

XGEVA- denosumab injection

Amgen Inc

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, Hypocalcemia (5.3) 02/2020

----- INDICATIONS AND USAGE -----

Xgeva is a RANK ligand (RANKL) inhibitor indicated for:

- Prevention of skeletal-related events in patients with multiple myeloma and in patients with bone metastases from solid tumors. (1.1)
- 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. (1.2, 14.3)
- Treatment of hypercalcemia of malignancy refractory to bisphosphonate therapy. (1.3)

----- DOSAGE AND ADMINISTRATION -----

- Xgeva is intended for subcutaneous route only and should not be administered intravenously, intramuscularly, or intradermally. (2.1)
- Multiple Myeloma and Bone Metastasis from Solid Tumors: Administer 120 mg every 4 weeks as a subcutaneous injection in the upper arm, upper thigh, or abdomen. (2.2)
- Giant Cell Tumor of Bone: Administer 120 mg 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. (2.3)
- Administer calcium and vitamin D as necessary to treat or prevent hypocalcemia. (2.2, 2.3)
- Hypercalcemia of Malignancy: Administer 120 mg 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. (2.4)

----- DOSAGE FORMS AND STRENGTHS -----

- Injection: 120 mg/1.7 mL (70 mg/mL) solution in a single-dose vial (3)

----- CONTRAINDICATIONS -----

- Hypocalcemia (4.1)
- Known clinically significant hypersensitivity to Xgeva (4.2)

----- WARNINGS AND PRECAUTIONS -----

- Same Active Ingredient: Patients receiving Xgeva should not take Prolia®. (5.1)
- Hypersensitivity reactions including anaphylaxis may occur. Discontinue permanently if a clinically significant reaction occurs. (5.2)
- Hypocalcemia: Xgeva can cause severe symptomatic hypocalcemia, and fatal cases have been reported. Correct hypocalcemia prior to initiating Xgeva. Monitor calcium levels during therapy, especially in the first weeks of initiating therapy, and adequately supplement all patients with calcium and vitamin D. (5.3)
- Osteonecrosis of the jaw (ONJ) has been reported in patients receiving Xgeva. Perform an oral examination prior to starting Xgeva. Monitor for symptoms. Avoid invasive dental procedures during treatment with Xgeva. (5.4)
- Atypical femoral fracture: Evaluate patients with thigh or groin pain to rule out a femoral fracture. (5.5)
- Hypercalcemia Following Treatment Discontinuation in Patients with Giant Cell Tumor of Bone and in Patients with Growing Skeletons: Monitor patients for signs and symptoms of hypercalcemia, and manage as clinically appropriate. (5.6, 8.4)
- Multiple Vertebral Fractures (MVF) Following Treatment Discontinuation: When Xgeva treatment is discontinued, evaluate the individual patient's risk for vertebral fractures. (5.7)
- Embryo-Fetal Toxicity: Can cause fetal harm. Advise females of reproductive potential of potential risk to the fetus and to use effective contraception. (5.8, 8.1, 8.3)

----- ADVERSE REACTIONS -----

- Bone Metastasis from Solid Tumors: Most common adverse reactions ($\geq 25\%$) were fatigue/asthenia,

hypophosphatemia, and nausea. (6.1)

- Multiple Myeloma: Most common adverse reactions ($\geq 10\%$) were diarrhea, nausea, anemia, back pain, thrombocytopenia, peripheral edema, hypocalcemia, upper respiratory tract infection, rash, and headache. (6.1)
- Giant Cell Tumor of Bone: Most common adverse reactions ($\geq 10\%$) were arthralgia, headache, nausea, back pain, fatigue, and pain in extremity. (6.1)
- Hypercalcemia of Malignancy: Most common adverse reactions ($> 20\%$) were nausea, dyspnea, decreased appetite, headache, peripheral edema, vomiting, anemia, constipation, and diarrhea. (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**-----

- Pediatric patients: Recommended only for treatment of skeletally mature adolescents with giant cell tumor of bone. (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: 6/2020

FULL PRESCRIBING INFORMATION: CONTENTS*

1 INDICATIONS AND USAGE

- 1.1 Multiple Myeloma and Bone Metastasis from Solid Tumors
- 1.2 Giant Cell Tumor of Bone
- 1.3 Hypercalcemia of Malignancy

2 DOSAGE AND ADMINISTRATION

- 2.1 Important Administration Instructions
- 2.2 Multiple Myeloma and Bone Metastasis from Solid Tumors
- 2.3 Giant Cell Tumor of Bone
- 2.4 Hypercalcemia of Malignancy
- 2.5 Preparation and Administration

3 DOSAGE FORMS AND STRENGTHS

4 CONTRAINDICATIONS

- 4.1 Hypocalcemia
- 4.2 Hypersensitivity

5 WARNINGS AND PRECAUTIONS

- 5.1 Drug Products with Same Active Ingredient
- 5.2 Hypersensitivity
- 5.3 Hypocalcemia
- 5.4 Osteonecrosis of the Jaw (ONJ)
- 5.5 Atypical Subtrochanteric and Diaphyseal Femoral Fracture
- 5.6 Hypercalcemia Following Treatment Discontinuation in Patients with Giant Cell Tumor of Bone and in Patients with Growing Skeletons
- 5.7 Multiple Vertebral Fractures (MVF) Following Treatment Discontinuation
- 5.8 Embryo-Fetal Toxicity

6 ADVERSE REACTIONS

- 6.1 Clinical Trials Experience
- 6.2 Postmarketing Experience
- 6.3 Immunogenicity

8 USE IN SPECIFIC POPULATIONS

- 8.1 Pregnancy
- 8.2 Lactation

- 8.3 Females and Males of Reproductive Potential
- 8.4 Pediatric Use
- 8.5 Geriatric Use
- 8.6 Renal Impairment

