PRODUCT MONOGRAPH

PrXGEVA®

(denosumab)

120 mg/1.7 mL solution for injection
Single-use Vial

Professed Standard

RANK Ligand Inhibitor
(Bone Metabolism Regulator)

Amgen Canada Inc.
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Mississauga, Ontario
L5N 0A4

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PrXGEVA®

(denosumab)

PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	Clinically Relevant Nonmedicinal Ingredients
Subcutaneous	120 mg denosumab in 1.7 mL solution in a single-use vial	Sorbitol, acetate, water for injection (USP) and sodium hydroxide *For a complete listing see Dosage Forms, Composition and Packaging section.*

DESCRIPTION

XGEVA (denosumab) is a fully human IgG2 monoclonal antibody with high affinity and specificity for human RANK Ligand (RANKL). Binding of XGEVA to RANKL inhibits RANKL from activating its only receptor, RANK, on the surface of osteoclasts and their precursors. Increased osteoclast activity, stimulated by RANKL, is a key mediator of bone disease in metastatic tumours and multiple myeloma. Prevention of RANKL-RANK interaction inhibits osteoclast formation, function and survival, thereby decreasing bone resorption and interrupting cancer-induced bone destruction. 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, colourless to slightly yellow solution formulated at pH 5.2. XGEVA is supplied as a single-use vial containing a deliverable dose of 120 mg denosumab.

INDICATIONS AND CLINICAL USE

- XGEVA (denosumab) is indicated for reducing the risk of developing skeletal-related events in patients with bone metastases from breast cancer, prostate cancer, non-small cell lung cancer, and other solid tumours.

  XGEVA is not indicated for reducing the risk of developing skeletal-related events in patients with multiple myeloma (see **CLINICAL TRIALS**).

- XGEVA is indicated for the treatment of adults and skeletally mature adolescents with giant cell tumour of bone that is unresectable or where surgical resection is likely to result in severe morbidity (see **CLINICAL TRIALS**).
- XGEVA is indicated for the treatment of hypercalcemia of malignancy that is refractory to intravenous bisphosphonate (see **CLINICAL TRIALS**).

Geriatrics (≥ 65 years of age)

Of the total number of patients in the pivotal clinical studies in patients with advanced cancer, 1260 patients (44.4%) treated with XGEVA, were ≥ 65 years old. No overall differences in safety or efficacy were observed between these patients and younger patients.

Pediatrics

The safety and efficacy of XGEVA have not been studied in pediatric populations other than skeletally mature adolescents (aged 13-17 years) with giant cell tumour of bone (GCTB). XGEVA is not indicated for use in pediatric patients other than skeletally mature adolescents with GCTB (see **WARNINGS AND PRECAUTIONS, Special Populations, Pediatrics**).

CONTRAINDICATIONS

Patients who are hypersensitive to this drug or to any ingredient in the formulation or component of the container. For a complete listing, see the **DOSAGE FORMS, COMPOSITION AND PACKAGING** section of the product monograph. Anaphylactic reactions have been reported (see **WARNINGS AND PRECAUTIONS**, **Hypersensitivity** and **ADVERSE REACTIONS, Postmarket Adverse Drug Reactions**).

Pre-existing hypocalcemia must be corrected prior to initiating therapy with XGEVA (see **WARNINGS AND PRECAUTIONS, Endocrine and Metabolism, Hypocalcemia**).

WARNINGS AND PRECAUTIONS

Osteonecrosis of the jaw (ONJ) (see **WARNINGS AND PRECAUTIONS, Other,** and **ADVERSE REACTIONS**)

General

XGEVA (denosumab) contains the same active ingredient as found in PROLIA®. Patients being treated with XGEVA should not be treated concomitantly with PROLIA.

Patients being treated with XGEVA should not be treated concomitantly with bisphosphonates.

Endocrine and Metabolism

Hypocalcemia

XGEVA can cause severe symptomatic hypocalcemia and fatal cases have been reported. Signs and symptoms of severe hypocalcemia may include, for example, altered mental status, tetany, seizures and QTc prolongation. Pre-existing hypocalcemia must be corrected prior to initiating therapy with XGEVA. Monitor calcium levels, (i) prior to the initial dose of XGEVA, (ii) within two weeks after the initial dose, and (iii) if suspected symptoms of hypocalcemia occur. Administer adequate calcium and vitamin D, and magnesium, as necessary. Additional monitoring should be considered during therapy in patients with risk factors for hypocalcemia, or if otherwise indicated based on the clinical condition of the patient. Monitor levels more frequently when XGEVA is administered with other drugs that can also lower calcium levels. If hypocalcemia occurs while receiving XGEVA, additional short-term calcium supplementation

and additional monitoring may be necessary (see **DOSAGE AND ADMINISTRATION,** and **ADVERSE REACTIONS, Hypocalcemia** and **Postmarketed Adverse Drug Reactions**).

An increased risk of hypocalcemia has been observed in patients with increasing degree of renal impairment. Patients with severe renal impairment (creatinine clearance less than 30 mL/min and/or receiving dialysis), are at a greater risk of developing hypocalcemia which is accompanied by an elevation in parathyroid hormone levels. Absence of calcium supplementation also plays a role in the increased risk of hypocalcemia development in patients with renal impairment. More frequent monitoring of calcium levels in these patients, within two weeks after administration of XGEVA, is especially important. If hypocalcemia occurs, administer adequate calcium, vitamin D, and magnesium, as necessary (see **Special Populations, Renal Impairment and ADVERSE REACTIONS**).

No dose adjustment is necessary in patients with renal impairment and there is no additional need for more frequent renal monitoring due to XGEVA administration (see **Special Populations, Renal Impairment**).

Hypercalcemia Following Treatment Discontinuation in Patients with Growing Skeletons

Clinically significant hypercalcemia has been reported in XGEVA-treated patients with growing skeletons weeks to months following treatment discontinuation. Monitor patients for signs and symptoms of hypercalcemia and treat appropriately (see **ADVERSE REACTIONS**).

Dermatologic

Skin Infections

An imbalance of skin infections leading to hospitalization was reported in a single placebo-controlled study of postmenopausal women with osteoporosis treated with denosumab 60 mg every 6 months (PROLIA 0.4%, placebo < 0.1%). These cases were predominantly cellulitis. In clinical trials in patients with advanced cancer treated with XGEVA or zoledronic acid, skin infections leading to hospitalization were reported more frequently in the XGEVA group (0.9%) compared with the zoledronic acid group (0.7%). Patients should be advised to seek prompt medical attention if they develop signs or symptoms of cellulitis.

Hypersensitivity

Clinically significant hypersensitivity reactions including anaphylaxis have been reported with XGEVA. Symptoms have included hypotension, dyspnea, throat tightness, facial and upper airway edema, pruritus, and urticaria.

If an anaphylactic or other clinically significant allergic reaction occurs, initiate appropriate treatment immediately and discontinue further use of XGEVA (see **CONTRAINDICATIONS and ADVERSE REACTIONS**).

Other

Osteonecrosis of the Jaw (ONJ)

ONJ has been reported in patients treated with denosumab or bisphosphonates, another class of anti-resorptive agents. ONJ can manifest 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, the incidence of ONJ was higher with longer duration of exposure (see **ADVERSE REACTIONS**). ONJ has also been diagnosed after treatment with XGEVA with the majority of cases occurring within 5 months after the last dose.

Poor oral hygiene, invasive dental procedures (e.g., tooth extraction, dental implants, oral surgery), treatment with anti-angiogenic medication, local gum or oral infection were risk factors for ONJ in patients receiving XGEVA in clinical trials. Other risk factors for ONJ include infections, older age, concomitant therapies (e.g., chemotherapy, corticosteroids, radiotherapy to the head and neck), smoking and previous treatment with bisphosphonates. In patients with risk factors for ONJ, an individual benefit-risk assessment should be performed before initiating therapy for XGEVA.

An oral exam should be performed by the prescriber prior to initiation of XGEVA treatment and a dental examination with appropriate preventive dentistry is recommended prior to treatment with XGEVA, especially in patients with risk factors for ONJ. Good oral hygiene practices should be maintained during treatment with XGEVA. Patients should receive routine dental check-ups, and immediately report any oral symptoms such as dental mobility, pain or swelling during treatment with XGEVA.

While on treatment, patients should avoid invasive dental procedures. For patients in whom invasive dental procedures cannot be avoided, the clinical judgment of the treating physician should guide the management plan of each patient based on individual benefit/risk assessment.

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. In patients who develop ONJ during treatment with XGEVA, a temporary interruption of treatment should be considered based on individual risk/benefit assessment until the condition resolves.

Atypical Femoral Fractures

Atypical femoral fracture has been reported with XGEVA. Atypical femoral fractures may occur with little or no trauma in the subtrochanteric and diaphyseal regions of the femur and may be bilateral. Specific radiographic findings characterize these events. Atypical femoral fractures have also been reported in patients with certain comorbid conditions (eg, vitamin D deficiency, rheumatoid arthiritis, hypophosphatasia) and with use of certain pharmaceutical agents (eg, bisphosphonates, glucocorticoids, proton pump inhibitors). These events have also occurred without antiresorptive therapy. During XGEVA treatment, patients should be advised to report new or unusual thigh, hip, or groin pain. Patients presenting with such symptoms should be evaluated for an incomplete femoral fracture, and the contralateral femur should also be examined.

Special Populations

Pregnant Women

The safety and efficacy of XGEVA in pregnant women have not been established.

Denosumab is not recommended for use in pregnant women.

At AUC exposures up to 16-fold higher than the human exposure (120 mg every 4 weeks), denosumab showed no evidence of impaired fertility in female cynomolgus monkeys.

In a study of cynomolgus monkeys dosed with denosumab during the period equivalent to the first trimester at AUC exposures up to 10-fold higher than the human dose (120 mg every 4 weeks), there was no evidence of maternal or fetal harm. In this study, fetal lymph nodes were not examined.

In another study, in utero denosumab exposure in cynomolgus monkeys at 50 mg/kg body weight every 4 weeks, from gestation day 20 through to parturition resulted in increased fetal loss, stillbirths and postnatal mortality. Findings in the infants included skeletal abnormalities resulting from impaired bone resorption during rapid growth, reduced bone strength and treatment-related bone fractures; reduced hematopoiesis; tooth malalignment and dental dysplasia (in the absence of adverse effects on tooth eruption); absence of peripheral lymph nodes; and decreased neonatal growth. There was no evidence of maternal toxicity. Maternal mammary gland development was normal.

In genetically engineered mice in which the gene for RANK ligand (RANKL) has been deleted (a "knockout mouse"), the absence of RANKL caused fetal lymph node agenesis and led to postnatal impairment of dentition and bone growth. Pregnant RANKL knockout mice also showed altered maturation of the maternal mammary gland, leading to impaired lactation postpartum (see **PART II, TOXICOLOGY**).

Women should be advised not to become pregnant during XGEVA therapy. Advise females of reproductive potential to use highly effective contraception during therapy, and for at least 5 months after the last dose of XGEVA.

