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PHARMACY / MEDICAL POLICY – 5.01.658

Denosumab Products

Effective Date:	Nov. 1, 2025	RELATED MEDICAL POLICIES:	
Last Revised:	Oct. 14, 2025	5.01.596	Pharmacologic Treatment of Osteoporosis
Replaces:	N/A		

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Introduction

Bone is living tissue, and the body constantly renews this living system by naturally breaking down and replacing bone. This is known as bone remodeling or bone turnover. As people age, however, bone remodeling changes. More old bone is lost than new bone is created. This can result in reduced bone mass. Osteoporosis, which means "porous bone," is a condition caused by the body's loss of too much bone. Osteoporosis leads to bones that are fragile. Thin, fragile bones are at high risk of fracture. Denosumab products are a RANK ligand inhibitor. This policy describes when denosumab drugs may be considered medically necessary.

Note: The Introduction section is for your general knowledge and is not to be taken as policy coverage criteria. The rest of the policy uses specific words and concepts familiar to medical professionals. It is intended for providers. A provider can be a person, such as a doctor, nurse, psychologist, or dentist. A provider also can be a place where medical care is given, like a hospital, clinic, or lab. This policy informs them about when a service may be covered.

Policy Coverage Criteria

Drug	Medical Necessity
• **Bildyos (denosumab-nxxp) SC**	**Bildyos (denosumab-nxxp), Conexxence (denosumab-bnht), Jubbonti (denosumab-bbdz), Ospomyv (denosumab-dssb), Prolia (denosumab), and Stoboclo (denosumab-bmwo) may be**

Drug	Medical Necessity
• **Conexxence (denosumab-bnht) SC** • **Jubbonti (denosumab-bbdz) SC** • **Ospomyv (denosumab-dssb) SC** • **Prolia (denosumab) SC** • **Stoboclo (denosumab-bmwo) SC**	**considered medically necessary when the following criteria are met:** • Treatment of osteoporosis when the individual has tried and failed or had intolerance to two generic bisphosphonates (either two oral medications or one oral medication and one IV medication) unless use of bisphosphonate medications are contraindicated* **OR** • Treatment to increase bone mass in men at high risk for fracture receiving androgen deprivation therapy (e.g., degarelix, goserelin, histrelin, leuprolide, triptorelin) for nonmetastatic prostate cancer **OR** • Treatment to increase bone mass in women at high risk for fracture receiving adjuvant aromatase inhibitor therapy (e.g., anastrozole, exemestane, letrozole) for breast cancer **AND** • The dose is limited to 60 mg every 6 months **Note:** Generic bisphosphonates include alendronate (oral), ibandronate (oral), risedronate (oral) and zoledronic acid (IV) **Note:** *In addition to contraindications in the prescribing information, oral bisphosphonates are considered contraindicated in individuals with esophageal disorders (e.g., achalasia, esophageal stricture, Barrett's esophagus, esophageal varices). Individuals with contraindications to oral bisphosphonates are only required to try and fail IV zoledronic acid.
• **Bilprevda (denosumab-nxxp) SC** • **Bomyntra (denosumab-bnht) SC** • **Osenvelt (denosumab-bmwo) SC** • **Wyost (denosumab-bbdz) SC** • **Xbryk (denosumab-dssb) SC** • **Xgeva (denosumab) SC**	**Bilprevda (denosumab-nxxp), Bomyntra (denosumab-bnht), Osenvelt (denosumab-bmwo), Wyost (denosumab-bbdz), Xbryk (denosumab-dssb), and Xgeva (denosumab) may be considered medically necessary for the prevention of skeletal-related events in an individual with bone metastases from solid tumors when:** • There is a documented inadequate response or intolerance to intravenous 4 mg zoledronic acid **AND** • For treatment of breast cancer, the individual has an expected survival of 3 months or greater