10 OVERDOSAGE

11 DESCRIPTION

12 CLINICAL PHARMACOLOGY

- 12.1 Mechanism of Action
- 12.2 Pharmacodynamics
- 12.3 Pharmacokinetics

13 NONCLINICAL TOXICOLOGY

- 13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
- 13.2 Animal Toxicology and/or Pharmacology

14 CLINICAL TRIALS

- 14.1 Bone Metastasis from Solid Tumors
- 14.2 Multiple Myeloma
- 14.3 Giant Cell Tumor of Bone
- 14.4 Hypercalcemia of Malignancy

16 HOW SUPPLIED/STORAGE AND HANDLING

17 PATIENT COUNSELING INFORMATION

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

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

1.1 Multiple Myeloma and Bone Metastasis from Solid Tumors

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

1.2 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 [see *Clinical Trials (14.2)*].

1.3 Hypercalcemia of Malignancy

Xgeva is indicated for the treatment of hypercalcemia of malignancy refractory to bisphosphonate therapy.

2 DOSAGE AND ADMINISTRATION

2.1 Important Administration Instructions

Xgeva is intended for subcutaneous route only and should not be administered intravenously, intramuscularly, or intradermally.

2.2 Multiple Myeloma and Bone Metastasis from Solid Tumors

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 (5.3)*].

2.3 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 [see *Warnings and Precautions (5.3)*].

2.4 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.

2.5 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-dose or entry.

3 DOSAGE FORMS AND STRENGTHS

Injection: 120 mg/1.7 mL (70 mg/mL) solution in a single-dose vial.

4 CONTRAINDICATIONS

4.1 Hypocalcemia

Pre-existing hypocalcemia must be corrected prior to initiating therapy with Xgeva [see *Warnings and Precautions (5.3)*].

4.2 Hypersensitivity

Xgeva is contraindicated in patients with known clinically significant hypersensitivity to Xgeva [see *Warnings and Precautions (5.2) and Adverse Reactions (6.2)*].

5 WARNINGS AND PRECAUTIONS

5.1 Drug Products with Same Active Ingredient

Xgeva includes the same active ingredient (denosumab) found in Prolia. Patients receiving Xgeva should not take Prolia.

5.2 Hypersensitivity

Clinically significant hypersensitivity including anaphylaxis has been reported with use of Xgeva. Reactions may include hypotension, dyspnea, upper airway edema, lip swelling, rash, pruritus, and urticaria. If an anaphylactic or other clinically significant allergic reaction occurs, initiate appropriate therapy and discontinue Xgeva therapy permanently [see *Contraindications (4.2) and Adverse Reactions (6.2)*].

5.3 Hypocalcemia

Xgeva can cause severe symptomatic hypocalcemia, and fatal cases have been reported. Correct pre-existing hypocalcemia prior to Xgeva treatment. Monitor calcium levels, throughout Xgeva therapy, especially in the first weeks of initiating therapy, and administer calcium, magnesium, and vitamin D as necessary. Concomitant use of calcimimetics and other drugs that can lower calcium levels may worsen hypocalcemia risk and serum calcium should be closely monitored. Advise patients to contact a healthcare provider for symptoms of hypocalcemia [see *Contraindications (4.1), Adverse Reactions (6.1, 6.2), and Patient Counseling Information (17)*].

An increased risk of hypocalcemia has been observed in clinical trials of patients with increasing renal dysfunction, most commonly with severe dysfunction (creatinine clearance less than 30 mL/min and/or on dialysis), and with inadequate/no calcium supplementation. Monitor calcium levels and calcium and vitamin D intake [see *Adverse Reactions (6.1), Use in Specific Populations (8.6), and Clinical Pharmacology (12.3)*].

5.4 Osteonecrosis of the Jaw (ONJ)

Osteonecrosis of the jaw (ONJ) has been reported 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 cancer, the incidence of ONJ was higher with longer duration of exposure [see *Adverse Reactions (6.1)*]. Seventy-nine percent of patients with ONJ had a history of tooth extraction, poor oral hygiene, or use of a dental appliance as a predisposing factor. Other risk factors for the development of ONJ include immunosuppressive therapy, treatment with angiogenesis inhibitors, systemic corticosteroids, diabetes, and gingival infections. Similarly, for Xgeva patients with multiple myeloma that developed ONJ, 58% had a history of invasive dental procedures as a predisposing factor.

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. Consider temporary discontinuation of Xgeva therapy if an invasive dental procedure must be performed. There are no data available to suggest the optimal duration of treatment interruption.

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. Clinical judgment of the treating healthcare provider should guide the management plan of each patient based on individual risk/benefit assessment.

5.5 Atypical Subtrochanteric and Diaphyseal Femoral Fracture

Atypical femoral fracture has been reported with Xgeva [see *Adverse Reactions (6.1)*]. These fractures can occur anywhere in the femoral shaft from just below the lesser

trochanter to above the supracondylar flare and are transverse or short oblique in orientation without evidence of comminution.

Atypical femoral fractures most commonly occur with minimal or no trauma to the affected area. They may be bilateral and many patients report prodromal pain in the affected area, usually presenting as dull, aching thigh pain, weeks to months before a complete fracture occurs. A number of reports note that patients were also receiving treatment with glucocorticoids (e.g. prednisone) at the time of fracture.

During Xgeva treatment, patients should be advised to report new or unusual thigh, hip, or groin pain. Any patient who presents with thigh or groin pain should be suspected of having an atypical fracture and should be evaluated to rule out an incomplete femur fracture. Patient presenting with an atypical femur fracture should also be assessed for symptoms and signs of fracture in the contralateral limb. Interruption of Xgeva therapy should be considered, pending a risk/benefit assessment, on an individual basis.

