrophage lineage, and by stimulating production of the receptor activator of nuclear factor kappa-B (RANK), which is required for osteoclastogenesis. High glucocorticoid levels also stimulate RANK ligand (RANKL) synthesis by pre-osteoblast/stromal cells, supporting osteoclast differentiation and net bone resorption. They also decrease intestinal calcium absorption in part by opposing the action of vitamin D and by decreasing the expression of calcium channels in the duodenum. With long-term use, the predominant effect of glucocorticoids on the skeleton is reduced bone formation. The decline in bone formation is mediated by direct inhibition of osteoblast proliferation and differentiation and by an increase in the apoptosis rates of mature osteoblasts and osteocytes. The reduction in bone formation is associated with a decrease in the mineral apposition rate and in serum and urine biochemical markers of bone formation. (10)

Denosumab
Denosumab is a human immunoglobulin - IgG2 - monoclonal antibody with affinity and specificity for human RANKL (receptor activator of nuclear factor kappa-B ligand). It binds to RANKL, a transmembrane or soluble protein essential for the formation, function and survival of osteoclasts, the cells responsible for bone resorption. It prevents RANKL from activating its receptor, RANK, on the surface of osteoclasts and their precursors. Prevention of the RANKL/ RANK interaction inhibits osteoclast formation, function, and survival, thereby decreasing bone

resorption and increasing bone mass and strength in both cortical and trabecular bone. (3, 4)

Regulatory Status
The U.S. Food and Drug Administration (FDA) approved denosumab (Prolia®) and associated biosimilars for the following indications: (1-6)

- Treatment of postmenopausal women with osteoporosis at high risk for fracture
- Treatment of bone loss in men with osteoporosis at high risk for fracture
- Glucocorticoid-induced osteoporosis
- Osteopenia in women at high risk of fracture receiving adjuvant aromatase inhibitor therapy for breast cancer
- Osteopenia in men at high risk of fracture receiving androgen deprivation therapy for nonmetastatic prostate cancer.

The following drugs have been approved by the U.S. FDA as biosimilars to Prolia:

- Jubbonti® (denosumab-bbdz) – March 2024
- Ospomyv™ (denosumab-dssb) – February 2025
- Stoboclo® (denosumab-bmwo) – February 2025
- Conexxence® (denosumab-bnht) – March 2025

This policy does not address the oncologic uses of denosumab.

Rationale

This medical policy is based on the Food and Drug Administration labeled indications of denosumab (Prolia®) and biosimilars for non-oncologic indications.

Prolia® and Associated Biosimilars (1-6)
Treatment of Postmenopausal Women with Osteoporosis
The efficacy and safety of denosumab in the treatment of postmenopausal osteoporosis was demonstrated in a 3-year, randomized, double-blind, placebo-controlled trial. Enrolled women had a baseline bone mass density (BMD) T-score between -2.5 and -4.0 at either the lumbar spine or total hip. Women with other diseases (such as rheumatoid arthritis, osteogenesis imperfecta, and Paget's disease) or on therapies that affect bone were excluded from this study. The 7808 enrolled women were aged 60 to 91 years with a mean age of 72 years. Overall, the mean baseline lumbar spine BMD T-score was -2.8, and 23% of women had a vertebral fracture at baseline. Women were randomized to receive subcutaneous injections of either placebo (N = 3906) or denosumab 60 mg (N = 3902) once every 6 months. All women received at least 1000 mg calcium and 400 international units (IU) vitamin D supplementation daily.

The primary efficacy variable was the incidence of new morphometric (radiologically diagnosed) vertebral fractures at 3 years. Vertebral fractures were diagnosed based on lateral spine

radiographs (T4-L4) using a semiquantitative scoring method. Secondary efficacy variables included the incidence of hip fracture and nonvertebral fracture, assessed at 3 years.

Effect on Vertebral Fractures

Denosumab significantly reduced the incidence of new morphometric vertebral fractures at 1, 2, and 3 years ($p < 0.0001$), as shown in Table 2. The incidence of new vertebral fractures at year 3 was 7.2% in the placebo-treated women compared to 2.3% for the denosumab-treated women. The absolute risk reduction was 4.8% and relative risk reduction was 68% for new morphometric vertebral fractures at year 3.

