Wellmark Advantage Health Plan

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Effective Date: 10/06/2022

Denosumab Products

Prolia® (denosumab)
Xgeva® (denosumab)

HCPCS: J0897

Policy:

Requests must be supported by submission of chart notes and patient specific documentation.

A. Coverage of the requested drug is provided when all the following are met:
   a. For the prevention of skeletal-related events in patients with multiple myeloma or with bone metastases from solid tumors (Xgeva only) when the below criteria are met:
      i. Documentation that at least one IV bisphosphonate has been ineffective, not tolerated or contraindicated
      OR
      ii. National Comprehensive Cancer Network (NCCN) supported category 1 preferred agent for prevention of skeletal related events in patients with bone metastases for the specific oncological diagnosis
   b. For the treatment of adults and skeletally mature adolescents with giant cell tumor of bone (Xgeva only) when these criteria have been met:
      i. Documentation of confirmed giant cell tumor of bone and radiologic evidence of measurable disease (via CT scan or MRI)
      ii. Bone is unresectable or surgical resection is likely to result in severe morbidity
   c. For the treatment of hypercalcemia of malignancy (HCM) refractory to bisphosphonate therapy (Xgeva only)
      i. Diagnosis of hypercalcemia secondary to a malignancy (including hematologic malignancies)
      ii. Albumin corrected serum calcium (CSC) ≥ 12mg/dL (3.0mmol/L)
      iii. Documentation that at least one IV bisphosphonate has been ineffective, not tolerated or contraindicated
   d. For the treatment of osteoporosis (Prolia only) when all of the criteria below are met:
      i. FDA approved diagnosis
      ii. At least one bisphosphonate (if patient has intolerance to oral administration, IV administration will be required) is not effective after at least a 12-month treatment period based on objective documentation except if:

a) Treatment with bisphosphonates (oral and intravenous formulations) are not tolerated or contraindicated

e. To increase bone mass in men at high risk for fracture receiving androgen deprivation therapy for nonmetastatic prostate cancer OR women at high risk for fracture receiving adjuvant aromatase inhibitor therapy for nonmetastatic breast cancer when all of the criteria below are met (Prolia only):
   i. When the 10-year probability of hip fracture is ≥ 3% or the 10-year probability of a major osteoporosis-related fracture is ≥ 20%.
   ii. At least one bisphosphonate (if patient has intolerance to oral administration, IV administration will be required) is not effective after at least a 12-month treatment period based on objective documentation except if:
      a) Treatment with bisphosphonates (oral and intravenous formulations) are not tolerated or contraindicated
f. Will NOT be used in combination with any anabolic bone modifying agent or bisphosphonate
g. Trial and failure of the preferred products as specified in the Wellmark Advantage Health Plan medical utilization management drug list

B. Quantity Limitations, Authorization Period and Renewal Criteria
   a. Quantity Limits: Align with FDA recommended dosing
   b. Authorization Period:
      i. For the prevention of skeletal-related events in patients with multiple myeloma or with bone metastases from solid tumors (Xgeva), quantity limit of 120 mg administered once every 4 weeks
      ii. For the treatment of giant cell tumor of bone (Xgeva), quantity limit of three 120 mg doses for the first month, followed by 120 mg every 4 weeks
      iii. For the treatment of hypercalcemia of malignancy (Xgeva), quantity limit of three 120 mg doses for the first month, followed by 120 mg every 4 weeks
   c. Renewal Criteria:
      i. Xgeva (multiple myeloma or bone metastases from solid tumors and breast cancer): If more than 1 fracture in the last 6 months alternative therapy is recommended
      ii. Xgeva (giant cell tumor of the bone): Goals of therapy have been met
      iii. Xgeva (hypercalcemia of malignancy): decrease in albumin CSC levels from baseline
      iv. Prolia: Documentation of improved or stable T-scores while on Prolia

***Note: Coverage may differ for Medicare Part B members based on any applicable criteria outlined in Local Coverage Determinations (LCD) or National Coverage Determinations (NCD) as determined by Center for Medicare and Medicaid Services (CMS). See the CMS website at http://www.cms.hhs.gov/. Determination of coverage of Part B drugs is based on medically accepted indications which have supported citations included or approved for inclusion determined by CMS approved compendia.

Background Information

- Denosumab is a fully human monoclonal antibody against the receptor activator of nuclear factor-kB ligand (RANKL). RANKL is a cytokine that is essential for the formation, function, and survival of osteoclasts. By binding RANKL, denosumab prevents the interaction of RANKL with its receptor on osteoclasts and osteoclast precursors and reversibly inhibits osteoclast-mediated bone resorption. As a monoclonal antibody, denosumab has potential safety risks/significant safety concerns that must be balanced against its potential benefits. Due to its mechanism of action, denosumab presents a novel approach to fracture prevention.