5.6 Hypercalcemia Following Treatment Discontinuation in Patients with Giant Cell Tumor of Bone and in Patients with Growing Skeletons

Clinically significant hypercalcemia requiring hospitalization and complicated by acute renal injury has been reported in Xgeva-treated patients with giant cell tumor of bone and patients with growing skeletons. Hypercalcemia has been reported within the first year after treatment discontinuation. After treatment is discontinued, monitor patients for signs and symptoms of hypercalcemia, assess serum calcium periodically, reevaluate the patient's calcium and vitamin D supplementation requirements and manage patients as clinically appropriate [see *Adverse Reactions (6)* and *Use in Specific Populations (8.4)*].

5.7 Multiple Vertebral Fractures (MVF) Following Treatment Discontinuation

Multiple vertebral fractures (MVF) have been reported following discontinuation of treatment with denosumab. Patients at higher risk for MVF include those with risk factors for or a history of osteoporosis or prior fractures.

When Xgeva treatment is discontinued, evaluate the individual patient's risk for vertebral fractures [see *Patient Counseling Information (17)*].

5.8 Embryo-Fetal Toxicity

Based on data from animal studies and its mechanism of action, Xgeva can cause fetal harm when administered to a pregnant woman. In animal reproduction studies, administration of denosumab to cynomolgus monkeys throughout pregnancy at a dose 25-fold higher than the recommended human dose of Xgeva based on body weight resulted in increased fetal loss, stillbirths, and postnatal mortality, along with evidence of absent peripheral lymph nodes, abnormal bone growth and decreased neonatal growth.

Verify the pregnancy status of females of reproductive potential prior to the initiation of Xgeva. Advise pregnant women and females of reproductive potential that exposure to Xgeva during pregnancy or within 5 months prior to conception can result in fetal harm. Advise females of reproductive potential to use effective contraception during therapy, and for at least 5 months after the last dose of Xgeva [see *Use in Specific Populations (8.1, 8.3)* and *Clinical Pharmacology (12.1)*].

6 ADVERSE REACTIONS

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

- Hypersensitivity [see *Warnings and Precautions (5.2)*]

- Hypocalcemia [see Warnings and Precautions (5.3) and Use in Specific Populations (8.6)]
- Osteonecrosis of the Jaw [see Warnings and Precautions (5.4)]
- Atypical Subtrochanteric and Diaphyseal Femoral Fracture [see Warnings and Precautions (5.5)]
- Hypercalcemia following treatment discontinuation in patients with giant cell tumor of bone and in patients with growing skeletons [see Warnings and Precautions (5.6) and Use in Specific Populations (8.4)]
- Multiple vertebral fractures (MVF) following treatment discontinuation [see Warnings and Precautions (5.7)]

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 the clinical trials of another drug and may not reflect the rates observed in practice.

Bone Metastasis from Solid Tumors

The safety of Xgeva was evaluated in three randomized, double-blind, double-dummy trials [see Clinical Trials (14.1)] 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 Studies 20050136, 20050244, and 20050103, 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.

The most common adverse reactions in patients (incidence greater than or equal to 25%) were fatigue/asthenia, hypophosphatemia, and nausea (see Table 1). The most common serious adverse reaction was dyspnea. The most common adverse reactions resulting in discontinuation of Xgeva were osteonecrosis and hypocalcemia.

Table 1. Selected^a Adverse Reactions of Any Severity (Studies 20050136, 20050244, and 20050103)

Body System	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 Studies 20050136, 20050244, and 20050103, 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 (5.3) 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 (ONJ)

In the primary treatment phases of Studies 20050136, 20050244, and 20050103, ONJ was confirmed in 1.8% of patients in the Xgeva group (median exposure of 12.0 months; range: 0.1-40.5) and 1.3% of patients in the zoledronic acid group. The trials in patients with breast (Study 20050136) or prostate (Study 20050103) cancer included an Xgeva open-label extension treatment phase where patients were offered Xgeva 120 mg once every 4 weeks (median overall exposure of 14.9 months; range: 0.1-67.2). The patient-year adjusted incidence (number of events per 100 patient years) of confirmed ONJ was 1.1% during the first year of treatment, 3.7% in the second year, and 4.6% per year thereafter. The median time to ONJ was 20.6 months (range: 4-53) [see *Warnings and Precautions (5.4)*].

In a placebo-controlled clinical trial with an extension treatment phase evaluating Xgeva for the prevention of bone metastases in patients with non-metastatic prostate cancer (a patient population for which Xgeva is not indicated), with longer treatment exposure of up to 7 years, the patient-year adjusted incidence (number of events per 100 patient years) of confirmed ONJ was 1.1% during the first year of treatment, 3.0% in the second year, and 7.1% per year thereafter.

Atypical Subtrochanteric and Diaphyseal Fracture

In the clinical trial program, atypical femoral fracture has been reported in patients treated with Xgeva and the risk increased with longer duration of treatment. Events have occurred during treatment and after treatment was discontinued [see *Warnings and Precautions (5.5)*].

Multiple Myeloma

The safety of Xgeva was evaluated in an international, randomized (1:1), double-blind, active-controlled trial of patients with newly diagnosed multiple myeloma with treatment through disease progression [see *Clinical Trials (14.2)*]. In this trial, patients received 120 mg Xgeva every 4 weeks as a subcutaneous injection (n = 850) or 4 mg (dose adjusted for renal function) of zoledronic acid intravenously (IV) every 4 weeks by IV infusion (n = 852). 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 16 months (range: 1-50) and median duration on-study was 17 months (range: 0-49). Of patients who received Xgeva, 46% were female, 83% percent were White, 13% Asian, 3% Black or African American, and 4% Hispanic/Latino. The median age of the patients randomized to Xgeva was 63 years (range: 29-91) and all patients who received Xgeva received concomitant anti-myeloma chemotherapy.