Table 2. The Effect of Denosumab on the Incidence of New Vertebral Fractures in Postmenopausal Women

	Proportion of Women with Fracture (%)[1]		**Absolute Risk of Reduction (%)[2] (95% CI)**	**Relative Risk of Reduction (%)[2] (95% CI)**
	Placebo N=3691 (%)	**Denosumab N=3702 (%)**		
0-1 Year	2.2	0.9	1.4 (0.8, 1.9)	61 (42, 74)
0-2 Years	5.0	1.4	3.5 (2.7, 4.3)	71 (61, 79)
0-3 Years	7.2	2.3	4.8 (3.9, 5.8)	68 (59, 74)

[1] Event rates based on crude rates in each interval.

[2] Absolute risk reduction and relative risk reduction based on Mantel-Haenszel method adjusting for age group variable.

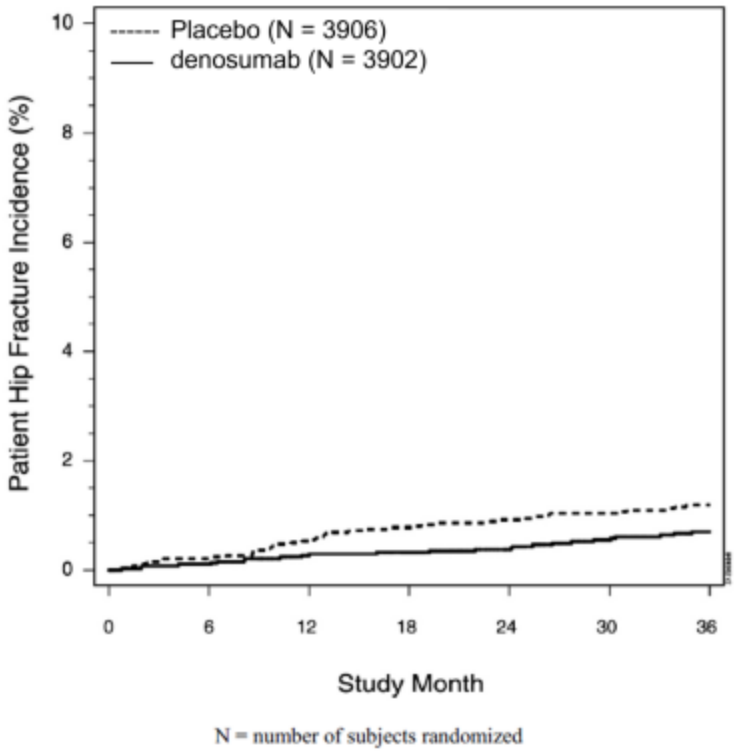
CI: confidence interval.

Denosumab was effective in reducing the risk for new morphometric vertebral fractures regardless of age, baseline rate of bone turnover, baseline BMD, baseline history of fracture, or prior use of a drug for osteoporosis.

Effect on Hip Fractures

The incidence of hip fracture was 1.2% for placebo-treated women compared to 0.7% for denosumab-treated women at year 3. The age-adjusted absolute risk reduction of hip fractures was 0.3% with a relative risk reduction of 40% at 3 years ($p = 0.04$) (Figure 1).

Figure 1. Cumulative Incidence of Hip Fractures Over 3 Years



Effect on Nonvertebral Fractures

Treatment with denosumab resulted in a significant reduction in the incidence of nonvertebral fractures (Table 3).

Table 3. The Effect of Denosumab on the Incidence of Nonvertebral Fractures at Year 3

	Proportion of Women with Fracture (%)[1]		**Absolute Risk Reduction (%) (95% CI)**	**Relative Risk Reduction (%) (95% CI)**
	Placebo N=3906 (%)	**Denosumab N=3902 (%)**		
Nonvertebral fracture[2]	8.0	6.5	1.5 (0.3, 2.7)	20 (5, 33)[3]

CI: confidence interval.

[1] Event rates based on Kaplan-Meier estimates at 3 years.

[2] Excluding those of the vertebrae (cervical, thoracic, and lumbar) skull, facial, mandible, metacarpus, and finger and toe phalanges.

[3] p-value = 0.01.

Effect on Bone Mineral Density (BMD)

Treatment with denosumab significantly increased BMD at all anatomic sites measured at 3 years. The treatment differences in BMD at 3 years were 8.8% at the lumbar spine, 6.4% at the total hip, and 5.2% at the femoral neck. Consistent effects on BMD were observed at the lumbar spine, regardless of baseline age, race, weight/body mass index (BMI), baseline BMD, and level of bone turnover.

After denosumab discontinuation, BMD returned to approximately baseline levels within 12 months.

Bone Histology and Histomorphometry
A total of 115 transiliac crest bone biopsy specimens were obtained from 92 postmenopausal women with osteoporosis at either month 24 and/or month 36 (53 specimens in denosumab group, 62 specimens in placebo group). Of the biopsies obtained, 115 (100%) were adequate for qualitative histology and 7 (6%) were adequate for full quantitative histomorphometry assessment.