Drug	Medical Necessity
	OR • For the treatment of prostate cancer, the individual has castration recurrent disease **Bilprevda (denosumab-nxxp), Bomyntra (denosumab-bnht), Osenvelt (denosumab-bmwo), Wyost (denosumab-bbdz), Xbryk (denosumab-dssb), and Xgeva (denosumab) may be considered medically necessary when there is a documented inadequate response or intolerance to intravenous 4 mg zoledronic acid:** • When used for the prevention of skeletal-related events in individuals with multiple myeloma **OR** • When used to treat hypercalcemia of malignancy **Bilprevda (denosumab-nxxp), Bomyntra (denosumab-bnht), Osenvelt (denosumab-bmwo), Wyost (denosumab-bbdz), Xbryk (denosumab-dssb), and Xgeva (denosumab) may be considered medically necessary when used to treat giant cell tumor of the bone**

Drug	Investigational
• **Bildyos (denosumab-nxxp)** • **Bilprevda (denosumab-nxxp)** • **Bomyntra (denosumab-bnht)** • **Conexxence (denosumab-bnht)** • **Jubbonti (denosumab-bbdz)** • **Osenvelt (denosumab-bmwo)** • **Ospomyv (denosumab-dssb)** • **Prolia (denosumab)**	**The medications listed in this policy are subject to the product's US Food and Drug Administration (FDA) dosage and administration prescribing information.** **All other uses of the medications listed in this policy for conditions not outlined in this policy are considered investigational.**

Drug	Investigational
• Stoboclo (denosumab-bmwo) • Wyost (denosumab-bbdz) • Xbryk (denosumab-dssb) • Xgeva (denosumab)	

Length of Approval	
Approval	**Criteria**
Initial authorization	**Non-formulary exception reviews for Bildyos (denosumab-nxxp), Bilprevda (denosumab-nxxp), Bomyntra (denosumab-bnht), Conexxence (denosumab-bnht), Jubbonti (denosumab-bbdz), Osenvelt (denosumab-bmwo), Ospomyv (denosumab-dssb), Prolia (denosumab), Stoboclo (denosumab-bmwo), Wyost (denosumab-bbdz), Xbryk (denosumab-dssb), and Xgeva (denosumab) may be approved up to 12 months.** **All other reviews for Bildyos (denosumab-nxxp), Conexxence (denosumab-bnht), Jubbonti (denosumab-bbdz), Ospomyv (denosumab-dssb), Prolia (denosumab), and Stoboclo (denosumab-bmwo) may be approved up to 2 years.** **All other reviews for Bilprevda (denosumab-nxxp), Bomyntra (denosumab-bnht), Osenvelt (denosumab-bmwo), Wyost (denosumab-bbdz), Xbryk (denosumab-dssb), and Xgeva (denosumab) listed in the policy may be approved up to 6 months.**
Re-authorization criteria	**Non-formulary exception reviews for Bildyos (denosumab-nxxp), Conexxence (denosumab-bnht), Jubbonti (denosumab-bbdz), Ospomyv (denosumab-dssb), Prolia (denosumab), and Stoboclo (denosumab-bmwo) may be approved up to 12 months in duration when there is documentation that the condition has stabilized or improved and the individual has not experienced serious or intolerable side effects.** **All other reviews for Bildyos (denosumab-nxxp), Conexxence (denosumab-bnht), Jubbonti (denosumab-bbdz), Ospomyv**

Length of Approval	
Approval	**Criteria**
	(denosumab-dssb), Prolia (denosumab), and Stoboclo (denosumab-bmwo) may be approved up to 2 years in duration when there is documentation that the condition has stabilized or improved and the individual has not experienced serious or intolerable side effects. **Non-formulary exception reviews and all other reviews for Bilprevda (denosumab-nxxp), Bomyntra (denosumab-bnht), Osenvelt (denosumab-bmwo), Wyost (denosumab-bbdz), Xbryk (denosumab-dssb), and Xgeva (denosumab) may be approved up to 12 months as long as the drug-specific coverage criteria are met and chart notes demonstrate that the individual continues to show a positive clinical response to therapy.**