The adverse reaction profile of Xgeva in patients with multiple myeloma, Study 20090482, was similar to that observed in Studies 20050136, 20050244, and 20050103. The most common adverse reactions (incidence $\geq 10\%$) were diarrhea (34%), nausea (32%), anemia (22%), back pain (21%), thrombocytopenia (19%), peripheral edema (17%), hypocalcemia (16%), upper respiratory tract infection (15%), rash (14%), and headache (11%). The most common serious adverse reaction (incidence $\geq 5\%$) was pneumonia (8%). The most common adverse reaction resulting in discontinuation of Xgeva ($\geq 1.0\%$) was osteonecrosis of the jaw.

Hypocalcemia and Hypophosphatemia

Severe hypocalcemia (corrected serum calcium less than 7 mg/dL or less than 1.75 mmol/L) and severe hypophosphatemia (serum phosphorus less than 2 mg/dL or less than 0.6 mmol/L) occurred in 2% and 21% patients treated with Xgeva, respectively.

Osteonecrosis of the Jaw (ONJ)

In the primary treatment phase of Study 20090482, ONJ was confirmed in 4.1% of patients in the Xgeva group (median exposure of 16 months; range: 1-50) and 2.8% of patients in the zoledronic acid group (median 15 months, range: 1-45 months). At the completion of the double-blind treatment phase of Study 20090482, the patient-year adjusted incidence (number of events per 100 patient years) of confirmed ONJ in the Xgeva group (median exposure of 19.4 months; range 1-52) was 2.0% during the first year of treatment, 5.0% in the second year, and 4.5% per year thereafter. The median time to ONJ was 18.7 months (range: 1-44) [see *Warnings and Precautions (5.4)*].

Giant Cell Tumor of Bone

The safety of Xgeva was evaluated in two single-arm trials (Study 20062004 and Study 20040215) [see *Clinical Trials (14.3)*] in which a total of 548 adult or skeletally mature

adolescent patients with giant cell tumor of bone received at least 1 dose of Xgeva. Patients received 120 mg Xgeva subcutaneously every 4 weeks with additional 120 mg doses on Days 8 and 15 of the first month of therapy. Patients receiving concurrent bisphosphonate therapy were excluded from enrollment in both studies. 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 were excluded from enrollment in Study 20040215. During the trial, serum chemistries including calcium and phosphorus were monitored every 4 weeks. Calcium and vitamin D supplementation was recommended but not required.

Of the 548 patients who received Xgeva, 467 patients were treated with Xgeva for ≥ 1 year, 323 patients for ≥ 2 years, and 255 patients for ≥ 3 years. The median number of doses received was 33 (range: 4-138 doses) and the median number of months on-study was 60 (range: 0-140 months). Fifty-seven percent of the enrolled patients were women and 82% were White. The median age was 33 years (range: 13-83 years); a total of 19 patients were skeletally mature adolescents (12 to <17 years of age).

The common adverse reaction profile of Xgeva in patients with giant cell tumor of bone was generally similar to that reported in Studies 20050136, 20050244, and 20050103. The most common adverse reactions in patients (incidence $\geq 10\%$) were arthralgia, back pain, pain in extremity, fatigue, headache, nausea, nasopharyngitis, musculoskeletal pain, toothache, vomiting, hypophosphatemia, constipation, diarrhea, and cough. The most frequent serious adverse reactions were osteonecrosis of the jaw (3.6%), bone giant cell tumor (1.5%), anemia (1.1%), pneumonia (0.9%), and back pain (0.9%). The most frequent adverse reactions resulting in discontinuation of Xgeva was osteonecrosis of the jaw (incidence of 3.6%). The adverse reaction profile appeared similar in skeletally mature adolescents and adults.

Hypocalcemia and Hypophosphatemia

- Moderate to severe hypocalcemia (corrected serum calcium less than 8 mg/dL or less than 2 mmol/L) occurred in 5% of patients treated with Xgeva.
- Severe hypophosphatemia (serum phosphorus less than 2 to 1 mg/dL or less than 0.6 to 0.3 mmol/L) occurred in 20% of patients treated with Xgeva.

Osteonecrosis of the Jaw (ONJ)

In Study 20062004 and Study 20040215, ONJ was confirmed in 6.6% of patients who received Xgeva. [see *Warnings and Precautions (5.4)*].

Atypical Subtrochanteric and Diaphyseal Fracture

Atypical femoral fracture has been reported with Xgeva and was observed in 0.9% of patients in the pooled safety population [see *Warnings and Precautions (5.5)*].

Hypercalcemia Following Treatment Discontinuation

In the pooled safety population, 0.7% of patients experienced serious adverse events of hypercalcemia > 30 days following treatment discontinuation that was recurrent in some patients [see *Warnings and Precautions (5.6)*].

Hypercalcemia of Malignancy

Xgeva was evaluated in an open-label, single-arm trial (Study 20070315) in which 33 patients with hypercalcemia of malignancy (with or without bone metastases) refractory to treatment with intravenous bisphosphonate therapy were enrolled [see *Clinical Trials (14.4)*].

The adverse reaction profile of Xgeva in patients with hypercalcemia of malignancy was similar to that reported in Studies 20050136, 20050244, 20050103, 20062004, and

20040215. Adverse reactions occurring in greater than 20% of patients were nausea (30%), dyspnea (27%), decreased appetite (24%), headache (24%), peripheral edema (24%), vomiting (24%), anemia (21%), constipation (21%), and diarrhea (21%). The following adverse reactions of Grade 3 or greater severity related to study therapy were reported on-study: fatigue (3%) and infection (6%). Grade 3 laboratory abnormalities included hypomagnesemia (3%), hypokalemia (3%), and hypophosphatemia (76%) of patients. No deaths on-study were related to Xgeva therapy.

