denosumab (Xgeva®, biosimilars)

Medicare Advantage Medical Policy #MA-047
Original Effective Date: 01/01/2025
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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 (Prolia®, biosimilars)‡ is addressed separately in medical policy MA-101.

When Services Are 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.*

Multiple Myeloma and Skeletal-Related Events Secondary to Bone Metastases from Solid Tumors

Based on review of available data, the Health Plan may consider the use of denosumab (Xgeva®)‡, denosumab-bbdz (Wyost)®‡, denosumab-nxxp (Bilprevda)®‡, denosumab-qbde (Xtrenbo)™‡, denosumab-bmwo (Osenvelt)®‡, denosumab-bnht (Bomyntra)®‡, denosumab-dssb (Xbryk)™‡, denosumab-kyqq (Aukelso)™‡, denosumab-desu (Jubereq)®‡, or denosumab-mobz (Oziltus)®‡ for the prevention of skeletal related events (SREs) in patients with multiple myeloma and in patients with bone metastases from solid tumors to be **eligible for coverage**.**

Patient Selection Criteria:

Coverage eligibility will be considered for the use of denosumab (Xgeva), denosumab-bbdz (Wyost), denosumab-nxxp (Bilprevda), denosumab-qbde (Xtrenbo), denosumab-bmwo (Osenvelt), denosumab-bnht (Bomyntra), denosumab-dssb (Xbryk), denosumab-kyqq (Aukelso), denosumab-desu (Jubereq), or denosumab-mobz (Oziltus) when the following criteria are met for the requested drug:

- Use in the prevention of SREs in patients with bone metastases from solid tumors; OR
- Use in the prevention of SREs in patients with multiple myeloma
- If the request is for denosumab (Xgeva), denosumab-bmwo (Osenvelt), denosumab-bnht (Bomyntra), denosumab-dssb (Xbryk), denosumab-kyqq (Aukelso), denosumab-desu (Jubereq), or denosumab-mobz (Oziltus), patient has tried and failed (e.g., intolerance or inadequate response) ALL of the following: denosumab-bbdz (Wyost), denosumab-nxxp (Bilprevda), AND denosumab-qbde (Xtrenbo) 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 120 mg subcutaneously every 4 weeks.

Giant Cell Tumor of the Bone

Based on review of available data, the Health Plan may consider the use of denosumab (Xgeva), denosumab-bbdz (Wyost), denosumab-nxxp (Bilprevda), denosumab-qbde (Xtrenbo), denosumab-bmwo (Osenvelt), denosumab-bnht (Bomyntra), denosumab-dssb (Xbryk), denosumab-kyqq (Aukelso), denosumab-desu (Jubereq), or denosumab-mobz (Oziltus) for the treatment of giant cell tumor of the bone to be **eligible for coverage**.**

Patient Selection Criteria:

Coverage eligibility will be considered for the use of denosumab (Xgeva), denosumab-bbdz (Wyost), denosumab-nxxp (Bilprevda), denosumab-qbde (Xtrenbo), denosumab-bmwo (Osenvelt), denosumab-bnht (Bomyntra), denosumab-dssb (Xbryk), denosumab-kyqq (Aukelso), denosumab-desu (Jubereq), or denosumab-mobz (Oziltus) when the following criteria are met for the requested drug:

- Patient has diagnosis of giant cell tumor of the bone; and
- Patient is an adult OR skeletally mature adolescent; and
- Giant cell tumor of the bone is unresectable OR surgical resection is likely to result in severe morbidity; AND
- If the request is for denosumab (Xgeva), denosumab-bmwo (Osenvelt), denosumab-bnht (Bomyntra), denosumab-dssb (Xbryk), denosumab-kyqq (Aukelso), denosumab-desu (Jubereq), or denosumab-mobz (Oziltus), patient has tried and failed (e.g., intolerance or inadequate response) ALL of the following: denosumab-bbdz (Wyost), denosumab-nxxp (Bilprevda), AND denosumab-qbde (Xtrenbo) 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 120 mg subcutaneously every 4 weeks. (Note: an additional dose of 120 mg on days 8 and 15 will be permitted for the first cycle only.)

