Application BLA 125320

This document contains: Label for XGEVA [Supplement 168, Action Date 06/08/2015]

Also available: Label for PROLIA (DENOSUMAB) [Supplement 174, Action Date 04/08/2015]

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----------

- Indications and Usage, Hypercalcemia of Malignancy (1.3) 12/2014
- Dosage and Administration, Important Administration Instructions (2.1) 12/2014
- Dosage and Administration, Hypercalcemia of Malignancy (2.4) 12/2014
- Warnings and Precautions, Hypocalcemia (5.3) xx/2015
- Warnings and Precautions, Osteonecrosis of the Jaw (ONJ) (5.4) xx/2015

---------- 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)
- 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, 14.2)
- Treatment of hypercalcemia of malignancy refractory to bisphosphonate therapy (1.3)

Limitation of use: Xgeva is not indicated for the prevention of skeletal-related events in patients with multiple myeloma

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

- Xgeva is intended for subcutaneous route only and should not be administered intravenously, intramuscularly, or intradermally (2.1)
- 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-use 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)
- Embryo-Fetal Toxicity: Can cause fetal harm. Advise females of reproductive potential of potential risk to the fetus and to use highly effective contraception (5.6, 8.1, 8.7)

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

- Bone Metastasis from Solid Tumors: Most common adverse reactions (per-patient incidence greater than or equal to 25%) were fatigue/asthenia, hypophosphatemia, and nausea (6.1)
- Giant Cell Tumor of Bone: Most common adverse reactions (per-patient incidence greater than or equal to 10%) were arthralgia, headache, nausea, back pain, fatigue, and pain in extremity (6.1)
- Hypercalcemia of Malignancy: Adverse reactions in greater than 20% of patients 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----------

- Nursing mothers: Discontinue drug or nursing taking into consideration importance of drug to mother (8.3)
- 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

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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.

Limitation of Use:
Xgeva is not indicated for the prevention of skeletal-related events in patients with multiple myeloma *[see Clinical Trials (14.1)]*.

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.

1.3 Hypercalcemia of Malignancy

Xgeva is indicated for the treatment of hypercalcemia of malignancy refractory to bisphosphonate therapy *[see Clinical Trials (14.3)]*.

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 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)]*.

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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-use or entry.

3 DOSAGE FORMS AND STRENGTHS

Injection: 120 mg/1.7 mL (70 mg/mL) solution in a single-use 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)]*.

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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. 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 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/minute 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 osseous metastasis, 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.

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 physician should guide the management plan of each patient based on individual risk/benefit assessment.

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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 Embryo-Fetal Toxicity

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) and (8.7)]*.

Advise females of reproductive potential to use highly effective contraception during therapy, and for at least 5 months after the last dose of Xgeva. Apprise the patient of the potential hazard to a fetus if Xgeva is used during pregnancy or if the patient becomes pregnant while patients are exposed to Xgeva. Advise patients to contact their healthcare provider if they become pregnant or a pregnancy is suspected during this time *[see Use in Specific Populations (8.1) and (8.7)]*.

6 ADVERSE REACTIONS

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

- Hypocalcemia *[see Warnings and Precautions (5.3)]*
- Osteonecrosis of the Jaw *[see Warnings and Precautions (5.4)]*

The most common adverse reactions in patients (per-patient 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.

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.

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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 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.

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

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 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 (5.3) 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 Trials 1, 2, and 3, 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 (Trial 1) or prostate (Trial 3) 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 of confirmed ONJ

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was 1.1% during the first year of treatment and 4.1% thereafter. The median time to ONJ was 20.6 months (range: 4–53) *[see Warnings and Precautions (5.4)]*.

Atypical Subtrochanteric and Diaphyseal Fracture
Atypical femoral fracture has been reported with Xgeva *[see Warnings and Precautions (5.5)]*.

Giant Cell Tumor of Bone
The safety of Xgeva was evaluated in two single arm trials (Trials 4 and 5) *[see Clinical Trials (14.2)]* in which a total of 304 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 Trial 5. 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 304 patients who received Xgeva, 145 patients were treated with Xgeva for ≥ 1 year, 44 patients for ≥ 2 years, and 15 patients for ≥ 3 years. The median number of doses received was 14 (range: 1 to 60 doses) and the median number of months on study was 11 (range: 0 to 54 months). Fifty-eight percent of the enrolled patients were women and 80% were White. The median age was 33 years (range: 13 to 83 years); a total of 10 patients were skeletally mature adolescents (13 to 17 years of age).

