Prescription only

Xgeva® Injection

(denosumab)

[COMPOSITION]

[Drug Product] 1 vial (1.7 mL) contains

Active Ingredient: denosumab (in-house) ……120 mg

Stabilizing agent: Polysorbate 20 ……0.17 mg

Excipients: Sorbitol, Glacial acetic acid, Sodium hydroxide, Water for injection

[APPEARANCE]

Colorless to slightly yellow, clear to slightly opalescent and practically free from particle injectable solution in vial.

[INDICATIONS]

1. Reduction of the risk for developing skeletal-related events in patients with bone metastases from solid tumors and multiple myeloma.

   Skeletal-related events refers to pathological fractures, radiation to bone, spinal cord compression, and bone surgery.

2. 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.

[DOSAGE AND ADMINISTRATION]

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

1. Multiple Myeloma and Bone Metastasis from Solid Tumors

Administer 1 vial of THIS DRUG (denosumab 120 mg) 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.

2. Giant Cell Tumor of Bone

Administer 1 vial of THIS DRUG (denosumab 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.

Administer calcium and vitamin D as necessary to treat or prevent hypocalcemia.

[PRECAUTIONS FOR USE]

1. Warning

Osteonecrosis of the Jaw (ONJ) has been reported in patients receiving THIS DRUG.

2. Contraindications

1) Patients with hypersensitivity to active ingredient and excipients of THIS DRUG.
2) Patients with severe un-treated hypocalcemia.

3. Adverse Reactions

The following adverse reactions are discussed below and 4. General Cautions in the labeling:

- Hypersensitivity
- Hypocalcemia
- Osteonecrosis of the Jaw (ONJ)
- Atypical Subtrochanteric and Diaphyseal Femoral Fracture
- Hypercalcemia following treatment discontinuation in patients with giant cell tumor of bone and in patients with growing skeletons
- Multiple vertebral fractures (MVF) following treatment discontinuation

1) Clinical Trials Experience

① Bone Metastasis from Solid Tumors

The safety of THIS DRUG was evaluated in three randomized, double-blind, double-dummy trials 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 THIS DRUG. In three trials, patients were randomized to receive either 120 mg of THIS DRUG 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.

The median duration of exposure to THIS DRUG was 12 months (range: 0.1 – 41) and median duration on-study was 13 months (range: 0.1 – 41). Of patients who received THIS DRUG, 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 THIS DRUG 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 THIS DRUG were osteonecrosis and hypocalcemia.

Table 1. Selected[a] Adverse Reactions of Any Severity

Body System	THIS DRUG 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

Body System	THIS DRUG n = 2841 %	Zoledronic Acid n = 2836 %
RESPIRATORY		
Dyspnea	21	18
Cough	15	15

[a] Adverse reactions reported in at least 10% of patients receiving THIS DRUG in three trials for bone metastases from solid tumors, and meeting one of the following criteria:

- At least 1% greater incidence in THIS DRUG-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 (not clinical trial for THIS DRUG, clinical trial for zoledronic acid compared to placebo)

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

Osteonecrosis of the Jaw (ONJ)

In the primary treatment phases of three trials for bone metastasis from solid tumors, ONJ was confirmed in 1.8% of patients in THIS DRUG treatment 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 or prostate cancer included a THIS DRUG open-label extension treatment phase where patients were offered THIS DRUG 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).

In a placebo-controlled clinical trial with an extension treatment phase evaluating THIS DRUG for the prevention of bone metastases in patients with non-metastatic prostate cancer (a patient population for which THIS DRUG 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 THIS DRUG and the risk increased with longer duration of treatment. Events have occurred during treatment and after treatment was discontinued.

② **Multiple Myeloma**

The safety of THIS DRUG 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. In this trial, patients received 120mg THIS DRUG 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, and 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 THIS DRUG was 16 months (range: 1 - 50) and median duration on-study was 17 months (range: 0.0 - 49). Of patients who received THIS DRUG, 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 THIS DRUG was 63 years (range: 29 -91) and all patients who received THIS DRUG received concomitant anti-myeloma chemotherapy.