Nursing Women

It is not known whether XGEVA is excreted into human milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from XGEVA, a decision should be made whether to discontinue nursing or discontinue the drug, taking into account the importance of the drug to the mother.

Maternal exposure to XGEVA during pregnancy may impair mammary gland development and lactation based on animal studies in pregnant mice lacking the RANK/RANKL signaling pathway which showed altered maturation of the maternal mammary gland, leading to impaired lactation postpartum (see **PART II, TOXICOLOGY**).

Pediatrics

The safety and efficacy of XGEVA have not been established in pediatric patients other than skeletally mature adolescents with GCTB.

XGEVA is not recommended for use in pediatric patients other than skeletally mature adolescents with GCTB.

XGEVA was studied in a Phase 2 open-label trial that enrolled a subset of 10 adolescent patients (aged 13-17 years) with GCTB who had reached skeletal maturity defined by at least 1 mature long bone (eg, closed epiphyseal growth plate of the humerus) and body weight ≥ 45 kg *(*see

INDICATIONS AND CLINICAL USE and **CLINICAL TRIALS**). The adverse reaction profile appeared similar in skeletally mature adolescents and adults.

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 (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 monkeys dosed with denosumab at 15 times (50 mg/kg dose) and 2.8 times (10 mg/kg dose) the area under the curve (AUC) exposure in adult humans dosed at 120 mg subcutaneously every 4 weeks had abnormal growth plates, considered to be consistent with the pharmacological activity of denosumab. In neonatal cynomolgus monkeys exposed in utero to denosumab at 50 mg/kg, there was increased postnatal mortality; skeletal abnormalities resulting from impaired bone resorption during rapid growth, reduced bone strength and treatment-related bone fractures; reduced hematopoiesis; tooth malalignment and dental dysplasia (in the absence of adverse effects on tooth eruption); absence of peripheral lymph nodes; and decreased neonatal growth. Following a recovery period from birth out to 6 months of age, findings still observed were mildly reduced bone length (femoral, vertebral, jaw), reduced cortical thickness with associated reduced strength; extramedullary hematopoiesis; dental dysplasia; and the absence or decreased size of some lymph nodes. One infant had minimal to moderate mineralization in multiple tissues. (see **PART II, TOXICOLOGY)**

Geriatrics (≥ 65 years of age)

Of the total number of patients in the pivotal clinical studies in patients with advanced cancer, 1260 patients (44.4%) treated with XGEVA were ≥ 65 years old. No overall differences in safety or efficacy were observed between these patients and younger patients.

Renal Impairment

Two clinical trials were conducted in subjects without cancer and with varying degrees of renal function. In one study, subjects (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 impairment (creatinine clearance less than 30 mL/minute and/or on dialysis) were given two 120 mg subcutaneous doses of denosumab. In both studies, there was a greater risk of developing hypocalcemia with increasing degree of renal impairment, and in the absence of, or inadequate calcium supplementation. The development of hypocalcemia in patients with severe renal impairment (creatinine clearance less than 30 mL/min and/or receiving dialysis) was accompanied by an elevation in parathyroid hormone levels.

No dose adjustment is necessary in patients with renal impairment and there is no additional need for more frequent renal monitoring due to XGEVA administration. Adequate intake of calcium and vitamin D is important in patients with severe renal impairment or receiving dialysis (see **WARNINGS AND PRECAUTIONS, ADVERSE REACTIONS,** and **ACTION AND CLINICAL PHARMACOLOGY**).

Hepatic Impairment

No clinical studies have been conducted to evaluate the effect of hepatic impairment on the pharmacokinetics of XGEVA.

Monitoring and Laboratory Tests

Monitor calcium levels, (i) prior to the initial dose of XGEVA, (ii) within two weeks after the initial dose, and (iii) if suspected symptoms of hypocalcemia occur. Additional monitoring should be considered during therapy in patients with risk factors for hypocalcemia, or if otherwise indicated based on the clinical condition of the patient. Calcium levels should be monitored more frequently when XGEVA is administered with other drugs that can also lower calcium levels. (See **WARNINGS AND PRECAUTIONS, Endocrine and Metabolism, Hypocalcemia**)

ADVERSE REACTIONS

Adverse Drug Reaction Overview

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

- Hypocalcemia (see **WARNINGS AND PRECAUTIONS, Endocrine and Metabolism, Hypocalcemia**)
- Osteonecrosis of the jaw [see **WARNINGS AND PRECAUTIONS, Other, Osteonecrosis of the Jaw (ONJ)**]

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

The most common serious adverse reaction in patients with bone metastasis from solid tumours receiving XGEVA was dyspnea.

The most common adverse reactions in patients with bone metastasis from solid tumours resulting in discontinuation of XGEVA were osteonecrosis and hypocalcemia.

The most common adverse reactions in patients with GCTB receiving XGEVA (per-patient incidence greater than or equal to 10%) were arthralgia, headache, nausea, fatigue, back pain, and pain in extremity.

The most common serious adverse reactions in patients with GCTB receiving XGEVA were osteonecrosis of the jaw and osteomyelitis (per-patient incidence of 0.7%).

The most common adverse reactions in patients with GCTB receiving XGEVA 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%).

Clinical Trial Adverse Drug Reactions

Because clinical trials are conducted under very specific conditions the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse drug reaction information

from clinical trials is useful for identifying drug-related adverse events and for approximating rates.

Bone Metastasis from Solid Tumours

The safety of XGEVA was evaluated in three randomized, double-blind, double-dummy trials (see **CLINICAL TRIALS**) in which a total of 2841 patients with bone metastasis from prostate cancer, breast cancer, or other solid tumours, or lytic bony lesions from multiple myeloma received at least one dose of XGEVA. In Studies 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.

The adverse events occurring during the studies were generally of a type and frequency expected in patients with cancer and bone metastases, many of whom were undergoing antineoplastic therapy. Table 1 describes adverse events occurring in ≥ 1% of patients in these studies.

Table 1. Percentage of Patients with Adverse Events ≥ 1% Reported in Patients with Advanced Malignancies Involving Bone by System Organ Class

SYSTEM ORGAN CLASS Preferred Term	Denosumab (N = 2841) n (%)	Zoledronic Acid (N = 2836) n (%)
BLOOD AND LYMPHATIC SYSTEM DISORDERS		
Anemia	771 (27.1)	859 (30.3)
Neutropenia	277 (9.8)	278 (9.8)
Thrombocytopenia	216 (7.6)	199 (7.0)
Leukopenia	165 (5.8)	177 (6.2)
Febrile neutropenia	58 (2.0)	72 (2.5)
Pancytopenia	29 (1.0)	34 (1.2)
CARDIAC DISORDERS		
Tachycardia	79 (2.8)	74 (2.6)
Cardiac failure	49 (1.7)	51 (1.8)
Atrial fibrillation	43 (1.5)	38 (1.3)
Palpitations	30 (1.1)	25 (0.9)
EAR AND LABYRINTH DISORDERS		
Vertigo	62 (2.2)	85 (3.0)
EYE DISORDERS		
Lacrimation increased	59 (2.1)	46 (1.6)
Vision blurred	53 (1.9)	48 (1.7)
Conjunctivitis	31 (1.1)	37 (1.3)
GASTROINTESTINAL DISORDERS		
Nausea	876 (30.8)	895 (31.6)
Constipation	603 (21.2)	670 (23.6)
Diarrhea	577 (20.3)	530 (18.7)
Vomiting	566 (19.9)	570 (20.1)
Abdominal pain	292 (10.3)	280 (9.9)
Abdominal pain upper	167 (5.9)	164 (5.8)
Stomatitis	146 (5.1)	115 (4.1)
Dyspepsia	132 (4.6)	147 (5.2)
Toothache	108 (3.8)	80 (2.8)
Ascites	68 (2.4)	53 (1.9)
Dysphagia	66 (2.3)	63 (2.2)
Abdominal distension	56 (2.0)	47 (1.7)
Dry mouth	53 (1.9)	57 (2.0)
Gastritis	51 (1.8)	59 (2.1)
Hemorrhoids	50 (1.8)	52 (1.8)
Gastroesophageal reflux disease	49 (1.7)	50 (1.8)
Flatulence	42 (1.5)	38 (1.3)
Gingival pain	36 (1.3)	29 (1.0)

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SYSTEM ORGAN CLASS Preferred Term	Denosumab (N = 2841) n (%)	Zoledronic Acid (N = 2836) n (%)
Rectal hemorrhage	32 (1.1)	37 (1.3)
Abdominal discomfort	30 (1.1)	26 (0.9)
Gingivitis	30 (1.1)	26 (0.9)
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS		
Fatigue	769 (27.1)	766 (27.0)
Asthenia	607 (21.4)	621 (21.9)
Edema peripheral	472 (16.6)	462 (16.3)
Pyrexia	409 (14.4)	562 (19.8)
Chest pain	263 (9.3)	247 (8.7)
Pain	222 (7.8)	243 (8.6)
General physical health deterioration	131 (4.6)	135 (4.8)
Mucosal inflammation	123 (4.3)	133 (4.7)
Edema	71 (2.5)	100 (3.5)
Chills	55 (1.9)	115 (4.1)
Influenza like illness	43 (1.5)	83 (2.9)
Malaise	41 (1.4)	36 (1.3)
Multi-organ failure	37 (1.3)	35 (1.2)
Gait disturbance	33 (1.2)	35 (1.2)
Face edema	29 (1.0)	17 (0.6)
Chest discomfort	26 (0.9)	31 (1.1)
Disease progression	25 (0.9)	31 (1.1)
HEPATOBILIARY DISORDERS		
Hepatic failure	41 (1.4)	31 (1.1)
Hepatic function abnormal	37 (1.3)	28 (1.0)
Jaundice	29 (1.0)	21 (0.7)
INFECTIONS AND INFESTATIONS		
Urinary tract infection	220 (7.7)	262 (9.2)
Nasopharyngitis	149 (5.2)	163 (5.7)
Pneumonia	147 (5.2)	130 (4.6)
Bronchitis	124 (4.4)	103 (3.6)
Influenza	118 (4.2)	97 (3.4)
Upper respiratory tract infection	110 (3.9)	116 (4.1)
Oral candidiasis	81 (2.9)	74 (2.6)
Sinusitis	70 (2.5)	50 (1.8)
Herpes zoster	54 (1.9)	49 (1.7)
Cellulitis	51 (1.8)	47 (1.7)
Rhinitis	46 (1.6)	40 (1.4)
Cystitis	44 (1.5)	48 (1.7)

