HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use XGEVA® safely and effectively. See full prescribing information for XGEVA.

Xgeva (denosumab)
injection, for subcutaneous use
Initial U.S. Approval: 2010

----------RECENT MAJOR CHANGES----------
- Warnings and Precautions (5.2) 09/2012
- Warnings and Precautions (5.3) 04/2012

---------- INDICATIONS AND USAGE----------
Xgeva is a RANK ligand (RANKL) inhibitor indicated for:
- Prevention of skeletal-related events in patients with bone metastases from solid tumors (1.1)

Important limitation of use: Xgeva is not indicated for the prevention of skeletal-related events in patients with multiple myeloma (1.2)

----------DOSAGE AND ADMINISTRATION----------
- Administer 120 mg every 4 weeks as a subcutaneous injection in the upper arm, upper thigh, or abdomen (2.1)
- Administer calcium and vitamin D as necessary to treat or prevent hypocalcemia (2.1)

----------DOSAGE FORMS AND STRENGTHS----------
- 120 mg/1.7 mL (70 mg/mL) single-use vial (3)

----------CONTRAINDICATIONS----------
- None (4)

----------WARNINGS AND PRECAUTIONS----------
- Hypocalcemia: Severe hypocalcemia can occur in patients receiving Xgeva. Correct hypocalcemia prior to initiating Xgeva. Monitor calcium levels and adequately supplement all patients with calcium and vitamin D (5.1)
- Osteonecrosis of the jaw can occur in patients receiving Xgeva. Perform an oral examination prior to starting Xgeva. Monitor for symptoms. Avoid invasive dental procedures during treatment with Xgeva (5.2)
- Pregnancy: Can cause fetal harm. Advise women of potential risk to the fetus (5.3, 8.1)

----------ADVERSE REACTIONS----------
- The most common adverse reactions in patients receiving Xgeva (per-patient incidence greater than or equal to 25%) were fatigue/asthenia, hypophosphatemia, and nausea (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Amgen Inc. at 1-800-77-AMGEN (1-800-772-6436) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

----------USE IN SPECIFIC POPULATIONS----------
- Nursing mothers: Discontinue drug or nursing taking into consideration importance of drug to mother (8.3)
- Pediatric patients: Safety and efficacy not established (8.4)
- Renal impairment: Patients with creatinine clearance less than 30 mL/min or receiving dialysis are at risk for hypocalcemia. Adequately supplement with calcium and vitamin D (8.6)

See 17 for PATIENT COUNSELING INFORMATION.

Revised: 09/2012

FULL PRESCRIBING INFORMATION: CONTENTS*

* Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

1.1 Bone Metastasis from Solid Tumors

Xgeva is indicated for the prevention of skeletal-related events in patients with bone metastases from solid tumors.

1.2 Important Limitation of Use

Xgeva is not indicated for the prevention of skeletal-related events in patients with multiple myeloma *[see Clinical Trials (14)]*.

2 DOSAGE AND ADMINISTRATION

2.1 Recommended Dosage

The recommended dose of Xgeva is 120 mg administered as a subcutaneous injection every 4 weeks in the upper arm, upper thigh, or abdomen.

Administer calcium and vitamin D as necessary to treat or prevent hypocalcemia *[see Warnings and Precautions (5.1)]*.

2.2 Preparation and Administration

Visually inspect Xgeva for particulate matter and discoloration prior to administration. Xgeva is a clear, colorless to pale yellow solution that may contain trace amounts of translucent to white proteinaceous particles. Do not use if the solution is discolored or cloudy or if the solution contains many particles or foreign particulate matter.

Prior to administration, Xgeva may be removed from the refrigerator and brought to room temperature (up to 25°C/77°F) by standing in the original container. This generally takes 15 to 30 minutes. Do not warm Xgeva in any other way *[see How Supplied/Storage and Handling (16)]*.

Use a 27-gauge needle to withdraw and inject the entire contents of the vial. Do not re-enter the vial. Discard vial after single-use or entry.

3 DOSAGE FORMS AND STRENGTHS

120 mg/1.7 mL (70 mg/mL) single-use vial.