Qualitative histology assessments showed normal architecture and quality with no evidence of mineralization defects, woven bone, or marrow fibrosis in patients treated with denosumab.

The presence of double tetracycline labeling in a biopsy specimen provides an indication of active bone remodeling, while the absence of tetracycline label suggests suppressed bone formation. In patients treated with denosumab, 35% had no tetracycline label present at the month 24 biopsy and 38% had no tetracycline label present at the month 36 biopsy, while 100% of placebo-treated patients had double label present at both time points. When compared to placebo, treatment with denosumab resulted in virtually absent activation frequency and markedly reduced bone formation rates. However, the long-term consequences of this degree of suppression of bone remodeling are unknown.

<u>Treatment to Increase Bone Mass in Men with Osteoporosis</u>
The efficacy and safety of denosumab in the treatment to increase bone mass in men with osteoporosis was demonstrated in a 1-year, randomized, double-blind, placebo-controlled trial. Enrolled men had a baseline BMD T-score between -2.0 and -3.5 at the lumbar spine or femoral neck. Men with a BMD T-score between -1.0 and -3.5 at the lumbar spine or femoral neck were also enrolled if there was a history of prior fragility fracture. Men with other diseases (such as rheumatoid arthritis, osteogenesis imperfecta, and Paget's disease) or on therapies that may affect bone were excluded from this study. The 242 men enrolled in the study ranged in age from 31 to 84 years with a mean age of 65 years. Men were randomized to receive SC injections of either placebo (n = 121) or denosumab 60 mg (n = 121) once every 6 months. All men received at least 1000 mg calcium and at least 800 IU vitamin D supplementation daily.

Effect on Bone Mineral Density (BMD)
The primary efficacy variable was percent change in lumbar spine BMD from baseline to 1-year. Secondary efficacy variables included percent change in total hip, and femoral neck BMD from baseline to 1-year.

Treatment with denosumab significantly increased BMD at 1-year. The treatment differences in BMD at 1-year were 4.8% (+0.9% placebo, +5.7% denosumab; (95% CI: 4.0, 5.6); $p < 0.0001$) at the lumbar spine, 2.0% (+0.3% placebo, +2.4% denosumab) at the total hip, and 2.2% (0.0% placebo, +2.1% denosumab) at femoral neck. Consistent effects on BMD were observed at the

lumbar spine regardless of baseline age, race, BMD, testosterone concentrations, and level of bone turnover.

Bone Histology and Histomorphometry
A total of 29 transiliac crest bone biopsy specimens were obtained from men with osteoporosis at 12 months (17 specimens in denosumab group, 12 specimens in placebo group). Of the biopsies obtained, 29 (100%) were adequate for qualitative histology and, in denosumab patients, 6 (35%) were adequate for full quantitative histomorphometry assessment. Qualitative histology assessments showed normal architecture and quality with no evidence of mineralization defects, woven bone, or marrow fibrosis in patients treated with denosumab. The presence of double tetracycline labeling in a biopsy specimen provides an indication of active bone remodeling, while the absence of tetracycline label suggests suppressed bone formation. In patients treated with denosumab, 6% had no tetracycline label present at the month 12 biopsy, while 100% of placebo-treated patients had double label present. When compared to placebo, treatment with denosumab resulted in markedly reduced bone formation rates. However, the long-term consequences of this degree of suppression of bone remodeling are unknown.

Treatment of Glucocorticoid-Induced Osteoporosis
The efficacy and safety of denosumab in the treatment of patients with glucocorticoid-induced osteoporosis was assessed in the 12-month primary analysis of a 2-year, randomized, multicenter, double-blind, parallel-group, active-controlled study (NCT01575873) of 795 patients (70% women and 30% men) aged 20 to 94 years (mean age of 63 years) treated with greater than or equal to 7.5 mg/day oral prednisone (or equivalent) for < 3 months prior to study enrollment and planning to continue treatment for a total of at least 6 months (glucocorticoid-initiating subpopulation; n = 290) or ≥ 3 months prior to study enrollment and planning to continue treatment for a total of at least 6 months (glucocorticoid-continuing subpopulation, n = 505). Enrolled patients < 50 years of age were required to have a history of osteoporotic fracture. Enrolled patients ≥ 50 years of age who were in the glucocorticoid-continuing subpopulation were required to have a baseline BMD T-score of ≤ -2.0 at the lumbar spine, total hip, or femoral neck; or a BMD T-score ≤ -1.0 at the lumbar spine, total hip, or femoral neck and a history of osteoporotic fracture.

