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Policy Number: 040.010

Title: Coverage Determination Policy for Bone-modifying agents:

- **Prolia, Xgeva (Denosumab); Evenity (Romosozumab-aqqg)**

Regions: ☒ **Texas** ☒ **New Mexico**

Impacted Areas:

☒ Network Management/Provider Services	☒ Utilization Management
☐ Member services	☐ Case management
☐ Quality Management	☐ Disease management
☐ Credentialing	☒ Claims
☐ IT	☐ Human resources
☐ Administration	☐ Finance
☐ Compliance/delegation	☒ Pharmacy
	☐ ALL

Available LCD/NCD/LCA: None

Disclaimer:

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Title: Coverage Determination Policy for Bone-modifying agents

Coverage Policy Number: 040.010

Line of Business: Medicare Part B

Policy Type: Prior Authorization

Coverage Determination:

Step Therapy Criteria

This policy supplements Medicare NCDs, LCDs, and manuals for the purpose of determining coverage under Medicare Part B medical benefits. This policy implements a prior authorization requirement for prescriptions or administrations of medical benefit injectables only. A member cannot be required under this policy to change a current drug/product. For the purposes of this policy, a current drug/product means the member has a paid claim for the drug/product within the past 365 days. For example, a new plan member currently using a particular drug/product will not be required to switch to the preferred drug/ product upon enrollment. Similarly, an existing member currently using a particular drug/product will not be required to change drugs/products in the event this policy is updated.

Bone Density Agents – Oncology
Preferred Drug(s)/Product(s): Ibandronate, Pamidronate, Zoledronic Acid
Non-Preferred Drug(s)/Product(s): Prolia, Xgeva

Xgeva Non-Preferred Product Step Therapy Criteria
Xgeva, when used for treatment of the following conditions:

- Prevention of skeletal related events in patients with multiple myeloma
- Prevention of skeletal related events in patients with bone metastases from solid tumors
- Hypercalcemia of malignancy
- Osteopenia/osteoporosis in patients with systemic mastocytosis with bone pain

May be covered when ANY of the criteria listed below are satisfied

A. History of use of an injectable bisphosphonate resulting in minimal clinical response to therapy
OR
B. History of contraindication, intolerance or adverse event(s) to an injectable bisphosphonate
OR
C. Continuation of prior therapy within the past 365 days

Prolia Non-Preferred Product Step Therapy Criteria
Prolia may be covered when ANY of the criteria listed below are satisfied:

A. History of use of an injectable bisphosphonate (e.g. Pamidronate, Zoledronic Acid) resulting in minimal clinical response to therapy
OR
B. History of contraindication, intolerance or adverse event(s) to an injectable bisphosphonate (e.g. Pamidronate, Zoledronic Acid)
OR
C. Continuation of prior therapy within the past 365 days

Bone Density Agents – Osteoporosis
Preferred Drug(s)/Product(s): Ibandronate, Pamidronate, Zoledronic Acid
Non-Preferred Drug(s)/Product(s): Evenity, Prolia

Evenity or Prolia may be covered for osteoporosis when the criteria in sections A, B, or C are met:

- **A.** History of use of an injectable bisphosphonate (e.g. Pamidronate, Zoledronic Acid) resulting in minimal clinical response to therapy
  OR
- **B.** History of contraindication, intolerance or adverse event(s) to an injectable bisphosphonate (e.g. Pamidronate, Zoledronic Acid)
  OR
- **C.** Continuation of prior therapy within the past 365 days

Initial/New Requests

If the above step therapy criteria is met, requests for Evenity and Prolia/Xgeva *will be covered when medically necessary as follows:*