4 CONTRAINDICATIONS

None.

5 WARNINGS AND PRECAUTIONS

5.1 Hypocalcemia

Xgeva can cause severe hypocalcemia. Correct pre-existing hypocalcemia prior to Xgeva treatment. Monitor calcium levels and administer calcium, magnesium, and vitamin D as necessary. Monitor levels more frequently when Xgeva is administered with other drugs that can also lower calcium levels. Advise patients to contact a healthcare professional for symptoms of hypocalcemia *[see Adverse Reactions (6.1) and Patient Counseling Information (17)]*.

Based on clinical trials using a lower dose of denosumab, patients with a creatinine clearance less than 30 mL/min or receiving dialysis are at greater risk of severe hypocalcemia compared to patients with normal renal function. In a trial of 55 patients, without cancer and with varying degrees of renal impairment, who received a single dose of 60 mg denosumab, 8 of 17 patients with a creatinine clearance less than 30 mL/min or receiving dialysis experienced corrected serum calcium levels less than 8.0 mg/dL as compared to 0 of 12 patients with normal renal function. The risk of hypocalcemia at the recommended dosing schedule of 120 mg every 4 weeks has not been evaluated in patients with a creatinine clearance less than 30 mL/min or receiving dialysis.

5.2 Osteonecrosis of the Jaw (ONJ)

Osteonecrosis of the jaw (ONJ) can occur in patients receiving Xgeva, manifesting as jaw pain, osteomyelitis, osteitis, bone erosion, tooth or periodontal infection, toothache, gingival ulceration, or gingival erosion. Persistent pain or slow healing of the mouth or jaw after dental surgery may also be manifestations of ONJ. In clinical trials in patients with osseous metastasis, 2.2% of patients receiving Xgeva developed ONJ after a median exposure of 13 doses; of these patients, 79% had a history of tooth extraction, poor oral hygiene, or use of a dental appliance *[see Adverse Reactions (6.1)]*. In a clinical trial conducted in patients with prostate cancer at high risk for osseous metastasis, a condition for which denosumab is not approved, 5.4% of patients developed ONJ after a median exposure of 20 doses.

Perform an oral examination and appropriate preventive dentistry prior to the initiation of Xgeva and periodically during Xgeva therapy. Advise patients regarding oral hygiene practices. Avoid invasive dental procedures during treatment with Xgeva.

Patients who are suspected of having or who develop ONJ while on Xgeva should receive care by a dentist or an oral surgeon. In these patients, extensive dental surgery to treat ONJ may exacerbate the condition.

5.3 Pregnancy

Xgeva can cause fetal harm when administered to a pregnant woman. Based on findings in animals, Xgeva is expected to result in adverse reproductive effects. In utero denosumab exposure in cynomolgus monkeys resulted in increased fetal loss, stillbirths, and postnatal mortality, along with evidence of absent peripheral lymph nodes, abnormal bone growth and decreased neonatal growth *[see Use in Specific Populations (8.1)]*.

There are no adequate and well-controlled studies with Xgeva in pregnant women. Women should be advised not to become pregnant when taking Xgeva. If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to the fetus.

6 ADVERSE REACTIONS

The following adverse reactions are discussed below and elsewhere in the labeling:

- Hypocalcemia *[see Warnings and Precautions (5.1)]*
- Osteonecrosis of the Jaw *[see Warnings and Precautions (5.2)]*

The most common adverse reactions in patients receiving Xgeva (per-patient incidence greater than or equal to 25%) were fatigue/asthenia, hypophosphatemia, and nausea (see Table 1).

The most common serious adverse reaction in patients receiving Xgeva was dyspnea.

The most common adverse reactions resulting in discontinuation of Xgeva were osteonecrosis and hypocalcemia.

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in other clinical trials and may not reflect the rates observed in practice.

