

denosumab (Prolia[®], biosimilars)

Medicare Advantage Medical Policy #MA-101

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Applies to all products administered or underwritten by the Health Plan, unless otherwise provided in the applicable contract. Medical technology is constantly evolving, and we reserve the right to review and update Medical Policy periodically.

Blue Advantage does not cover investigational or experimental services, including any drug, device, procedure, or service provided under the investigational arm of a clinical trial or study unless mandated by the Centers for Medicare and Medicaid Services. Coverage is limited to routine services for Category A IDE studies and to devices and related services for Category B IDE studies when not supplied by the trial sponsor. Approved IDE studies are posted on www.cms.gov/medicare/coverage/evidence.

Note: Denosumab (Xgeva[®], biosimilars)[‡] is addressed separately in medical policy MA-047.

When Services May Be Eligible for Coverage

Coverage for eligible medical treatments or procedures, drugs, devices or biological products may be provided only if:

- *Benefits are available in the member's contract/certificate, and*
- *Medical necessity criteria and guidelines are met.*

Women

Based on review of available data, the Health Plan may consider the use of denosumab (Prolia[®])[‡], denosumab-bbdz (Jubbonti)^{®‡}, denosumab-nxxp (Bildyos)^{®‡}, denosumab-qbde (Enoby)^{™‡}, denosumab-bmwo (Stoboclo)^{®‡}, denosumab-bnht (Conexxence)^{®‡}, denosumab-dssb (Ospomyv)^{™‡}, denosumab-kyqq (Bosaya)^{™‡}, denosumab-desu (Osvyrti)^{®‡}, or denosumab-mobz (Boncresa)^{®‡} for the treatment of postmenopausal women with osteoporosis at high risk for fracture OR to increase bone mass in women at high risk for fracture receiving adjuvant aromatase inhibitor (AI) therapy for breast cancer to be **eligible for coverage**.**

Patient Selection Criteria

Coverage eligibility for the use of denosumab (Prolia), denosumab-bbdz (Jubbonti)^{®‡}, denosumab-nxxp (Bildyos)^{®‡}, denosumab-qbde (Enoby)^{™‡}, denosumab-bmwo (Stoboclo)^{®‡}, denosumab-bnht (Conexxence)^{®‡}, denosumab-dssb (Ospomyv)^{™‡}, denosumab-kyqq (Bosaya)^{™‡}, denosumab-desu (Osvyrti)^{®‡}, or denosumab-mobz (Boncresa)^{®‡} for the treatment of women will be considered when the following criteria are met for the requested drug:

- Patient is a woman with high risk for fracture (i.e., has a history of osteoporotic or fragility fracture, has a pre-treatment T-score of -1 or lower, has multiple risk factors for fracture, or has failed or is intolerant to other available osteoporosis therapy) and is receiving adjuvant AI therapy for breast cancer; OR
- Patient is a postmenopausal woman who meets ONE of the following diagnostic criteria for osteoporosis:
 - Presence of a central dual x-ray absorptiometry (DXA) bone mineral density (BMD) T-score less than or equal to -2.5, confirming osteoporosis; OR

denosumab (Prolia[®], biosimilars)

Medicare Advantage Medical Policy #MA-101

Original Effective Date: 06/01/2025

Current Effective Date: 05/01/2026

- Patient has experienced a fragility fracture [defined as a major osteoporotic fracture, sustained as a result of a low-level trauma (e.g., a fall from standing height or less) that is associated with low BMD, including vertebral (spine), hip, forearm (wrist/distal radius), and proximal humerus (shoulder) fractures]; OR
- Patient has a BMD T-score between -1.0 and -2.5 with an increased fracture risk (Defined as fracture risk assessment tool [FRAX[®]][†] 10-year probability of major osteoporotic fracture greater than or equal to 20% or 10-year probability of hip fracture greater than or equal to 3%); AND
- Patient has or has had 1 of the following:
 - An inability to take bisphosphonates; OR
 - A 12-month trial of oral bisphosphonates with documentation of new fractures or significant loss of bone mineral density; OR
 - Patient has experienced a fracture within the past 12 months; OR
 - Patient has a history of multiple fractures; OR
 - Patient has a T score less than -3.0; OR
 - Patient is at high risk of falls or has a history of falls; OR
 - Patient has a FRAX 10-year probability of major osteoporotic fracture greater than 30%; OR
 - Patient has a FRAX 10-year probability of hip fracture greater than 4.5%; AND
- If the request is for denosumab (Prolia), denosumab-bmwo (Stoboclo), denosumab-bnht (Conexence), denosumab-dssb (Ospomyv), denosumab-kyqq (Bosaya), denosumab-desu (Osvyrti), or denosumab-mobz (Boncresa), patient has tried and failed (e.g., intolerance or inadequate response) ALL of the following: denosumab-bbdz (Jubbonti), denosumab-nxxp (Bildyos), AND denosumab-qbde (Enoby) unless there is clinical evidence or patient history that suggests the use of these products will be ineffective or cause an adverse reaction to the patient ***; AND
- The requested dose does not exceed 60 mg subcutaneously once every 6 months.