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SYSTEM ORGAN CLASS Preferred Term	Denosumab (N = 2841) n (%)	Zoledronic Acid (N = 2836) n (%)
Respiratory tract infection	40 (1.4)	36 (1.3)
Sepsis	37 (1.3)	34 (1.2)
Pharyngitis	35 (1.2)	41 (1.4)
Gastroenteritis	30 (1.1)	26 (0.9)
Oral herpes	30 (1.1)	24 (0.8)
Tooth abscess	29 (1.0)	16 (0.6)
Lower respiratory tract infection	20 (0.7)	29 (1.0)
INJURY, POISONING AND PROCEDURAL COMPLICATIONS		
Rib fracture	158 (5.6)	166 (5.9)
Thoracic vertebral fracture	149 (5.2)	154 (5.4)
Lumbar vertebral fracture	107 (3.8)	111 (3.9)
Contusion	61 (2.1)	57 (2.0)
Fall	54 (1.9)	48 (1.7)
Femur fracture	33 (1.2)	37 (1.3)
INVESTIGATIONS		
Hypophosphatemia (laboratory-derived)	912 (32.1)	555 (19.6)
Weight decreased	330 (11.6)	332 (11.7)
Blood creatinine increased	105 (3.7)	134 (4.7)
Aspartate aminotransferase increased	76 (2.7)	95 (3.3)
Blood alkaline phosphatase increased	74 (2.6)	76 (2.7)
Alanine aminotransferase increased	62 (2.2)	82 (2.9)
Hemoglobin decreased	56 (2.0)	60 (2.1)
Weight increased	48 (1.7)	55 (1.9)
Platelet count decreased	39 (1.4)	36 (1.3)
Prostatic specific antigen increased	37 (1.3)	19 (0.7)
METABOLISM AND NUTRITION DISORDERS		
Decreased appetite	656 (23.1)	694 (24.5)
Hypocalcemia	265 (9.3)	134 (4.7)
Dehydration	179 (6.3)	164 (5.8)
Hypokalemia	130 (4.6)	156 (5.5)
Hyperglycemia	108 (3.8)	107 (3.8)
Hypophosphatemia	61 (2.1)	32 (1.1)
Hypomagnesemia	56 (2.0)	46 (1.6)
Hyponatremia	50 (1.8)	64 (2.3)
Hypoalbuminemia	48 (1.7)	44 (1.6)
Hyperkalemia	45 (1.6)	50 (1.8)
Hypercalcemia	39 (1.4)	51 (1.8)
Cachexia	35 (1.2)	37 (1.3)
Hypoglycemia	29 (1.0)	32 (1.1)

Table 1. Percentage of Patients with Adverse Events ≥ 1% Reported in Patients with Advanced Malignancies Involving Bone by System Organ Class

SYSTEM ORGAN CLASS Preferred Term	Denosumab (N = 2841) n (%)	Zoledronic Acid (N = 2836) n (%)
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS		
Back pain	718 (25.3)	747 (26.3)
Arthralgia	570 (20.1)	632 (22.3)
Bone pain	564 (19.9)	639 (22.5)
Pain in extremity	524 (18.4)	550 (19.4)
Musculoskeletal pain	357 (12.6)	385 (13.6)
Musculoskeletal chest pain	186 (6.5)	188 (6.6)
Myalgia	150 (5.3)	195 (6.9)
Neck pain	125 (4.4)	144 (5.1)
Muscle spasms	121 (4.3)	96 (3.4)
Muscular weakness	111 (3.9)	140 (4.9)
Pain in jaw	108 (3.8)	83 (2.9)
Osteonecrosis	52 (1.8)	34 (1.2)
Groin pain	48 (1.7)	63 (2.2)
Flank pain	31 (1.1)	34 (1.2)
Musculoskeletal stiffness	30 (1.1)	45 (1.6)
Joint swelling	29 (1.0)	25 (0.9)
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS)		
Metastases to central nervous system	137 (4.8)	122 (4.3)
Malignant neoplasm progression	130 (4.6)	129 (4.5)
Metastases to liver	103 (3.6)	88 (3.1)
Metastases to bone	94 (3.3)	97 (3.4)
Prostate cancer	47 (1.7)	66 (2.3)
Metastases to spine	40 (1.4)	41 (1.4)
Metastases to lung	33 (1.2)	32 (1.1)
NERVOUS SYSTEM DISORDERS		
Headache	360 (12.7)	382 (13.5)
Dizziness	232 (8.2)	254 (9.0)
Paraesthesia	168 (5.9)	204 (7.2)
Neuropathy peripheral	147 (5.2)	142 (5.0)
Hypoesthesia	109 (3.8)	118 (4.2)
Dysgeusia	104 (3.7)	102 (3.6)
Spinal cord compression	96 (3.4)	118 (4.2)
Peripheral sensory neuropathy	89 (3.1)	86 (3.0)
Somnolence	57 (2.0)	69 (2.4)
Syncope	50 (1.8)	50 (1.8)
Lethargy	44 (1.5)	51 (1.8)
Sciatica	37 (1.3)	40 (1.4)

Table 1. Percentage of Patients with Adverse Events ≥ 1% Reported in Patients with Advanced Malignancies Involving Bone by System Organ Class

SYSTEM ORGAN CLASS Preferred Term	Denosumab (N = 2841) n (%)	Zoledronic Acid (N = 2836) n (%)
Tremor	27 (1.0)	46 (1.6)
Convulsion	27 (1.0)	32 (1.1)
Neuralgia	27 (1.0)	30 (1.1)
PSYCHIATRIC DISORDERS		
Insomnia	302 (10.6)	324 (11.4)
Anxiety	196 (6.9)	184 (6.5)
Depression	186 (6.5)	182 (6.4)
Confusional state	87 (3.1)	87 (3.1)
Agitation	20 (0.7)	35 (1.2)
RENAL AND URINARY DISORDERS		
Hematuria	115 (4.0)	118 (4.2)
Urinary retention	112 (3.9)	109 (3.8)
Dysuria	111 (3.9)	102 (3.6)
Renal failure	74 (2.6)	104 (3.7)
Pollakiuria	59 (2.1)	69 (2.4)
Hydronephrosis	56 (2.0)	47 (1.7)
Urinary incontinence	40 (1.4)	54 (1.9)
Renal failure acute	34 (1.2)	44 (1.6)
Renal impairment	26 (0.9)	34 (1.2)
Nocturia	23 (0.8)	36 (1.3)
REPRODUCTIVE SYSTEM AND BREAST DISORDERS		
Pelvic pain	80 (2.8)	79 (2.8)
Breast pain	28 (1.0)	31 (1.1)
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS		
Dyspnea	585 (20.6)	507 (17.9)
Cough	437 (15.4)	419 (14.8)
Pleural effusion	153 (5.4)	137 (4.8)
Epistaxis	109 (3.8)	107 (3.8)
Oropharyngeal pain	96 (3.4)	81 (2.9)
Respiratory failure	96 (3.4)	78 (2.8)
Dyspnea exertional	58 (2.0)	53 (1.9)
Pulmonary embolism	57 (2.0)	65 (2.3)
Hemoptysis	47 (1.7)	51 (1.8)
Dysphonia	46 (1.6)	49 (1.7)
Productive cough	35 (1.2)	37 (1.3)
Nasal congestion	30 (1.1)	23 (0.8)
Hypoxia	29 (1.0)	21 (0.7)
Rhinorrhea	24 (0.8)	31 (1.1)

Table 1. Percentage of Patients with Adverse Events ≥ 1% Reported in Patients with Advanced Malignancies Involving Bone by System Organ Class

SYSTEM ORGAN CLASS Preferred Term	Denosumab (N = 2841) n (%)	Zoledronic Acid (N = 2836) n (%)
SKIN AND SUBCUTANEOUS TISSUE DISORDERS		
Alopecia	265 (9.3)	266 (9.4)
Rash	193 (6.8)	201 (7.1)
Pruritus	107 (3.8)	111 (3.9)
Palmar-plantar erythrodysesthesia syndrome	101 (3.6)	109 (3.8)
Nail disorder	66 (2.3)	72 (2.5)
Hyperhidrosis	66 (2.3)	36 (1.3)
Erythema	64 (2.3)	70 (2.5)
Dry skin	58 (2.0)	60 (2.1)
Night sweats	32 (1.1)	33 (1.2)
Dermatitis	31 (1.1)	20 (0.7)
Skin ulcer	30 (1.1)	19 (0.7)
SURGICAL AND MEDICAL PROCEDURES		
Tooth extraction	43 (1.5)	24 (0.8)
VASCULAR DISORDERS		
Hypertension	148 (5.2)	153 (5.4)
Hypotension	112 (3.9)	99 (3.5)
Hot flush	95 (3.3)	98 (3.5)
Deep vein thrombosis	51 (1.8)	55 (1.9)
Lymphoedema	47 (1.7)	43 (1.5)
Phlebitis	31 (1.1)	31 (1.1)

N = Number of subjects who received ≥ 1 active dose of investigational product
n = Number of subjects reporting ≥ 1 event
Includes only treatment-emergent adverse events
System organ classes are sorted alphabetically and preferred terms are sorted by descending order of frequency in the Denosumab group and coded using MedDRA version 12.1

Less Common Clinical Trial Adverse Events (< 1%) in Patients with Advanced Malignancies Involving Bone by System Organ Class

BLOOD AND LYMPHATIC SYSTEM DISORDERS: *leukocytosis, lymphadenopathy, lymphopenia, coagulopathy, neutrophilia, disseminated intravascular coagulation, thrombocytosis, splenomegaly, lymph node pain, hemorrhagic diathesis, anemia of chronic disease, lymphadenopathy mediastinal, macrocytosis, iron deficiency anemia*

CARDIAC DISORDERS: *Arrhythmia, pericardial effusion, cardiac failure congestive, angina pectoris, cardiac arrest, cardio-respiratory arrest, myocardial ischemia, cardiopulmonary failure, myocardial infarction, sinus tachycardia, acute myocardial infarction, cardiac failure acute, mitral valve incompetence, pericarditis, coronary artery disease, left ventricular hypertrophy, supraventricular tachycardia, cardiomyopathy, cardiogenic shock, bradycardia, left ventricular failure, tricuspid valve incompetence, angina unstable, bundle branch block right, ventricular tachycardia, cardiomegaly, acute coronary syndrome, extrasystoles, atrial flutter, cardiovascular insufficiency, cardiovascular disorder, diastolic dysfunction*

CONGENITAL, FAMILIAL AND GENETIC DISORDERS: *phimosis*

EAR AND LABYRINTH DISORDERS: *ear pain, tinnitus, hypoacusis, hearing impaired, deafness, cerumen impaction, ear pruritus, vertigo positional, ear discomfort*

ENDOCRINE DISORDERS: *cushingoid, hypothyroidism, goiter, hyperthyroidism, cushing's syndrome, adrenal insufficiency*

EYE DISORDERS: *visual acuity reduced, visual impairment, diplopia, dry eye, cataract, eye pain, eye irritation, eye hemorrhage, eyelid ptosis, eye pruritus, conjunctival hemorrhage, eyelid edema, eye swelling, myodesopsia, exophthalmos, blepharitis, eye inflammation, photophobia, photopsia, conjunctivitis allergic, keratoconjunctivitis sicca, retinal detachment, blindness unilateral, eye disorder, keratitis, ophthalmoplegia, eye edema, ocular hyperemia, glaucoma, amaurosis, lacrimal disorder*