The safety of Xgeva was evaluated in three randomized, double-blind, double-dummy trials *[see Clinical Trials (14)]* in which a total of 2841 patients with bone metastasis from prostate cancer, breast cancer, or other solid tumors, or lytic bony lesions from multiple myeloma received at least one dose of Xgeva. In Trials 1, 2, and 3, patients were randomized to receive either 120 mg of Xgeva every 4 weeks as a subcutaneous injection or 4 mg (dose adjusted for reduced renal function) of zoledronic acid every 4 weeks by intravenous (IV) infusion. Entry criteria included serum calcium (corrected) from 8 to 11.5 mg/dL (2 to 2.9 mmol/L) and creatinine clearance 30 mL/min or greater. Patients who had received IV bisphosphonates were excluded, as were patients with prior history of ONJ or osteomyelitis of the jaw, an active dental or jaw condition requiring oral surgery, non-healed dental/oral surgery, or any planned invasive dental procedure. During the study, serum chemistries including calcium and phosphorus were monitored every 4 weeks. Calcium and vitamin D supplementation was recommended but not required.

The median duration of exposure to Xgeva was 12 months (range: 0.1 – 41) and median duration on-study was 13 months (range: 0.1 – 41). Of patients who received Xgeva, 46% were female. Eighty-five percent were White, 5% Hispanic/Latino, 6% Asian, and 3% Black. The median age was 63 years (range: 18 – 93). Seventy-five percent of patients who received Xgeva received concomitant chemotherapy.

Table 1. Per-patient Incidence of Selected[a] Adverse Reactions of Any Severity (Trials 1, 2, and 3)

	Xgeva n = 2841 %	Zoledronic Acid n = 2836 %
GASTROINTESTINAL		
Nausea	31	32
Diarrhea	20	19
GENERAL		
Fatigue/Asthenia	45	46
INVESTIGATIONS		
Hypocalcemia[b]	18	9
Hypophosphatemia[b]	32	20
NEUROLOGICAL		
Headache	13	14
RESPIRATORY		
Dyspnea	21	18
Cough	15	15

[a] Adverse reactions reported in at least 10% of patients receiving Xgeva in Trials 1, 2, and 3, and meeting one of the following criteria:

- At least 1% greater incidence in Xgeva-treated patients, or
- Between-group difference (either direction) of less than 1% and more than 5% greater incidence in patients treated with zoledronic acid compared to placebo (US Prescribing Information for zoledronic acid)

[b] Laboratory-derived and below the central laboratory lower limit of normal [8.3 – 8.5 mg/dL (2.075 – 2.125 mmol/L) for calcium and 2.2 – 2.8 mg/dL (0.71 – 0.9 mmol/L) for phosphorus]

Severe Mineral/Electrolyte Abnormalities

- Severe hypocalcemia (corrected serum calcium less than 7 mg/dL or less than 1.75 mmol/L) occurred in 3.1% of patients treated with Xgeva and 1.3% of patients treated with zoledronic acid. Of patients who experienced severe hypocalcemia, 33% experienced 2 or more episodes of severe hypocalcemia and 16% experienced 3 or more episodes *[see Warnings and Precautions (5.1) and Use in Specific Populations (8.6)]*.

- Severe hypophosphatemia (serum phosphorus less than 2 mg/dL or less than 0.6 mmol/L) occurred in 15.4% of patients treated with Xgeva and 7.4% of patients treated with zoledronic acid.

Osteonecrosis of the Jaw

In the primary treatment phases of Trials 1, 2, and 3, ONJ was confirmed in 1.8% of patients in the Xgeva group and 1.3% of patients in the zoledronic acid group *[see Warnings and Precautions (5.2)]*. When events occurring during an extended treatment phase of approximately 4 months in each trial are included, the incidence of confirmed ONJ was 2.2% in patients who received Xgeva. The median time to ONJ was 14 months (range: 4 – 25).

6.2 Immunogenicity

As with all therapeutic proteins, there is potential for immunogenicity. Using an electrochemiluminescent bridging immunoassay, less than 1% (7/2758) of patients with osseous metastases treated with denosumab doses ranging from 30-180 mg every 4 weeks or every 12 weeks for up to 3 years tested positive for binding antibodies. No patient with positive binding antibodies tested positive for neutralizing antibodies as assessed using a chemiluminescent cell-based *in vitro* biological assay. There was no evidence of altered pharmacokinetic profile, toxicity profile, or clinical response associated with binding antibody development.