Diagnosis- Specific Criteria

1. **Treatment of osteoporosis**:
   A. **Evenity** is proven for the treatment of **osteoporosis in postmenopausal patients at high risk for fracture** when **ALL** of the following criteria are met:
      I. Diagnosis of postmenopausal osteoporosis; and
      II. Patient is at high risk for fracture (e.g., history of osteoporotic fracture, multiple risk factors for fracture, patients who have failed or are intolerant to other available osteoporosis therapy); and
      III. Dosing is in accordance with the United States Food and Drug Administration approved labeling;
   B. **Prolia** is proven for the treatment of **postmenopausal patients with osteoporosis or to increase bone mass in patients with osteoporosis at high risk for fracture** when **ALL** of the following criteria are met:
      I. Diagnosis of osteoporosis; and
      II. Patient is at high risk for fracture (e.g., history of osteoporotic fracture, multiple risk factors for fracture, patients who have failed or are intolerant to other available osteoporosis therapy); and
      III. Dosing is in accordance with the United States Food and Drug Administration approved labeling;

2. **Treatment of glucocorticoid-induced osteoporosis: Prolia** is proven to treat **glucocorticoid-induced osteoporosis in patients at high risk for fracture** when **ALL** of the following criteria are met:
   A. Diagnosis of glucocorticoid-induced osteoporosis
   B. Patient is at high risk for fracture (e.g., history of osteoporotic fracture, multiple risk factors for fracture, patients who have failed or are intolerant to other available osteoporosis therapy); and
   C. Dosing is in accordance with the United States Food and Drug Administration approved labeling;
3. **Treatment to increase bone mass in men at high risk for fracture that are receiving androgen deprivation therapy (ADT) for non-metastatic prostate cancer: Prolia** is medically necessary when **ALL** of the following criteria are met:
   A. Diagnosis of non-metastatic prostate cancer
   B. Patient is receiving androgen deprivation therapy
   C. Dosing is in accordance with the United States Food and Drug Administration approved labeling

4. **Treatment to increase bone mass in women at high risk for fracture that are receiving an aromatase inhibitor therapy for breast cancer: Prolia** is medically necessary when **ALL** of the following criteria are met:
    A. Diagnosis of breast cancer
    B. Patient is receiving aromatase inhibitor therapy
    C. Dosing is in accordance with the United States Food and Drug Administration approved labeling
5. **Treatment of bone metastasis from solid tumors AND for the prevention of skeletal-related events in patients with multiple myeloma: Xgeva** is medically necessary when **ALL** of the following criteria are met:
    A. ONE of the following:
        I. Patient is ≥ 18 yrs of age
        II. Patient is a skeletally mature adolescent as defined by having at least 1 mature long bone (e.g., closed epiphyseal growth plate of the humerus)
    B. ONE of the following:
        I. Diagnosis of multiple myeloma
        II. Presence of metastatic disease secondary to a solid tumor (e.g., bladder, breast, kidney, lung, ovarian, thyroid, etc.)
    C. Individual has an expected survival of 3 months or greater
    D. Dosing is in accordance with the United States Food and Drug Administration approved labeling;
6. **Treatment of giant cell tumor of the bone: Xgeva** is medically necessary when **ALL** of the following criteria are met:
    A. Patient has ONE of the following:
        I. Patient is ≥ 18 years of age
        II. Patient is a skeletally mature adolescent as defined by having at least 1 mature long bone (e.g., closed epiphyseal growth plate of the humerus)
    B. Diagnosis of localized, recurrent or metastatic giant cell tumor of the bone
    C. Disease is ONE of the following:
        I. Unresectable
        II. Surgical resection is likely to result in severe morbidity
    D. Dosing is in accordance with the United States Food and Drug Administration approved labeling