6.2 Postmarketing Experience

The following adverse reactions have been identified during post approval use of Xgeva. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

- Hypocalcemia: Severe symptomatic hypocalcemia, including fatal cases [see *Contraindications (4.1) and Warnings and Precautions (5.3)*].
- Hypercalcemia: Severe symptomatic hypercalcemia following treatment discontinuation can occur [see *Adverse Reactions (6) and Warnings and Precautions (5.6)*].
- Hypersensitivity, including anaphylactic reactions [see *Contraindications (4.2) and Warnings and Precautions (5.2)*].
- Musculoskeletal pain, including severe musculoskeletal pain. Positive re-challenge has been reported.
- Lichenoid drug eruptions (e.g., lichen planus-like reactions).
- Alopecia.

6.3 Immunogenicity

As with all therapeutic proteins, there is potential for immunogenicity. The detection of antibody formation is highly dependent on the sensitivity and specificity of the assay. Additionally, the observed incidence of antibody (including neutralizing antibody) positivity in an assay 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 the incidence of antibodies to denosumab in the studies described below with the incidence of antibodies to other studies or to other products may be misleading.

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 against denosumab. None of the 37 patients with giant cell tumor of bone in Study 20040215 tested positive for binding antibodies against denosumab. Three of the 506 patients with giant cell tumor of bone in Study 20062004 tested positive for transient binding antibodies following treatment with denosumab. In multiple myeloma patients in Study 20090482, 1 out of 199 patients with a post-baseline result, tested positive for binding antibodies against denosumab. 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 to denosumab associated with binding antibody development.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Based on findings in animals and its mechanism of action, Xgeva can cause fetal harm when administered to a pregnant woman [see *Clinical Pharmacology (12.1)*]. There are insufficient data with denosumab use in pregnant women to inform any drug associated risks for adverse developmental outcomes. *In utero* denosumab exposure from cynomolgus monkeys dosed monthly with denosumab throughout pregnancy at a dose 25-fold higher than the recommended human dose of Xgeva based on body weight resulted in increased fetal loss, stillbirths, and postnatal mortality; and absent lymph nodes, abnormal bone growth, and decreased neonatal growth [see *Data*].

Apprise pregnant women of the potential risk to the fetus.

The background rate of major birth defects and miscarriage is unknown for the indicated population. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively.

Data

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 starting at gestational day 20 and at a pharmacologically active dose 25-fold higher than the recommended human dose of Xgeva based on body weight, 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. 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.

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)*].

8.2 Lactation

Risk Summary

There is no information regarding the presence of Xgeva (denosumab) in human milk, the effects on the breastfed child, or the effects on milk production. Denosumab was

detected in the maternal milk of cynomolgus monkeys up to 1 month after the last dose of denosumab ($\leq 0.5\%$ milk:serum ratio) and maternal mammary gland development was normal, with no impaired lactation. However, pregnant RANKL knockout mice showed altered maturation of the maternal mammary gland, leading to impaired lactation [see *Use in Specific Populations (8.1)* and *Nonclinical Toxicology (13.2)*]. Consider the developmental and health benefits of breastfeeding along with the mother's clinical need for Xgeva treatment and any potential adverse effects on the breastfed child from Xgeva or from the underlying maternal condition.

8.3 Females and Males of Reproductive Potential

Based on findings in animals and its mechanism of action, Xgeva can cause fetal harm when administered to a pregnant woman [see *Use in Specific Populations (8.1)*].

Pregnancy Testing

Verify the pregnancy status of females of reproductive potential prior to initiating Xgeva treatment.

Contraception

Females

Advise females of reproductive potential to use effective contraception during therapy, and for at least 5 months after the last dose of Xgeva.

8.4 Pediatric Use

The safety and efficacy of Xgeva have not been established in pediatric patients except in skeletally mature adolescents (aged 12–16 years) with giant cell tumor of bone. Xgeva is recommended only for treatment of skeletally mature adolescents (aged 12–16 years) with giant cell tumor of bone [see *Indications and Usage (1.2)*]. Clinically significant hypercalcemia after treatment discontinuation has been reported in pediatric patients with growing skeletons who received denosumab for giant cell tumor of bone or for unapproved indications [see *Adverse Reactions (6.2)* and *Warnings and Precautions (5.6)*].

Xgeva was studied in an open-label trial that enrolled a subset of 19 adolescent patients (aged 12–16 years) with giant cell tumor of bone who had reached skeletal maturity, defined by at least 1 mature long bone (e.g., closed epiphyseal growth plate of the humerus), and had a body weight ≥ 45 kg [see *Indications and Usage (1.2)* and *Clinical Trials (14.3)*]. A total of one of five (20%) evaluable adolescent patients had an objective response by retrospective independent assessment of radiographic response according to modified Response Evaluation Criteria in Solid Tumors (RECIST 1.1). The adverse reaction profile and efficacy results appeared to be similar in skeletally mature adolescents and adults [see *Adverse Reactions (6.1)* and *Clinical Trials (14.3)*].

Animal Data

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 the total number of patients in clinical studies that received Xgeva (n = 2841) in Studies 20050136, 20050244, and 20050103, 1271 (44%) were \geq 65 years old, while 473 patients (17%) were \geq 75 years old. Of the 859 patients in Study 20090482 that received Xgeva, 387 patients (45%) were \geq 65 years old, while 141 patients (16%) were \geq 75 years old. No overall differences in safety or efficacy were observed between older and younger patients.

8.6 Renal Impairment

Two clinical trials were conducted in patients without cancer and with varying degrees of renal function.