Hypercalcemia of Malignancy

Based on review of available data, the Health Plan may consider the use of denosumab (Xgeva), denosumab-bbdz (Wyost), denosumab-nxxp (Bilprevda), denosumab-qbde (Xtrenbo), denosumab-bmwo (Osenvelt), denosumab-bnht (Bomyntra), denosumab-dssb (Xbryk), denosumab-kyqq (Aukelso), denosumab-desu (Jubereq), or denosumab-mobz (Oziltus) for the treatment of hypercalcemia of malignancy to be **eligible for coverage**.**

Patient Selection Criteria:

Coverage eligibility will be considered for the use of denosumab (Xgeva), denosumab-bbdz (Wyost), denosumab-nxxp (Bilprevda), denosumab-qbde (Xtrenbo), denosumab-bmwo (Osenvelt), denosumab-bnht (Bomyntra), denosumab-dssb (Xbryk), denosumab-kyqq (Aukelso), denosumab-

desu (Jubereq), or denosumab-mobz (Oziltus) when the following criteria are met for the requested drug:

- Patient has a diagnosis of hypercalcemia of malignancy that is refractory to intravenous (IV) bisphosphonate therapy (e.g. Zometa [zoledronic acid], pamidronate); AND
- If the request is for denosumab (Xgeva), denosumab-bmwo (Osenvelt), denosumab-bnht (Bomyntra), denosumab-dssb (Xbryk), denosumab-kyqq (Aukelso), denosumab-desu (Jubereq), or denosumab-mobz (Oziltus), patient has tried and failed (e.g., intolerance or inadequate response) ALL of the following: denosumab-bbdz (Wyost), denosumab-nxxp (Bilprevda), AND denosumab-qbde (Xtrenbo) 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 120 mg subcutaneously every 4 weeks. (Note: an additional dose of 120 mg on days 8 and 15 will be permitted for the first cycle only.)

When Services Are Considered Not Medically Necessary

Based on review of available data, the Company considers the use of denosumab (Xgeva), denosumab-bmwo (Osenvelt), denosumab-bnht (Bomyntra), denosumab-dssb (Xbryk), denosumab-kyqq (Aukelso), denosumab-desu (Jubereq), or denosumab-mobz (Oziltus) when the patient has not tried and failed ALL of the following: denosumab-bbdz (Wyost), denosumab-nxxp (Bilprevda), AND denosumab-qbde (Xtrenbo) 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 (Xgeva), denosumab-bbdz (Wyost), denosumab-nxxp (Bilprevda), denosumab-qbde (Xtrenbo), denosumab-bmwo (Osenvelt), denosumab-bnht (Bomyntra), denosumab-dssb (Xbryk), denosumab-kyqq (Aukelso), denosumab-desu (Jubereq), or denosumab-mobz (Oziltus) when patient selection criteria are not met OR for any other use not mentioned above to be **investigational.***

Background/Overview

Xgeva is a monoclonal antibody that works to inhibit RANKL (receptor activator of nuclear factor kappa-B ligand) or nuclear factor kB ligand. Denosumab-bbdz (Wyost), denosumab-nxxp (Bilprevda), denosumab-qbde (Xtrenbo), denosumab-bmwo (Osenvelt), denosumab-bnht (Bomyntra), denosumab-dssb (Xbryk), denosumab-kyqq (Aukelso), denosumab-desu (Jubereq), and denosumab-mobz (Oziltus) are biosimilar to Xgeva. 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 indicated for the prevention of SREs in patients with bone metastases from solid tumors and in patients with multiple myeloma. Denosumab is also indicated for the treatment of giant cell tumor of the bone that is unresectable or in an area where surgical resection is likely to result in severe morbidity. and for use in hypercalcemia of malignancy refractory to bisphosphonate therapy. In general, RANKL binds to the RANK receptor to increase differentiation and maturation of an osteoclastic precursor into a mature osteoclast. Osteoclasts work to increase bone resorption (in other words, increase the destruction of bone cells in order to release mineral contents within the bone cells). Under normal physiological situations, osteoclastic activity is important in bone development. When the activity is out of control, bone resorption can occur and make the bone more prone to fracture. Denosumab prevents RANKL from activating its receptor, RANK, on the surface of osteoclasts, their precursors, and osteoclast-like giant cells.