Patients were randomized (1:1) to receive either an oral daily bisphosphonate (active control, risedronate 5 mg once daily) (n = 397) or denosumab 60 mg subcutaneously once every 6 months (n = 398) for one year. Randomization was stratified by gender within each subpopulation. Patients received at least 1000 mg calcium and 800 IU vitamin D supplementation daily.

Effect on Bone Mineral Density (BMD)
In the glucocorticoid-initiating subpopulation, denosumab significantly increased lumbar spine BMD compared to the active-control at one year (Active-control 0.8%, denosumab 3.8%) with a treatment difference of 2.9% ($p < 0.001$). In the glucocorticoid-continuing subpopulation, denosumab significantly increased lumbar spine BMD compared to active-control at 1 year

(Active-control 2.3%, denosumab 4.4%) with a treatment difference of 2.2% ($p < 0.001$). Consistent effects on lumbar spine BMD were observed regardless of gender; race; geographic region; menopausal status; and baseline age, lumbar spine BMD T-score, and glucocorticoid dose within each subpopulation.

Bone Histology
Bone biopsy specimens were obtained from 17 patients (11 in the active-control treatment group and 6 in the denosumab treatment group) at Month 12. Of the biopsies obtained, 17 (100%) were adequate for qualitative histology. Qualitative assessments showed bone of normal architecture and quality without mineralization defects or bone marrow abnormality. The presence of double tetracycline labeling in a biopsy specimen provides an indication of active bone remodeling, while the absence of tetracycline label suggests suppressed bone formation. In patients treated with active-control, 100% of biopsies had tetracycline label. In patients treated with denosumab, 1 (33%) had tetracycline label and 2 (67%) had no tetracycline label present at the 12-month biopsy. Evaluation of full quantitative histomorphometry including bone remodeling rates was not possible in the glucocorticoid-induced osteoporosis population treated with denosumab. The long-term consequences of this degree of suppression of bone remodeling in glucocorticoid-treated patients is unknown.

Practice Guidelines and Position Statements
<u>The North American Menopause Society</u>
In 2021, the North American Menopause Society (NAMS) updated their 2010 position statement regarding the management of osteoporosis in postmenopausal women. (11) The position statement recommendations include in part:

- Evaluate bone mineral density (BMD) in all women:
  - Aged 65 years and older;
  - With a history of fracture (other than skull, facial bone, ankle, finger, and toe) after menopause;
  - With medical causes of bone loss such as adverse event (AE) therapy and systemic glucocorticoid therapy of more than 3 months.
- Consider BMD testing for postmenopausal women aged younger than 65 years who have 1 or more of more of these risk factors:
  - Discontinued estrogen with additional risk factors for fracture;
  - Thinness (body weight <127 lb. [57.7 kg] or body mass index [BMI] <21 kg/m^2);
  - History of hip fracture in a parent;
  - Current smoking;
  - Excessive alcohol intake;
  - Long-term use of medications associated with bone loss such as prednisone or an aromatase inhibitor (AI).
- Drug therapy is recommended to prevent bone loss in postmenopausal women with:
  - Premature menopause, at least until the average age of natural menopause;
  - Low BMD (T-score < -1.0) and experiencing relatively rapid bone loss because of acute estrogen deficiency in the menopause transition or on discontinuing estrogen therapy;

- Low BMD (T-score < -1.0) and other risk factors for fracture (e.g., family history) but who do not meet the criteria for osteoporosis treatment.

- Drug therapy is recommended to treat osteoporosis in these populations:
  - All postmenopausal women who have had a vertebral or hip fracture.
  - All postmenopausal women who have BMD values consistent with osteoporosis (i.e., T-scores <-2.5) at the lumbar spine, femoral neck, or total hip (LS, FN, or TH) region.
  - All postmenopausal women who have T-scores from -1.0 to -2.5 and any one of:
    - History of fracture of proximal humerus, pelvis, or distal forearm.
    - History of multiple fractures at other sites (excluding face, feet, and hands).
    - Increased fracture risk according to country-specific thresholds using FRAX. In the United States, those thresholds are a 10-year risk of major osteoporotic fracture (spine, hip, shoulder, and wrist) of at least 20% or of hip fracture of at least 3%.