The adverse reaction profile of THIS DRUG in patients with multiple myeloma was similar to that observed in three trials. The most common adverse reactions (incidence ≥ 10%) were diarrhea (denosumab 34%, zoledronic acid 32%), nausea (32%, 30%), anemia (22%, 21%), back pain (21%, 20%), thrombocytopenia (19%, 16%), peripheral edema (17%, 16%), hypocalcemia (16%, 12%), upper respiratory tract infection (15%, 13%), rash (14%, 11%), and headache (11%, 9%). The most frequently reported serious adverse events (more than 2% in either treatment group) was pneumonia (denosumab 8.4%, zoledronic acid 8.1%),

plasma cell myeloma (2.8%, 3.1%), pyrexia (2.6%, 2.5%), febrile neutropenia (2.5%, 2.7%), and acute kidney injury (2.0%, 2.5%), sepsis (1.9%, 2.5%), and anemia (1.1%, 2.8%). No events were reported with a difference of more than 2% between treatment groups. The most common adverse reaction resulting in discontinuation of THIS DRUG (more than 1%) 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 THIS DRUG, respectively.

Osteonecrosis of the Jaw (ONJ)

In the primary treatment phase of the trial, ONJ was confirmed in 4.1% of patients in the THIS DRUG group (median exposure of 16 months; range: 1 – 50) and 2.8% of patients in zoledronic acid group (median exposure of 15 months; range: 1 – 45). At the completion of the double-blind treatment phase of the trial, the patient-year adjusted incidence (number of events per 100 patient years) of confirmed ONJ in the THIS DRUG 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).

③ Giant Cell Tumor of Bone

The safety of THIS DRUG was evaluated in two single arm trials in which a total of 548 adult or skeletally mature adolescent patients with giant cell tumor of bone received at least 1 dose of THIS DRUG. Patients received 120 mg THIS DRUG 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 one trial. 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 THIS DRUG, 467 patients were treated with THIS DRUG 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 to 140 months). Fifty-seven percent of the enrolled patients were women and 82% were White. The median age was 33 years (range: 13 to 83 years); a total of 19 patients were skeletally mature adolescents (12 to 17 years of age).

The common adverse event profile of THIS DRUG in patients with giant cell tumor of bone was generally similar to that reported in three trials for bone metastases from solid tumors. The most common adverse events in patients (incidence ≥ 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 events 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 events resulting in discontinuation of THIS DRUG 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 THIS DRUG.
- Severe hypophosphatemia (serum phosphorus less than 1 to 2 mg/dL or less than 0.3 to 0.6 mmol/L) occurred in 20% of patients treated with THIS DRUG.

Osteonecrosis of the Jaw (ONJ)

In two trials with giant cell tumor of bone, ONJ was confirmed in 6.6% of patients who received THIS DRUG.

Atypical Subtrochanteric and Diaphyseal Fracture

Atypical femoral fracture has been reported with THIS DRUG and was observed in 0.9% of patients in the pooled safety population.

④ **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.

2) Postmarketing Experience

The following adverse reactions have been identified during post-approval use of THIS DRUG.

- Hypocalcemia: Severe symptomatic hypocalcemia, including fatal cases.
- Hypercalcemia: Severe symptomatic hypercalcemia following treatment discontinuation can occur.
- Hypersensitivity, including anaphylactic reactions.
- Musculoskeletal pain, including severe musculoskeletal pain. Positive re-challenge has been reported.

- Lichenoid drug eruptions (e.g., lichen planus-like reactions)
- Alopecia

3) Immunogenicity

As with all therapeutic proteins, there is potential for immunogenicity. Less than 1% (7/2758) of patients with osseous metastases treated with THIS DRUG doses ranging from 30 – 180 mg every 4 weeks or every 12 weeks for up to 3 years tested positive for binding antibodies against THIS DRUG. None of the 37 patients with giant cell tumor of bone in one clinical trial tested positivie for binding antibodies against THIS DRUG. Three of the 506 patients with giant cell tumor of bone in another clinical trials tested positive for transient binding antibodies following treatment with THIS DRUG. In multiple myeloma patients, 1 out of 199 patients with a post baseline result, tested positive for binding antibodies against THIS DRUG. No patient with positive binding antibodies tested positive for neutralizing antibodies. There was no evidence of altered pharmacokinetic profile, toxicity profile, or clinical response to THIS DRUG associated with binding antibody development.