7. **Treatment of hypercalcemia of malignancy: Xgeva** is medically necessary when **ALL** of the following criteria are met:
   A. Patient has ONE of the following:
      I. Patient is ≥ 18 years of age
      II. Patient is a skeletally mature adolescent as defined by having at least 1 mature long bone (e.g., closed epiphyseal growth plate of the humerus)
   B. Diagnosis of hypercalcemia of malignancy (i.e., albumin-corrected serum calcium level greater than 12.5 mg/dL)
   C. No pre-existing hypocalcemia (i.e., serum calcium or corrected calcium within normal limits per laboratory reference)
   D. Refractory (within the past 30 days), contraindication (including renal insufficiency), or intolerance to treatment with intravenous bisphosphonate therapy (e.g., pamidronate, zoledronic acid)
   E. Dosing is in accordance with the United States Food and Drug Administration approved labeling
8. **Prevention of skeletal-related events in men with castration-resistant prostate cancer who have bone metastases: Xgeva** is medically necessary for the prevention of skeletal-related events in men with castration resistant prostate cancer who have bone metastases when **ALL** of the following criteria are met:
   A. Diagnosis of castration-resistant prostate cancer
   B. Presence of metastatic disease
   C. Refractory (within the past 30 days), contraindication (including renal insufficiency), or intolerance to treatment with intravenous bisphosphonate therapy (e.g., pamidronate, zoledronic acid)
   D. Dosing is in accordance with the United States Food and Drug Administration approved labeling
9. **Treatment of osteopenia/osteoporosis in patients with systemic mastocytosis with bone pain not responding to bisphosphonates: Xgeva** is medically necessary for the treatment of osteopenia/osteoporosis in patients with systemic mastocytosis with bone pain not responding to bisphosphonates when **ALL** of the following criteria are met:
   A. Diagnosis of systemic mastocytosis
   B. Patient has bone pain
   C. Diagnosis of osteoporosis or osteopenia
   D. Dosing is in accordance with the United States Food and Drug Administration approved labeling

Unproven/Not Medically Necessary

Denosumab is unproven and not medically necessary for the following indications:

- Combination therapy of denosumab and intravenous bisphosphonates
- Bone loss associated with hormone-ablation therapy (other than aromatase inhibitors) in breast/prostate cancer
- Cancer pain
- Central giant cell granuloma
- Hyper-parathyroidism
- Immobilization hypercalcemia
- Osteogenesis imperfecta
- Osteopenia

Impaired renal function as indicated by drug specific creatinine clearance values listed in the following table	
Drug and Availability	**Contraindication Cutoff**
Alendronate (Fosamax®, Binosto®) (PO only)	CrCl less than 35 mL/min
Risedronate (Actonel®, Atelvia®) (PO only)	CrCl less than 30 mL/min
Ibandronate (Boniva®) (PO and IV)	CrCl less than 30 mL/min
Zoledronic Acid (Zometa®, Reclast®) (IV only)	CrCl less than 35 mL/min
Pamidronate (IV only)	Serum Creatinine > 3 mg/dL or CrCl <30 mL/min single doses should not exceed 90 mg and infused over 4-6 hours; withhold pamidronate if albuminuria occurs.
Etidronate (PO only)	Serum creatinine >2.5mg/dL – use with caution Serum creatinine >5 mg/dL - not recommended

Renewal Requests/Continuation of Therapy

1. For RENEWAL of **Prolia, ALL** of the following:
   A. Documentation of positive clinical response to therapy; and
   B. Dosing is in accordance with the United States Food and Drug Administration approved labeling
   C. For diagnosis of increase bone mass in patients at high risk for fracture receiving androgen deprivation therapy OR to treat patients at high risk for fracture receiving adjuvant aromatase inhibitor therapy patient must be receiving androgen deprivation therapy or aromatase inhibitor therapy respectively for renewals
2. For RENEWAL of **Xgeva, ALL** of the following:
   A. Positive response to therapy (e.g. absence of fractures, stable disease, absence of hypocalcemia, absence of hypersensitivity to product)
   B. Dosing is in accordance with the United States Food and Drug Administration approved labeling
   C. ** For diagnosis of prevention of skeletal-related events in patients with multiple myeloma and with bone metastases from solid tumors Individual has an expected survival of 3 months or greater **
3. For RENEWAL of **Evenity, ALL** of the following:
   A. The clinical benefit of Evenity has not been demonstrated beyond 12 months in phase 3 clinical trials. The continued use of Evenity beyond 12 months is unproven and not medically necessary.