- Bisphosphonates are currently the most predominantly prescribed treatments and have a proven history of safety and efficacy. Due to the many available traditional options and with lack of robust clinical evidence of superior ability to reduce fractures or treat bone metastases, along with significant safety concerns, denosumab should not be used as a first-line therapy.

- Osteoporosis

  - Approximately 54 million people in the United States have osteoporosis or another form of low bone mass. Breakdown of bone structure may be the result of natural aging and calcium deficiency (e.g., senile osteoporosis) or due to hormonal changes as in post-menopause. The decrease in bone mass and deterioration of bone tissue in osteoporosis can result in bone fragility and potential for fractures. Fractures related to osteoporosis and bone loss are a concern because of the high morbidity and mortality rate and economic burden. The National Osteoporosis Foundation estimates that 1 in 2 women and 1 in 4 men over 50 years of age will break a bone as a result of osteoporosis, resulting in $19 billion in related costs every 2 years and 2 million broken bones. With the aging population, these numbers are estimated to rise to 3 million fractures and $25.3 billion in costs annually by 2025.

  - Denosumab (Prolia) has not been proven in reliable clinical studies to be more effective than bisphosphonates.

  - There is a large number of randomized controlled trials (RCTs) assessing the efficacy of denosumab. However, only one trial studied the clinically meaningful endpoint of fracture prevention. All other efficacy trials used percent change in bone mineral density (BMD) as the primary endpoint. BMD is a surrogate marker and change in BMD is poorly correlated to fracture prevention. There is one placebo-controlled trial that established the efficacy of denosumab (Prolia) with regard to decreased fracture risk. Denosumab (Prolia) reduces the risk of vertebral, hip, and non-vertebral fractures in post-menopausal women with osteoporosis over 36 months when compared to placebo.

  - There are trials comparing denosumab (Prolia) to weekly alendronate for the treatment of osteoporosis in post-menopausal women. The primary endpoint of these trials is BMD changes at 12 months which is not as clinically relevant as fracture data.

  - The FRAX® tool (www.shef.ac.uk/FRAX) was developed by the World Health Organization (WHO) to evaluate fracture risk of patients. It integrates clinical risk factors with BMD at the femoral neck. The FRAX® tool provides the 10-year probability of fracture. The output is a 10-year probability of hip fracture and a 10-year probability of major osteoporotic fracture (forearm, shoulder, or clinical vertebral fracture).

  - Treatment should be considered if the 10-year risk is 3% or more for hip fracture or 20% or more for "major" osteoporosis-related fracture based on the US-adapted WHO algorithm (FRAX® tool).

  - The American Association for Clinical Endocrinology guidelines (2020) define osteoporosis as a BMD T-score at or lower than -2.5. However, a non- or low-traumatic fracture (fragility fracture) is considered osteoporosis regardless of T-score. The AACE guidelines include the following recommendations:

    - The AACE recommend either bisphosphonates (IV or oral) or denosumab as initial treatment options for patients with high-risk osteoporosis without prior fracture. Guidelines do not give preference to one anti-resorptive therapy over another. Bisphosphonates decrease the breakdown of bone and have been shown to increase BMD and reduce the incidence of fractures in patients with osteoporosis. Contraindications to bisphosphonates include hypocalcemia and severe renal impairment. In addition, oral bisphosphonates are contraindicated in patients with the inability to stand or sit upright for at least 30 minutes and may not be an appropriate option in patients with underlying gastrointestinal issues. However, use of IV bisphosphonates is still appropriate in these situations.

    - There is evidence supporting superiority of anabolic agents, such as parathyroid hormone analogs and romosozumab (Evenity®), over anti-resorptive therapies such as bisphosphonates and

denosumab in reducing vertebral fracture risk in patients with a very high risk of fracture, such as those with T-score less than -3.0. Guidelines recommend sequential treatment with anti-resorptive osteoporosis therapies to maintain BMD gains and reduce fracture risk after completing a course of treatment with anabolic drugs.

- Sequential treatment with a bisphosphonate or denosumab is recommended after discontinuation of an anabolic agent to prevent bone density decline and loss of fracture efficacy.

- There are no studies showing that combination treatment with two or more osteoporosis drugs has a greater effect on fracture reduction than treatment with a single agent. Therefore, AACE does not recommend concomitant use of these agents for prevention or treatment of osteoporosis in postmenopausal women.