GASTROINTESTINAL DISORDERS: *abdominal pain lower, oesophagitis, dental caries, oral pain, mouth ulceration, periodontitis, ileus, tooth disorder, hematochezia, loose tooth, hypoesthesia oral, odynophagia, intestinal obstruction, aphthous stomatitis, gastrointestinal hemorrhage, hematemesis, proctalgia, colitis, gingival bleeding, hiatus hernia, periodontal disease, diverticulum, hemorrhoidal hemorrhage, gingival recession, sensitivity of teeth, paresthesia oral, melena, glossodynia, epigastric discomfort, tooth loss, upper gastrointestinal hemorrhage, gastrointestinal disorder, cheilitis, irritable bowel syndrome, small intestinal obstruction, mouth hemorrhage, fecal incontinence, duodenal ulcer, inguinal hernia, hyperchlorhydria, gastric ulcer, oral discomfort, salivary hypersecretion, lip dry, lip swelling, lower gastrointestinal hemorrhage, oral disorder, retching, gingival ulceration, gastritis erosive, duodenitis, gastrointestinal obstruction, anal hemorrhage, fecaloma, abdominal tenderness, peritonitis, gastrointestinal motility disorder, gingival disorder, subileus, gastrointestinal edema, anal fissure, feces discoloured, diverticulum intestinal, eructation, gingival swelling, intestinal perforation, esophageal stenosis, colonic polyp, proctitis, umbilical hernia, anal pruritus, gingival erythema, edema mouth, rectal tenesmus, reflux gastritis, frequent bowel movements, gastric ulcer hemorrhage, obstruction gastric, oral dysesthesia, reflux esophagitis, anorectal discomfort, gastrointestinal hypomotility, gastrointestinal pain, enteritis, tongue discolouration, tongue disorder*

GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS: *performance status decreased, death, local swelling, catheter related complication, hyperthermia, axillary pain, generalised edema, localised edema, facial pain, catheter site pain, injection site pain, injection site reaction, feeling cold, inflammation, adverse drug reaction, extravasation, non-cardiac chest pain, xerosis, temperature intolerance, thirst, early satiety, sudden death, nodule, suprapubic pain, abasia, impaired healing, injection site pruritus, cyst, irritability, catheter site hematoma, infusion site pain, catheter site inflammation, feeling hot, swelling, catheter site hemorrhage, hernia, catheter site erythema, catheter thrombosis, injection site hematoma, drug withdrawal syndrome, infusion site extravasation, discomfort, injection site hemorrhage, drug intolerance, hypothermia, mucosal dryness, organ failure, induration*

HEPATOBILIARY DISORDERS: *hyperbilirubinemia, hepatomegaly, cholelithiasis, hepatic pain, hepatic steatosis, liver disorder, cholecystitis, cholestasis, hepatitis toxic, hepatorenal failure, bile duct obstruction, hepatic cyst, hepatotoxicity, hepatic lesion*

IMMUNE SYSTEM DISORDERS: *hypersensitivity, drug hypersensitivity, seasonal allergy*

INFECTIONS AND INFESTATIONS: *tooth infection, localised infection, lung infection, catheter related infection, infection, erysipelas, candidiasis, paronychia, oral fungal infection, septic shock, respiratory tract infection viral, viral infection, lobar pneumonia, skin infection, onychomycosis, nail infection, urosepsis, diverticulitis, wound infection, ear infection, herpes virus infection, eye infection, vaginal infection, pyelonephritis, subcutaneous abscess, laryngitis, bronchopneumonia, osteomyelitis, gastroenteritis viral, fungal skin infection, oral infection, tinea pedis, catheter site infection, gingival infection, vulvovaginal mycotic infection, furuncle, neutropenic sepsis, esophageal candidiasis, fungal infection, tracheitis, clostridial infection, tonsillitis, postoperative wound infection, Clostridium difficile colitis, Staphylococcal infection, viral upper respiratory tract infection, breast cellulitis, staphylococcal sepsis, gastrointestinal infection, bacteremia, infected bites, lymphangitis, folliculitis, gingival abscess, otitis media, vulvovaginal candidiasis, abscess limb, Escherichia bacteremia, lung abscess, pyelonephritis acute, hordeolum, infected skin ulcer, labyrinthitis, mastitis, orchitis, soft tissue infection, gangrene, genital infection fungal, pyelonephritis chronic, acarodermatitis, pulpitis dental, febrile infection, kidney infection, skin candida, herpes simplex, abscess, catheter site cellulitis, Enterococcal infection, pneumonia Klebsiella*

INJURY, POISONING AND PROCEDURAL COMPLICATIONS: *procedural pain, radiation skin injury, cervical vertebral fracture, tooth fracture, wound, pelvic fracture, fractured ischium, fracture, ilium fracture, skin laceration, fractured sacrum, limb injury, humerus fracture, muscle strain, thermal burn, clavicle fracture, subdural hematoma, excoriation, joint sprain, radius fracture, drug toxicity, head injury, joint injury, arthropod bite, scapula fracture, tooth injury, tibia fracture, fibula fracture, gastroenteritis radiation, medical device complication, post-traumatic pain, sternal fracture, wound complication, post procedural hemorrhage, radiation pneumonitis, sunburn, contrast media reaction, ulna fracture, seroma, device breakage, transfusion reaction, eye injury, radiation injury, skeletal injury, subdural hemorrhage, concussion, post procedural complication, wound dehiscence, face injury, joint dislocation, poisoning, tendon rupture, animal bite, facial bones fracture, overdose, radiation associated pain*

INVESTIGATIONS: *blood bilirubin increased, white blood cell count decreased, gamma-glutamyltransferase increased, blood alkaline phosphatase, body temperature increased, blood calcium decreased, blood urea increased, blood pressure increased, blood glucose increased, blood potassium increased, blood potassium decreased, international normalised ratio increased, neutrophil count decreased, hemoglobin, blood albumin decreased, hepatic enzyme increased, liver function test abnormal, blood lactate dehydrogenase increased, blood phosphorus decreased, hematocrit decreased, white blood cell count increased, blood magnesium decreased, blood bicarbonate decreased, blood creatinine, urine output decreased, cardiac murmur, red blood cell count decreased, blood sodium decreased, blood uric acid increased, blood urine present, blood iron decreased, transaminases increased, blood creatine increased, heart rate increased, neutrophil count, platelet count increased, creatinine renal clearance decreased, blood creatinine decreased, bone density decreased, electrocardiogram QT prolonged, occult blood positive, protein total decreased, C-reactive protein increased, breath sounds abnormal, prothrombin time prolonged, activated partial thromboplastin time prolonged, blood calcium increased, Eastern Cooperative Oncology Group performance status worsened, ejection fraction decreased, neutrophil count increased*

METABOLISM AND NUTRITION DISORDERS: *diabetes mellitus, malnutrition, hypercholesterolemia, hyperuricemia, hypoproteinemia, metabolic acidosis, gout, fluid retention, hypercreatininemia, failure to thrive, hypertriglyceridemia, electrolyte imbalance, dyslipidemia, hypermagnesemia, hypophagia, hypovolemia, fluid overload, iron deficiency, hyperlipidemia, diabetes mellitus inadequate control, type 2 diabetes mellitus, acidosis, vitamin D deficiency, polydipsia, tumour lysis syndrome, appetite disorder, vitamin B12 deficiency*

MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS: *osteoarthritis, musculoskeletal discomfort, joint stiffness, joint range of motion decreased, arthritis, coccydynia, pubic pain, intervertebral disc protrusion, bone lesion, limb discomfort, spinal osteoarthritis, tendonitis, myopathy, mobility decreased, muscle tightness, jaw disorder, rotator cuff syndrome, osteolysis, bursitis, periarthritis, sensation of heaviness, hypercreatinemia, muscle fatigue, osteoporosis, osteitis, tendon disorder, exostosis, amyotrophy, intervertebral disc degeneration, dupuytren's contracture, rheumatoid arthritis, trigger finger, arthropathy, muscle atrophy, joint effusion, osteopenia, pathological fracture, plantar fasciitis, muscle twitching, spinal disorder, spondylolisthesis, scoliosis, muscle contracture, joint crepitation, lumbar spinal stenosis, muscle rigidity, tenosynovitis, trismus*

NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS): *metastasis, cancer pain, breast cancer, metastases to lymph nodes, benign neoplasm of skin, prostate cancer metastatic, metastatic pain, malignant pleural effusion, metastases to meninges, breast cancer metastatic, metastases to bone marrow, metastatic neoplasm, lung cancer metastatic, basal cell carcinoma, malignant ascites, seborrheic keratosis,*

tumour pain, metastases to pleura, benign neoplasm, paraneoplastic syndrome, skin papilloma, metastases to peritoneum, colon cancer metastatic, gastric cancer, metastases to bladder, rectal cancer, benign neoplasm of thyroid gland, meningioma, metastases to gastrointestinal tract, metastases to skin, neoplasm progression, squamous cell carcinoma, lip neoplasm benign, tumour associated fever

NERVOUS SYSTEM DISORDERS: *cerebrovascular accident, peripheral motor neuropathy, balance disorder, facial palsy, memory impairment, ataxia, polyneuropathy, amnesia, dysarthria, loss of consciousness, dysesthesia, monoparesis, migraine, paraparesis, hyperaesthesia, neurotoxicity, hemiparesis, presyncope, cerebral ischemia, brain edema, intracranial pressure increased, transient ischemic attack, cervical cord compression, speech disorder, hemiplegia, cognitive disorder, sensory disturbance, disturbance in attention, ageusia, vocal cord paralysis, carpal tunnel syndrome, coma, epilepsy, restless legs syndrome, sinus headache, hypertonia, burning sensation, aphasia, paraplegia, hypotonia, aphonia, monoplegia, dizziness postural, motor dysfunction, cerebral hemorrhage, hydrocephalus, dementia, encephalopathy, paresis, parosmia, paralysis, poor quality sleep, depressed level of consciousness, hepatic encephalopathy, ischemic stroke, cerebrovascular disorder, cervical root pain, cranial neuropathy, facial paresis, epiduritis, grand mal convulsion, sensory loss, autonomic nervous system imbalance, cauda equina syndrome, cerebellar syndrome, neurological decompensation, partial seizures, cerebral atrophy, cerebral infarction, trigeminal neuralgia, hypogeusia, mental impairment, nervous system disorder, vascular encephalopathy, peroneal nerve palsy, hemorrhage intracranial, horner's syndrome, coordination abnormal, dyskinesia, hypersomnia, formication, hemorrhagic stroke, radiculopathy, sedation, radicular pain, diplegia*

PSYCHIATRIC DISORDERS: *sleep disorder, disorientation, mental status changes, depressed mood, hallucination, mood altered, restlessness, nervousness, delirium, affect lability, abnormal behaviour, libido decreased, nightmare, bruxism, neurosis, adjustment disorder, fear, mental disorder, panic attack, mood swings, apathy, stress, hallucination (visual), aggression*

RENAL AND URINARY DISORDERS: *urinary tract obstruction, urinary tract disorder, oliguria, renal cyst, nephrolithiasis, proteinuria, micturition urgency, incontinence, renal pain, renal failure chronic, urinary bladder hemorrhage, micturition disorder, urinary hesitation, urine flow decreased, bladder spasm, bladder obstruction, polyuria, anuria, hemorrhage urinary tract, ureteric obstruction, calculus bladder, bladder pain, renal colic, calculus ureteric, urethral stenosis, hypertonic bladder, urethral obstruction, bladder disorder, choluria, azotemia, chromaturia, obstructive uropathy, renal disorder, bladder neck obstruction, strangury*