Men

Based on review of available data, the Health Plan may consider the use of denosumab (Prolia), denosumab-bbdz (Jubbonti), denosumab-nxxp (Bildyos), denosumab-qbde (Enoby), denosumab-bmwo (Stoboclo), denosumab-bnht (Conexence), denosumab-dssb (Ospomyv), denosumab-kyqq (Bosaya), denosumab-desu (Osvyrti), or denosumab-mobz (Boncresa) for the treatment of men with osteoporosis at high risk for fracture **or** to increase bone mass in men at high risk for fracture receiving androgen deprivation therapy (ADT) for nonmetastatic prostate cancer to be **eligible for coverage**.**

Patient Selection Criteria

Coverage eligibility for the use of denosumab (Prolia), denosumab-bbdz (Jubbonti), denosumab-nxxp (Bildyos), denosumab-qbde (Enoby), denosumab-bmwo (Stoboclo), denosumab-bnht (Conexence), denosumab-dssb (Ospomyv), denosumab-kyqq (Bosaya), denosumab-desu (Osvyrti), or denosumab-mobz (Boncresa) for the treatment of men will be considered when the following criteria are met for the requested drug:

Medicare Advantage Medical Policy: MA-101

Last Reviewed: 03/17/2026

denosumab (Prolia[®], biosimilars)

Medicare Advantage Medical Policy #MA-101

Original Effective Date: 06/01/2025

Current Effective Date: 05/01/2026

- Patient is a man at high risk for fracture (i.e., has a history of osteoporotic or fragility fracture, has pre-treatment T-score of -1 or lower, has multiple risk factors for fracture, or has failed or is intolerant to other available osteoporosis therapy) and is receiving androgen deprivation therapy for nonmetastatic prostate cancer; OR
- Patient is a man who meets ONE of the following diagnostic criteria for osteoporosis:
 - Presence of a central dual x-ray absorptiometry (DXA) bone mineral density (BMD) T-score less than or equal to -2.5, confirming osteoporosis; OR
 - Patient has experienced a fragility fracture [defined as a major osteoporotic fracture, sustained as a result of a low-level trauma (e.g., a fall from standing height or less) that is associated with low BMD, including vertebral (spine), hip, forearm (wrist/distal radius), and proximal humerus (shoulder) fractures]; OR
 - Patient has a BMD T-score between -1.0 and -2.5 with an increased fracture risk (Defined as a FRAX 10-year probability of major osteoporotic fracture greater than or equal to 20% or 10-year probability of hip fracture greater than or equal to 3%); AND
- Patient has or has had 1 of the following:
 - An inability to take bisphosphonates; OR
 - A 12-month trial of oral bisphosphonates with documentation of new fractures or significant loss of bone mineral density; OR
 - Patient has experienced a fracture within the past 12 months; OR
 - Patient has a history of multiple fractures; OR
 - Patient has a T score less than -3.0; OR
 - Patient is at high risk of falls or has a history of falls; OR
 - Patient has a FRAX 10-year probability of major osteoporotic fracture greater than 30%; OR
 - Patient has a FRAX 10-year probability of hip fracture greater than 4.5%; AND
- If the request is for denosumab (Prolia), denosumab-bmwo (Stoboclo), denosumab-bnht (Conexence), denosumab-dssb (Ospomyv), denosumab-kyqq (Bosaya), denosumab-desu (Osvyrti), or denosumab-mobz (Boncrea), patient has tried and failed (e.g., intolerance or inadequate response) ALL of the following: denosumab-bbdz (Jubbonti), denosumab-nxxp (Bildyos), AND denosumab-qbde (Enoby) unless there is clinical evidence or patient history that suggests the use of these products will be ineffective or cause an adverse reaction to the patient ***; AND
- The requested dose does not exceed 60 mg subcutaneously once every 6 months.