The adverse reaction profile of Xgeva in patients with giant cell tumor of bone was similar to that reported in Trials 1, 2, and 3. The most common adverse reactions in patients (per-patient incidence ≥ 10%) were arthralgia, headache, nausea, back pain, fatigue, and pain in extremity. The most common serious adverse reactions were osteonecrosis of the jaw and osteomyelitis (per-patient incidence of 0.7%). The most common adverse reactions resulting in discontinuation of Xgeva were osteonecrosis of the jaw (per-patient incidence of 0.7%), and tooth abscess or tooth infection (per-patient incidence of 0.7%). The adverse reaction profile appeared similar in skeletally mature adolescents and adults.

Hypocalcemia and Hypophosphatemia
- Moderate hypocalcemia (corrected serum calcium less than 8 to 7 mg/dL or less than 2 to 1.75 mmol/L) occurred in 2.6% 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 29 patients (9.5%).

Osteonecrosis of the Jaw (ONJ)
In Trials 4 and 5, ONJ was confirmed in 4 of 304 (1.3%) patients who received Xgeva. The median time to ONJ was 16 months (range: 13 to 20 months) *[see Warnings and Precautions (5.4)]*.

Hypercalcemia of Malignancy
Xgeva was evaluated in an open-label, single-arm trial (Trial 6) 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 (14.3)]*.

The adverse reaction profile of Xgeva in patients with hypercalcemia of malignancy was similar to that reported in Trials 1, 2, 3, 4, and 5. 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

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(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 postapproval 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)]*.
- Hypersensitivity, including anaphylactic reactions *[see Contraindications (4.2) and Warnings and Precautions (5.2)]*.
- Musculoskeletal pain, including severe musculoskeletal pain. Positive rechallenge has been reported.

6.3 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 and none of the 304 patients with giant cell tumor of bone in Trials 4 and 5 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.

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.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category D *[see Warnings and Precautions (5.6)]*

<u>Risk Summary</u>
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

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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

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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

The safety and efficacy of Xgeva have not been established in pediatric patients except in skeletally mature adolescents with giant cell tumor of bone. Xgeva is recommended only for treatment of skeletally mature adolescents with giant cell tumor of bone *[see Indications and Usage (1.2)]*.

Xgeva was studied in an open-label trial that enrolled a subset of 10 adolescent patients (aged 13-17 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 (14.2)]*. A total of two of six (33%) 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) criteria. 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 (14.2)]*.

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

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/minute

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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)]*.

8.7 Females and Males of Reproductive Potential

Contraception

Females

Counsel patients on pregnancy planning and prevention. Advise females of reproductive potential to use highly effective contraception during therapy, and for at least 5 months after the last dose of Xgeva. Advise patients to contact their healthcare provider if they become pregnant, or a pregnancy is suspected, during treatment or within 5 months after the last dose of Xgeva *[see Use in Specific Populations (8.1) and Patient Counseling Information (17)]*.

Males

The extent to which denosumab is present in seminal fluid is unknown. There is potential for fetal exposure to denosumab when a male treated with Xgeva has unprotected sexual intercourse with a pregnant partner. Advise males of this potential risk.

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, acetate (18 mM), 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.

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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 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 (± standard deviation) serum steady-state trough concentration of 20.5 (± 13.5) mcg/mL was achieved by 6 months.

With the 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 (± standard deviation) serum trough concentrations on Day 8, 15, and one month after the first dose were 19.0 (± 24.1), 31.6 (± 27.3), 36.4 (± 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 (± 12.1) mcg/mL. The mean elimination half-life was 28 days.

<u>Special Populations</u>
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: The pharmacokinetics of denosumab in pediatric patients has 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 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)]*.

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.

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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

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.

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

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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).

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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.

14.2 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 (Trial 4 and 5) that enrolled patients with histologically confirmed measurable giant cell tumor of bone that was either recurrent, unresectable, or for which planned surgery was likely to result in severe morbidity. Patients received 120 mg Xgeva subcutaneously every 4 weeks with additional doses on Days 8 and 15 of the first cycle of therapy.

Trial 4 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

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enrollment. Patients enrolled in Trial 4 underwent CT or MRI assessment of giant cell tumor of bone at baseline and quarterly during Xgeva treatment.

Trial 5 was a parallel-cohort, proof of concept, and safety trial conducted in 282 adult or skeletally mature adolescent patients with histologically confirmed giant cell tumor of bone and evidence of measurable active disease. Trial 5 enrolled 10 patients who were 13 – 17 years of age *[see Use in Specific Populations (8.4)]*. Patients enrolled into one of three cohorts: Cohort 1 enrolled 170 patients with surgically unsalvageable disease (e.g., sacral or spinal sites of disease, or pulmonary metastases); Cohort 2 enrolled 101 patients with surgically salvageable disease where the investigator determined that the planned surgery was likely to result in severe morbidity (e.g., joint resection, limb amputation, or hemipelvectomy); Cohort 3 enrolled 11 patients who previously participated in Trial 4. Patients underwent imaging assessment of disease status at intervals determined by their treating physician.