- The goal of monitoring osteoporosis therapy is to identify those who have significant bone loss. AACE recommends a repeat DXA scan 1 to 2 years after initiation of therapy until bone density is stable. Bone turnover markers (BTMs) are also useful for assessing patient compliance and efficacy of therapy. Reductions in BTMs are conferred by antiresorptive therapy and are associated with fracture reduction. Significant increases in BTMs indicate good response to anabolic therapy.

- Glucocorticoid-Induced Osteoporosis

  - A 24-month international, multi-center, double-blind, active controlled, double-dummy, non-inferiority study compared denosumab to risedronate. Of the 795 patients enrolled, 505 were glucocorticoid-continuing and 290 were initiating therapy. Denosumab was both non-inferior and superior to risedronate at 12 months for effect on BMD at the lumbar spine in both glucocorticoid-continuing (4·4% [95% CI 3·8–5·0] vs 2·3% [1·7–2·9]; p<0·0001) and glucocorticoid-initiating (3·8% [3·1–4·5] vs 0·8% [0·2–1·5]; p<0·0001) subpopulations. Incidence of adverse events, serious adverse events (including infections), and fractures was similar between treatment groups.

  - Guidelines from the American College of Rheumatology (ACR) for the prevention and treatment of glucocorticoid-induced osteoporosis (2017) include the following recommendations:

    - For adults with moderate- or high-risk of fracture, the ACR recommends treatment with an oral bisphosphonate over IV bisphosphonates, denosumab, teriparatide, or raloxifene.

    - Oral bisphosphonates are preferred as first-line treatment due to established safety and lower cost. Additionally, the ACR guidelines note that there is a lack of safety data for denosumab in patients treated with immunosuppressive agents.

- Prevention of Osteoporosis Due to Hormone Suppression

  - In breast and prostate cancer patients on hormone suppression therapy, hormone suppression increases bone turnover and decreases bone mineral density (BMD). Oral bisphosphonates are the best value for the prevention of osteoporosis in patients on hormone suppression therapy.

  - There is a limited body of evidence for fracture prevention during hormone suppression therapy. Trials were designed to demonstrate an increase in BMD without evidence of fracture prevention. BMD is a surrogate for fracture risk, the more clinically meaningful measure of efficacy.

  - There are two denosumab trials in the prevention of bone loss due to hormone ablation therapy in prostate and breast cancer. There is low confidence in the results of both of the trials because they used change in BMD as the primary endpoint and were not comparative trials. Despite the shortcoming of the trials there

was a decrease in new vertebral fractures compared to placebo. There are many other treatment options available including generics for the prevention of bone loss.

- For prevention of osteoporosis in patients with prostate cancer during androgen deprivation therapy (ADT): there is evidence that denosumab, pamidronate, zoledronic acid and alendronate increase BMD during ADT. NCCN Prostate Cancer guidelines (2022) recommend denosumab every 6 months, zoledronic acid once annually, or alendronate 70 mg once weekly when risk of fracture warrants treatment. Zoledronic acid increases BMD when administered every three months OR annually. There is no comparative evidence that demonstrates that more frequent dosing is more effective.

- There is evidence to support the use of anti-resorptive agents (bisphosphonates and denosumab) to maintain or improve bone mineral density and reduce the risk of fractures in postmenopausal women who are receiving adjuvant aromatase inhibitor therapy. The NCCN Breast Cancer guidelines (2022) recommend bisphosphonate therapy for postmenopausal patients receiving adjuvant endocrine therapy.

- There is no comparative evidence among bisphosphonates or denosumab, for prevention of osteoporosis in patients with breast cancer during hormone suppression therapy. Bisphosphonate treatment for prevention of bone loss, regardless of cause, is the standard of care due to the body of evidence supporting efficacy and track record of safety.

- Cancer-Related Bone Metastases

  - Zoledronic acid (Zometa) provides the best value for prevention of skeletal complications, decreasing the incidence and rate of skeletal events, and delaying skeletal events in women with breast cancer with bone metastases. The effectiveness of denosumab was evaluated in 5,732 patients with various advanced cancers including metastatic breast, prostate, and various other solid tumor cancers. There are three randomized controlled trials comparing denosumab (Xgeva) with zoledronic acid (Zometa) for the prevention of skeletal-related events related to bone metastases.

  - Skeletal-related events (SRE) related to bone metastases were defined as bone pain, pathologic fractures, spinal cord compression, and bone complications that required radiation or surgery. Denosumab (Xgeva) and zoledronic acid (Zometa) appear to be at least similar in delaying the time to first SRE in patients with metastases from solid tumor cancers.

  - The quality of the evidence is insufficient to differentiate denosumab (Xgeva) and zoledronic acid (Zometa) for the delay of SREs in patients with metastatic hormone-resistant prostate cancer or metastatic advanced solid tumor cancers.