The incidence of antibody formation is highly dependent on the sensitivity and specificity of the assay. Additionally, the observed incidence of a positive antibody (including neutralizing antibody) test result may be influenced by several factors, including assay methodology, sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, comparison of antibodies to denosumab with the incidence of antibodies to other products may be misleading.

7 DRUG INTERACTIONS

No formal drug-drug interaction trials have been conducted with Xgeva.

In clinical trials in patients with breast cancer metastatic to bone, Xgeva was administered in combination with standard anticancer treatment. Serum denosumab concentrations at 1 and 3 months and reductions in the bone turnover marker uNTx/Cr (urinary N-terminal telopeptide corrected for creatinine) at 3 months were similar in patients with and without prior intravenous bisphosphonate therapy.

There was no evidence that various anticancer treatments affected denosumab systemic exposure and pharmacodynamic effect. Serum denosumab concentrations at 1 and 3 months were not altered by concomitant chemotherapy and/or hormone therapy. The median reduction in uNTx/Cr from baseline to month 3 was similar between patients receiving concomitant chemotherapy and/or hormone therapy *[see Clinical Pharmacology (12.2)]*.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category D *[see Warnings and Precautions (5.3)]*

Risk Summary

Xgeva can cause fetal harm when administered to a pregnant woman based on findings in animals. In utero denosumab exposure in cynomolgus monkeys resulted in increased fetal loss, stillbirths, and postnatal mortality, along with evidence of absent lymph nodes, abnormal bone growth and decreased neonatal growth.

There are no adequate and well-controlled studies with Xgeva in pregnant women. Women should be advised not to become pregnant when taking Xgeva. If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to the fetus.

Women who become pregnant during Xgeva treatment are encouraged to enroll in Amgen's Pregnancy Surveillance Program. Patients or their physicians should call 1-800-77-AMGEN (1-800-772-6436) to enroll.

Clinical Considerations
The effects of Xgeva are likely to be greater during the second and third trimesters of pregnancy. Monoclonal antibodies are transported across the placenta in a linear fashion as pregnancy progresses, with the largest amount transferred during the third trimester.

If the patient becomes pregnant during Xgeva therapy, consider the risks and benefits in continuing or discontinuing treatment with Xgeva.

Animal Data
The effects of denosumab on prenatal development have been studied in both cynomolgus monkeys and genetically engineered mice in which RANK ligand (RANKL) expression was turned off by gene removal (a "knockout mouse"). In cynomolgus monkeys dosed subcutaneously with denosumab throughout pregnancy at a pharmacologically active dose, there was increased fetal loss during gestation, stillbirths, and postnatal mortality. Other findings in offspring included absence of axillary, inguinal, mandibular, and mesenteric lymph nodes; abnormal bone growth, reduced bone strength, reduced hematopoiesis, dental dysplasia and tooth malalignment; and decreased neonatal growth. At birth out to one month of age, infants had measurable blood levels of denosumab (22-621% of maternal levels).

Following a recovery period from birth out to 6 months of age, the effects on bone quality and strength returned to normal; there were no adverse effects on tooth eruption, though dental dysplasia was still apparent; axillary and inguinal lymph nodes remained absent, while mandibular and mesenteric lymph nodes were present, though small; and minimal to moderate mineralization in multiple tissues was seen in one recovery animal. There was no evidence of maternal harm prior to labor; adverse maternal effects occurred infrequently during labor. Maternal mammary gland development was normal. There was no fetal NOAEL (no observable adverse effect level) established for this study because only one dose of 50 mg/kg was evaluated.

In RANKL knockout mice, absence of RANKL (the target of denosumab) also caused fetal lymph node agenesis and led to postnatal impairment of dentition and bone growth. Pregnant RANKL knockout mice showed altered maturation of the maternal mammary gland, leading to impaired lactation *[see Use in Specific Populations (8.3) and Nonclinical Toxicology (13.2)]*.

