Drug and Biologic Coverage Policy

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Coverage Policy Number 1212

Denosumab

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Related Coverage Resources

Bone Mineral Density Measurement
Step Therapy

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Coverage Policy

Denosumab (Prolia) is considered medically necessary when ANY of the following criteria are met:

- Osteoporosis in a man or postmenopausal woman meeting **BOTH** of the following:
  - Candidate for pharmacologic therapy meeting **ANY** of the following:
    - History of fragility (non-traumatic) or osteoporotic fracture
    - Bone mineral density (BMD) T-score less than or equal to -2.5 in the lumbar spine, femoral neck, total hip, and/or 33% (one third) radius [wrist]
    - T-score between –1.0 and –2.5 if the FRAX® 10-year probability for major osteoporotic fracture is at least 20% or the 10-year probability of hip fracture is at least 3% (see Appendix 1)
  - Documentation of **EITHER** of the following:
    - History of beneficial clinical response with denosumab (Prolia)
    - **EITHER** of the following:
      - Failure / Inadequate response to at least **ONE** oral **OR** intravenous bisphosphonate product (for example, osteoporotic fracture while receiving bisphosphonate therapy, ongoing loss of BMD, lack of continued BMD increase)
      - Contraindication per FDA label, intolerance, inability to take, or not a candidate for oral **AND** intravenous bisphosphonate therapy

- Bone loss in non-metastatic prostate cancer meeting **BOTH** of the following:
    - Receiving androgen deprivation therapy
    - High risk for fractures as defined by **ANY** of the following:
        - History of fragility (non-traumatic) or osteoporotic fracture
        - Bone mineral density (BMD) T-score less than or equal to -2.5 in the lumbar spine, femoral neck, total hip, and/or 33% (one third) radius [wrist]
        - T-score between –1.0 and –2.5 if the FRAX® 10-year probability for major osteoporotic fracture is at least 20% or the 10-year probability of hip fracture is at least 3% (see Appendix 1)

- Bone loss in a woman for breast cancer and BOTH of the following:
    - Receiving adjuvant aromatase inhibitor therapy
    - High risk for fractures (for example, bone mineral density [BMD] T-score less than or equal to -1.0)

- Treatment of Glucocorticoid-Induced Osteoporosis when **BOTH** of the following criteria are met:
    - Individual is initiating or continuing treatment with a medium or high dose systemic glucocorticoid (for example, greater than or equal to 7.5mg/day oral prednisone) and expected to remain on therapy for at least 6 months
    - Documentation of **EITHER** of the following:
        - History of beneficial clinical response with denosumab (Prolia)
        - **EITHER** of the following:
            - Failure / Inadequate response to at least ONE oral **OR** intravenous bisphosphonate product (for example, osteoporotic fracture while receiving bisphosphonate therapy, ongoing loss of BMD, lack of continued BMD increase)
            - Contraindication per FDA label, intolerance, inability to take, or not a candidate for oral **AND** intravenous bisphosphonate therapy

Denosumab (Xgeva) is considered medically necessary when ANY of the following criteria are met:

- Prevention of skeletal-related events in an individual with bone metastases from solid tumors AND the following criteria (when applicable):
    - EITHER of the following:
        - History of beneficial clinical response with denosumab (Xgeva)
        - Documented failure/inadequate response, contraindication per FDA label, intolerance or not a candidate for zoledronic acid
    - If breast cancer, individual has an expected survival of 3 months or greater
    - If prostate cancer, individual has castration recurrent disease (meaning disease is no longer responsive to androgen deprivation therapy)
- Prevention of skeletal-related events in patients with multiple myeloma AND EITHER of the following:
    - History of beneficial clinical response with denosumab (Xgeva)
    - Documented failure/inadequate response, contraindication per FDA label, intolerance or not a candidate for zoledronic acid
- Treatment of giant cell tumor of bone
- Treatment of hypercalcemia of malignancy when there is a failure of intravenous bisphosphonate therapy

Initial authorization is up to 12 months unless otherwise stated.

When coverage is available and medically necessary, the dosage, frequency, duration of therapy, and site of care should be reasonable, clinically appropriate, and supported by evidence-based literature and adjusted based upon severity, alternative available treatments, and previous response to therapy.