Documentation Requirements
The patient's medical records submitted for review for all conditions should document that medical necessity criteria are met. The record should include the following: • Office visit notes that contain the diagnosis and medication history

Coding

Code	Description
HCPCS	
J0897	Injection, denosumab (Prolia/Xgeva/Osenbelt) 1 mg
J3590	Unclassified biologics (use to report: Bildyos and Bilprevda)
Q5136	Injection, denosumab-bbdz (Jubbonti/Wyost), biosimilar, 1 mg
Q5157	Injection, denosumab-bmwo (Stoboclo/Osenvelt), biosimilar, 1 mg (new code effective 10/01/25).
Q5158	Injection, denosumab-bnht (Bomyntra/Conexxence), biosimilar, 1 mg (new code effective 10/01/25).
Q5159	Injection, denosumab-dssb (Ospomyv/Xbryk), biosimilar, 1 mg (new code effective 10/01/25).

Note: CPT codes, descriptions and materials are copyrighted by the American Medical Association (AMA). HCPCS codes, descriptions and materials are copyrighted by Centers for Medicare Services (CMS).

Related Information

Benefit Application

Bildyos (denosumab-nxxp), Conexxence (denosumab-bnht), Jubbonti (denosumab-bbdz), Ospomyv (denosumab-dssb), Prolia (denosumab), and Stoboclo (denosumab-bmwo) is administered by a healthcare professional subcutaneously every six months and is managed through the medical benefit and pharmacy benefit. Bilprevda (denosumab-nxxp), Bomyntra (denosumab-bnht), Osenvelt (denosumab-bmwo), Wyost (denosumab-bbdz), Xbryk (denosumab-dssb), and Xgeva (denosumab) is managed through the medical benefit.

Consideration of Age

Age limits specified in this policy are determined according to the US Food and Drug Administration (FDA) -approved indications, where applicable.

Evidence Review

Background

Osteoporosis is a pathological condition characterized by bone fragility and increased risk of fracture. The National Osteoporosis Foundation's (NOF) estimated in 2014 that nearly half the total adult U.S. population was affected by osteoporosis and low bone mass (T-score <-1.0). Approximately 10.2 million Americans ≥50 years of age (8.2 million women and 2.0 million men) were estimated to have osteoporosis and an additional 43.4 million (27.3 million women and 16.1 million men) to have low bone mass at the femoral neck (FN) or lumbar spine (LS) (NOF 2014). The prevalence of these conditions is expected to increase as the U.S. population ages.

The NOF also estimates approximately 2 million osteoporotic fractures occur in the U.S. each year (NOF 2014). Hip fracture is associated with the highest morbidity and mortality. Up to 24%

of individuals ≥50 years of age with hip fracture die in the year following the event (NOF 2015). Each year, of nearly 300,000 hip fracture individuals, one-quarter end up in nursing homes and half never regain previous function (NOF 2015). In total, osteoporotic fractures cost individuals, families, and the American healthcare system $19 billion annually, with Medicare paying a majority of these costs (NOF 2015).

Bone is constantly remodeled (broken down and replaced). Frequently, as people age creation of new bone does not keep up with removal of the old, resulting in reduced bone mass and increased risk for fracture.

The goal of therapy for osteoporosis is to prevent fractures. There are six classes of products currently indicated for use in osteoporosis in the U.S.

Denosumab (Prolia)

Treatment of Osteoporosis in Postmenopausal Women at High Risk for Fracture

Evidence showed that treatment with denosumab reduces radiographic vertebral, nonvertebral, and hip fractures compared with placebo in postmenopausal osteoporotic women. One Japanese trial and its 1-year open-label extension study included postmenopausal osteoporotic women with prevalent radiographic vertebral fractures and showed that denosumab protected against radiographic vertebral fractures.