REPRODUCTIVE SYSTEM AND BREAST DISORDERS: *gynecomastia, vaginal hemorrhage, vulvovaginal dryness, scrotal edema, nipple pain, penile edema, edema genital, vaginal discharge, benign prostatic hyperplasia, erectile dysfunction, ovarian cyst, prostatitis, vulvovaginal pruritus, amenorrhea, prostatism, scrotal pain, metrorrhagia, genital hemorrhage, breast edema, breast mass, breast tenderness, balanitis, breast discomfort, dyspareunia, menstruation irregular, vaginal inflammation, vulvovaginal pain, perineal pain, genital discharge, penile pain, testicular pain, breast hemorrhage, breast swelling, pruritus genital, menorrhagia, pelvic discomfort*

RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS: *wheezing, hydrothorax, atelectasis, chronic obstructive pulmonary disease, hiccups, rhinitis allergic, lung infiltration, pleurisy, pulmonary edema, pleuritic pain, bronchospasm, sinus congestion, respiratory tract congestion, lung disorder, pneumothorax, acute respiratory failure, postnasal drip, respiratory distress, rhonchi, pneumonitis, rales, acute respiratory distress syndrome, bronchitis chronic, nasal dryness, asthma, respiratory disorder, tachypnea, dry throat, increased bronchial secretion, pulmonary hypertension, paranasal sinus hypersecretion, orthopnea, emphysema, sinus disorder, hydropneumothorax, hemothorax, throat irritation, increased upper airway secretion, pulmonary hemorrhage, bronchial obstruction, asphyxia, nasal discomfort, pharyngeal inflammation, respiratory tract hemorrhage, apnea, pulmonary fibrosis, respiratory arrest, upper airway obstruction, acute pulmonary edema, hypoventilation, pulmonary congestion, interstitial lung disease, aspiration*

SKIN AND SUBCUTANEOUS TISSUE DISORDERS: *skin lesion, hypoesthesia facial, decubitus ulcer, urticaria, ecchymosis, swelling face, skin reaction, skin hyperpigmentation, skin exfoliation, dermatitis allergic, acne, onycholysis, skin discolouration, rash erythematous, eczema, nail discolouration, blister, petechiae, skin disorder, periorbital edema, dermatitis contact, skin nodule, subcutaneous nodule, skin irritation, onychoclasis, rash popular, rash pruritic, skin fissures, ingrowing nail, rash macular, actinic keratosis, pain of skin, dermatitis acneiform, pigmentation disorder, pruritus generalized, nail toxicity, drug eruption, seborrheic dermatitis, cold sweat, hyperkeratosis, rash generalized, skin atrophy, skin edema, xeroderma, skin toxicity, exfoliative rash, nail*

dystrophy, dermal cyst, skin hemorrhage, purpura, intertrigo, onychomadesis, increased tendency to bruise, psoriasis, photodermatosis, ingrown hair, scar

SOCIAL CIRCUMSTANCES: *immobile*

SURGICAL AND MEDICAL PROCEDURES: *mastectomy, catheter placement, endodontic procedure, bladder catheterization, cataract operation, transurethral prostatectomy, central venous catheterization*

VASCULAR DISORDERS: *hematoma, thrombosis, flushing, thrombophlebitis, pallor, hemorrhage, hypertensive crisis, lymphostasis, orthostatic hypotension, peripheral coldness, venous thrombosis, arteriosclerosis, varicose vein, circulatory collapse, venous thrombosis limb, jugular vein thrombosis, superior vena caval occlusion, aortic aneurysm, aortic arteriosclerosis, venous insufficiency, subclavian vein thrombosis, intermittent claudication, phlebitis superficial, hypovolemic shock, thrombophlebitis superficial, vasculitis, embolism, vein pain*

Giant Cell Tumour of Bone

The safety of XGEVA was evaluated in two Phase 2 open-label, single arm studies (Study 4 and 5) (see **CLINICAL TRIALS**) in which a total of 304 patients with GCTB received at least 1 dose of XGEVA. Patients received 120 mg XGEVA subcutaneously every 4 weeks with a loading dose of 120 mg on days 8 and 15. Of the 304 patients who received XGEVA, 147 patients were treated with XGEVA for ≥ 1 year, 46 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 subjects were women. The majority of subjects were white (80.3%). The median (range) age was 33 (13 to 83) years; 10 subjects were skeletally mature adolescents (aged 13 to 17 years).

Table 2 describes adverse events occurring in ≥ 1% of patients in these studies.

Table 2. Percentage of Patients with Adverse Events ≥ 1% Reported in Patients with Giant Cell Tumour of Bone by System Organ Class

SYSTEM ORGAN CLASS Preferred Term	Denosumab (N=304) n (%)
BLOOD AND LYMPHATIC SYSTEM DISORDERS	
Anemia	12 (3.9)
CARDIAC DISORDERS	
Palpitations	5 (1.6)
Tachycardia	4 (1.3)
EAR AND LABYRINTH DISORDERS	
Vertigo	10 (3.3)
GASTROINTESTINAL DISORDERS	
Nausea	54 (17.8)
Vomiting	28 (9.2)
Constipation	22 (7.2)
Diarrhea	21 (6.9)
Toothache	17 (5.6)
Abdominal pain	16 (5.3)
Abdominal pain upper	11 (3.6)
Dyspepsia	8 (2.6)
Abdominal distension	6 (2.0)
Dental caries	5 (1.6)
Stomatitis	5 (1.6)
Tooth disorder	5 (1.6)
Abdominal discomfort	4 (1.3)
Dry mouth	4 (1.3)
Gastroesophageal reflux disease	4 (1.3)
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	
Fatigue	51 (16.8)
Edema peripheral	24 (7.9)
Non-cardiac chest pain	16 (5.3)
Pyrexia	14 (4.6)
Asthenia	12 (3.9)
Influenza like illness	11 (3.6)
Local swelling	8 (2.6)
Pain	7 (2.3)
Chills	5 (1.6)
Injection site hematoma	4 (1.3)
INFECTIONS AND INFESTATIONS	
Nasopharyngitis	24 (7.9)

Table 2. Percentage of Patients with Adverse Events ≥ 1% Reported in Patients with Giant Cell Tumour of Bone by System Organ Class

SYSTEM ORGAN CLASS Preferred Term	Denosumab (N=304) n (%)
Upper respiratory tract infection	23 (7.6)
Urinary tract infection	11 (3.6)
Influenza	9 (3.0)
Gastroenteritis	8 (2.6)
Sinusitis	7 (2.3)
Cystitis	6 (2.0)
Bronchitis	5 (1.6)
Tooth abscess	5 (1.6)
Pharyngitis	4 (1.3)
Tooth infection	4 (1.3)
INJURY, POISONING AND PROCEDURAL COMPLICATIONS	
Procedural pain	13 (4.3)
Contusion	4 (1.3)
INVESTIGATIONS	
Weight increased	19 (6.3)
Weight decreased	6 (2.0)
Aspartate aminotransferase increased	4 (1.3)
METABOLISM AND NUTRITION DISORDERS	
Hypophosphatemia	17 (5.6)
Hypocalcemia	13 (4.3)
Decreased appetite	11 (3.6)
Hypercalcemia	6 (2.0)
Hyperglycemia	5 (1.6)
Hypokalemia	4 (1.3)
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS	
Arthralgia	64 (21.1)
Back pain	53 (17.4)
Pain in extremity	49 (16.1)
Musculoskeletal pain	26 (8.6)
Muscle spasms	17 (5.6)
Bone pain	16 (5.3)
Myalgia	16 (5.3)
Neck pain	15 (4.9)
Pain in jaw	10 (3.3)
Muscular weakness	6 (2.0)
Musculoskeletal chest pain	5 (1.6)
Musculoskeletal stiffness	5 (1.6)
Joint swelling	4 (1.3)

Table 2. Percentage of Patients with Adverse Events ≥ 1% Reported in Patients with Giant Cell Tumour of Bone by System Organ Class

SYSTEM ORGAN CLASS Preferred Term	Denosumab (N=304) n (%)
Osteonecrosis of jaw	4 (1.3)
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS)	
Tumour pain	9 (3.0)
NERVOUS SYSTEM DISORDERS	
Headache	56 (18.4)
Paraesthesia	16 (5.3)
Dizziness	15 (4.9)
Hypoaesthesia	10 (3.3)
Neuralgia	8 (2.6)
Lethargy	4 (1.3)
Peripheral sensory neuropathy	4 (1.3)
Somnolence	4 (1.3)
PSYCHIATRIC DISORDERS	
Insomnia	16 (5.3)
Depression	14 (4.6)
Anxiety	8 (2.6)
RENAL AND URINARY DISORDERS	
Dysuria	4 (1.3)
Urinary incontinence	4 (1.3)
REPRODUCTIVE SYSTEM AND BREAST DISORDERS	
Pelvic pain	6 (2.0)
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	
Cough	19 (6.3)
Dyspnea	11 (3.6)
Oropharyngeal pain	10 (3.3)
Nasal congestion	6 (2.0)
Rhinorrhea	4 (1.3)
SKIN AND SUBCUTANEOUS TISSUE DISORDERS	
Rash	15 (4.9)
Pruritus	9 (3.0)
Eczema	7 (2.3)
Acne	6 (2.0)
Dry skin	6 (2.0)
Alopecia	5 (1.6)

Table 2. Percentage of Patients with Adverse Events ≥ 1% Reported in Patients with Giant Cell Tumour of Bone by System Organ Class

SYSTEM ORGAN CLASS Preferred Term	Denosumab (N=304) n (%)
VASCULAR DISORDERS	
Hot flush	12 (3.9)
Hypertension	4 (1.3)

N = Number of subjects who received ≥ 1 active dose of investigational product
N = Number of subjects reporting ≥ 1 event
Includes only treatment-emergent adverse events
System organ classes are sorted alphabetically and preferred terms are sorted by descending order of frequency and coded using MedDRA version 14.1
Subjects who rolled over from Study 4 to Study 5 or who discontinued Study 4 and re-entered Study 5 are counted only once and their analysis period will start from Study 4 and end at Study 5.