FDA Approved Dose and Indication

Drug	FDA Approved Dose
Prolia (Denosumab)	60mg subcutaneously every 6 months (All FDA approved indications indicated above)
Xgeva (Denosumab)	Giant cell tumor of bone and hypercalcemia of malignancy: • 120 mg subQ every 4 weeks, with additional 120-mg doses on days 8 and 15 of first month of therapy Multiple Myeloma and Bone Metastasis from Solid Tumors: • 120 mg subQ every 4 weeks
Evenity (Romosozumab-aqqg)	210mg SubQ once monthly for **12 months** Each monthly dose consists of 2 consecutive SubQ injections

FDA Approved Indications	Prolia	Xgeva	Evenity
Treatment of Osteoporosis in postmenopausal women at high risk for fracture	X		X
Treatment of Osteoporosis in Men at high risk for fracture	X		
Treatment to increase bone mass in women at high risk for fracture that receiving aromatase inhibitor (exemastine, anastrazole, letrozole) therapy for breast cancer	X		
Treatment to increase bone mass in men at high risk for fracture that are receiving androgen deprivation therapy (ADT) for non-metastatic prostate cancer	X		
Bone metastasis associated with solid tumors - Disorder of skeletal system; Prophylaxis		X	
Hypercalcemia of malignancy, Refractory to Bisphosphonates		X	
Disorder of skeletal system; Prophylaxis - Multiple Myeloma		X	
Giant cell tumor of bone, Unresectable or where surgical resection is likely to result in severe Morbidity		X	
Treatment of glucocorticoid-induced osteoporosis in men and women at high risk for fracture	X		

General Background

Osteoporosis is characterized by low bone mass, microarchitectural disruption, and increased skeletal fragility. The Word Health Organization (WHO) established diagnostic thresholds for bone mineral density (BMD) by dual-energy x-ray absorptiometry (DXA) according to the standard deviation (SD) difference between a patient's BMD and that of a young adult reference population (T-score). A T-score of -2.5 SD or below is defined as osteoporosis, provided that other causes of low BMD have been ruled out, and a T-score between -1 and -2.5 SD is defined as osteopenia. Additionally, guidelines state that osteoporosis can be diagnosed by one of the following1: (1) Presence of fragility fractures in the absence of other metabolic bone disorders; (2) T-score ≤ −2.5 SD in the lumbar spine (antero-posterior), femoral neck, total hip, or one-third radius; or (3) T- score between −1.0 and −2.5 and increased fracture risk using the FRAX® (fracture risk assessment tool) country-specific thresholds. The FRAX tool is designed to assist clinicians in predicting the ten-year probability of hip fracture and 10-year probability of a major osteoporotic fracture (spine, forearm, hip or shoulder fracture) with or without the addition of femoral neck BMD.7 In the United States, a clinical diagnosis of osteoporosis may be made when the FRAX 10-year probability of major osteoporotic fracture (hip, clinical spine, proximal humerus, or forearm) is greater than or equal to 20 percent or the FRAX 10-year probability of hip fracture is greater than or equal to 3 percent.

Denosumab binds to RANKL, a transmembrane or soluble protein essential for the formation, function, and survival of osteoclasts, the cells responsible for bone resorption, thereby modulating calcium release from bone. Denosumab prevents RANKL from activating its receptor, RANK, on the surface of osteoclasts, their precursors, and osteoclast-like giant cells. 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. Increased osteoclast activity, stimulated by RANKL, is a mediator of bone pathology in solid tumors with osseous metastases. Similarly, giant cell tumors of bone consist of stromal cells expressing RANKL and osteoclast-like giant cells expressing RANK receptor, and signaling through the RANK receptor contributes to

Romosozumab is a human monoclonal antibody that binds and inhibits sclerostin. Sclerostin is a negative regulator of bone formation that is secreted by osteocytes, inhibiting Wnt pathway signaling, down-regulating the stimulus for osteoblast development and function. When romosozumab binds to sclerostin, sclerostin cannot bind to the LRP-5 and LRP-6 receptors, preventing its inhibitory effect. The therapeutic effect of sclerostin inhibition promotes the dual effect of increasing bone formation and decreasing bone resorption.