Denosumab is considered experimental, investigational or unproven for ANY other use including the following:

- Individuals with thalassemia-induced osteoporosis (in those individuals who do not meet the above criteria for denosumab coverage for osteoporosis)
- Concomitant use with bisphosphonates

Note: Receipt of sample product does not satisfy any criteria requirements for coverage

FDA Approved Indications

Brand Name	Approved Indications
Prolia	**Treatment of Postmenopausal Women with Osteoporosis at High Risk for Fracture** Prolia is indicated for the treatment of postmenopausal women with osteoporosis at high risk for fracture, defined as a history of osteoporotic fracture, or multiple risk factors for fracture; or patients who have failed or are intolerant to other available osteoporosis therapy. In postmenopausal women with osteoporosis, Prolia reduces the incidence of vertebral, nonvertebral, and hip fractures. **Treatment to Increase Bone Mass in Men with Osteoporosis** Prolia is indicated for treatment to increase bone mass in men with osteoporosis at high risk for fracture, defined as a history of osteoporotic fracture, or multiple risk factors for fracture; or patients who have failed or are intolerant to other available osteoporosis therapy. **Treatment of Bone Loss in Men Receiving Androgen Deprivation Therapy for Prostate Cancer** Prolia is indicated as a treatment to increase bone mass in men at high risk for fracture receiving androgen deprivation therapy for nonmetastatic prostate cancer. In these patients Prolia also reduced the incidence of vertebral fractures. **Treatment of Bone Loss in Women Receiving Adjuvant Aromatase Inhibitor Therapy for Breast Cancer** Prolia is indicated as a treatment to increase bone mass in women at high risk for fracture receiving adjuvant aromatase inhibitor therapy for breast cancer. **Treatment of Glucocorticoid-Induced Osteoporosis** Prolia is indicated for the treatment of glucocorticoid-induced osteoporosis in men and women at high risk of fracture who are either initiating or continuing systemic glucocorticoids in a daily dosage equivalent to 7.5 mg or greater of prednisone and expected to remain on glucocorticoids for at least 6 months. High risk of fracture is defined as a history of osteoporotic fracture, multiple risk factors for fracture, or patients who have failed or are intolerant to other available osteoporosis therapy
Xgeva	**Multiple Myeloma and Bone Metastasis from Solid Tumors** Xgeva is indicated for the prevention of skeletal-related events in patients with multiple myeloma and bone metastases from solid tumors. **Giant Cell Tumor of Bone** Xgeva is indicated for the treatment of adults and skeletally mature adolescents with giant cell tumor of bone that is unresectable or where surgical resection is likely to result in severe morbidity. **Hypercalcemia of Malignancy** Xgeva is indicated for the treatment of hypercalcemia of malignancy refractory to bisphosphonate therapy.

Recommended Dosing

FDA Recommended Dosing

Brand Name	Recommended Dosing
Prolia	Prolia should be administered by a healthcare professional. The recommended dose of Prolia is 60 mg administered as a single subcutaneous injection once every 6 months. All patients should receive calcium 1000 mg daily and at least 400 IU vitamin D daily. If a dose of Prolia is missed, administer the injection as soon as the patient is available. Thereafter, schedule injections every 6 months from the date of the last injection.
Xgeva	Xgeva is intended for subcutaneous route only and should not be administered intravenously, intramuscularly, or intradermally. **Multiple Myeloma and Bone Metastasis from Solid Tumors** The recommended dose of Xgeva is 120 mg administered as a subcutaneous injection every 4 weeks. Administer calcium and vitamin D as necessary to treat or prevent hypocalcemia. **Giant Cell Tumor of Bone** The recommended dose of Xgeva is 120 mg administered every 4 weeks with additional 120 mg doses on Days 8 and 15 of the first month of therapy. Administer subcutaneously in the upper arm, upper thigh, or abdomen. Administer calcium and vitamin D as necessary to treat or prevent hypocalcemia. **Hypercalcemia of Malignancy** The recommended dose of Xgeva is 120 mg administered every 4 weeks with additional 120 mg doses on Days 8 and 15 of the first month of therapy. Administer subcutaneously in the upper arm, upper thigh, or abdomen.