Treatment to Increase Bone Mass in Men with Osteoporosis at High Risk for Fracture

Despite the prevalence of osteoporosis among older men and potential severity of its health consequences, osteoporosis in men is significantly understudied compared with women. The systematic review and meta-analysis published by the Journal of the American Geriatrics Society looked at two studies that evaluated the effect of denosumab vs. placebo in men with osteoporosis. Both studies did not demonstrate evidence of statistically significant reduction in vertebral fracture risk for men with denosumab.

Treatment of Glucocorticoid-Induced Osteoporosis (GIOP) in Men and Women at High Risk for Fracture

The efficacy of denosumab in the treatment of individuals with GIOP was assessed in the 12-month primary analysis of a 2-year, randomized, multicenter, double-blind parallel-group,

active-controlled study of 795 individuals (70% women and 30% men). Eligible individuals were aged 18 years or older and were receiving glucocorticoids (≥7·5 mg prednisone daily, or equivalent) for at least 3 months (glucocorticoid continuing) or less than 3 months (glucocorticoid initiating) before screening. Individuals were randomized (1:1) to receive either 5 mg risedronate daily (n =397) or denosumab 60 mg subcutaneously once every 6 months (n = 398) for one year. Denosumab was both non-inferior and superior to risedronate at 12 months for effect on BMD at the lumbar spine in both glucocorticoid-continuing and glucocorticoid-initiating subpopulations.

Treatment to Increase Bone Mass in Men at High Risk for Fracture Receiving Androgen Deprivation Therapy for Nonmetastatic Prostate Cancer

A placebo-controlled trial showed the benefits of denosumab in men with early prostate cancer receiving ADT; after 36 months of treatment, denosumab increased spine, hip, and distal radius BMD and decreased the incidence of vertebral fractures by 62%.

Treatment to Increase Bone Mass in Women at High Risk for Fracture Receiving Adjuvant Aromatase Inhibitor Therapy for Breast Cancer

For women taking aromatase inhibitors, denosumab has been shown to improve BMD and reduce the risk of clinical fractures compared to placebo. Efficacy was established in two trials. In both trials, women in the denosumab group had significant increase BMD at the LS, total hip, and femoral neck. In the Adjuvant Denosumab in Breast Cancer Trial (ABCSG-18), denosumab was shown to delay the time to first clinical fracture and reduce the incidence of new vertebral fractures when compared to placebo.

Xgeva (denosumab)

Clinical data from the pivotal Xgeva multiple myeloma ‘482 study demonstrated that Xgeva is non-inferior to zoledronic acid in delaying time to first on-study skeletal-related events (SREs). The median time to first on-study SRE was 22.83 months for Xgeva vs 23.98 months for zoledronic acid. Xgeva delayed the time to first SRE following randomization as compared to zoledronic acid in individuals with breast or castration-resistant prostate cancer (CRPC). In individuals with bone metastasis due to other solid tumors, Xgeva was noninferior to zoledronic

acid in delaying the time to first SRE following randomization. Overall survival and progression-free survival were similar between arms in all three trials.

Practice Guidelines and Position Statements

American College of Physicians Guideline

The American College of Physicians Guideline on the Treatment of Low Bone Density or Osteoporosis to Prevent Fractures in Men and Women recommended that clinicians:

- Offer pharmacologic treatment with alendronate, risedronate, zoledronic acid, or denosumab to reduce the risk for hip and vertebral fractures in women who have known osteoporosis. (Grade: strong recommendation; high-quality evidence)
- Treat osteoporotic women with pharmacologic therapy for 5 years. (Grade: weak recommendation; low-quality evidence)
- Offer pharmacologic treatment with bisphosphonates to reduce the risk for vertebral fracture in men who have clinically recognized osteoporosis. (Grade: weak recommendation; low-quality evidence)

American Association of Clinical Endocrinologists (AACE)/American College of Endocrinology (ACE) Clinical Practice Guideline