Clinical Evidence

Prolia

Postmenopausal Patients with Osteoporosis

In a post-hoc analysis of the 7-year FREEDOM Extension trial, Kendler et al, analyzed whether women who experienced fracture while on denosumab was due to inadequate treatment response, or whether the risk of fracture remains low while continuing denosumab treatment. During the extension trial, all study participants were to receive denosumab. The authors of this analysis compared subsequent osteoporotic fracture rates between denosumab treated subjects during the initial FREEDOM or the extension and placebo-treated subjects in FREEDOM. During FREEDOM, 438 placebo- and 272 denosumab-treated subjects had an osteoporotic fracture. Exposure-adjusted subject incidence per 100 subject-years was lower for denosumab (6.7) vs placebo (10.1). Combining all subjects on denosumab from FREEDOM and the Extension for up to 10 years (combined denosumab), 794 (13.7%) had an osteoporotic fracture while on denosumab. One or more subsequent fractures occurred in 144 (18.1%) subjects, with an exposure-adjusted incidence of 5.8 per 100 subject-years, similar to FREEDOM denosumab (6.7 per 100 subject-years) and lower than FREEDOM placebo (10.1 per 100 subject years). Adjusting for prior fracture, the risk of having a subsequent on-study osteoporotic fracture was lower in the combined denosumab group vs placebo (hazard ratio [95% CI]: 0.59 [0.43–0.81]; p = 0.0012). The authors concluded that the post-hoc analysis demonstrates that denosumab decreases the risk of subsequent fracture and a fracture sustained while on denosumab, and not necessarily due to inadequate treatment response.21

Brown JP et al compared the efficacy and safety of denosumab with alendronate in postmenopausal women with low bone mass in a phase 3, multicenter, double-blind study.11 Participants included postmenopausal women with a T-score < or = -2.0 at the lumbar spine or total hip and received subcutaneous denosumab injections (60 mg every 6 months [Q6M]) plus oral placebo weekly (n = 594) or oral alendronate weekly (70 mg) plus subcutaneous placebo injections Q6M (n = 595). Efficacy was measured by assessing changes in BMD at the total hip, femoral neck, trochanter, lumbar spine, and one-third radius at 6 and 12 months. Additionally, bone turnover markers at months 1, 3, 6, 9, and 12 were assessed. Adverse events were monitored to evaluate safety. Denosumab significantly increased BMD at month 12 (3.5% versus 2.6%; p < 0.0001 for the total hip). Significantly greater increases in BMD were observed with denosumab at all measured skeletal sites over the twelve month treatment period. Denosumab showed significantly greater reduction of bone turnover markers compared to alendronate. Adverse events and laboratory values were similar for the two treatment groups. The authors conclude that denosumab showed a significantly larger gain in BMD and greater reduction in bone turnover markers compared with alendronate. Overall, the safety profile was similar for both treatment groups.

Men with Low Bone Mineral Density

Langdahl BL et al evaluated denosumab therapy in men with low bone mineral density (BMD) in a multicenter, phase 3 study.9 The study consisted of 2 treatment periods including a 12-month double-blind, placebo-controlled phase and a 12-month open-label phase. Participants from the

original denosumab (long-term) and placebo (crossover) groups received 60 mg of denosumab subcutaneous every 6 months. During the open-label phase, the following BMD increases occurred with long-term denosumab treatment (2.2% lumbar spine, 0.9% total hip, 1.3% femoral neck, 1.3% trochanter, and 0.2% 1/3 radius), resulting in cumulative 24-month gains from baseline of 8.0%, 3.4%, 3.4%, 4.6%, and 0.7%, respectively (all $p < .01$). The crossover group showed BMD gains similar to the long-term treatment group during the first 12 months of treatment. Similar adverse event rates were seen in both groups. The authors conclude that in the study population, denosumab treatment for a second year continued to increase BMD, maintained reductions in bone resorption, and was well tolerated. These results were similar to previous results in postmenopausal women with osteoporosis and in men with prostate cancer receiving androgen deprivation therapy.
Orwoll E. et al evaluated the safety and efficacy of denosumab compared with placebo in men with low BMD after 1 year of treatment in a placebo-controlled, phase 3 study.10 The primary endpoint was the percent change of BMS from baseline in lumbar spine (LS) at one year. After 12 months, denosumab resulted in BMD increases of 5.7% at the LS, 2.4% at the total hip, 2.1% at the femoral neck, 3.1% at the trochanter, and 0.6% at the one third radius (adjusted $p \leq 0.0144$ for BMD percent differences at all sites compared with placebo). The incidence of adverse events was similar between groups. The authors conclude that 12 months of treatment with denosumab in men with low BMD was well tolerated and resulted in a reduction in bone resorption and significant increases in BMD at all skeletal sites assessed.