Drug Availability

Brand Name	Drug Availability
Prolia	Prolia is supplied in a single-use prefilled syringe with a safety guard or in a single-use vial as 60 mg/1 mL (1 syringe or vial per carton). A Risk Evaluation and Mitigation Strategy (REMS) program is in place with a goal of informing healthcare providers and patients about the risks of hypocalcemia, osteonecrosis of the jaw, atypical femoral fractures, serious infections, and dermatologic reactions associated with Prolia (denosumab). The REMS program includes a medication guide and communication plan.
Xgeva	Xgeva is supplied in a single-use vial as 120 mg/1.7 mL (70 mg/mL) (1 vial per carton).

General Background

Pharmacology
Prolia and Xgeva (denosumab) bind and inhibit RANKL, a protein required for the differentiation and growth of osteoclasts. The effect of denosumab is limited to the duration of treatment. Discontinuation of denosumab is associated with a significant bone turnover rebound and a rapid loss of bone mass. Caution should be exerted against sudden interruption of denosumab. (Meier, 2017) Denosumab may exacerbate or cause hypocalcemia. Hypocalcemia is a contraindication to the use of denosumab and pre-existing hypocalcemia must be corrected prior to initiating therapy with Prolia or Xgeva.

Professional Societies/Organizations
Prolia
American Association of Clinical Endocrinologists and American College of Endocrinology

American Association of Clinical Endocrinologists (AACE) and American College of Endocrinology (ACE) published updated guidelines in 2016 addressing diagnosis and treatment of postmenopausal osteoporosis. This update expanded the diagnosis of osteoporosis to include patients with osteopenia and an increased fracture risk using FRAX® country-specific thresholds (for the US, 10-year probability of hip fracture of 3% or greater or major osteoporotic fracture of 20% or greater) in accord with the definition of osteoporosis published by the National Bone Health Alliance. (Camacho, 2016; Siris, 2014) Other groups meeting the definition for diagnosis of osteoporosis include those with a prior fragility fracture in the absence of other metabolic bone disorders or a T-score of – 2.5 or lower in the lumbar spine, femoral neck, total hip, and/or 33% radius.

AACE/ACE strongly recommends pharmacologic treatment for those with osteopenia and a history of fragility fracture of the hip or spine; T-score of – 2.5 or lower in the spine, femoral neck, total hip, or 33% radius; and T-score of -1.0 to -2.5 and a FRAX® 10-year probability for major osteoporotic fracture of at least 20% and hip fracture of at least 3% for the U.S. Denosumab, along with the bisphosphonates alendronate, risedronate, and zoledronic acid, are recommended as initial therapy for most with high risk of fracture. Denosumab, teriparatide, and zoledronic acid are options when the patient is unable to use oral therapy or as an initial therapy for those at especially high fracture risk. AACE/ACE notes that a drug holiday is not recommended with denosumab. (Camacho, 2016)

American College of Obstetricians and Gynecologists
American College of Obstetricians and Gynecologists (ACOG) published a clinical practice bulletin with guidelines for the management of osteoporosis. ACOG suggest that bisphosphonates are generally first-line therapy and denosumab is an option for the treatment of women at high risk of fracture (Committee on Practice Bulletins, 2012).

American College of Rheumatology
American College of Rheumatology (ACR) Guideline for the Prevention and Treatment of Glucocorticoid-Induced Osteoporosis suggest that numerous risk calculators can be applied to provide estimates of risk of major Osteoporosis fracture and hip fracture clinically diagnosed, with adjustment for glucocorticoid (GC) dose used in some calculators. Most stratify glucocorticoid use into 2 categories: low (prednisone less than or equal to 7.5 mg/day) or high (greater than 7.5 mg/day). These comprehensive guidelines stratify recommendations by patient characteristics, such as age, fracture risk, and special populations. Most recommendations are conditional and based on benefit versus harm and risk. Use of bisphosphonate is recommended prior to the use of denosumab in patients who are on long term GC treatment. (Buckley, 2017)

Endocrine Society
Endocrine Society lists denosumab as one of the FDA-approved treatment options for men with osteoporosis at a high risk of fracture and for treatment in men receiving androgen deprivation therapy for prostate cancer. (Watts, 2012)