The AACE/ACE Clinical Practice Guidelines For The Diagnosis and Treatment of Postmenopausal Osteoporosis were updated in 2020. The AACE/ACE guidelines are based on diligent reviews of the clinical evidence and the 2020 updated guideline contains 52 recommendations. Recommendations on which medications should be used to treat osteoporosis include the following:

- Offer approved agents with efficacy to reduce hip, nonvertebral, and spine fractures including alendronate, denosumab, risedronate, and zoledronate are appropriate as initial therapy for most osteoporotic individuals with high fracture risk
- Abaloparatide, denosumab, romosozumab, teriparatide, and zoledronate should be considered for individuals unable to use oral therapy and as initial therapy for individuals at very high fracture risk

Recommendations on how long individuals should be treated include the following:

- Limit treatment with abaloparatide and teriparatide to 2 years and follow abaloparatide or teriparatide therapy with a bisphosphonate or denosumab
- Limit treatment with romosozumab to 1 year and follow with a drug intended for long-term use, such as a bisphosphonate or denosumab
- For oral bisphosphonates, consider a bisphosphonate holiday after 5 years of treatment if fracture risk is no longer high (such as when the T score is greater than -2.5, or the individual has remained fracture free), but continue treatment up to an additional 5 years if fracture risk remains high
- For oral bisphosphonates, consider a bisphosphonate holiday after 6 to 10 years of stability in individuals with very high fracture risk
- For zoledronate, consider a bisphosphonate holiday after 3 years in high-risk individuals or until fracture risk is no longer high, and continue for up to 6 years in very-high risk individuals
- The ending of a bisphosphonate holiday should be based on individual patient circumstances such as an increase in fracture risk, a decrease in bone mineral density beyond the least significant change (LSC) of the dual-energy X-ray absorptiometry (DXA) machine, or an increase in bone turnover markers
- A holiday is not recommended for non-bisphosphonate antiresorptive drugs, and treatment with such agents should be continued for as long as clinically appropriate
- If denosumab therapy is discontinued, individuals should be transitioned to another antiresorptive

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14. Xgeva (denosumab) [prescribing information]. Thousand Oaks, CA; Amgen, Inc. Revised June 2020.
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18. Conexxence (denosumab-bnht) [prescribing information]. Lake Zurich, IL; Fresenius Kabi USA, LLC. Revised March 2025.
19. Stoboclo (denosumab-bmwo) [prescribing information]. Jersey City, NJ; Celltrion USA, Inc. Revised September 2025.
20. Osenvelt (denosumab-bmwo) [prescribing information]. Jersey City, NJ; Celltrion USA, Inc. Revised September 2025.
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22. Xbryk (denosumab-dssb) [prescribing information]. Incheon, Korea; Samsung Bioepis. Revised February 2025.
23. Jubbonti (denosumab-bbdz) [prescribing information]. Princeton, NJ; Sandoz Inc. March 2024.
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History

Date	Comments
11/01/25	New policy, approved October 14, 2025. Moved Prolia (denosumab) from policy 5.01.596 Pharmacologic Treatment of Osteoporosis to 5.01.658 Denosumab Products. Moved Xgeva (denosumab) from policy 5.01.540 Miscellaneous Oncology Drugs to 5.01.658 Denosumab Products. Added coverage criteria for Bildyos (denosumab-nxxp),

Date	Comments
	Bilprevda (denosumab-nxxp), Bomyntra (denosumab-bnht), Conexxence (denosumab-bnht), Jubbonti (denosumab-bbdz), Osenvelt (denosumab-bmwo), Ospomyv (denosumab-dssb), Stoboclo (denosumab-bmwo), Wyost (denosumab-bbdz), and Xbryk (denosumab-dssb).

Scope: Medical policies are systematically developed guidelines that serve as a resource for Company staff when determining coverage for specific medical procedures, drugs or devices. Coverage for medical services is subject to the limits and conditions of the member benefit plan. Members and their providers should consult the member benefit booklet or contact a customer service representative to determine whether there are any benefit limitations applicable to this service or supply. This medical policy does not apply to Medicare Advantage.