American College of Physicians

In the 2008 guidelines on screening for osteoporosis in men, the American College of Physicians state, "Key risk factors for low BMD include mediated fracture include increased age, low body weight, weight loss, physical inactivity, prolonged corticosteroid use, previous osteoporotic fracture, and androgen deprivation therapy….The clinical diagnosis of osteoporosis is made in two ways: occurrence of an osteoporotic fracture or BMD more than 2.5 standard deviations (T-score, −2.5) below that of a young, healthy population." (12)

Coding

Procedure codes on Medical Policy documents are included **only** as a general reference tool for each policy. **They may not be all-inclusive.**

The presence or absence of procedure, service, supply, or device codes in a Medical Policy document has no relevance for determination of benefit coverage for members or reimbursement for providers. **Only the written coverage position in a Medical Policy should be used for such determinations.**

Benefit coverage determinations based on written Medical Policy coverage positions must include review of the member's benefit contract or Summary Plan Description (SPD) for defined coverage vs. non-coverage, benefit exclusions, and benefit limitations such as dollar or duration caps.

CPT Codes	None
HCPCS Codes	C9399, J0897, J3490, J3590, J9999, Q5136, Q5157, Q5158, Q5159, Q5161, Q5162, Q5166, Q5167, Q5171

*Current Procedural Terminology (CPT®) ©2024 American Medical Association: Chicago, IL.

References

Food and Drug Administration Labels:

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Centers for Medicare and Medicaid Services (CMS)

The information contained in this section is for informational purposes only. HCSC makes no representation as to the accuracy of this information. It is not to be used for claims adjudication for HCSC Plans.

The Centers for Medicare and Medicaid Services (CMS) does not have a national Medicare coverage position. Coverage may be subject to local carrier discretion.

A national coverage position for Medicare may have been developed since this medical policy document was written. See Medicare's National Coverage at <https://www.cms.hhs.gov>.

Policy History/Revision	
Date	**Description of Change**
01/01/2026	Document updated. The following changes were made to Coverage: 1) Removed language on Continuation Therapy; 2) Removed all content related to Xgeva® and its biosimilars, and all oncology indications with addition of NOTE referring to RX502.061 for oncology use; 3) Revised conditional coverage criteria; and 4) Revised the experimental, investigational and/or unproven statement. Reference 3-5 & 12 added; others updated/removed. Title changed from "Denosumab (Prolia & Xgeva) and Associated Biosimilars."
07/01/2025	Document updated. The following change was made to Coverage: Updated coverage criteria to include the biosimilar denosumab-dssb (i.e., Ospomyv™ and Xbryk™). Added references 19 and 20.
06/01/2025	Document updated with literature review. The following change was made to Coverage: Modified Prolia criteria specific to breast cancer to replace "adjuvant endocrine therapy" with "an aromatase inhibitor". Added references 3, 10, 11, 15, and 16; others updated.
10/01/2024	Document updated. The following change was made to Coverage: Updated coverage criteria to include the biosimilar denosumab-bbdz (i.e., Jubbonti® and Wyost®). Added references 14 and 15. Title changed from "Denosumab (Prolia & Xgeva)".
06/01/2024	Document updated. The following change was made to Continuation Therapy in Coverage: removed "through a previously authorized pharmacy or medical benefit" in the statement "Continuation of Prolia/Xgeva may be considered medically necessary for all members (including new members…" Now reads: Continuation of Prolia/Xgeva may be considered medically necessary for all Members (including new members): who are currently receiving the requested medication for an indication listed below, AND who are experiencing benefit from therapy as evidenced by disease stability or disease improvement, AND when dosing is in accordance with an authoritative source." No new references added.
04/01/2024	New medical document. Denosumab (Prolia® and Xgeva®) may be considered medically necessary based on the indications listed in the coverage. Continuation of denosumab (Prolia/Xgeva) therapy is considered medically necessary for all members (including new members) who are currently receiving the requested medication through a previously authorized pharmacy or medical benefit, when dosing is in accordance with an authoritative source, and who are experiencing benefit from therapy as evidenced by disease stability or disease improvement. Denosumab (Prolia or Xgeva) is considered experimental, investigational and/or unproven for all

	other indications, including but not limited to combination therapy of denosumab and intravenous bisphosphonates; patients with uncorrected preexisting hypocalcemia; bone loss associated with hormone-ablation therapy (other than aromatase inhibitors) in breast cancer; cancer pain; central giant cell granuloma; hyper-parathyroidism; immobilization hypercalcemia; osteogenesis imperfecta; osteopenia (other than due to systemic mastocytosis); Paget's disease of bone; primary bone sarcomas (e.g., Ewing's sarcoma and osteosarcoma); rheumatoid arthritis.