In one study, patients (N = 55) with varying degrees of renal function (ranging from normal through end-stage renal disease requiring dialysis) received a single 60 mg subcutaneous dose of denosumab. In a second study, patients (N = 32) with severe renal dysfunction (creatinine clearance less than 30 mL/min and/or on dialysis) were given two 120 mg subcutaneous doses of denosumab. In both studies, greater risk of developing hypocalcemia was observed with increasing renal impairment, and with inadequate/no calcium supplementation. Hypocalcemia was mild to moderate in severity in 96% of patients. Monitor calcium levels and calcium and vitamin D intake [see *Warnings and Precautions (5.3)*, *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-dose vial of Xgeva contains 120 mg denosumab, acetate (18 mM), polysorbate 20 (0.01%), sorbitol (4.6%), 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, thereby modulating calcium release from 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 osteolysis and tumor growth. Xgeva prevents RANKL from activating its receptor, RANK, on the surface of osteoclasts, their precursors, and osteoclast-like giant cells.

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 Studies 20050136, 20050244, and 20050103, the median reduction in uNTx/Cr from baseline to Month 3 was approximately 80% in 2075 Xgeva-treated patients.

In a phase 3 study of patients with newly diagnosed multiple myeloma who received subcutaneous doses of Xgeva 120 mg every 4 weeks (Q4W), median reductions in uNTx/Cr of approximately 75% were observed by week 5. Reductions in bone turnover markers were maintained, with median reductions of 74% to 79% for uNTx/Cr from weeks 9 to 49 of continued 120 mg Q4W dosing.

In adult and skeletally mature adolescent patients with giant cell tumor of bone who received subcutaneous doses of Xgeva 120 mg Q4W with a 120 mg loading dose on Days 8 and 15, median reductions in uNTx/Cr from baseline were 84% at Week 13 and 82% at Week 25.

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 once every 4 weeks, up to 2.8-fold accumulation in serum denosumab concentrations was observed and steady-state was achieved by 6 months. A mean (\pm standard deviation) serum steady-state trough concentration of 20.5 (\pm 13.5) mcg/mL was achieved by 6 months. The mean elimination half-life was 28 days.

In patients with newly diagnosed multiple myeloma who received 120 mg every 4 weeks, denosumab concentrations appear to reach steady-state by month 6. In patients with giant cell tumor of bone, after administration of subcutaneous doses of 120 mg once every 4 weeks with additional 120 mg doses on Days 8 and 15 of the first month of therapy, mean (\pm standard deviation) serum trough concentrations on Day 8, 15, and one month after the first dose were 19.0 (\pm 24.1), 31.6 (\pm 27.3), 36.4 (\pm 20.6) mcg/mL, respectively. Steady-state was achieved in 3 months after initiation of treatment with a mean serum trough concentration of 23.4 (\pm 12.1) mcg/mL.

Special Populations

Body Weight: 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.

Age, Gender and Race: The pharmacokinetics of denosumab was not affected by age, gender, and race.

Pediatrics: In skeletally-mature adolescent patients (12 to 16 years of age) with giant cell tumor of bone (GCTB) who received 120 mg every 4 weeks with a 120 mg loading dose

on Days 8 and 15, the pharmacokinetics of denosumab were comparable to those observed in adult patients with GCTB.

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

Renal Impairment: In clinical trials of 87 patients with varying degrees of renal dysfunction, including patients on dialysis, the degree of renal impairment had no effect on the pharmacokinetics and pharmacodynamics of denosumab [see *Use in Specific Populations (8.6)*].

Drug Interactions

No formal drug-drug interaction trials have been conducted with Xgeva. There was no evidence that various anticancer treatments affected denosumab systemic exposure and pharmacodynamic effect. 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 and were not altered by concomitant chemotherapy and/or hormone therapy.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

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

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 information on the pharmacodynamic properties of denosumab. RANK/RANKL knockout mice 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). Neonatal RANK/RANKL knockout mice exhibited reduced bone growth and lack of tooth eruption. A corroborative study in 2-week-old rats given the RANKL inhibitor OPG-Fc also 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.

14 CLINICAL TRIALS

14.1 Bone Metastasis from Solid Tumors

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.

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 (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.

Table 2. Efficacy Results for Xgeva Compared to Zoledronic Acid

	Study 20050136 Metastatic Breast Cancer		Study 20050244 Metastatic Solid Tumors or Multiple Myeloma		Study 20050103 Metastatic CRPC^a	
	Xgeva	Zoledronic Acid	Xgeva	Zoledronic Acid	Xgeva	Zoledronic Acid

	N = 1026	N = 1020	N = 886	N = 890	N = 950	N = 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 \geq 21 days after preceding event.

^e Adjusted p-values are presented.

14.2 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).

Table 3. Efficacy Results for Xgeva Compared to Zoledronic Acid

	Study 20090482 Multiple Myeloma	
	Xgeva N = 859	Zoledronic Acid N = 859
First On-study SRE		
Number of Patients who had SREs (%)	376 (43.8)	383 (44.6)
Components of First SRE		
Radiation to Bone	47 (5.5)	62 (7.2)
Pathological Fracture	342 (39.8)	338 (39.3)
Surgery to Bone	37 (4.3)	48 (5.6)
Spinal Cord Compression	6 (0.7)	4 (0.5)
Median Time to SRE (months) (95% CI)	22.8 (14.7, NE ^a)	24 (16.6, 33.3)
Hazard Ratio (95% CI)	0.98 (0.85, 1.14)	

^a NE = not estimable

14.3 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 20040215 (NCT00396279) and Study 20062004 (NCT00680992)] 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 a loading dose on Days 8 and 15 of the first cycle of therapy. Patients who discontinued Xgeva then entered the safety follow-up phase for a minimum of 60 months. Retreatment with Xgeva while in safety follow-up was allowed for patients who initially demonstrated a response to Xgeva (e.g., in the case of recurrent disease).