Glucocorticoid Induced Osteoporosis

Based on review of available data, the Health Plan may consider the use of denosumab (Prolia), denosumab-bbdz (Jubbonti), denosumab-nxxp (Bildyos), denosumab-qbde (Enoby), denosumab-bmwo (Stoboclo), denosumab-bnht (Conexence), denosumab-dssb (Ospomyv), denosumab-kyqq (Bosaya), denosumab-desu (Osvyrti), or denosumab-mobz (Boncrea) for the treatment of men and women with glucocorticoid induced osteoporosis to be **eligible for coverage**.**

denosumab (Prolia[®], biosimilars)

Medicare Advantage Medical Policy #MA-101

Original Effective Date: 06/01/2025

Current Effective Date: 05/01/2026

Patient Selection Criteria:

Coverage eligibility will be considered for the treatment of patients with glucocorticoid induced osteoporosis with denosumab (Prolia), denosumab-bbdz (Jubbonti), denosumab-nxxp (Bildyos), denosumab-qbde (Enoby), denosumab-bmwo (Stoboclo), denosumab-bnht (Conexxence), denosumab-dssb (Ospomyv), denosumab-kyqq (Bosaya), denosumab-desu (Osvyrti), or denosumab-mobz (Boncresa) when the following criteria are met for the requested drug:

- Patient is 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; AND
- Patient meets ONE of the following:
 - Presence of a central DXA BMD T-score less than or equal to -2.5, confirming osteoporosis; OR
 - Patient has experienced a fragility fracture [defined as a major osteoporotic fracture, sustained as a result of a low-level trauma (e.g., a fall from standing height or less) that is associated with low BMD, including vertebral (spine), hip, forearm (wrist/distal radius), and proximal humerus (shoulder) fractures]; OR
 - Patient has a BMD T-score between -1.0 and -2.5 with an increased fracture risk (Defined as a FRAX 10-year probability of major osteoporotic fracture greater than or equal to 20% or 10-year probability of hip fracture greater than or equal to 3%); AND
- Patient has or has had 1 of the following:
 - An inability to take bisphosphonates; OR
 - A 12-month trial of oral bisphosphonates with documentation of new fractures or significant loss of bone mineral density; OR
 - Patient has experienced a fracture within the past 12 months; OR
 - Patient has a history of multiple fractures; OR
 - Patient has a T score less than -3.0; OR
 - Patient is at high risk of falls or has a history of falls; OR
 - Patient has a FRAX 10-year probability of major osteoporotic fracture greater than 30%; OR
 - Patient has a FRAX 10-year probability of hip fracture greater than 4.5%; AND
- If the request is for denosumab (Prolia), denosumab-bmwo (Stoboclo), denosumab-bnht (Conexxence), denosumab-dssb (Ospomyv), denosumab-kyqq (Bosaya), denosumab-desu (Osvyrti), or denosumab-mobz (Boncresa), patient has tried and failed (e.g., intolerance or inadequate response) ALL of the following: denosumab-bbdz (Jubbonti), denosumab-nxxp (Bildyos), AND denosumab-qbde (Enoby) unless there is clinical evidence or patient history that suggests the use of these products will be ineffective or cause an adverse reaction to the patient ***; AND
- The requested dose does not exceed 60 mg subcutaneously once every 6 months.

denosumab (Prolia[®], biosimilars)

Medicare Advantage Medical Policy #MA-101

Original Effective Date: 06/01/2025

Current Effective Date: 05/01/2026

When Services Are Considered Not Medically Necessary

Based on review of available data, the Health Plan considers the use of denosumab (Prolia), denosumab-bbdz (Jubbonti), denosumab-nxxp (Bildyos), denosumab-qbde (Enoby), denosumab-bmwo (Stoboclo), denosumab-bnht (Conexxence), denosumab-dssb (Ospomyv), denosumab-kyqq (Bosaya), denosumab-desu (Osvyrti), or denosumab-mobz (Boncresa) when the following criteria are NOT met to be **not medically necessary**.**

- Patient has an inability to take bisphosphonates; OR
- Patient has a 12-month trial of oral bisphosphonates with documentation of new fractures or significant loss of bone mineral density; OR
- Patient has experienced a fracture within the past 12 months; OR
- Patient has a history of multiple fractures; OR
- Patient has a T-score less than -3.0; OR
- Patient is at high risk of falls or has a history of falls; OR
- Patient has a FRAX 10-year probability of major osteoporotic fracture greater than 30%; OR
- Patient has a FRAX 10-year probability of hip fracture greater than 4.5%.