8.3 Nursing Mothers

It is not known whether Xgeva is excreted into human milk. Measurable concentrations of denosumab were present in the maternal milk of cynomolgus monkeys up to 1 month after the last dose of denosumab (≤ 0.5% milk:serum ratio). Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from Xgeva, a decision should be made whether to discontinue nursing or discontinue the drug, taking into account the importance of the drug to the mother.

Maternal exposure to Xgeva during pregnancy may impair mammary gland development and lactation based on animal studies in pregnant mice lacking the RANK/RANKL signaling pathway that have shown altered maturation of the maternal mammary gland, leading to impaired lactation postpartum. However, in cynomolgus monkeys treated with denosumab throughout pregnancy, maternal mammary gland development was normal, with no impaired lactation. Mammary gland histopathology at 6 months of age was normal in female offspring exposed to denosumab in utero; however, development and lactation have not been fully evaluated *[see Nonclinical Toxicology (13.2)]*.

8.4 Pediatric Use

Xgeva is not recommended in pediatric patients. The safety and effectiveness of Xgeva in pediatric patients have not been established.

Treatment with Xgeva may impair bone growth in children with open growth plates and may inhibit eruption of dentition. In neonatal rats, inhibition of RANKL (the target of Xgeva therapy) with a construct of osteoprotegerin bound to Fc (OPG-Fc) at doses ≤ 10 mg/kg was associated with inhibition of bone growth and tooth eruption. Adolescent primates treated with denosumab at doses 5 and 25 times (10 and 50 mg/kg dose) higher than the recommended human dose of 120 mg administered once every 4 weeks, based on body weight (mg/kg), had abnormal growth plates, considered to be consistent with the pharmacological activity of denosumab.

Cynomolgus monkeys exposed in utero to denosumab exhibited bone abnormalities, reduced hematopoiesis, tooth malalignment, decreased neonatal growth, and an absence of axillary, inguinal, mandibular, and mesenteric lymph nodes. Some bone abnormalities recovered once exposure was ceased following birth; however, axillary and inguinal lymph nodes remained absent 6 months post-birth *[see Use in Specific Populations (8.1)]*.

8.5 Geriatric Use

Of patients who received Xgeva in Trials 1, 2, and 3, 1260 (44%) were 65 years of age or older. No overall differences in safety or efficacy were observed between these patients and younger patients.

8.6 Renal Impairment

In a trial of 55 patients without cancer and with varying degrees of renal function who received a single dose of 60 mg denosumab, patients with a creatinine clearance of less than 30 mL/min or receiving dialysis were at greater risk of severe hypocalcemia with denosumab compared to patients with normal renal function. The risk of hypocalcemia at the recommended dosing schedule of 120 mg every 4 weeks has not been evaluated in patients with a creatinine clearance of less than 30 mL/min or receiving dialysis *[see Warnings and Precautions (5.1), Adverse Reactions (6.1), and Clinical Pharmacology (12.3)]*.

10 OVERDOSAGE

There is no experience with overdosage of Xgeva.

11 DESCRIPTION

Xgeva (denosumab) is a human IgG2 monoclonal antibody that binds to human RANKL. Denosumab has an approximate molecular weight of 147 kDa and is produced in genetically engineered mammalian (Chinese hamster ovary) cells.

Xgeva is a sterile, preservative-free, clear, colorless to pale yellow solution.

Each single-use vial of Xgeva contains 120 mg denosumab, 4.6% sorbitol, 18 mM acetate, Water for Injection (USP), and sodium hydroxide to a pH of 5.2.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Xgeva binds to RANKL, a transmembrane or soluble protein essential for the formation, function, and survival of osteoclasts, the cells responsible for bone resorption. Xgeva prevents RANKL from activating its receptor, RANK, on the surface of osteoclasts and their precursors. Increased osteoclast activity, stimulated by RANKL, is a mediator of bone pathology in solid tumors with osseous metastases.

12.2 Pharmacodynamics

In patients with breast cancer and bone metastases, the median reduction in uNTx/Cr was 82% within 1 week following initiation of Xgeva 120 mg administered subcutaneously. In Trials 1, 2, and 3, the median reduction in uNTx/Cr from baseline to month 3 was approximately 80% in 2075 Xgeva-treated patients.