Less Common Clinical Trial Adverse Events (< 1%) in Patients with Giant Cell Tumour of Bone by System Organ Class

BLOOD AND LYMPHATIC SYSTEM DISORDERS: *Leukopenia, Lymphadenopathy, Hypochromic anaemia,Iron deficiency anaemia, Lymph node pain, Spleen disorder, Splenomegaly*

CARDIAC DISORDERS*: Sinus tachycardia, Pericarditis*

EAR AND LABYRINTH DISORDERS: *Ear pain, Eustachian tube obstruction, Tympanic membrane perforation,*

ENDOCRINE DISORDERS*: Hyperthyroidism, Goitre, Hyperparathyroidism, Hypothyroidism, Toxic nodular goitre*

EYE DISORDERS: *Cataract, Dry eye, Eye irritation, Visual impairment, Abnormal sensation in eye, Astigmatism, Diplopia, Eye oedema, Eye pruritus, Lacrimation increased, Myopia, Ocular hyperaemia, Periorbital oedema, Photophobia, Visual acuity reduced*

GASTROINTESTINAL DISORDERS: *Abdominal pain lower, Flatulence, Haematochezia, Rectal haemorrhage, Sensitivity of teeth, Abdominal rigidity, Aphthous stomatitis, Chapped lips, Cheilitis, Gingival bleeding, Gingival disorder, Gingivitis, Lip ulceration, Odynophagia, Oral pain, Pancreas lipomatosis, Periodontitis, Tooth discolouration, Umbilical hernia*

GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS: *Feeling cold, Oedema, Atrophy, Axillary pain, Cyst, Device failure, Gait disturbance, Hyperthermia, Injection site erythema, Injection site irritation, Localised oedema, Mucosal inflammation, Nodule, Sensation of pressure, Temperature intolerance*

HEPATOBILIARY DISORDERS: *Cholelithiasis, Hepatic steatosis*

IMMUNE SYSTEM DISORDERS: *Allergy to animal, Hypersensitivity, Seasonal allergy*

INFECTIONS AND INFESTATIONS: *Oral herpes, Osteomyelitis, Skin infection, Viral upper respiratory tract infection, Abscess oral, Acarodermatitis, Acute tonsillitis, Appendicitis, Dental fistula, Device related infection, Eye infection, Folliculitis, Gastritis bacterial, Genital candidiasis, Genital herpes, Helicobacter infection, Infected cyst, Infection, Infectious mononucleosis, Injection site infection, Localised infection, Measles, Oral candidiasis, Orchitis, Post procedural infection, Postoperative wound infection, Rhinitis, Tonsillitis, Urinary tract infection enterococcal*

INJURY, POISONING AND PROCEDURAL COMPLICATIONS: *Arthropod bite, Ligament sprain, Post procedural complication, Tibia fracture, Wound, Endotracheal intubation complication, Fractured sacrum, Gun shot wound, Hand fracture, Head injury, Humerus fracture, Joint injury, Limb injury, Meniscus lesion, Mouth injury, Muscle strain, Nail injury, Nerve injury, Post procedural discomfort, Post procedural haemorrhage, Post-traumatic pain, Procedural vomiting, Rib fracture, Spinal compression fracture, Stress fracture, Tooth injury, Vena cava injury, Wound dehiscence*

INVESTIGATIONS: *Blood calcium decreased, Blood pressure increased, Breath sounds abnormal, Neutrophil count decreased, Blood iron decreased, Blood lactate dehydrogenase increased, C-reactive protein increased, Cardiac murmur, Computerised tomogram thorax abnormal, Haemoglobin decreased, Occult blood*

METABOLISM AND NUTRITION DISORDERS: *Cell death, Hyperlipidaemia, Iron deficiency*

MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS: *Bursitis, Joint range of motion decreased, Joint warmth, Tendonitis, Wrist deformity, Chondropathy, Flank pain, Intervertebral disc protrusion, Joint effusion, Limb discomfort, Muscle contracture, Muscle fatigue, Osteoarthritis, Osteonecrosis, Periarthritis, Plantar fasciitis, Temporomandibular joint syndrome, Tenosynovitis*

NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS*): Benign neoplasm of skin, Skin papilloma, Basal cell carcinoma, Benign lung neoplasm, Benign neoplasm, Bone giant cell tumour, Bone neoplasm, Ganglioneuroma, Lipoma, Neoplasm progression, Parathyroid tumour benign, Sarcoma, Spindle cell sarcoma, Thyroid cancer, Tumour haemorrhage*

NERVOUS SYSTEM DISORDERS: *Presyncope, Sinus headache, Amnesia, Carpal tunnel syndrome, Central nervous system lesion, Dysgeusia, Hyperaesthesia, Intercostal neuralgia, Lumbar radiculopathy, Memory impairment, Mental impairment, Muscle contractions involuntary, Nerve compression, Nystagmus, Peroneal nerve palsy, Restless legs syndrome, Tension headache, Transient ischaemic attack*

PSYCHIATRIC DISORDERS: *Bruxism, Libido decreased, Mood altered, Affect lability, Depressed mood, Emotional disorder, Euphoric mood, Mood swings, Sleep disorder, Stress, Suicidal ideation*

RENAL AND URINARY DISORDERS: *Pollakiuria, Nocturia, Polyuria, Urine odour abnormal*

REPRODUCTIVE SYSTEM AND BREAST DISORDERS: *Amenorrhoea, Breast cyst, Breast discharge, Breast pain, Cervical dysplasia, Dysmenorrhoea, Vaginal discharge, Vaginal haemorrhage*

RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS: *Paranasal sinus hypersecretion, Pleuritic pain, Rhinitis allergic, Bronchial hyperreactivity, Dyspnoea exertional, Hiccups, Oropharyngeal blistering, Pharyngeal disorder, Productive cough, Respiratory failure, Respiratory tract congestion, Sinus congestion, Sneezing, Upper-airway cough syndrome*

SKIN AND SUBCUTANEOUS TISSUE DISORDERS: *Erythema, Onychoclasis, Scar pain, Skin chapped, Skin discolouration, Skin hyperpigmentation, Cold sweat, Dermal cyst, Dermatitis, Dermatitis acneiform, Dermatitis allergic, Ecchymosis, Keratosis pilaris, Nail disorder, Petechiae, Pruritus generalised, Rash erythematous, Rash pruritic, Seborrhoeic dermatitis, Skin irritation, Subcutaneous nodule*

VASCULAR DISORDERS: *Flushing, Lymphoedema,*

Hypercalcemia of Malignancy Refractory to Intravenous Bisphosphonate

The safety of XGEVA was evaluated in an open-label, single-arm trial (Study 6) in which 33 patients were enrolled with hypercalcemia of malignancy (with or without bone metastases) refractory to treatment with intravenous bisphosphonate. Patients received XGEVA subcutaneously every 4 weeks with additional 120 mg doses on Days 8 and 15 of the first month of therapy.

Of the 33 patients who received XGEVA, 33 patients were treated with XGEVA for ≥ 1 month, 5 patients for ≥ 6 months, and 3 patients for ≥ 1 year. The median number of doses received was 4 (range: 1 to 25 doses) and the median number of months on study was 1.8 (range: 0 to 23 months). Sixty-four percent of enrolled patients were men and 70% were White. The median age was 63 years (range: 22 to 89 years).

The adverse event profile of XGEVA in patients with hypercalcemia of malignancy was similar to that reported in Studies 1, 2, 3, 4, and 5 (Table 3). The most common adverse events were nausea (10 patients, 30%), dyspnea (9 patients, 27%), and decreased appetite, headache, peripheral edema, and vomiting, each of which occurred in 8 patients (24%). The patient

incidence of fatal adverse events was 78.8%. The most frequently reported serious adverse events were worsening hypercalcemia (5 subjects, 15%), dyspnea (3 subjects, 9%), and metastatic breast cancer (3 subjects, 9%). No adverse events leading to discontinuation were reported as related to XGEVA treatment.

Table 3. Treatment-Emergent Adverse Events by Preferred Term in Descending Order of Frequency (≥ 5% Patient Incidence)

Preferred Term	Denosumab (N=33) n (%)
Number of patients reporting adverse events	32 (97.0)
Nausea	10 (30.3)
Dyspnoea	9 (27.3)
Decreased appetite	8 (24.2)
Headache	8 (24.2)
Oedema peripheral	8 (24.2)
Vomiting	8 (24.2)
Anaemia	7 (21.2)
Constipation	7 (21.2)
Diarrhoea	7 (21.2)
Cough	6 (18.2)
Fatigue	6 (18.2)
Hypercalcaemia	6 (18.2)
Hypotension	5 (15.2)
Pleural effusion	5 (15.2)
Pyrexia	5 (15.2)
Arthralgia	4 (12.1)
Back pain	4 (12.1)
Confusional state	4 (12.1)
Fluid overload	4 (12.1)
Hypophosphataemia	4 (12.1)
Pulmonary oedema	4 (12.1)
Weight decreased	4 (12.1)
Abdominal distension	3 (9.1)
Abdominal pain	3 (9.1)
Alopecia	3 (9.1)
Breast cancer metastatic	3 (9.1)
Epistaxis	3 (9.1)
Haemoglobin decreased	3 (9.1)
Hypocalcaemia	3 (9.1)
Hypokalaemia	3 (9.1)
Hyponatraemia	3 (9.1)
Myalgia	3 (9.1)
Oropharyngeal pain	3 (9.1)

Table 3. Treatment-Emergent Adverse Events by Preferred Term in Descending Order of Frequency (≥ 5% Patient Incidence)

Preferred Term	Denosumab (N=33) n (%)
Pneumonia	3 (9.1)
Rash	3 (9.1)
Renal failure acute	3 (9.1)
Tachycardia	3 (9.1)
Thrombocytopenia	3 (9.1)
Asthenia	2 (6.1)
Breast cancer	2 (6.1)
Clostridium difficile colitis	2 (6.1)
Dehydration	2 (6.1)
Depressed level of consciousness	2 (6.1)
Dizziness	2 (6.1)
Dry mouth	2 (6.1)
Dysphonia	2 (6.1)
Fall	2 (6.1)
Febrile neutropenia	2 (6.1)
Head and neck cancer	2 (6.1)
Hyperkalaemia	2 (6.1)
Hypomagnesaemia	2 (6.1)
Hypoxia	2 (6.1)
Insomnia	2 (6.1)
Lethargy	2 (6.1)
Lung neoplasm malignant	2 (6.1)
Musculoskeletal pain	2 (6.1)
Neutropenia	2 (6.1)
Non-small cell lung cancer	2 (6.1)
Pain in extremity	2 (6.1)
Palmar-plantar erythrodysaesthesia syndrome	2 (6.1)
Plasma cell myeloma	2 (6.1)
Rash pruritic	2 (6.1)
Rhinorrhoea	2 (6.1)

N = Number of patients who received ≥ 1 dose of denosumab; n = Number of patients reporting ≥ 1 adverse event; Includes only treatment-emergent adverse events; Preferred terms are sorted by descending order of frequency and coded using MedDRA version 16.0.