Based on review of available data, the Company considers the use of denosumab (Prolia), denosumab-bmwo (Stoboclo), denosumab-bnht (Conexxence), denosumab-dssb (Ospomyv), denosumab-kyqq (Bosaya), denosumab-desu (Osvyrti), or denosumab-mobz (Boncresa) when the patient has not tried and failed ALL of the following: denosumab-bbdz (Jubbonti), denosumab-nxxp (Bildyos), AND denosumab-qbde (Enoby) to be **not medically necessary**.**

When Services Are Considered Investigational

Coverage is not available for investigational medical treatments or procedures, drugs, devices or biological products.

Based on review of available data, the Health Plan considers the use of denosumab (Prolia), denosumab-bbdz (Jubbonti), denosumab-nxxp (Bildyos), denosumab-qbde (Enoby), denosumab-bmwo (Stoboclo), denosumab-bnht (Conexxence), denosumab-dssb (Ospomyv), denosumab-kyqq (Bosaya), denosumab-desu (Osvyrti), or denosumab-mobz (Boncresa) when patient selection criteria are not met (with the exception of those denoted above as **not medically necessary****) OR for use in any other indication than those listed above to be **investigational**.*

Background/Overview

Osteoporosis is a major metabolic bone disease that causes fractures in 40% of aging women and 15% of aging men over their lifetimes. Osteoporosis can be diagnosed based on DXA scans revealing a T-score less than or equal to -2.5, or presence of a fragility fracture (regardless of T-score), or a T-score between -1.0 and -2.5 with an increased fracture risk using FRAX score. A fragility fracture is a major osteoporotic fracture, sustained as a result of a low-level trauma (e.g., a fall from standing height or less) that is associated with low BMD, including vertebral (spine), hip, forearm (wrist/distal

denosumab (Prolia[®], biosimilars)

Medicare Advantage Medical Policy #MA-101

Original Effective Date: 06/01/2025

Current Effective Date: 05/01/2026

radius), and proximal humerus (shoulder) fractures. The fracture risk assessment tool (FRAX) estimates the 10-year probability of hip fracture and major osteoporotic fracture (hip, clinical spine, proximal humerus, or forearm) in untreated patients aged 40 to 90 years using easily obtainable clinical risk factors for fracture and femoral neck BMD when available. The data used by the FRAX was collected in large, prospective, observational studies across world regions. The tool has been validated in approximately 26 independent cohorts, and its country-specific prediction algorithms are available for many countries online. The United States FRAX can be accessed at <https://frax.shef.ac.uk/FRAX/tool.aspx?country=9>.

Recent studies have shown that estrogen deficiency is the cause of both the early and the late forms of osteoporosis in postmenopausal women and contributes to the development of osteoporosis in aging men. Estrogen deficiency is associated with an increase in bone resorption over bone formation, leading to excessive and sustained bone loss. The increase in bone resorption is due both to increased osteoclastogenesis and to decreased osteoclast apoptosis. Receptor activator of nuclear factor-kappaB (RANK ligand or RANKL) is a key mediator of bone resorption in normal and pathological states. In normal bone turnover and in bone metastasis, RANKL stimulates the formation and activity of bone-removing cells, osteoclasts.

Prolia is known as a RANK Ligand inhibitor; it works by decreasing the breakdown of bone by osteoclasts. Denosumab-bbdz (Jubbonti), denosumab-nxxp (Bildyos), denosumab-qbde (Enoby), denosumab-bmwo (Stoboclo), denosumab-bnht (Conexxence), denosumab-dssb (Ospomyv), denosumab-kyqq (Bosaya), denosumab-desu (Osvyrti), and denosumab-mobz (Boncresa) are biosimilar to Prolia. A biosimilar product is a biological product that is approved based on demonstration that it is highly similar to an already approved biological reference product. The biosimilar must also demonstrate that it has no clinically meaningful differences in terms of safety and effectiveness from the reference product. Only minor differences in clinically inactive components are allowable in biosimilar products. Biosimilar products can only be approved by the U.S. Food and Drug Administration (FDA) if they have the same mechanism of action, route of administration, dosage form, and strengths as the reference product as well as only the indications and conditions of use that have been approved by the FDA for the reference product. Denosumab is a highly specific monoclonal antibody produced in genetically engineered mammalian (Chinese hamster ovary) cells. Denosumab binds to RANKL, a transmembrane or soluble protein essential for the formation, function, and survival of osteoclasts, the cells responsible for bone resorption. Denosumab 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. Denosumab is dosed 60 mg every 6 months as a subcutaneous injection in the upper arm, upper thigh, or abdomen.