National Comprehensive Cancer Network
National Comprehensive Cancer Network (NCCN) suggests that denosumab is a treatment option for men on androgen deprivation therapy for non-metastatic prostate cancer at high risk of fracture to increase bone density. NCCN advises screening and treating osteoporosis in accord with guidelines from the National Osteoporosis Foundation and treating with denosumab, zoledronic acid, or alendronate when fracture risk constitutes drug therapy (NCCN, 2017e). To preserve or improve BMD and decrease fracture risk, denosumab is also recommended in postmenopausal invasive breast cancer patients who are being treated with adjuvant endocrine therapy and concomitant calcium and vitamin D. (NCCN, 2017b)

National Osteoporosis Foundation
National Osteoporosis Foundation (NOF) lists denosumab as one of the FDA approved pharmacologic treatment options for osteoporosis. NOF advises treatment for those with hip or vertebral fractures; T-scores less than – 2.5 in the femoral neck, total hip, or lumbar spine, and for postmenopausal women and men 50 years and older with a T-score of – 1.0 to – 2.5 (osteopenia) and a 10-year hip fracture probability of at least 3% or major osteoporotic fracture of at least 20%. The organization advises that therapeutic categories are intended to be guidelines and that assessment for treatment should be individualized, taking into consideration other comorbidities and factors not taken into account by risk estimate models, such as falls. (Cosman, 2014)

Xgeva

American Society of Clinical Oncology - Cancer Care Ontario

American Society of Clinical Oncology (ASCO) - Cancer Care Ontario (CCO) joint guidelines focus on the role of bone-modifying agents (BMA; denosumab, pamidronate, or zoledronic acid) in metastatic breast cancer. The guidelines recommend that BMAs be used in individuals with breast cancer who have bone metastases. In regards to bone pain, the group does not recommend monotherapy treatment with BMAs, but rather employing supportive care and pain management, such as analgesia, surgery, radiotherapy and systemic chemotherapy. The panel does not recommend one BMA over another. (Van Poznak, 2017)

American Urological Association

American Urological Association (AUA) states that either denosumab or zoledronic acid are options when choosing a preventative treatment for skeletal related events for bone metastases in castration-resistant prostate cancer. (Cookson, 2014)

National Comprehensive Cancer Network

National Comprehensive Cancer Network (NCCN) suggests the use of denosumab for bone metastases in breast cancer (when expected survival is at least 3 months), kidney cancer, non-small cell lung cancer, castration-recurrent (i.e., disease no longer responsive to androgen deprivation therapy) prostate cancer, and thyroid carcinoma (NCCN, 2017b; NCCN, 2017c; NCCN, 2017d; NCCN, 2017e; NCCN, 2017f). NCCN also suggests a role for denosumab in giant cell tumor of the bone as a single-agent for localized or metastatic disease or in combination with interferon alfa or radiation therapy for localized disease (NCCN, 2017a). NCCN recommends either bisphosphonates or denosumab as options to prevent skeletal related events in bone metastases. (NCCN, 2018)

The American Board of Internal Medicine's (ABIM) Foundation Choosing Wisely® Initiative:

No recommendations are available for denosumab (Prolia or Xgeva).

Centers for Medicare & Medicaid Services - National Coverage Determinations (NCDs)

There are no CMS National Coverage Determinations for denosumab (Prolia or Xgeva).

Clinical Efficacy

Prolia

Osteoporosis

The Agency for Healthcare Research and Quality (AHRQ) published a systematic review on the comparative effectiveness of pharmacologic treatments for fracture prevention in osteoporosis in 2007 with subsequent updates in 2012 and 2014. A total of 315 articles (including trials, observational studies, and systematic reviews) were included. The authors concluded that denosumab, along with bisphosphonates (alendronate, ibandronate, risedronate, and zoledronic acid), teriparatide, and raloxifene have strong evidence supporting efficacy in prevention of vertebral fractures in women with osteoporosis (number needed to treat of 60-89 to prevent 1 fracture over 1-3 years of treatment). Regarding prevention of non-vertebral fractures in women with osteoporosis, the authors conclude that denosumab, alendronate, risedronate, zoledronic acid, and teriparatide have strong evidence with a number needed to treat of 50-60 to prevent 1 fracture over 1-3 years of treatment. For men with osteoporosis, the authors summarize that zoledronic acid has moderate evidence for prevention of fractures. Regarding adverse events and denosumab, the authors' state there is moderate evidence of infection with denosumab (number needed to harm of 118). (Crandall, 2014)