  - There is low confidence in the evidence that denosumab (Xgeva) is superior to zoledronic acid (Zometa) because the difference between the products cannot be accurately quantified from clinical trials.

  - Denosumab (Xgeva) extends the time to first SRE by six months in patients with metastatic breast cancer. As a secondary endpoint the number of SREs was reported (number of SREs is the more commonly reported endpoint in efficacy trials). In the metastatic breast cancer trial, 30.7% of denosumab (Xgeva) subjects had an SRE compared with 36.5% of zoledronic acid (Zometa) subjects. This small difference of 5.8%, coupled with the dropout rate of 18% could have influenced the magnitude of difference between the products. It is unclear that that the treatment effect would be as robust if the subjects who left the trial early had completed the trial.

  - The claim of superiority in other metastatic solid tumor cancers including prostate cancer is uncertain due to the small treatment effect and high drop-out rates. The drop-out rate (patients who did not complete the trial for reasons other than having an on-study SRE, death or disease progression) was greater than 22% in

both trials. Therefore, it is uncertain that study groups remained adequately randomized and balanced by the end of the trials for a fair comparison.

- Prevention of Skeletal Related Events in patients with Multiple Myeloma

  - A randomized, double blind, active controlled, noninferiority trial compared denosumab and zoledronic acid. It enrolled 1,718 patients with newly diagnosed multiple myeloma (MM). The study met its primary endpoint. Denosumab was found to be non-inferior to zoledronic acid in delaying the time to first SRE following randomization, with a median time of 22.8 months for denosumab and 24 months for zoledronic acid (HR = 0.98, 95% CI, 0.85-1.14). An SRE was defined as a pathologic fracture, radiation therapy to bone, surgery to bone, or spinal cord compression. The results for overall survival (OS) were comparable between Xgeva and zoledronic acid treatment groups with a hazard ratio of 0.90 (95% CI: 0.70, 1.16).

- Clinical Efficacy in hypercalcemia of malignancy

  - HCM is a serious complication that is indicative of poor malignancy prognosis. It results from cancer-driven increases in bone resorption, and if untreated, can lead to renal failure, progressive mental impairment, coma, and death.

  - The classification of severity of hypercalcemia is as follows:

    - Mild hypercalcemia: albumin CSC <12 mg/dL

    - Moderate hypercalcemia: albumin CSC between 12 and 14 mg/dL

    - Severe hypercalcemia: albumin CSC >14 mg/dL

  - Denosumab (Xgeva) acts by inhibiting the osteoclast-mediated bone resorption, which results in decrease in bone destruction and calcium release thus lowering calcium levels in HCM patients.

  - An open-label, single-arm study evaluated 33 patients with advanced cancer and persistent hypercalcemia (CSC of 12.5mg/dL or higher) after recent bisphosphonate treatment. The primary endpoint was the proportion of patients with a response (defined as albumin-corrected serum calcium (CSC) <11.5 mg/dL within 10 days after the first dose of Xgeva)

  - The secondary endpoints included the proportion of patients who experienced a complete response (defined as CSC <10.8 mg/dL by day 10), time to response, and response duration (defined as the number of days from the first occurrence of CSC <11.5 mg/dL)

Table 1: Efficacy of Xgeva in Patient with HCM Refractory to Bisphosphonate Therapy

	N = 33	Proportion (%)
All Responders (CSC≤ 11.5 mg/dL) by day 10	21	63.6
All Responders by Day 57	23	69.7
Complete Responders (CSC≤ 10.8 mg/dL) by day 10	12	36.4
All Complete Responders by Day 57	21	63.6

References:

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7. FDA Approves Xgeva (denosumab) for Hypercalcemia of Malignancy Refractory to Bisphosphonate Therapy. http://www.drugs.com/newdrugs/fda-approves-xgeva-denosumab-hypercalcemia-malignancy-refractory-bisphosphonate-therapy-4117.html. Accessed Jan 16, 2015.
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13. NCCN Guidelines Version 4.2022. Breast Cancer. Published June 21, 2022.
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Policy History		
#	Date	Change Description
1.1	Effective Date: 10/06/2022	Shortened duration of bisphosphonate trial to 12 months for osteoporosis indication for Prolia; removed requirement for calcium/vitamin D supplementation for all indications; will not allow for combination therapy with bisphosphonates in addition to anabolic therapies
1.0	Effective Date: 01/01/2022	New Policy

** The prescribing information for a drug is subject to change. To ensure you are reading the most current information it is advised that you reference the most updated prescribing information by visiting the drug or manufacturer website or http://dailymed.nlm.nih.gov/dailymed/index.cfm.*