An independent review committee evaluated objective response in 187 patients enrolled and treated in Trials 4 and 5 for whom baseline and at least one post-baseline radiographic assessment were available (27 of 37 patients enrolled in Trial 4 and 160 of 270 patients enrolled in Cohorts 1 and 2 of Trial 5). The primary efficacy outcome measure was objective response rate using modified Response Evaluation Criteria in Solid Tumors (RECIST 1.1).

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

14.3 Hypercalcemia of Malignancy

The safety and efficacy of Xgeva was demonstrated in an open-label, single-arm trial (Trial 6) 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 3. Concurrent chemotherapy did not appear to affect response to Xgeva.

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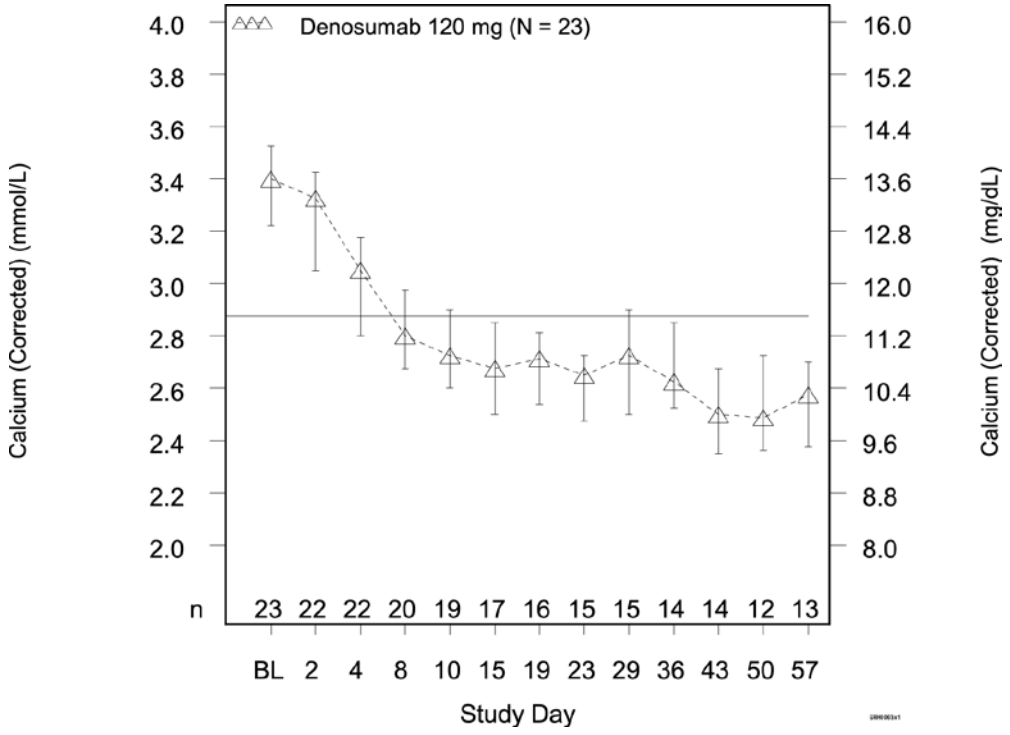
Figure 1: Corrected Serum Calcium by Visit in Responders (Median and Interquartile Range)



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

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Table 3: Efficacy in Patients with Hypercalcemia of Malignancy Refractory to Bisphosphonate Therapy

	N = 33	**Proportion (%) (95% CI)**
All Responders (CSC ≤ 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 ≤ 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 ≤ 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 ≤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-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 a hypersensitivity reaction, including rash, urticaria, pruritus, lip swelling, shortness of breath, hypotension and respiratory tract edema. *[see Contraindications (4.2), Warnings and Precautions (5.2), and Adverse Reactions (6.2)]*
- Symptoms of hypocalcemia, including paresthesias or muscle stiffness, twitching, spasms, or cramps *[see Contraindications (4.1), Warnings and Precautions (5.3), 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 (5.4) and Adverse Reactions (6.1)]*

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- Persistent pain or slow healing of the mouth or jaw after dental surgery *[see Warnings and Precautions (5.4)]*
- Symptoms of atypical femoral fracture, including new or unusual thigh, hip, or groin pain *[see Warnings and Precautions (5.5)]*
- Pregnancy or nursing *[see Warnings and Precautions (5.6) and Use in Specific Populations (8.1, 8.3)]*

Advise patients of the need for:

- Avoiding therapy with Xgeva if a serious allergic reaction occurred with prior Xgeva or Prolia therapy *[see Contraindications (4.2) and Warnings and Precautions (5.2)]*
- Proper oral hygiene and routine dental care
- Informing their dentist that they are receiving Xgeva
- Avoiding invasive dental procedures during treatment with Xgeva
- The use of highly effective contraception during and for at least 5 months after treatment with Xgeva for females of reproductive potential.

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 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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