Other medications that have been approved for similar indications as denosumab include Zometa and Aredia. Mechanisms are unclear and differ for each drug. Denosumab is administered subcutaneously every four weeks in a 120 mg dose for the prevention of SREs secondary to bone metastases from solid tumors or multiple myeloma. In patients with giant cell tumor of the bone or hypercalcemia of malignancy refractory to bisphosphonate therapy, denosumab is dosed at 120mg every 4 weeks with additional 120mg doses on days 8 and 15 of the first month of therapy.

SREs are defined as pathologic fractures, surgical/radiotherapy interventions to bone lesions, spinal cord compression and hypercalcemia of malignancy. SREs result in negative quality of life and a worsening of prognosis. Bisphosphonates are a standard of care for patients with bone metastasis.

Bone Metastases

Pathophysiology

Sites of bone metastasis are predominantly the axial skeleton, particularly the spine, pelvis, and ribs, where red marrow is most abundant. Bone metastases are classified as either osteolytic (destructive of normal bone) or osteoblastic (involving deposition of new bone) based upon the predominant radiologic appearance. In both types of lesions there is dysregulation of the normal bone remodeling process. Both breast cancer and prostate cancer bone metastases tend to be mixed osteoblastic and osteolytic, although osteolytic lesions generally predominate in breast cancer and osteoblastic lesions generally predominate in prostate cancer.

The bone destruction observed in osteolytic metastases is primarily mediated by osteoclasts and is not a direct effect of tumor cells. In breast cancer, a reciprocal interaction between breast cancer cells and the bone microenvironment results in a "vicious cycle" that increases both bone destruction and tumor burden. Tumor cells produce factors that directly or indirectly induce osteoclast formation. The resulting bone resorption caused by osteoclasts releases growth factors from the bone matrix that stimulate both tumor growth and further bone destruction.

The pathogenesis of osteoblastic metastasis is less well understood than that of osteolytic lesions. Prostate specific antigen (PSA), released from prostate cancer cells, may lead to blockade of tumor-induced bone resorption and to release of osteoblastic growth factors in the bone microenvironment.

Clinical Presentation
Bone metastases can cause a wide range of symptoms that can impair the quality of life or shorten survival. Direct complications of bone involvement include severe pain, pathologic fractures, and epidural spinal cord compression. In addition to these local effects, osteolytic metastases can result in life-threatening hypercalcemia.

Metastatic bone pain is typically described as aching, with insidious onset and gradual increase in severity over weeks to months. However, there are exceptions, such as the sudden onset of back pain that accompanies the collapse of a cancer-containing vertebral body. Nerve root entrapment, a common complication associated with vertebral metastases, may cause a burning and/or radiating type of pain.

Diagnosis
Pain by itself is not a reliable indicator of the presence of bone metastases. Confusion with benign pathology is particularly a problem for elderly patients, in whom degenerative disease and osteoporosis are common. The differential diagnosis of new or increasing bone pain in a patient with malignancy includes:

- Worsening pain from nonmalignant conditions, such as arthritis, disc injury, osteoporosis, degenerative disease, and Paget's disease
- Musculoskeletal discomfort related to physical exertion
- Treatment-related complications, such as nerve root compression from vertebral body collapse

Structural information on skeletal damage from metastatic bone disease is best obtained by skeletal radiography supplemented by computerized tomography or magnetic resonance imaging (MRI). Isotope bone scanning is a sensitive but non-specific test to detect the presence of skeletal pathology. Preferential uptake of tracer occurs at sites of active bone formation and is influenced by osteoblastic activity and skeletal vascularity. The bone scan, therefore, reflects not only neoplastic but also traumatic and inflammatory processes. A false-negative scan will occur when there is pure lytic disease.

Serum and urinary levels of several biochemical markers of bone metabolism (e.g., C-telopeptide [CTx] and N-telopeptide [NTx], the C-terminal and N-terminal peptides, respectively, of mature type I collagen) are being investigated for their diagnostic and prognostic utility in patients with metastatic bone disease. Urinary NTx levels may have particular clinical relevance.