12.3 Pharmacokinetics

Following subcutaneous administration, bioavailability was 62%. Denosumab displayed nonlinear pharmacokinetics at doses below 60 mg, but approximately dose-proportional increases in exposure at higher doses. With multiple subcutaneous doses of 120 mg every 4 weeks in patients with cancer metastatic to the bone, up to 2.8-fold accumulation in serum denosumab concentrations was observed and steady state was achieved by 6 months. At steady state, the mean ± SD serum trough concentration was 20.5 ± 13.5 mcg/mL at the recommended Xgeva dose, and the mean elimination half-life was 28 days.

A population pharmacokinetic analysis was performed to evaluate the effects of demographic characteristics. Denosumab clearance and volume of distribution were proportional to body weight. The steady-state exposure following repeat subcutaneous administration of 120 mg every 4 weeks to 45 kg and 120 kg subjects were, respectively, 48% higher and 46% lower than exposure of the typical 66 kg subject.

Specific Populations

The pharmacokinetics of denosumab were not affected by age, gender, and race. The pharmacokinetics of denosumab in pediatric patients have not been assessed.

Hepatic Impairment: No clinical trials have been conducted to evaluate the effect of hepatic impairment on the pharmacokinetics of denosumab.

Renal Impairment: In a trial of 55 subjects with varying degrees of renal function, including subjects on dialysis, the degree of renal impairment had no effect on the pharmacokinetics and pharmacodynamics of denosumab *[see Use in Specific Populations (8.6)]*.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenicity
The carcinogenic potential of denosumab has not been evaluated in long-term animal studies.

Mutagenicity
The genotoxic potential of denosumab has not been evaluated.

Impairment of Fertility
Denosumab had no effect on female fertility or male reproductive organs in monkeys at doses that were 6.5- to 25-fold higher than the recommended human dose of 120 mg subcutaneously administered once every 4 weeks, based on body weight (mg/kg).

13.2 Animal Toxicology and/or Pharmacology

Denosumab is an inhibitor of osteoclastic bone resorption via inhibition of RANKL.

Because the biological activity of denosumab in animals is specific to nonhuman primates, evaluation of genetically engineered (knockout) mice or use of other biological inhibitors of the RANK/RANKL pathway, OPG-Fc and RANK-Fc, provided additional safety information on the inhibition of the RANK/RANKL pathway in rodent models. A study in 2-week-old rats given the RANKL inhibitor OPG-Fc showed reduced bone growth, altered growth plates, and impaired tooth eruption. These changes were partially reversible in this model when dosing with the RANKL inhibitors was discontinued. Neonatal RANK/RANKL knockout mice also exhibited reduced bone growth and lack of tooth eruption. RANK/RANKL knockout mice also exhibited absence of lymph node formation, as well as an absence of lactation due to inhibition of mammary gland maturation (lobulo-alveolar gland development during pregnancy) *[see Use in Specific Populations (8.3, 8.4)]*.

14 CLINICAL TRIALS

The safety and efficacy of Xgeva for the prevention of skeletal-related events in patients with bone metastases from solid tumors was demonstrated in three international, randomized (1:1), double-blind, active-controlled, noninferiority trials comparing Xgeva with zoledronic acid. In all three trials, patients were randomized to receive 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.

Trial 1 enrolled 2046 patients with advanced breast cancer and bone metastasis. Randomization was stratified by a history of prior SRE (yes or no), receipt of chemotherapy within 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.

Trial 2 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.

Trial 3 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 (Table 2). In patients with bone metastasis due to other solid tumors or lytic lesions due to multiple myeloma, Xgeva was noninferior to zoledronic acid in delaying the time to first SRE following randomization.

Overall survival and progression-free survival were similar between arms in all three trials. Mortality was higher with Xgeva in a subgroup analysis of patients with multiple myeloma (hazard ratio [95% CI] of 2.26 [1.13, 4.50]; n = 180).