4) Postmarketing surveillance results in Korea

As result of postmarketing surveillance conducted for re-evaluation with 316 patients for 6 years in Korea, incidence of adverse events is reported as 37.3% (118/316 patients, total 267 cases), regardless of causal relationship. Out of these, serious adverse reactions for which a causal relationship cannot be ruled out and unexpected adverse reactions for which a causal relationship cannot be ruled out are listed in the table below, depending on the frequency of occurrence.

		Serious adverse drug reactions 0.3% (1/316 patients, 1 case)	Unexpected adverse drug reactions 3.2% (10/316 patients, 11 case)
Sometimes (0.1 to less than 5%)	General disorders and administration site	Pyrexia	Chill, pain
	Musculoskeletal and connective tissue disorders	-	Musculoskeletal chest pain, pain in jaw, myalgia
	Skin and subcutaneous tissue disorders	-	Urticaria
	Various gastrointestinal disorders	-	Gum discomfort
	Various mental disorder	-	Anxiety

4. General Cautions

1) Drug Products with Same Active Ingredient

THIS DRUG includes the same active ingredient (denosumab) found in Prolia pre-filled syringes. Patients receiving THIS DRUG should not take Prolia pre-filled syringes.

2) Hypersensitivity

Clinically significant hypersensitivity including anaphylaxis has been reported with use of THIS DRUG. 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 THIS DRUG therapy permanently.

3) Hypocalcemia

THIS DRUG can cause severe symptomatic hypocalcemia, and fatal cases have been reported. Correct pre-existing hypocalcemia prior to THIS DRUG treatment. Monitor calcium levels, throughout THIS DRUG therapy, especially in the first weeks of initiating therapy, and administer calcium, magnesium, and vitamin D as necessary. Monitor levels more frequently when THIS DRUG is administered with other drugs that can also lower calcium levels. Advise patients to contact a healthcare provider for symptoms of hypocalcemia.

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.

4) Osteonecrosis of the Jaw (ONJ)

Osteonecrosis of the jaw (ONJ) has been reported in patients receiving THIS DRUG, 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. 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 THIS DRUG 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 THIS DRUG and periodically during THIS DRUG therapy. Advise patients regarding oral hygiene practices. Avoid invasive dental procedures during treatment with THIS DRUG.

Good oral hygiene practices should be maintained during treatment with THIS DRUG. Consider temporary discontinuation of THIS DRUG 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 THIS DRUG 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) Atypical Subtrochanteric and Diaphyseal Femoral Fracture

Atypical femoral fracture has been reported with THIS DRUG. 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 THIS DRUG 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 THIS DRUG therapy should be considered, pending a risk/benefit assessment, on an individual basis.

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 THIS DRUG-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.

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 THIS DRUG treatment is discontinued, evaluate the individual patient's risk for vertebral fractures.

5. Drug-Drug Interactions

1) No formal drug-drug interaction trials have been conducted with THIS DRUG.
2) 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.

6. Use in Pregnancy and Nursing Mothers

1) Pregnancy

There are no adequate and well-controlled studies with THIS DRUG in pregnant women.

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. 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 THIS DRUG based 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.

Based on finding in animals and its mechanism of action, THIS DRUG can cause fetal harm when administered to a pregnant woman. 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.

2) Lactation

There is no information regarding the presence of THIS DRUG 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 (≤ 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. Because of the potential for serious adverse reactions in nursing infants from THIS DRUG, a decision should be made whether to discontinue nursing or discontinue the drug, taking into account the importance of the drug to the mother.