A systematic review/meta-analysis (4 trials; n=1942) was performed to compare (head-to-head) the efficacy and safety profile between denosumab 60 mg subcutaneous (SQ) every 6 months and 70 mg alendronate orally every week. The results suggested that within 1 year denosumab 60 mg SQ every 6 months was more effective in increasing bone mass but could not reduce the fracture risk to a greater extent than 70 mg alendronate weekly therapy. The authors also noted that denosumab did not increase the risks of neoplasms and infections compared to alendronate weekly. The authors concluded that the analysis of the relevant clinical outcome demonstrated inconclusive benefits of denosumab over alendronate. (Lin, 2012)

In the absence of head-to head randomized controlled trials, several network meta-analyses techniques/studies have been published that use indirect methods to (e.g., mixed treatment comparison, indirect treatment comparison) to evaluate the comparative effectiveness of available agents to treat osteoporosis with variable techniques and results. One evaluated 9 randomized controlled trials in an attempt to simultaneously compare alendronate, risedronate, ibandronate, zoledronate and denosumab in the prevention of vertebral fractures in a Bayesian meta-analysis for assessing indirect comparisons. The authors concluded that although the mixed treatment comparisons among these agents did not show a statistically significant difference, their analysis suggests that zoledronate, compared to placebo, is expected to provide the highest rate of reduction in vertebral fractures. (Migliore, 2013)

Another meta-analysis evaluated 33 RCTs comparing fracture outcomes for pharmacologic therapies versus placebo (fixed and random effects models); adjusted indirect comparisons and mixed treatment comparison (MTC) assessed fracture risk in postmenopausal women treated with denosumab versus other agents. Random effects meta-analysis showed that all agents (alendronate, risedronate, ibandronate, zoledronic acid, strontium ranelate, teriparatide, raloxifene, denosumab), except etidronate, significantly reduced risk of new vertebral fractures compared to placebo. Denosumab, risedronate, and zoledronic acid significantly reduced non-vertebral and hip fracture while alendronate, strontium ranelate, and teriparatide significantly reduced risk for non-vertebral fractures. MTC showed denosumab as more effective than strontium ranelate, raloxifene, alendronate, and risedronate in preventing new vertebral fractures. (Freemantle, 2013)

A network meta-analysis was performed that included 116 trials to evaluate the efficacy of bisphosphonates, teriparatide, selective estrogen receptor modulators, denosumab, or calcium and vitamin D in reducing the risk of fragility fractures. The authors indicate that teriparatide had the highest risk reduction of fractures and the highest probability of being ranked first for efficacy (probabilities of 42, 49, and 79% for hip, vertebral, and nonvertebral fractures, respectively; however, differences to denosumab, zoledronate, risedronate, ibandronate, and alendronate were not statistically significant. Raloxifene and bazedoxifene were noted to likely be less effective, although these data were limited. The authors concluded that teriparatide, bisphosphonates, and denosumab are most effective in reducing risk of fragility fractures. The authors noted that due both to the limited number of direct head-to-head trials and the small number of fracture outcomes in trials available for analysis, their data is insufficient to determine the comparative efficacy of each of the available osteoporosis therapies with respect to fracture outcomes. The authors concluded that teriparatide, bisphosphonates, and denosumab are most effective in reducing the risk of fragility fracture. Differences in efficacy across drugs are noted to be small; therefore patients and clinicians need to consider their associated harms and costs. (Murad, 2012)