Table 2. Efficacy Results for Xgeva Compared to Zoledronic Acid

	Trial 1 Metastatic Breast Cancer		**Trial 2 Metastatic Solid Tumors or Multiple Myeloma**		**Trial 3 Metastatic CRPC[a]**	
	Xgeva	Zoledronic Acid	Xgeva	Zoledronic Acid	Xgeva	Zoledronic Acid
N	1026	1020	886	890	950	951
First On-study SRE						
Number of Patients who had SREs (%)	315 (30.7)	372 (36.5)	278 (31.4)	323 (36.3)	341 (35.9)	386 (40.6)
Components of First SRE						
Radiation to Bone	82 (8.0)	119 (11.7)	119 (13.4)	144 (16.2)	177 (18.6)	203 (21.3)
Pathological Fracture	212 (20.7)	238 (23.3)	122 (13.8)	139 (15.6)	137 (14.4)	143 (15.0)
Surgery to Bone	12 (1.2)	8 (0.8)	13 (1.5)	19 (2.1)	1 (0.1)	4 (0.4)
Spinal Cord Compression	9 (0.9)	7 (0.7)	24 (2.7)	21 (2.4)	26 (2.7)	36 (3.8)
Median Time to SRE (months)	NR[b]	26.4	20.5	16.3	20.7	17.1
Hazard Ratio (95% CI)	0.82 (0.71, 0.95)		0.84 (0.71, 0.98)		0.82 (0.71, 0.95)	
Noninferiority p-value	< 0.001		< 0.001		< 0.001	
Superiority p-value[c]	0.010		0.060		0.008	
First and Subsequent SRE[d]						
Mean Number/Patient	0.46	0.60	0.44	0.49	0.52	0.61
Rate Ratio (95% CI)	0.77 (0.66, 0.89)		0.90 (0.77, 1.04)		0.82 (0.71, 0.94)	
Superiority p-value [e]	0.001		0.145		0.009	

[a]CRPC = castrate-resistant prostate cancer.
[b]NR = not reached.
[c]Superiority testing performed only after denosumab demonstrated to be noninferior to zoledronic acid within trial.
[d]All skeletal events postrandomization; new events defined by occurrence ≥ 21 days after preceding event.
[e]Adjusted p-values are presented.

16 HOW SUPPLIED/STORAGE AND HANDLING

Xgeva is supplied in a single-use vial.

120 mg/1.7 mL	1 vial per carton	NDC 55513-730-01

Store Xgeva in a refrigerator at 2°C to 8°C (36°F to 46°F) in the original carton. Do not freeze. Once removed from the refrigerator, Xgeva must not be exposed to temperatures above 25°C/77°F or direct light and must be used within 14 days. Discard Xgeva if not used within the 14 days. Do not use Xgeva after the expiry date printed on the label.

Protect Xgeva from direct light and heat.

Avoid vigorous shaking of Xgeva.

17 PATIENT COUNSELING INFORMATION

Advise patients to contact a healthcare professional for any of the following:

- Symptoms of hypocalcemia, including paresthesias or muscle stiffness, twitching, spasms, or cramps *[see Warnings and Precautions (5.1) and Adverse Reactions (6.1)]*
- Symptoms of ONJ, including pain, numbness, swelling of or drainage from the jaw, mouth, or teeth *[see Warnings and Precautions (5.2) and Adverse Reactions (6.1)]*
- Persistent pain or slow healing of the mouth or jaw after dental surgery *[see Warnings and Precautions (5.2)]*
- Pregnancy or nursing *[see Warnings and Precautions (5.3) and Use in Specific Populations (8.1, 8.3)]*

Advise patients of the need for:

- Proper oral hygiene and routine dental care
- Informing their dentist that they are receiving Xgeva
- Avoiding invasive dental procedures during treatment with Xgeva

Advise patients that denosumab is also marketed as Prolia®. Patients should inform their healthcare provider if they are taking Prolia.

AMGEN®

Xgeva® (denosumab)

Manufactured by:
Amgen Manufacturing Limited, a subsidiary of Amgen Inc.
One Amgen Center Drive
Thousand Oaks, California 91320-1799

This product, its production, and/or its use may be covered by one or more U.S. Patents, including U.S. Patent Nos. 6,740,522; 7,411,050; 7,097,834; and 7,364,736, as well as other patents or patents pending.

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