FDA or Other Governmental Regulatory Approval

U.S. Food and Drug Administration (FDA)

Prolia was approved in 2010 for the treatment of postmenopausal women with osteoporosis at high risk for fracture. In 2011, Prolia received indications for the treatment of men or women with a high

denosumab (Prolia[®], biosimilars)

Medicare Advantage Medical Policy #MA-101

Original Effective Date: 06/01/2025

Current Effective Date: 05/01/2026

risk of fracture that are undergoing hormone ablation therapy in either prostate or breast cancer. In 2012, Prolia was approved for the treatment of osteoporosis in men. In 2018, Prolia received the additional indication for the treatment of glucocorticoid-induced osteoporosis in men and women at high risk for fracture.

In 2024, denosumab-bbdz (Jubbonti) became the first biosimilar for Prolia to be approved. Several other biosimilar products were approved throughout 2025 including denosumab-nxxp (Bilydos), denosumab-qbde (Enoby), denosumab-bmwo (Stoboclo), denosumab-bnht (Conexxence), denosumab-dssb (Ospomyv), denosumab-kyqq (Bosaya), denosumab-desu (Osvyrti), and denosumab-mobz (Boncresa).

Rationale/Source

This medical policy was developed through consideration of peer-reviewed medical literature generally recognized by the relevant medical community, U.S. Food and Drug Administration approval status, nationally accepted standards of medical practice and accepted standards of medical practice in this community, technology evaluation centers, reference to federal regulations, other plan medical policies, and accredited national guidelines.

Postmenopausal Women with Osteoporosis

The efficacy and safety of Prolia in the treatment of postmenopausal osteoporosis was demonstrated in a 3-year, randomized, double-blind, placebo-controlled trial. Enrolled women had a baseline 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 Prolia 60 mg (N = 3902) once every 6 months. All women received at least 1000 mg calcium and 400 IU vitamin D supplementation daily.

The primary efficacy variable was the incidence of new morphometric (radiologically-diagnosed) vertebral fractures at three 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 three years.

Prolia significantly reduced the incidence of new morphometric vertebral fractures at 1, 2 and 3 years ($p < 0.0001$). The incidence of new vertebral fractures at year 3 was 7.2% in the placebo-treated women compared to 2.3% for the Prolia-treated women. The absolute risk reduction was 4.8% and relative risk reduction was 68% for new morphometric vertebral fractures at year 3. The incidence of hip fracture was 1.2% for placebo-treated women compared to 0.7% for Prolia-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 ($p = 0.04$). Treatment with Prolia resulted in a significant reduction in the incidence of nonvertebral fractures at year 3. Treatment with Prolia significantly increased

denosumab (Prolia[®], biosimilars)

Medicare Advantage Medical Policy #MA-101

Original Effective Date: 06/01/2025

Current Effective Date: 05/01/2026

BMD at all anatomic sites measured at three 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.

Treatment to Increase Bone Mass in Men with Osteoporosis

The efficacy and safety of Prolia 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 Prolia 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. 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 Prolia significantly increased BMD at 1 year. The treatment differences in BMD at 1 year were 4.8% (+0.9% placebo, +5.7% Prolia; (95% confidence interval [CI]: 4.0, 5.6); p < 0.0001) at the lumbar spine, 2.0% (+0.3% placebo, +2.4% Prolia) at the total hip, and 2.2% (0.0% placebo, +2.1% Prolia) 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.

Treatment of Bone Loss in Men with Prostate Cancer

The efficacy and safety of Prolia in the treatment of bone loss in men with nonmetastatic prostate cancer receiving ADT were demonstrated in a 3-year, randomized (1:1), double blind, placebo-controlled, multinational study. Men less than 70 years of age had either a BMD T-score at the lumbar spine, total hip, or femoral neck between -1.0 and -4.0, or a history of an osteoporotic fracture. The mean baseline lumbar spine BMD T-score was -0.4, and 22% of men had a vertebral fracture at baseline. The 1468 men enrolled ranged in age from 48 to 97 years (median 76 years). Men were randomized to receive subcutaneous injections of either placebo (n = 734) or Prolia 60 mg (n = 734) once every 6 months for a total of 6 doses. Randomization was stratified by age (< 70 years vs. ≥ 70 years) and duration of ADT at trial entry (≤ 6 months vs. > 6 months). Seventy-nine percent of patients received ADT for more than 6 months at study entry. All men received at least 1000 mg calcium and 400 IU vitamin D supplementation daily. The primary efficacy variable was percent change in lumbar spine BMD from baseline to month 24. An additional key secondary efficacy variable was the incidence of new vertebral fracture through month 36 diagnosed based on x-ray evaluation by two independent radiologists. Lumbar spine BMD was higher at 2 years in Prolia-treated patients as compared to placebo-treated patients [-1.0% placebo, +5.6% Prolia; treatment difference 6.7% (95% CI: 6.2, 7.1); p < 0.0001]. With approximately 62% of patients followed for 3 years, treatment differences in BMD at 3 years were 7.9% (-1.2% placebo, +6.8% Prolia) at the lumbar spine, 5.7% (-2.6% placebo, +3.2% Prolia) at the total hip, and 4.9% (-1.8%