A systematic literature review was conducted that identified randomized, placebo-controlled trials with nine drugs for post-menopausal women deriving odds ratio and 95% credibility intervals for the rates of hip, non-vertebral, vertebral, and wrist fractures for each drug and between drugs using a Bayesian approach. A drug was ranked as the most efficacious if it had the highest posterior odds ratio, or had the highest effect size. 30 studies reported fracture rates for nine drugs: alendronate (6 studies), denosumab (1 study), etidronate (8 studies), ibandronate (4 studies), raloxifene (1 study), risedronate (7 studies), strontium (2 studies), teriparatide (1 study), and zoledronic acid (1 study). The drugs with the highest probability of reducing non-vertebral fractures was etidronate and teriparatide while the drugs with the highest probability of reducing vertebral, hip or wrist fractures were teriparatide, zoledronic acid and denosumab. The drugs with the largest effect size for vertebral fractures were zoledronic acid, teriparatide, and denosumab while the drugs with the highest effect size for non-vertebral, hip or wrist fractures were alendronate or risedronate. The authors concluded that teriparatide, zoledronic acid, and denosumab have the highest probabilities of being most efficacious for non-vertebral and vertebral fractures, and have the greatest effect sizes. (Hopkins, 2011)

In summary, there is insufficient comparative evidence to prove or disprove superiority of any one bisphosphonate or any agent for the prevention of fractures.

Treatment of Glucocorticoid-Induced Osteoporosis

Saag et al evaluated denosumab versus risendronate in glucocorticoid-induced osteoporosis. They conducted a multicenter, randomized, double-blind, active-controlled, non-inferiority study in 795 patients aged 20 to 94 years that were using greater than or equal to 7.5 mg/day oral prednisone or its equivalent for less than 3 months prior to study enrollment and planning to continue treatment for a total of at least 6 months (defined as the

glucocorticoid-initiating subpopulation) or greater than or equal to 3 months prior to study enrollment and planning to continue treatment for a total of at least 6 months (defined as the glucocorticoid-continuing subpopulation). Participants were randomly assigned (1:1) to either 60 mg subcutaneous denosumab every 6 months and oral placebo daily for 24 months, or 5 mg oral risedronate daily and subcutaneous placebo every 6 months for 24 months. Enrolled patients who were less than 50 years of age were required to have a history of osteoporotic fracture. Enrolled patients who were greater than or equal to 50 years of age who were defined as being in the glucocorticoid-continuing subpopulation were required to have a baseline BMD T-score of ≤ -2.0 at the lumbar spine, total hip, or femoral neck or both a (1) BMD T-score ≤ -1.0 at the lumbar spine, total hip, or femoral neck and (2) a history of osteoporotic fracture. In the population defined as glucocorticoid-initiating, Prolia significantly increased lumbar spine BMD compared to the active-control at one year (Active-control 2.3%, Prolia 4.4%). In the population defined as glucocorticoid-continuing, Prolia significantly increased lumbar spine BMD compared to active-control at one year (Active-control 0.8%, Prolia 3.8%). (Saag, 2018)

Xgeva

Multiple Myeloma

The efficacy of Xgeva for the prevention of skeletal-related events in newly diagnosed multiple myeloma patients with treatment through disease progression, was evaluated in Study 20090482 (NCT01345019), an international, randomized (1:1), double-blind, active-controlled, noninferiority trial comparing Xgeva with zoledronic acid. In this trial, patients were randomized to receive 120 mg Xgeva subcutaneously every 4 weeks or 4 mg zoledronic acid intravenously (IV) every 4 weeks (dose adjusted for reduced renal function). Patients with creatinine clearance less than 30 mL/min were excluded. In this trial, the main efficacy outcome measure was noninferiority of time to first skeletal-related event (SRE). Additional efficacy outcome measures were superiority 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.

Study 20090482 enrolled 1718 newly diagnosed multiple myeloma patients with bone lesions. Randomization was stratified by a history of prior SRE (yes or no), the anti-myeloma agent being utilized/planned to be utilized in first-line therapy (novel therapy-based or non-novel therapy-based [novel therapies include bortezomib, lenalidomide, or thalidomide]), intent to undergo autologous PBSC transplantation (yes or no), stage at diagnosis (International Staging System I or II or III) and region Japan (yes or no). At study enrollment, 96% of the patients were receiving or planning to receive novel therapy based first-line anti-myeloma therapy, 55% of the patients intended to undergo autologous PBSC transplantation, 61% of patients had a previous SRE, 32% were at ISS stage I, 38% were at ISS stage II and 29% were at ISS Stage III, and 2% were enrolled from Japan. Median age was 63 years, 82% of patients were White, and 46% of patients were women. The median number of doses administered was 16 for Xgeva and 15 for zoledronic acid.