Patients at High Risk for Fracture Receiving Androgen Deprivation Therapy for Non-Metastatic Prostate Cancer

Smith ME et al investigated the effects of denosumab in a double-blind, multicenter study, on bone mineral density and fractures in patients with non-metastatic prostate cancer who are receiving androgen-deprivation therapy.8 Patients were randomly assigned to receive denosumab at a dose of 60 mg subcutaneously every 6 months or placebo (n = 734 per group). The primary end point was percent change in bone mineral density at the lumbar spine at 24 months. Secondary end points included percent change in bone mineral densities at the femoral neck and total hip at 24 months and at all three sites at 36 months, as well as frequency of new vertebral fractures. At 24 months, patients receiving denosumab experienced an increase in bone mineral density of the lumbar spine by 5.6% as compared with a loss of 1.0% in the placebo group ($p < 0.001$). Significant differences between the placebo and denosumab groups were seen at 1 month and continued through 36 months. Treatment was also associated with significant increases in bone mineral density at the total hip, femoral neck, and distal third of the radius. Patients who received denosumab had a decreased incidence of new vertebral fractures at 36 months (1.5%, vs. 3.9% with placebo) (relative risk, 0.38; 95% confidence interval, 0.19 to 0.78; $p = 0.006$). Similar rates of adverse events were reported in the two groups. The authors conclude that denosumab is associated with increased bone mineral density at all sites and a reduction in the incidence of new vertebral fractures among patients receiving androgen-deprivation therapy for non-metastatic prostate cancer. (ClinicalTrials.gov number, NCT00089674)

Glucocorticoid-Induced Osteoporosis in Patients at High Risk for Fracture

Saag et al assessed the efficacy and safety of denosumab compared with risedronate in

glucocorticoid-induced osteoporosis in a 24-month, double-blind, active-controlled, double-dummy, non-inferiority study.18 The study enrolled patients aged 18 years or older who were receiving ≥ 7.5 mg prednisone daily or equivalent, for at least 3 months (glucocorticoid continuing) or less than 3 months (glucocorticoid initiating). Patients under 50 years of age were required to have a history of osteoporosis-related fracture. Patients 50 years and older needed a lumbar spine, total hip, or femoral neck bone mineral density T score of -2.0 or less, or -1.0 or less if they had a history of osteoporosis-related fracture. Study patients received either 60 mg subcutaneous denosumab every 6 months and oral placebo daily for, or 5 mg oral risedronate daily and subcutaneous placebo every 6 months for 24 months. The primary outcome was non-inferiority of denosumab to risedronate in terms of percentage change from baseline in lumbar spine bone mineral density at 12 months based on non-inferiority margins. In addition, superiority was also assessed. The safety analysis included all study patients who received one dose or more of their assigned investigational product. This study is registered with ClinicalTrials.gov (NCT01575873). Denosumab was both non-inferior and superior to risedronate at 12 months for effect on bone mineral density 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 and fractures was similar between treatment groups. The most common adverse events in both groups included back pain and arthralgia. Serious infection occurred in 15 (4%) patients in the risedronate group and 17 (4%) patients in the denosumab group. The authors conclude that denosumab could be a useful treatment option for patients taking glucocorticoids who are at risk for fractures.