Table 4. Investigational Product Related Adverse Events by Preferred Term in Descending Order of Frequency

Preferred Term	Denosumab (N=33) n (%)
Number of subjects reporting investigational product related adverse events	13 (39.4)
Hypophosphataemia	4 (12.1)
Nausea	4 (12.1)
Oedema peripheral	3 (9.1)
Arthralgia	2 (6.1)
Constipation	2 (6.1)
Diarrhoea	2 (6.1)
Hypocalcaemia	2 (6.1)
Myalgia	2 (6.1)
Pneumonia	2 (6.1)
Rash	2 (6.1)
Rash pruritic	2 (6.1)
Rhinorrhoea	2 (6.1)
Vomiting	2 (6.1)
Abdominal distension	1 (3.0)
Abdominal pain	1 (3.0)
Abdominal pain lower	1 (3.0)
Aspartate aminotransferase increased	1 (3.0)
Back pain	1 (3.0)
Bone pain	1 (3.0)
Cardiac arrest	1 (3.0)
Cardiac murmur	1 (3.0)
Clostridium difficile colitis	1 (3.0)
Coccydynia	1 (3.0)
Colitis	1 (3.0)
Contusion	1 (3.0)
Dysgeusia	1 (3.0)
Dyspepsia	1 (3.0)
Electrocardiogram QT prolonged	1 (3.0)
Fatigue	1 (3.0)
Fluid overload	1 (3.0)
Headache	1 (3.0)
Hypertension	1 (3.0)
Lung infection	1 (3.0)
Musculoskeletal pain	1 (3.0)
Musculoskeletal stiffness	1 (3.0)
Oropharyngeal pain	1 (3.0)
Pharyngitis	1 (3.0)
Pollakiuria	1 (3.0)

Table 4. Investigational Product Related Adverse Events by Preferred Term in Descending Order of Frequency

Preferred Term	Denosumab (N=33) n (%)
Respiratory tract infection	1 (3.0)
Temporomandibular joint syndrome	1 (3.0)
Toothache	1 (3.0)
Urinary retention	1 (3.0)
Ventricular tachycardia	1 (3.0)
Vision blurred	1 (3.0)

N = Number of subjects who received ≥ 1 dose of investigational product
n = Number of subjects reporting ≥ 1 event
Includes only treatment-emergent adverse events for which the investigator indicated there was a reasonable possibility they may have been caused by investigational product
Preferred terms are sorted by descending order of frequency and coded using MedDRA version 15.1.

One fatal event (cardiac arrest) and 1 serious grade 4 colitis were reported by the investigator to be related to XGEVA therapy. The XGEVA therapy-related grade 3 events of fatigue, infections and hypophosphatemia were reported in 3%, 6.1% and 9.1% of the patients, respectively.

Hypocalcemia

In clinical trials in patients with advanced cancer and adequate renal function (defined as estimated creatinine clearance ≥ 30 mL/min), hypocalcemia was reported as an adverse event in 9.6% of patients in the XGEVA group and 5.0% of patients in the zoledronic acid group.

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, Hypocalcemia**).

In clinical trials in patients with GCTB, 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.

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

In one study, subjects (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. Hypocalcemia was observed in 8 subjects (15%), 1 (2%) of whom was symptomatic. Two subjects (4%) each experienced an adverse event of hypocalcemia that was classified as serious. Both subjects had severe chronic kidney disease (CKD) and were enrolled before the protocol required supplementation of calcium and vitamin D.

In a second study, patients (N=32) with severe renal impairment (creatinine clearance less than 30 mL/minute and/or on dialysis) were given two 120 mg subcutaneous doses (Days 1 and 29) of denosumab. Two patients overall (1 in each group) had symptomatic hypocalcemia, based on clinical adverse events and concomitant symptoms. One patient in the severe CKD group had concomitant muscle spasms and 1 patient in the CKD on dialysis group had concomitant paresthesia. Hence, the overall incidence of clinically significant hypocalcemia (corrected serum calcium less than 1.75 mmol/L or symptomatic hypocalcemia) was 9.4%: 1 of 16 patients (6.3%) in the severe group and 2 of 16 patients (12.5%) in the CKD on dialysis group. Both events of symptomatic hypocalcemia were mild in severity. Accompanying increases in parathyroid hormone (PTH) have also been observed in patients receiving XGEVA with severe renal impairment or receiving dialysis. At baseline, median (range) intact PTH (iPTH) values were 6.1 pmol/L (1.06 pmol/L, 13.2 pmol/L) and 16.3 pmol/L (0.3 pmol/L, 37.0 pg/mL) in the severe CKD and CKD on dialysis groups, respectively. At end of study (Day 113), median (range) iPTH values were 7.1 pmol/L (0.85 pmol/L, 372.2 pmol/L) and 31.5 pmol/L (1.3 pmol/L, 136.1 pmol/mL) in the severe CKD and CKD on dialysis groups, respectively. The median percent change from baseline to end of study (Day 113) was 15.0% in the severe CKD group and 107.5% in the CKD on dialysis group. The median (range) maximal elevation of PTH was 19.4 pmol/L (2.8 pmol/L, 372.2 pmol/L) in the severe CKD group and 64.2 pmol/L (1.3 pmol/L, 396.1 pmol/L) in the CKD on dialysis group. The median (range) % change of the maximal elevation of PTH values from baseline was 164.8% (28.2%, 2729.0%) in the severe CKD group and 256.1% (46.8%, 1681.9%) in the CKD on dialysis group. The median (range) time to reach maximal elevation of PTH was 22.5 days (3 days, 115 days) in the severe CKD group and 64.0 days (6 days, 115 days) in the CKD dialysis group. The median duration (range) of the elevation (20% above baseline) of PTH was 41.0 days (3.0 days, 112.0 days) in the severe CKD group and 79.5 days (11.0 days, 216.0 days) in the CKD on dialysis group.

In both studies, there was a greater risk of developing hypocalcemia with increasing degree of renal impairment, and in the absence of, or inadequate calcium supplementation.

Osteonecrosis of the Jaw (ONJ)

In clinical trials in patients with advanced cancer, 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 (see **WARNINGS AND PRECAUTIONS**). Fifty-eight percent of subjects in the XGEVA group and 65% of subjects in the zoledronic acid group had a prior or concurrent tooth extraction, 42% of subjects in the XGEVA group and 27% of subjects in the zoledronic acid group had used a denture or other dental appliance, and 31% of subjects in the XGEVA group and 32% of subjects in the zoledronic acid group had poor oral hygiene.

The trials in patients with breast or prostate cancer included an XGEVA extension treatment phase (median overall exposure of 14.9 months; range 0.1 – 67.2) (see **CLINICAL TRIALS**). For patients who were randomized to XGEVA and continued on XGEVA in the open label extension phase, the patient-year adjusted incidence of confirmed ONJ was 1.1% during the first year of treatment (0 – 12 months) and 4.1% thereafter (> 12 months, up to 67.2 months). The median time to ONJ was 20.6 months (range: 4 – 53) (**see WARNINGS AND PRECAUTIONS**).

In clinical trials in patients with GCTB, 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**).

Atypical Femoral Fractures

Atypical femoral fracture has been reported with XGEVA.

Malignancies

In a pooled safety analysis of clinical trials in cancer patients with bone metastases, the overall incidence of new primary malignancies was 0.99% (28 out of 2841 patients) in the XGEVA group and 0.63% (18 out of 2836 patients) in the zoledronic acid group. In the breast cancer trial, the incidence was 0.5 % in both XGEVA (5/1020 patients) and zoledronic acid groups (5/1013 patients). In other solid tumours or multiple myeloma, the incidence was 0.6% (5/878 patients) and 0.3% (3/878 patients) in the XGEVA and zoledronic acid groups, respectively. In the prostate cancer trial, the incidence was 1.9% (18/943 patients) in the XGEVA group and 1.1% (10/945 patients) in the zoledronic acid group.

Immunogenicity

Denosumab is a human monoclonal antibody. As with all therapeutic proteins, there is potential for immunogenicity. Using an electrochemiluminescent bridging immunoassay, less than 1% of patients treated with XGEVA for up to 3 years tested positive for binding antibodies (including pre-existing, transient, and developing antibodies). None of the patients 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.

Abnormal Hematologic and Clinical Chemistry Findings

In clinical trials in cancer patients with bone metastases, a grade 3 decrease in serum calcium levels was experienced in 2.5% of patients treated with XGEVA and 1.2% of patients treated with zoledronic acid. A grade 4 decrease in serum calcium levels was experienced in 0.6% of patients treated with XGEVA and 0.2% of patients treated with zoledronic acid (see **WARNINGS AND PRECAUTIONS**, **Special Populations, Renal Impairment**). In studies, the development of hypocalcemia in patients with severe renal impairment (creatinine clearance less than 30 mL/min and/or receiving dialysis) was accompanied by an elevation in parathyroid hormone levels.

Severe hypophosphatemia (Grade 3) occurred in 15.4% of patients treated with XGEVA and 7.4% of patients treated with zoledronic acid.

In clinical trials in patients with GCTB, the subject incidence of grade 2 calcium decreases was 2.6%. No grade 3 or grade 4 decreases in calcium were observed.

CTCAE grade 3 low phosphorus values were observed for 29 patients (9.5%). No grade 4 decreases in serum phosphorus were observed.

Postmarket Adverse Drug Reactions

Hypocalcemia

Severe symptomatic hypocalcemia, including fatal cases, has been reported in patients receiving XGEVA.

Hypersensitivity Reactions

Hypersensitivity, including anaphylactic reactions.

Musculoskeletal Pain

Musculoskeletal pain, including severe cases, has been reported in patients receiving XGEVA.

DRUG INTERACTIONS

Overview

No formal drug interaction studies have been conducted with XGEVA.

Drug-Drug Interactions

Interactions with other drugs have not been established.

In clinical trials, XGEVA has been administered in combination with standard anti-cancer treatment and in patients previously receiving bisphosphonates. Apparent differences in the pharmacokinetics and pharmacodynamics of denosumab with concomitant chemotherapy and/or hormone therapy, or previous exposure to intravenous bisphosphonate were small in relation to inherent inter-subject variability within a patient population.

Drug-Food Interactions

Interactions with food have not been established.

Drug-Herb Interactions

Interactions with food herbal products have not been established.

Drug-Laboratory Interactions

Interactions with laboratory tests have not been established.

DOSAGE AND ADMINISTRATION

Substitution by any other biological medicinal product requires the consent of the prescribing physician.

Dosing Considerations

All patients, except those with hypercalcemia, should receive at least 500 mg calcium daily and at least 400 IU vitamin D daily.

Recommended Dose

Bone Metastasis from Solid Tumours

The recommended dose of XGEVA is 120 mg administered as a single subcutaneous injection once every 4 weeks.

Giant Cell Tumour of Bone

The recommended dose of XGEVA is 120 mg administered as a subcutaneous injection once every 4 weeks with a loading dose of 120 mg on days 8 and 15 of the first month of therapy.

Hypercalcemia of Malignancy Refractory to Intravenous Bisphosphonate

The recommended dose of XGEVA is 120 mg administered as a subcutaneous injection once every 4 weeks with a loading dose of 120 mg on days 8 and 15 of the first month of therapy.

Missed Dose

If a dose of XGEVA is missed, administer the injection as soon as the patient is available. Thereafter, injections should be scheduled every 4 weeks from the date of the last injection.

Administration

Prior to administration, XGEVA 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 XGEVA in any other way (see **STORAGE AND STABILITY**).

Visually inspect XGEVA for particulate matter and discolouration prior to administration. XGEVA is a clear, colourless to slightly yellow solution that may contain trace amounts of translucent to white proteinaceous particles. Do not use if the solution is discoloured or cloudy or if the solution contains many particles or foreign particulate matter.