Xgeva was 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 (OS) were comparable between Xgeva and zoledronic acid treatment groups with a hazard ratio of 0.90 (95% CI: 0.70, 1.16).

Bone Metastases from solid tumors

The safety and efficacy of Xgeva for the prevention of skeletal-related events in patients with bone metastases from solid tumors were 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 120 mg Xgeva subcutaneously every 4 weeks or 4 mg zoledronic acid intravenously (IV) every 4 weeks (dose adjusted for reduced renal function). Patients with creatinine clearance less than 30 mL/min were excluded. In each trial, the main outcome measure was demonstration of noninferiority of time to first skeletal-related event (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.

Study 20050136 (NCT00321464) 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 6 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 6 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.

Study 20050244 (NCT00330759) enrolled 1776 adults with solid tumors other than breast and castrate-resistant prostate cancer 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 7 for both denosumab and zoledronic acid.

Study 20050103 (NCT00321620) enrolled 1901 men with castrate-resistant prostate cancer and bone metastasis. Randomization was stratified by previous SRE, PSA level (less than 10 ng/mL or 10 ng/mL or greater) and receipt of chemotherapy within 6 weeks prior to randomization (yes or no). Twenty-six percent of patients had a previous SRE, 15% of patients had PSA less than 10 ng/mL, and 14% received chemotherapy within 6 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 castrate-resistant prostate cancer (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.

Giant Cell Tumor of 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 [Study 20062004 (NCT00680992) and Study 20040215 (NCT00396279)] 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.

Study 20040215 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. Study 20040215 enrolled 10 patients who were 13 - 17 years of age. Patients enrolled into one of three cohorts: Cohort 1 enrolled170 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 Study 20062004. 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 Study 20062004 and Study 20040215 for whom baseline and at least one post-baseline radiographic assessment were available (27 of 37 patients enrolled in Study 20062004 and 160 of 270 patients enrolled in Cohorts 1 and 2 of Study 20040215). 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
Efficacy of denosumab, at a dose of 120 mg subcutaneously every 4 weeks (with additional doses given on days 8 and 15 of the first month of therapy), for the treatment of hypercalcemia of malignancy was established in an open-label, phase 2, single-arm study. This trial enrolled 33 patients who were refractory to intravenous bisphosphonate therapy (defined as the corrected serum calcium not decreasing to less than or equal to 11.5 mg/dL 7-30 days following treatment with an intravenous bisphosphonate). (Hu, 2014)

Experimental, Investigational, Unproven Uses
There are no studies showing that combination treatment with osteoporosis drugs has a greater effect on fracture reduction compared to treatment with a single agent. The American Association of Clinical Endocrinologists (AACE) and American College of Endocrinology (ACE) postmenopausal osteoporosis guidelines recommend against the use combination therapy for prevention or treatment of postmenopausal osteoporosis until it is known what effect concomitant use has on fracture risk. (Camacho, 2016)

The double-blind, placebo-controlled phase 2b clinical trial evaluated denosumab in patients with transfusion-dependent thalassemia osteoporosis. 63 patients were deemed eligible for inclusion if they had transfusion-dependent thalassemia and a T score between −2.5 and −4.0 in at least 1 of the 3 examined sites (lumbar spine, femoral neck, and wrist bone). Inclusion criteria also included only adults over 30 years of age that were described as skeletally mature. The patients were randomly assigned 1:1 to receive 60 mg of denosumab or placebo administered subcutaneously every 6 months for 12 months, for a total of 2 doses. The primary outcome was to evaluate the effect of denosumab on lumbar spine bone mineral density. At 12 months, the mean percentage increase of lumbar spine bone mineral density was 5.92% with denosumab compared to 2.92% with placebo; the difference was statistically significant (*P* = .043). Results are promising but further studies are needed to validate these findings. (Voskaridou, 2018)

APPENDIX 1 – FRAX®
The FRAX® tool is utilized to evaluate fracture risk and is available at: https://www.shef.ac.uk/FRAX/

Coding/Billing Information

Note: 1) This list of codes may not be all-inclusive.
2) Deleted codes and codes which are not effective at the time the service is rendered may not be eligible for reimbursement.

Considered Medically Necessary when criteria in the applicable policy statements listed above are met:

HCPCS Codes	Description
J0897	Injection, denosumab, 1 mg

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