Medicare Advantage Medical Policy: MA-101

Last Reviewed: 03/17/2026

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Medicare Advantage Medical Policy #MA-101

Original Effective Date: 06/01/2025

Current Effective Date: 05/01/2026

placebo, +3.0% Prolia) at the femoral neck. Consistent effects on BMD were observed at the lumbar spine in relevant subgroups defined by baseline age, BMD, and baseline history of vertebral fracture. Prolia significantly reduced the incidence of new vertebral fractures at 3 years ($p = 0.0125$).

Treatment of Bone Loss in Women with Breast Cancer

The efficacy and safety of Prolia in the treatment of bone loss in women receiving adjuvant AI therapy for breast cancer was assessed in a 2-year, randomized (1:1), double-blind, placebo controlled, multinational study. Women had baseline BMD T-scores between -1.0 to -2.5 at the lumbar spine, total hip, or femoral neck, and had not experienced fracture after age 25. The mean baseline lumbar spine BMD T-score was -1.1, and 2.0% of women had a vertebral fracture at baseline. The 252 women enrolled ranged in age from 35 to 84 years (median 59 years). Women were randomized to receive subcutaneous injections of either placebo ($n = 125$) or Prolia 60 mg ($n = 127$) once every 6 months for a total of 4 doses. Randomization was stratified by duration of adjuvant AI therapy at trial entry (≤ 6 months vs. > 6 months). Sixty-two percent of patients received adjuvant AI therapy for more than 6 months at study entry. All women received at least 1000 mg calcium and 400 IU vitamin D supplementation daily. The primary efficacy variable was percent change in lumbar spine BMD from baseline to month 12. Lumbar spine BMD was higher at 12 months in Prolia-treated patients as compared to placebo-treated patients [-0.7% placebo, +4.8% Prolia; treatment difference 5.5% (95% CI: 4.8, 6.3); $p < 0.0001$]. With approximately 81% of patients followed for 2 years, treatment differences in BMD at 2 years were 7.6% (-1.4% placebo, +6.2% Prolia) at the lumbar spine, 4.7 % (-1.0% placebo, +3.8% Prolia) at the total hip, and 3.6% (-0.8% placebo, +2.8% Prolia) at the femoral neck.

Glucocorticoid Induced Osteoporosis

The efficacy and safety of Prolia 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 of 795 patients. Included patients were aged 20 to 94 years of age and 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) or ≥ 3 months prior to study enrollment and planning to continue treatment for a total of at least 6 months (glucocorticoid-continuing subpopulation). 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 or Prolia 60 mg subcutaneously once every 6 months for 1 year. Patients received at least 1000 mg calcium and 800 IU vitamin D supplementation daily.

In the glucocorticoid-initiating subpopulation, Prolia significantly increased lumbar spine BMD compared to the active control at one year (Active control 2.3%, Prolia 4.4%) with a treatment difference of 2.2% ($p < 0.001$). In the glucocorticoid-continuing subpopulation, Prolia significantly increased lumbar spine BMD compared to active-control at one year (Active control 0.8%, Prolia

denosumab (Prolia[®], biosimilars)

Medicare Advantage Medical Policy #MA-101

Original Effective Date: 06/01/2025

Current Effective Date: 05/01/2026

3.8%) with a treatment difference of 2.9% (p<0.001). Consistent effects on lumbar spine BMD were observed regardless of gender, race, geographic region, menopausal status, baseline age, lumbar spine BMD T-score, and glucocorticoid dose within each subpopulation.