Study 20040215 was a single-arm, pharmacodynamic, and proof of concept trial conducted in 37 adult patients with unresectable or recurrent giant cell tumor of bone.

Patients were required to have histologically confirmed giant cell tumor of bone and radiologic evidence of measurable disease from a computed tomography (CT) or magnetic resonance imaging (MRI) obtained within 28 days prior to study enrollment. Patients enrolled in Study 20040215 underwent CT or MRI assessment of giant cell tumor of bone at baseline and quarterly during Xgeva treatment.

Study 20062004 was a parallel-cohort, proof of concept, and safety trial conducted in 535 adult or skeletally mature adolescent patients with histologically confirmed giant cell tumor of bone and evidence of measurable active disease. Study 20062004 enrolled 19 patients who were 12-16 years of age [see *Use in Specific Populations (8.4)*]. Patients enrolled into one of three cohorts: Cohort 1 enrolled 268 patients with surgically unsalvageable disease (e.g., sacral or spinal sites of disease, or pulmonary metastases); Cohort 2 enrolled 252 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 15 patients who previously participated in Study 20040215. Patients underwent imaging assessment of disease status at intervals determined by their treating physician.

A retrospective interim analysis concluded by an independent review committee evaluated objective response in 187 patients enrolled and treated in Study 20040215 and Study 20062004 for whom baseline and at least one post-baseline radiographic assessment were available (27 of 37 patients enrolled in Study 20040215 and 160 of 270 patients enrolled in Cohorts 1 and 2 of Study 20062004). The primary efficacy outcome measure was objective response rate using Response Evaluation Criteria in Solid Tumors (RECIST) v 1.1.

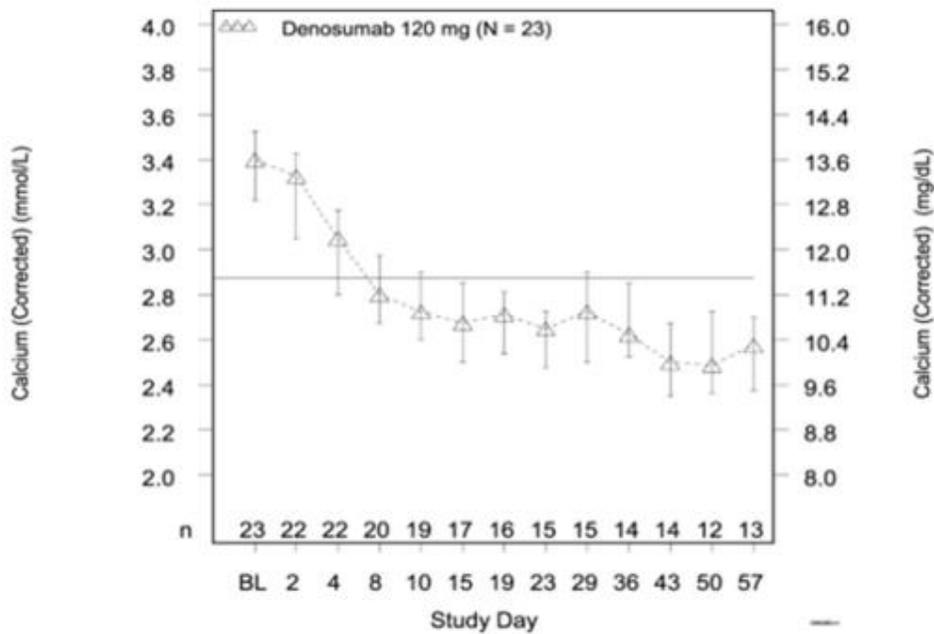
The overall objective response rate (RECIST 1.1) was 25% (95% CI: 19, 32). All responses were partial responses. The estimated median time to response was 3 months. In the 47 patients with an objective response, the median duration of follow-up was 20 months (range: 2-44 months), and 51% (24/47) had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

14.4 Hypercalcemia of Malignancy

The safety and efficacy of Xgeva was demonstrated in an open-label, single-arm trial [Study 20070315 (NCT00896454)] that enrolled 33 patients with hypercalcemia of malignancy (with or without bone metastases) refractory to treatment with intravenous bisphosphonate therapy. Patients received Xgeva subcutaneously every 4 weeks with additional 120 mg doses on Days 8 and 15 of the first month of therapy.

In this trial, refractory hypercalcemia of malignancy was defined as an albumin-corrected calcium of > 12.5 mg/dL (3.1 mmol/L) despite treatment with intravenous bisphosphonate therapy in 7-30 days prior to initiation of Xgeva therapy. The primary outcome measure was the proportion of patients achieving a response, defined as corrected serum calcium (CSC) ≤ 11.5 mg/dL (2.9 mmol/L), within 10 days after Xgeva administration. Efficacy data are summarized in Figure 1 and Table 4. Concurrent chemotherapy did not appear to affect response to Xgeva.

Figure 1. Corrected Serum Calcium by Visit in Responders (Median and Interquartile Range)



N = Number of responders who received ≥ 1 dose of investigational product
n = Number of responders who had no missing data at baseline and the time point of interest

Table 4. Efficacy in Patients with Hypercalcemia of Malignancy Refractory to Bisphosphonate Therapy

	N = 33	Proportion (%) (95% CI)
All Responders (CSC \leq 11.5 mg/dL) by Day 10	21	63.6 (45.1, 79.6)
All Responders by Day 57	23	69.7 (51.3, 84.4)
Complete Responders (CSC \leq 10.8 mg/dL) by Day 10	12	36.4 (20.4, 54.9)
All Complete Responders by Day 57	21	63.6 (45.1, 79.6)

Median time to response (CSC \leq 11.5 mg/dL) was 9 days (95% CI: 8, 19), and the median duration of response was 104 days (95% CI: 7, not estimable). Median time to complete response (CSC \leq 10.8 mg/dL) was 23 days (95% CI: 9, 36), and the median duration of complete response was 34 days (95% CI: 1, 134).