Giant Cell Tumor of the Bone
Giant cell tumor of the bone is a very rare disease and is typically located towards the end of a bone. The disease is characterized by the presence of multinucleated giant cells and imaging would provide

classic features of malignant destruction (lytic destruction, cortical destruction, soft-tissue extension, and pathologic fracture).

Hypercalcemia of Malignancy
Hypercalcemia is not uncommon in patients with malignancy. There are typically three mechanisms by which the hypercalcemia can occur. These include osteolytic metastases, tumor secretion of parathyroid hormone related protein, or tumor production of 1.25-dihydroxyvitamin D. There are two IV bisphosphonates approved for the treatment of hypercalcemia of malignancy (zoledronic acid and pamidronate).

FDA or Other Governmental Regulatory Approval

U.S. Food and Drug Administration (FDA)
In November 2010, the FDA approved Xgeva for the prevention of SREs in patients with bone metastasis from solid tumors. In June 2013, Xgeva was approved for the treatment of giant cell tumor of the bone that is unresectable or in an area where surgical resection is likely to result in severe morbidity. In late 2014, Xgeva was approved for the treatment of hypercalcemia of malignancy that is refractory to bisphosphonate therapy. In January 2018, Xgeva was approved for the prevention of SREs in patients with multiple myeloma.

In 2024, denosumab-bbdz (Wyost) became the first biosimilar for Xgeva to be approved. Several other biosimilar products were approved throughout 2025 including denosumab-nxxp (Bilprevda), denosumab-qbde (Xtrenbo), denosumab-bmwo (Osenvelt), denosumab-bnht (Bomyntra), denosumab-dssb (Xbryk), denosumab-kyqq (Aukelso), denosumab-desu (Jubereq), and denosumab-mobz (Oziltus).

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.

Skeletal Related Events Secondary to Bone Metastases from Solid Tumors
The safety and efficacy of Xgeva for the prevention of SREs in patients with bone metastases from solid tumors was demonstrated in three international, randomized (1:1), double-blind, active-controlled, noninferiority trials comparing Xgeva with zoledronic acid. In all three trials, patients were randomized to receive 120mg Xgeva subcutaneously every four weeks or 4mg zoledronic acid IV every four weeks (dose adjusted for reduced renal function). Patients with creatinine clearance less than 30mL/min were excluded. In each trial, the main outcome measure was demonstration of noninferiority of time to first SRE as compared to zoledronic acid. Supportive outcome measures were superiority of time to first SRE and superiority of time to first and subsequent SRE; testing for these outcome measures occurred if the main outcome measure was statistically significant. An SRE

was defined as any of the following: pathologic fracture, radiation therapy to bone, surgery to bone, or spinal cord compression.

Trial 1 enrolled 2046 patients with advanced breast cancer and bone metastasis. Randomization was stratified by a history of prior SRE (yes or no), receipt of chemotherapy within six weeks prior to randomization (yes or no), prior oral bisphosphonate use (yes or no), and region (Japan or other countries). Forty percent of patients had a previous SRE, 40% received chemotherapy within six weeks prior to randomization, 5% received prior oral bisphosphonates, and 7% were enrolled from Japan. Median age was 57 years, 80% of patients were white, and 99% of patients were women. The median number of doses administered was 18 for denosumab and 17 for zoledronic acid.

Trial 2 enrolled 1776 adults with solid tumors other than breast and castrate-resistant prostate cancer (CRPC) with bone metastasis and multiple myeloma. Randomization was stratified by previous SRE (yes or no), systemic anticancer therapy at time of randomization (yes or no), and tumor type (non-small cell lung cancer, myeloma, or other). Eighty-seven percent were receiving systemic anticancer therapy at the time of randomization, 52% had a previous SRE, 64% of patients were men, 87% were White, and the median age was 60 years. A total of 40% of patients had non-small cell lung cancer, 10% had multiple myeloma, 9% had renal cell carcinoma, and 6% had small cell lung cancer. Other tumor types each comprised less than 5% of the enrolled population. The median number of doses administered was seven for both denosumab and zoledronic acid.