3) Females and Males of Reproductive Potential

Based on finding in animals and its mechanism of action, THIS DRUG can cause fetal harm when administered to a pregnant woman.

Verify the pregnancy status of females of reproductive potential prior to initiating THIS DRUG treatment. Advise pregnant women and females of reproductive potential that exposure to THIS DRUG during pregnancy or within 5 months prior to conception can result in fetal harm. In addition, advise females of reproductive potential to use effective contraception during therapy, and for at least 5 months after the last dose of THIS DRUG.

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 THIS DRUG has unprotected sexual intercourse with a pregnant partner. Advise males of this potential risk.

7. Pediatric Use

The safety and efficacy of THIS DRUG have not been established in pediatric patients except in skeletally mature adolescents (aged 12-16 years) with giant cell tumor of bone. THIS DRUG is recommended only for treatment of skeletally mature adolescents (aged 12-16 years) with giant cell tumor of bone. 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.

THIS DRUG 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. The adverse reaction profile and efficacy results appeared to be similar in skeletally mature adolescents and adults.

Animal Data

Treatment with THIS DRUG 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 THIS DRUG 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 THIS DRUG.

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.

8. Geriatric Use

Of the total number of patients in clinical studies that received THIS DRUG (n=2841) in three clinical trials, 1271 (44%) were ≥ 65 years old, while 473 patients (17%) were ≥ 75 years old. Of the 859 patients in multiple myeloma trial that received THIS DRUG, 387 patients (45%) were ≥ 65 years old, while 141 patients (16%) were ≥ 75 years old. No overall differences in safety or efficacy were observed between older and younger patients.

9. 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.

10. Overdosage

There is no experience with overdosage of THIS DRUG.

11. Cautions in Administration

1) Visually inspect THIS DRUG for particulate matter and discoloration prior to administration. THIS DRUG 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.
2) Prior to administration, THIS DRUG may be removed from the refrigerator and brought to room temperature (up to 25°C) by standing in the original container. This generally takes 15 to 30 minutes. Do not warm THIS DRUG in any other way.
3) 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.
4) This is supplied in a single-use vial.

12. Cautions for Storage and Handling

1) Store THIS DRUG in a refrigerator at 2°C to 8°C in the original carton. Do not freeze.
2) Once removed from the refrigerator, THIS DRUG must not be exposed to temperatures above 25°C or direct light and must be used within 14 days. Discard THIS DRUG if not used within the 14 days. Do not use THIS DRUG after the expiry date printed on the label.
3) Protect THIS DRUG from direct light and heat.
4) Avoid vigorous shaking of THIS DRUG.

[STORAGE CONDITION]

Hermetic container, store in refrigerator (2°C to 8°C) and protect from light

[PACKAGING UNIT]

1 × vial (1.7 mL)/Box

[EXPIRY DATE]

Refer to the outer package (YY/MM/DD)

[PRODUCT LICENSE HOLDER]

Amgen Inc.

One Amgen Center Drive, Thousand Oaks, CA 91320, USA

[MANUFACTURER]

1) Drug Substance

Amgen Singapore Manufacturing Pte. Ltd (ASM)

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2) Drug Product, Packaging and Labeling

Amgen Manufacturing Limited (AML)

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[IMPORTER]

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- If products are decomposed, deteriorated, damaged, contaminated or expired, they can be exchanged at the pharmacy, clinic, hospital, or wholesaler where purchased. Please contact the facility where you bought the product for return or exchange.
- You will be compensated for consumers' damages as per the Consumer Injury Compensation Rule.
- Relief of injury from adverse drug reaction: Korea Institute of Drug Safety & Risk Management (Tel: 1644-6223, www.drugsafe.or.kr)
- You can find the latest product information after the following revision date on the MFDS medicines integrated information system (http://nedrug.mfds.go.kr) or the Amgen Korea Limited website (www.amgen.co.kr).
- Amgen Korea Limited contact phone: 00798 611 3554 (toll free) / 02-3434-4899 / medinfo.JAPAC@amgen.com

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