References

1. Prolia (denosumab) [package insert]. Thousand Oaks, CA: Amgen, Inc. May 2025.
2. Camacho PM, Petak SM, Binkley N, et al. American Association of Clinical Endocrinologists/ American College of Endocrinology Clinical Practice Guidelines for the Diagnosis and Treatment of Postmenopausal Osteoporosis. *Endocr Pract* 2020;26(1):1-44.
3. Osteoporotic Fracture Risk Assessment. UpToDate. Updated Dec. 2024.
4. Jubbonti (denosumab-bbdz) [package insert]. Princeton, NJ: Sandoz, Inc. October 2025.
5. BILDYOS (denosumab-nxxp) [package insert]. Jersey City, NJ: Organon, LLC. October 2025.
6. Enoby (denosumab-qbde) [package insert]. Cherry Hill, NJ: Hikma Pharmaceuticals USA, Inc. September 2025.
7. Stoboclo (denosumab-bmwo) [package insert]. Jersey City, NJ: Celltrion USA, Inc. October 2025.
8. Coneexence (denosumab-bnht) [package insert]. Lake Zurich, IL: Fresenius Kabi USA, LLC. October 2025.
9. Ospomyv (denosumab-dssb) [package insert]. Incheon, Republic of Korea: Samsung Bioepis Co., Ltd. October 2025.
10. Bosaya (denosumab-kyqq) [package insert]. Cambridge, MA: Biocon Biologics, Inc. September 2025.
11. Osvyrti (denosumab-desu) [package insert]. Raleigh, NC: Accord BioPharma, Inc. October 2025.
12. Boncresa (denosumab-mobz) [package insert]. Piscataway, NJ: Amneal Pharmaceuticals, LLC. December 2025.

Policy History

Original Effective Date: 06/01/2025

Current Effective Date: 05/01/2026

03/18/2025 UM Committee review and approval. New policy.

09/16/2025 UM Committee review. Coding update.

03/17/2026 UM Committee review. Added new biosimilar products, denosumab-bbdz (Jubbonti), denosumab-nxxp (BILDYOS), denosumab-qbde (Enoby), denosumab-bmwo (Stoboclo), denosumab-bnht (Coneexence), denosumab-dssb (Ospomyv), denosumab-kyqq (Bosaya), denosumab-desu (Osvyrti), and denosumab-mobz (Boncresa) to the policy. Added criterion requiring trial and failure of denosumab-bbdz (Jubbonti), denosumab-nxxp (BILDYOS), AND denosumab-qbde (Enoby) prior to the approval of denosumab (Prolia), denosumab-bmwo (Stoboclo), denosumab-bnht (Coneexence), denosumab-dssb (Ospomyv), denosumab-kyqq (Bosaya), denosumab-desu (Osvyrti), or denosumab-mobz (Boncresa). Updated criteria to clarify that doses above the labeled maximum dose are considered investigational. Title changed from “denosumab (Prolia)” to “denosumab (Prolia, biosimilars)”.

Medicare Advantage Medical Policy: MA-101

Last Reviewed: 03/17/2026

denosumab (Prolia[®], biosimilars)

Medicare Advantage Medical Policy #MA-101

Original Effective Date: 06/01/2025

Current Effective Date: 05/01/2026

Next Scheduled Review Date: 03/2027

Coding

The five character codes included in the Health Plan Medical Policy Coverage Guidelines are obtained from Current Procedural Terminology (CPT[®])[‡], copyright 2025 by the American Medical Association (AMA). CPT is developed by the AMA as a listing of descriptive terms and five character identifying codes and modifiers for reporting medical services and procedures performed by physician.

The responsibility for the content of the Health Plan Medical Policy Coverage Guidelines is with the Health Plan and no endorsement by the AMA is intended or should be implied. The AMA disclaims responsibility for any consequences or liability attributable or related to any use, nonuse or interpretation of information contained in the Health Plan Medical Policy Coverage Guidelines. Fee schedules, relative value units, conversion factors and/or related components are not assigned by the AMA, are not part of CPT, and the AMA is not recommending their use. The AMA does not directly or indirectly practice medicine or dispense medical services. The AMA assumes no liability for data contained or not contained herein. Any use of CPT outside of the Health Plan Medical Policy Coverage Guidelines should refer to the most current Current Procedural Terminology which contains the complete and most current listing of CPT codes and descriptive terms. Applicable FARS/DFARS apply.

CPT is a registered trademark of the American Medical Association.