Trial 3 enrolled 1901 men with CRPC and bone metastasis. Randomization was stratified by previous SRE, PSA level (less than 10ng/mL or 10ng/mL or greater) and receipt of chemotherapy within six weeks prior to randomization (yes or no). Twenty-six percent of patients had a previous SRE, 15% of patients had PSA less than 10ng/mL, and 14% received chemotherapy within six weeks prior to randomization. Median age was 71 years and 86% of patients were white. The median number of doses administered was 13 for denosumab and 11 for zoledronic acid.

Xgeva delayed the time to first SRE following randomization as compared to zoledronic acid in patients with breast or CRPC with osseous metastases. In patients with bone metastasis due to other solid tumors or lytic lesions due to multiple myeloma, 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. Mortality was higher with Xgeva in a subgroup analysis of patients with multiple myeloma (hazard ratio [95% confidence interval or CI] of 2.26 [1.13, 4.50]; n=180).

Giant Cell Tumor of the Bone
The safety and efficacy of Xgeva for the treatment of giant cell tumor of bone in adults or skeletally mature adolescents were demonstrated in two open-label trials (Trial 4 and 5) that enrolled patients with histologically confirmed measurable giant cell tumor of bone that was either recurrent, unresectable, or for which planned surgery was likely to result in severe morbidity. Patients received 120 mg Xgeva subcutaneously every 4 weeks with additional doses on Days 8 and 15 of the first cycle of therapy.

Trial 4 was a single arm, pharmacodynamic, and proof of concept trial conducted in 37 adult patients with unresectable or recurrent giant cell tumor of bone. Patients were required to have histologically confirmed giant cell tumor of bone and radiologic evidence of measurable disease from a computed tomography (CT) or MRI obtained within 28 days prior to study enrollment. Patients enrolled in Trial 4 underwent CT or MRI assessment of giant cell tumor of bone at baseline and quarterly during Xgeva treatment.
Trial 5 was a parallel-cohort, proof of concept, and safety trial conducted in 282 adult or skeletally mature adolescent patients with histologically confirmed giant cell tumor of bone and evidence of measurable active disease. Trial 5 enrolled 10 patients who were 13–17 years of age. Patients enrolled into one of three cohorts: Cohort 1 enrolled 170 patients with surgically unsalvageable disease (e.g., sacral or spinal sites of disease, or pulmonary metastases); Cohort 2 enrolled 101 patients with surgically salvageable disease where the investigator determined that the planned surgery was likely to result in severe morbidity (e.g., joint resection, limb amputation, or hemipelvectomy); Cohort 3 enrolled 11 patients who previously participated in Trial 4. Patients underwent imaging assessment of disease status at intervals determined by their treating physician.

An independent review committee evaluated objective response in 187 patients enrolled and treated in Trials 4 and 5 for whom baseline and at least one post-baseline radiographic assessment were available (27 of 37 patients enrolled in Trial 4 and 160 of 270 patients enrolled in Cohorts 1 and 2 of Trial 5). The primary efficacy outcome measure was objective response rate using modified Response Evaluation Criteria in Solid Tumors (RECIST 1.1).

The overall objective response rate (RECIST 1.1) was 25% (95% CI: 19, 32). All responses were partial responses. The estimated median time to response was 3 months. In the 47 patients with an objective response, the median duration of follow-up was 20 months (range: 2 to 44 months), and 51% (24/47) had a duration of response lasting at least 8 months. Three patients experienced disease progression following an objective response.

Hypercalcemia of Malignancy
The safety and efficacy of Xgeva was demonstrated in an open-label, single-arm trial (Trial 6) that enrolled 33 patients with hypercalcemia of malignancy (with or without bone metastases) refractory to treatment with IV bisphosphonate therapy. Patients received Xgeva subcutaneously every 4 weeks with additional 120 mg doses on Days 8 and 15 of the first month of therapy. The primary outcome measure was the proportion of patients achieving a response, defined as corrected serum calcium (CSC) ≤ 11.5 mg/dL (2.9 mmol/L), within 10 days after Xgeva administration. The proportion of responders achieving a response by day 10 was 63.6%. The proportion of patients that were responders by day 57 was 69.7%. Median time to response (CSC < 11.5 mg/dL) was 9 days (95% CI: 8, 19), and the median duration of response was 104 days (95% CI: 7, not estimable). Median time to complete response (CSC <10.8 mg/dL) was 23 days (95% CI: 9, 36), and the median duration of complete response was 34 days (95% CI: 1, 134). Concurrent chemotherapy did not appear to affect response to Xgeva.