Xgeva

In an ad hoc analysis of the phase 3 clinical trial of 1,776 patients with metastases from solid tumors or multiple myeloma, where it was shown that denosumab was non-inferior to zoledronic acid (ZA) in delaying or preventing SREs, Henry et al reports outcomes in the subgroup of 1,597 patients with solid tumors, excluding multiple myeloma.17 In the ad hoc analysis, denosumab significantly delayed time to first on-study SRE compared to ZA (HR, 0.81; 95% CI, 0.68–0.96) and time to first-and-subsequent SREs (RR, 0.85; 95% CI, 0.72–1.00). Denosumab also significantly delayed time to development of moderate or severe pain (HR, 0.81; 95% CI, 0.66–1.00), pain worsening (HR, 0.83; 95% CI, 0.71–0.97), and worsening pain interference in patients with no/mild baseline pain (HR, 0.77; 95% CI, 0.61–0.96). Overall survival was similar in both groups. The median KM estimate was 10.7 months for denosumab-treated patients and 10.0 months for ZA-treated patients (HR, 0.92; 95% CI, 0.81–1.05: $p = 0.215$). Similarly, there was no difference between groups in time to disease progression. The median KM estimate was 5.3 (4.9, 5.7) months for denosumab-treated and 5.4 (4.8, 5.7) months for ZA-treated patients (HR, 0.96; 95% CI, 0.85–1.08: $p = 0.497$). The authors concluded that denosumab was more effective in delaying the incidence of SREs, however did not significantly affect the overall incidence or disease progression or overall survival.

In a double-blind, double-dummy, phase III clinical trial, Henry et al compared denosumab with zoledronic acid (ZA) for delaying or preventing skeletal-related events (SRE) in patients with advanced cancer and bone metastases (excluding breast and prostate) or myeloma.16 Patients were randomly assigned to receive either monthly subcutaneous denosumab 120mg (n = 886) or intravenous ZA 4mg (dose adjustment for renal impairment; n = 890). The primary end point

was time to first on-study SRE (pathologic fracture, radiation or surgery to bone, or spinal cord compression). The trial demonstrated that denosumab was noninferior to ZA in delaying time to first on-study SRE (hazard ratio, 0.84; 95% CI, 0.71 to 0.98; p = 0.0007). Denosumab was not statistically superior to ZA in delaying time to first on-study SRE (p = 0.03 unadjusted; p = 0.06 adjusted for multiplicity) or time to first-and-subsequent (multiple) SRE (rate ratio, 0.90; 95% CI, 0.77 to 1.04; p = 0.14). Overall survival and disease progression were similar between groups. Hypocalcemia occurred more frequently with denosumab. Osteonecrosis of the jaw occurred at similarly low rates in both groups. Acute-phase reactions after the first dose occurred more frequently with ZA, as did renal adverse events and elevations in serum creatinine. The authors concluded that denosumab was noninferior to ZA in preventing or delaying first on-study SRE in patients with advanced cancer metastatic to bone or myeloma.

Fizazi et al evaluated the comparison of denosumab with zoledronic acid (ZA) for the prevention of skeletal-related events in men with bone metastases from castration-resistant prostate cancer.20 In a phase 3 clinical study, 1904 men with castration-resistant prostate cancer had no previous exposure to IV bisphosphonate were randomized 1:1 to either receive 120mg subcutaneous denosumab plus IV placebo (n = 950), or 4mg IV ZA plus subcutaneous placebo (n = 951) every 4 weeks. The primary endpoint was time to first on-study skeletal related event (pathological fracture, radiation therapy, surgery to bone, or spinal cord compression), and was assessed for non-inferiority. The same outcome was further assessed for superiority as a secondary endpoint. Efficacy analysis was by intention to treat. Median time to first on-study skeletal-related event was 20.7 months (95% CI 18.8–24.9) with denosumab compared with 17.1 months (15.0–19.4) with zoledronic acid (hazard ratio 0.82, 95% CI 0.71–0.95; p = 0.0002 for non-inferiority; p = 0.008 for superiority). While there was a three-month increase in the time to first skeletal-related events observed with denosumab in men with prostate cancer, there was no clinically meaningful difference in skeletal-related events for denosumab as compared with zoledronic acid: Overall confirmed events (ZA vs. denosumab) 41% vs. 36%; radiation to bone (21% vs. 19%); pathological fracture (15% vs. 14%); spinal cord compression (4% vs. 3%); surgery to bone (< 1% vs. < 1%). The authors concluded that denosumab was better than ZA for delaying the time to first SRE, however, was not significantly better at preventing the overall incidence of SREs versus zoledronic acid.