16 HOW SUPPLIED/STORAGE AND HANDLING

Xgeva is supplied in a single-dose vial.

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

Drug Products with Same Active Ingredient

Advise patients that denosumab is also marketed as Prolia, and if taking Xgeva, they should not receive Prolia [see *Warnings and Precautions (5.1)*].

Hypersensitivity

Advise patients to seek prompt medical attention if signs or symptoms of hypersensitivity reactions occur. Advise patients who have had signs or symptoms of systemic hypersensitivity reactions that they should not receive denosumab (Xgeva or Prolia) [see *Warnings and Precautions (5.2)* and *Contraindications (4.2)*].

Hypocalcemia

Adequately supplement patients with calcium and vitamin D and instruct them on the importance of maintaining serum calcium levels while receiving Xgeva [see *Warnings and Precautions (5.3)* and *Use in Specific Populations (8.6)*]. Advise patients to seek prompt medical attention if they develop signs or symptoms of hypocalcemia.

Osteonecrosis of the Jaw

Advise patients to maintain good oral hygiene during treatment with Xgeva and to inform their dentist prior to dental procedures that they are receiving Xgeva. Patients should avoid invasive dental procedures during treatment with Xgeva and inform their healthcare provider or dentist if they experience persistent pain and/or slow healing of the mouth or jaw after dental surgery [see *Warnings and Precautions (5.4)*].

Atypical Subtrochanteric and Diaphyseal Femoral Fracture

Advise patients to report new or unusual thigh, hip, or groin pain [see *Warnings and Precautions (5.5)*].

Hypercalcemia Following Treatment Discontinuation in Patients with Giant Cell Tumor of Bone and in Patients with Growing Skeletons

Advise patients to report nausea, vomiting, headache, and decreased alertness following treatment discontinuation [see *Warnings and Precautions (5.6)* and *Use in Specific Populations (8.4)*].

Multiple Vertebral Fractures (MVF) Following Treatment Discontinuation

Advise patients that after treatment with Xgeva is stopped there may be an increased risk of having broken bones in the spine especially in patients who have had a fracture or who have had osteoporosis. Advise patients not to interrupt Xgeva therapy without their physician's advice [see *Warnings and Precautions (5.7)*].

Embryo-Fetal Toxicity

Advise females of reproductive potential that Xgeva can cause harm to a fetus and to inform their healthcare provider of a known or suspected pregnancy [see *Warnings and*

Precautions (5.8) and Use in Specific Populations (8.1, 8.3)].

Advise females of reproductive potential to use effective contraception during treatment and for at least 5 months after the last dose of Xgeva [see Use in Specific Populations (8.3)].

Xgeva® (denosumab)

Manufactured by:

Amgen Inc.
One Amgen Center Drive
Thousand Oaks, California 91320-1799
U.S. License No. 1080

Patent: <http://pat.amgen.com/xgeva/>

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1xxxxx - v20

PRINCIPAL DISPLAY PANEL - 1.7 mL Vial Carton

AMGEN®

120
mg/1.7mL

XGEVA®
(denosumab)

120 mg/1.7 mL
(70 mg/mL)

Injection

For Subcutaneous Use Only

Single-Dose Vial. Discard Unused Portion.

<p>GTIN: SN: LOT: EXP:</p>	<p>1 x 120 mg Single-Dose Vial NDC 55513-730-01</p>	<p>Sterile Solution – No Preservative Refrigerate at 2° to 8°C (36° to 46°F). Do not freeze. Avoid excessive shaking. Protect from direct light. Manufactured by: Amgen Inc. Thousand Oaks, CA 91320-1799 U.S. License No. 1080 Product of Singapore</p>	
	<p>Each vial contains: 120 mg denosumab, acetate (18 mM), polysorbate 20 (0.01%), sorbitol (4.6%), Water for Injection, USP, and sodium hydroxide to adjust pH to 5.2.</p>	 <p>3 55513 73001 3</p>	 <p>120 mg/1.7mL Injection For Subcutaneous Use Only Single-Dose Vial. Discard Unused Portion.</p>

XGEVA

denosumab injection

Product Information

Product Type	HUMAN PRESCRIPTION DRUG	Item Code (Source)	NDC:55513-730
Route of Administration	SUBCUTANEOUS		

Active Ingredient/Active Moiety

Ingredient Name	Basis of Strength	Strength
DENOSUMAB (UNII: 4EQZ6YO2HI) (DENOSUMAB - UNII:4EQZ6YO2HI)	DENOSUMAB	120 mg in 1.7 mL

Inactive Ingredients

Ingredient Name	Strength
SODIUM ACETATE (UNII: 4550K0SC9B)	1.8 mg in 1.7 mL
POLYSORBATE 20 (UNII: 7T1F30V5YH)	0.17 mg in 1.7 mL
SORBITOL (UNII: 506T60A25R)	78.1 mg in 1.7 mL
WATER (UNII: 059QF0K00R)	
SODIUM HYDROXIDE (UNII: 55X04QC32I)	

Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:55513-730-01	1 in 1 CARTON	11/18/2010	
1		1.7 mL in 1 VIAL, SINGLE-USE; Type 0: Not a Combination Product		

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
BLA	BLA125320	11/18/2010	

Labeler - Amgen Inc (039976196)

Establishment

Name	Address	ID/FEI	Business Operations
Amgen Manufacturing Ltd		785800020	ANALYSIS(55513-730) , MANUFACTURE(55513-730) , PACK(55513-730) , LABEL(55513-730)

Revised: 1/2024

Amgen Inc