Multiple Myeloma
The efficacy of Xgeva for the prevention of SREs was evaluated in an international, randomized, double-blind, active-controlled, noninferiority trial comparing Xgeva with zoledronic acid in 1718 newly diagnosed multiple myeloma patients with bone lesions. Patients were randomized 1:1 to receive 120 mg Xgeva subcutaneously every 4 weeks or 4 mg zoledronic acid intravenously every 4 weeks. The main efficacy outcome measure was noninferiority of time to first SRE, time to first and subsequent SRE, and overall survival. An SRE was defined as any of the following: pathologic fracture, radiation therapy to bone, surgery to bone, or spinal cord compression.

Xgeva was found to be noninferior to zoledronic acid in delaying the time to first SRE following randomization (HR=0.98, 95%CI, 0.85-1.14). the results for overall survival were comparable between Xgeva and zoledronic acid treatment groups with a hazard ratio of 0.9 (95% CI: 0.7, 1.16).

References

1. U. S. Food and Drug Administration. Labeling of the drug denosumab (Xgeva). June 2014. http://www.fda.gov
2. Xgeva. [package insert]. Amgen: Thousand Oaks, California. May 2025.
3. Wyost (denosumab-bbdz) [package insert]. Princeton, NJ: Sandoz, Inc. October 2025.
4. Bilprevda (denosumab-nxxp) [package insert]. Jersey City, NJ: Organon, LLC. October 2025.
5. Xtrenbo (denosumab-qbde) [package insert]. Cherry Hill, NJ: Hikma Pharmaceuticals USA, Inc. September 2025.
6. Osenvelt (denosumab-bmwo) [package insert]. Jersey City, NJ: Celltrion USA, Inc. October 2025.
7. Bomyntra (denosumab-bnht) [package insert]. Lake Zurich, IL: Fresenius Kabi USA, LLC. October 2025.
8. Xbryk (denosumab-dssb) [package insert]. Incheon, Republic of Korea: Samsung Bioepis Co., Ltd. October 2025.
9. Aukelso (denosumab-kyqq) [package insert]. Cambridge, MA: Biocon Biologics, Inc. September 2025.
10. Jubereq (denosumab-desu) [package insert]. Raleigh, NC: Accord BioPharma, Inc. October 2025.
11. Oziltus (denosumab-mobz) [package insert]. Piscataway, NJ: Amneal Pharmaceuticals, LLC. December 2025.

Policy History

Original Effective Date: 01/01/2025
Current Effective Date: 05/01/2026

10/15/2024	UM Committee review and approval. New policy.
12/30/2024	Coding update
09/16/2025	UM Committee review. Coding update.
03/17/2026	UM Committee review. Added new biosimilar products, denosumab-bbdz (Wyost), denosumab-nxxp (Bilprevda), denosumab-qbde (Xtrenbo), denosumab-bmwo

(Osenvelt), denosumab-bnht (Bomyntra), denosumab-dssb (Xbryk), denosumab-kyqq (Aukelso), denosumab-desu (Jubereq), and denosumab-mobz (Oziltus) to the policy. Added criterion requiring trial and failure of denosumab-bbdz (Wyost), denosumab-nxxp (Bilprevda), AND denosumab-qbde (Xtrenbo) prior to the approval of denosumab (Xgeva), denosumab-bmwo (Osenvelt), denosumab-bnht (Bomyntra), denosumab-dssb (Xbryk), denosumab-kyqq (Aukelso), denosumab-desu (Jubereq), or denosumab-mobz (Oziltus). Updated criteria to clarify that doses above the labeled maximum dose are considered investigational. Title changed from "denosumab (Xgeva)" to "denosumab (Xgeva, biosimilars)".

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.

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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 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.

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.

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.