Codes used to identify services associated with this policy may include (but may not be limited to) the following:

Code Type	Code
CPT	No codes
HCPCS	J0897, Q5136, Q5157, Q5158, Q5159 Add codes effective 05/01/2026: C9399, J3490, J3590, Q5161, Q5162
ICD-10 Diagnosis	All related diagnoses

*Investigational – A medical treatment, procedure, drug, device, or biological product is Investigational if the effectiveness has not been clearly tested and it has not been incorporated into standard medical practice. Any determination we make that a medical treatment, procedure, drug, device, or biological product is Investigational will be based on a consideration of the following:

- A. Whether the medical treatment, procedure, drug, device, or biological product can be lawfully marketed without approval of the U.S. Food and Drug Administration (FDA) and whether such approval has been granted at the time the medical treatment, procedure, drug, device, or biological product is sought to be furnished; or
- B. Whether the medical treatment, procedure, drug, device, or biological product requires further studies or clinical trials to determine its maximum tolerated dose, toxicity, safety, effectiveness, or effectiveness as compared with the standard means of treatment or

denosumab (Prolia[®], biosimilars)

Medicare Advantage Medical Policy #MA-101

Original Effective Date: 06/01/2025

Current Effective Date: 05/01/2026

diagnosis, must improve health outcomes, according to the consensus of opinion among experts as shown by reliable evidence, including:

1. Consultation with technology evaluation center(s);
2. Credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community; or
3. Reference to federal regulations.

****Medically Necessary (or “Medical Necessity”)** - Health care services, treatment, procedures, equipment, drugs, devices, items or supplies that a Provider, exercising prudent clinical judgment, would provide to a patient for the purpose of preventing, evaluating, diagnosing or treating an illness, injury, disease or its symptoms, and that are:

- A. In accordance with nationally accepted standards of medical practice;
- B. Clinically appropriate, in terms of type, frequency, extent, level of care, site and duration, and considered effective for the patient's illness, injury or disease; and
- C. Not primarily for the personal comfort or convenience of the patient, physician or other health care provider, and not more costly than an alternative service or sequence of services at least as likely to produce equivalent therapeutic or diagnostic results as to the diagnosis or treatment of that patient's illness, injury or disease.

For these purposes, “nationally accepted standards of medical practice” means standards that are based on credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community, Physician Specialty Society recommendations and the views of Physicians practicing in relevant clinical areas and any other relevant factors.

*******According to the US Food and Drug Administration (FDA), a biosimilar is a biological product that has no clinically meaningful differences from the existing FDA-approved reference product. All biosimilar products meet the FDA’s rigorous standards for approval for the indications described in the product labeling. Once a biosimilar has been approved by the FDA, the safety and effectiveness of these products have been established, just as they have been for the reference product. Coverage of a biosimilar product as an alternate to a reference product is not considered a form of step therapy by the Health Plan.

‡ Indicated trademarks are the registered trademarks of their respective owners.

NOTICE: If the Patient’s health insurance contract contains language that differs from the Health Plan Medical Policy definition noted above, the definition in the health insurance contract will be relied upon for specific coverage determinations.

NOTICE: Medical Policies are scientific based opinions, provided solely for coverage and informational purposes. Medical Policies should not be construed to suggest that the Health Plan recommends, advocates, requires, encourages, or discourages any particular treatment, procedure, or service, or any particular course of treatment, procedure, or service.

denosumab (Prolia[®], biosimilars)

Medicare Advantage Medical Policy #MA-101

Original Effective Date: 06/01/2025

Current Effective Date: 05/01/2026

NOTICE: Federal and State law, as well as contract language, including definitions and specific contract provisions/exclusions, take precedence over Medical Policy and must be considered first in determining eligibility for coverage.

NOTICE: All codes listed on the Medical Policy require prior authorization. This ensures appropriate utilization and alignment with current clinical guidelines.

NOTICE: If an authorization for an ongoing course of treatment has been provided to a member and the member changes from one health plan to another health plan (e.g., a member moves from carrier A to Blue Advantage), Blue Advantage may honor the previous health plan's authorization for the same service under the same type of in-network benefit for a 90-day transition period. Documentation of the authorization for the ongoing course of treatment from the previous health plan must be provided to us by the member or their provider and the services provided for the course of treatment must otherwise be a covered service under the Blue Advantage health plan.

Medicare Advantage Members

Established coverage criteria for Medicare Advantage members can be found in Medicare coverage guidelines in statutes, regulations, National Coverage Determinations (NCD)s, and Local Coverage Determinations (LCD)s. To determine if a National or Local Coverage Determination addresses coverage for a specific service, refer to the Medicare Coverage Database at the following link: <https://www.cms.gov/medicare-coverage-database/search.aspx>. You may wish to review the Guide to the MCD Search here: <https://www.cms.gov/medicare-coverage-database/help/mcd-bene-help.aspx>.

When coverage criteria are not fully established in applicable Medicare statutes, regulations, NCDs or LCDs, internal coverage criteria may be developed. This policy is to serve as the summary of evidence, a list of resources and an explanation of the rationale that supports the adoption of this internal coverage criteria.