Professional Societies

National Comprehensive Cancer Network Clinical Practice Guidelines in Oncology (NCCN Guidelines®)

Several National Comprehensive Cancer Network Clinical Practice Guidelines in Oncology (NCCN Guidelines®) include denosumab as a treatment for several conditions related to malignant disease. The following NCCN Guidelines® state: 15

- For non-small cell lung cancer, the NCCN recommends (Category 2A) denosumab to be considered in patients with bone metastases.
- For ductal carcinoma, invasive breast cancer or inflammatory breast cancer, the NCCN recommends (Category 2A) denosumab to be considered in postmenopausal (natural or induced) patients receiving adjuvant aromatase inhibition therapy along with calcium and vitamin D supplementation to maintain or improve bone mineral density and reduce risk of fractures.
- For invasive or inflammatory breast cancer, the NCCN recommends (Category 1)

denosumab to be used with calcium and vitamin D supplementation in addition to chemotherapy or endocrine therapy for bone metastasis in patients with expected survival ≥ 3 months with adequate renal function.

- For kidney cancer, the NCCN recommends (Category 2A) denosumab to be used as a component of best supportive care for bony metastases.
- For systemic mastocytosis, the NCCN recommends (Category 2A) denosumab as second-line therapy for osteopenia/osteoporosis in patients with bone pain not responding to bisphosphonates or for patients who are not candidates for bisphosphonates because of renal insufficiency.
- For thyroid carcinoma (anaplastic, follicular, medullary, oncocytic, papillary), the NCCN recommends (Category 2A) denosumab to be considered for bone metastases or palliative care for bone metastases (anaplastic).
- For giant cell tumor of the bone, the NCCN recommends (Category 2A) denosumab as a single agent or combined with serial embolization (preferred), and/or radiation therapy for resectable disease with unacceptable morbidity and/or unresectable axial lesions for patients with localized disease, metastases at presentation, or recurrence, denosumab is also recommended as a single agent for unresectable metastatic disease, unresectable metastatic recurrence or considered prior to surgery for resectable local recurrence.
- For prostate cancer, the NCCN recommends (Category 2A) denosumab for prevention or treatment of osteoporosis during androgen deprivation therapy (ADT) for patients with high fracture risk, denosumab is also recommended (Category 1) as the preferred agent for the prevention of skeletal-related events in patients with castration-resistant prostate cancer who have documented bone metastases and creatinine clearance greater than 30 ml/min.
- For multiple myeloma, the NCCN recommends (Category 2A) denosumab to be used in combination with primary myeloma therapy and is the preferred agent in patients with renal insufficiency.

Fracture Risk Calculation

The FRAX® algorithms give the 10-year probability of fracture. The output is a 10-year probability of hip fracture and the 10-year probability of a major osteoporotic fracture (clinical spine, forearm, hip or shoulder fracture). High risk is considered to be a 10-year probability of hip fracture ≥3 percent or a 10-year probability of a major osteoporosis-related fracture ≥20%. While the FRAX® was initially created for untreated patients, results from a large, prospective cohort study suggest that FRAX® can similarly predict fracture in women currently or previously treated for osteoporosis. The FRAX® calculation tool can be accessed online at the following link: https://www.sheffield.ac.uk/FRAX/tool.aspx?country=9

HCPCS Code

HCPCS Code	Description	Dosage Form & Route of Administration
J0897	Injection, denosumab, 1mg	**Prolia:** Injection: Single-dose prefilled syringe containing 60 mg in a 1 mL solution **Xgeva:** Injection:120mg/1.7mL (70mg/mL) solution in a single-dose vial
J3111	Injection, romosozumab-aqqg, 1 mg	Injection: 105 mg/1.17 mL solution in a single-use prefilled syringe. A full dose of EVENITY requires two single-use prefilled syringes.

Acronyms

BMD = Bone mineral density

WHO= World Health Organization

SD = Standard deviation

BMA = Bone modifying agent

CRPC = Castration-resistant prostate cancer

FRAX = Fracture Risk Assessment Tool

GFR = Glomerular Filtration Rate

SubQ = Subcutaneous

CrCl = Creatinine Clearance

ADT Androgen-Deprivation Therapy

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