Use a 27-gauge needle to withdraw and inject the entire contents of the vial. The vial is filled to ensure a deliverable dose of 120 mg. Do not re-enter the vial. Discard vial and any liquid remaining in the vial.

XGEVA is intended for use under the guidance and supervision of physicians who have fully familiarized themselves with the efficacy/safety profile of XGEVA. After an initial training in proper subcutaneous injection technique, patients may self-inject XGEVA if a physician determines that is appropriate and with medical follow-up as necessary.

XGEVA is intended for subcutaneous route only and should not be administered intravenously, intramuscularly, or intradermally. Administer XGEVA via subcutaneous injection in the upper arm, the upper thigh, or the abdomen.

OVERDOSAGE

For management of a suspected drug overdose, contact your regional Poison Control Centre.

There is no experience with overdosage of XGEVA.

ACTION AND CLINICAL PHARMACOLOGY

Mechanism of Action

Bone Metastasis from Solid Tumours

XGEVA binds to RANK Ligand (RANKL), a transmembrane or soluble protein essential for the formation, function, and survival of osteoclasts, the cells responsible for bone resorption. XGEVA prevents RANKL from activating its receptor, RANK, on the surface of osteoclasts and their precursors. Increased osteoclast activity, stimulated by RANKL, is a key mediator of bone disease in metastatic tumours and multiple myeloma. Prevention of the RANKL/RANK interaction inhibits osteoclast formation, function, and survival, thereby decreasing bone resorption and interrupting cancer-induced bone destruction.

Giant Cell Tumour of Bone

GCTB are characterized by stromal cells expressing RANKL and osteoclast-like giant cells expressing RANK. In patients with GCTB, XGEVA binds to RANKL, significantly reducing or eliminating osteoclast-like giant cells. Consequently, osteolysis is reduced and proliferative tumour stroma is replaced with non-proliferative, differentiated, densely woven new bone.

Hypercalcemia of Malignancy Refractory to Intravenous Bisphosphonates

The primary etiology of both skeletal and humoral HCM is increased bone resorption, which leads to elevated calcium concentrations in the extracellular fluid. The increase in bone resorption is initiated by the release of signaling molecules such as PTHrP, prostaglandins, and cytokine by malignant and stromal cells. These molecules stimulate osteoblasts and other stromal cells to express RANK ligand (RANKL), which upon binding its receptor RANK upregulates osteoclast recruitment and differentiation and thus bone resorption, with a resultant increase in calcium concentrations of the extracellular fluid and serum. XGEVA binds to RANKL preventing RANK/RANKL mediated osteoclast formation, function, and survival thereby lowering serum calcium levels.

Pharmacodynamics

In a phase 2 study of patients with breast cancer and bone metastases who had not previously received intravenous (IV) bisphosphonate therapy, subcutaneous (SC) doses of XGEVA 120 mg every 4 weeks caused a rapid reduction in markers of bone resorption (uNTX/creatinine and serum CTx) with a median reduction of 82% for uNTX/Cr within 1 week. Reductions in bone turnover markers were maintained, with median uNTX/Cr reductions of 74% to 82% from weeks

2 to 25 of continued 120 mg every 4 weeks dosing. In phase 3 clinical studies of patients with advanced cancer who had not previously received IV bisphosphonate therapy, median reductions of approximately 80% in uNTx/Cr from baseline after 3 months of treatment were observed across 2075 XGEVA-treated advanced cancer patients (breast, prostate, multiple myeloma or other solid tumours).

Similarly, in a phase 2 study of patients with solid tumours and bone metastases (including patients with multiple myeloma and bone disease) who were receiving IV bisphosphonate therapy, yet had uNTX/Cr levels > 50 nM/mM, SC dosing of XGEVA administered either every 4 weeks or every 12 weeks caused an approximate 80% reduction in uNTX/creatinine from baseline after 3 and 6 months of treatment.

In a phase 2 study of patients with GCTB who received SC doses of XGEVA 120 mg every 4 weeks (Q4W) with loading doses on days 8 and 15, median reductions in uNTx/Cr and sCTx of approximately 80% were observed by week 9. Reductions in bone turnover markers were maintained, with median reductions of 56% to 77% for uNTx/Cr and 79% to 83% for sCTx from weeks 5 to 25 of continued 120 mg Q4W dosing.

Pharmacokinetics

Following SC administration, bioavailability was 62% based on a population PK analysis. Relative AUC exposure ratios for SC vs. IV dosing were 78% and 75% for doses of 1.0 and 3.0 mg/kg in postmenopausal women. Denosumab displayed non-linear pharmacokinetics with dose over a wide dose range, but approximately dose-proportional increases in exposure for doses of 60 mg (or 1 mg/kg) and higher (for example, 3.8- to 4.0-fold increases in mean C_{max} and AUC values for a 3-fold increase in dose from 60 to 180 mg). In subjects with advanced cancer, who received multiple SC doses of 120 mg every 4 weeks an approximate 2.5-fold accumulation in serum denosumab AUC(0-tau) exposures was observed and steady-state was achieved on or after 6 doses. These results indicate that denosumab pharmacokinetics does not change with time or multiple dosing. In subjects with GCTB who received 120 mg every 4 weeks with a loading dose on days 8 and 15, steady-state levels were achieved within the first month of treatment. Between weeks 9 and 49, median trough levels varied by less than 9%. At steady-state in these subjects, the mean serum trough concentration was 20.6 mcg/mL (range, 0.456 to 56.9 mcg/mL). In patients who discontinued 120 mg every 4 weeks dosing, the mean half-life was 28 days (range 14 to 55 days).

A population pharmacokinetic analysis was performed to evaluate the effects of demographic characteristics. This analysis suggested that there were no notable differences in various pharmacokinetics parameters (clearance, volume of distribution, absorption rate, bioavailability) with age (18 to 87 years), race, body weight (36 to 174 kg), or across patients with solid tumours and GCTB. Denosumab pharmacokinetics and pharmacodynamics were similar in men and women and in patients transitioning from IV bisphosphonate therapy. Denosumab pharmacokinetics and pharmacodynamics were not affected by the formation of binding antibodies to denosumab.

Special Populations and Conditions

Gender

The pharmacokinetics of denosumab was not different in men and women.

Pediatrics

The pharmacokinetics of denosumab in pediatric patients has not been assessed.

Geriatrics

The pharmacokinetics of denosumab was not affected by age from 18 years to 87 years.

Race

The pharmacokinetics of denosumab was not affected by race.

Hepatic Impairment

No clinical studies have been conducted to evaluate the effect of hepatic impairment on the pharmacokinetics of denosumab.

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. Hypocalcemia was observed in 8 subjects (15%), 1 (2%) of whom was symptomatic. Two patients (4%) each experienced an adverse event of hypocalcemia that was classified as serious. Both patients had severe chronic kidney disease (CKD) and were enrolled before the protocol required supplementation of calcium and vitamin D.

In a second study, patients (N=32) with severe renal impairment (creatinine clearance less than 30 mL/minute and/or on dialysis) were given two 120 mg subcutaneous doses (Days 1 and 29) of denosumab. Two patients overall (1 in each group) had symptomatic hypocalcemia, based on clinical adverse events and concomitant symptoms. One patient in the severe CKD group had concomitant muscle spasms and 1 patient in the CKD on dialysis group had concomitant paresthesia. Hence, the overall incidence of clinically significant hypocalcemia (corrected serum calcium less than 1.75 mmol/L or symptomatic hypocalcemia) was 9.4%: 1 of 16 patients (6.3%) in the severe group and 2 of 16 patients (12.5%) in the CKD on dialysis group. Both events of symptomatic hypocalcemia were mild in severity.

Accompanying increases in parathyroid hormone have also been observed in patients receiving XGEVA with severe renal impairment or receiving dialysis.

In both studies in patients with varying degrees of renal function, including patients on dialysis, the degree of renal impairment had no effect on the pharmacokinetics and pharmacodynamics of denosumab. The risk of developing hypocalcemia increased with increasing degree of renal impairment, and in the absence of, or inadequate calcium supplementation.

Dose adjustment for renal impairment is not required and there is no additional need for more frequent renal monitoring due to XGEVA administration.

STORAGE AND STABILITY

Store XGEVA in a refrigerator at 2°C to 8°C in the original carton. Do not freeze.

Prior to administration, XGEVA may be allowed to reach room temperature (up to 25°C) in the original container. Once removed from the refrigerator, XGEVA must not be exposed to temperatures above 25°C and must be used within 30 days. If not used within the 30 days, XGEVA should be discarded.

Do not use XGEVA after the expiry date printed on the label.

Protect XGEVA from direct light and heat.

Avoid vigorous shaking of XGEVA.

DOSAGE FORMS, COMPOSITION AND PACKAGING

XGEVA is a sterile, preservative-free, clear, colourless to slightly yellow solution, formulated at pH 5.2.

XGEVA is supplied in a single-use vial containing 120 mg denosumab, 4.6% sorbitol, 18 mM acetate, water for injection (USP), and sodium hydroxide to a pH of 5.2.

XGEVA is supplied in a carton containing 1 vial.

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

Drug Substance

Proper name:	denosumab
Molecular mass:	147 kDa
Structural formula:	Denosumab is a fully human IgG2 monoclonal antibody heterotetramer consisting of 2 heavy chains of the gamma 2 subclass (447 amino acids per chain) and 2 light chains of the kappa subclass (215 amino acids per chain)

CLINICAL TRIALS

Bone Metastasis from Solid Tumours

Study demographics and trial design

Table 5. Summary of Patient Demographics for Clinical Studies in Patients with Advanced Malignancies Involving Bone

Study #	Trial design	Dosage, route of administration and duration*	Study subjects (n = number)	Mean age (Range)	Gender (Female:Male) %
Study 1	Phase 3, randomized, double-blind, active-controlled	XGEVA 120 mg SC and zoledronic acid placebo IV Q4W or zoledronic acid 4mg IV and denosumab placebo SC Q4W	2046 adults with advanced breast cancer and bone metastasis (XGEVA: 1026 Zoledronic acid: 1020)	57 (24, 91)	XGEVA (99.2:0.8) Zoledronic acid (99.1:0.9)
Study 2	Phase 3, randomized, double-blind, active-controlled	XGEVA 120 mg SC and zoledronic acid placebo IV Q4W or zoledronic acid 4mg IV and denosumab placebo SC Q4W	1776 adults with advanced cancers including solid tumours [excluding breast and prostate], multiple myeloma, and lymphoma (XGEVA: 886 Zoledronic acid: 890)	60 (18, 89)	XGEVA (33.6:66.4) Zoledronic acid (38.0:62.0)
Study 3	Phase 3, randomized, double-blind, active-controlled	XGEVA 120 mg SC and zoledronic acid placebo IV Q4W or zoledronic acid 4mg IV and denosumab placebo SC Q4W	1901 adult men with castrate-resistant prostate cancer and bone metastasis (XGEVA: 950 Zoledronic acid: 951)	71 (38, 93)	XGEVA (0:100) Zoledronic acid (0:100)

* Studies were event-driven: the length of the primary double-blind treatment phase was determined by the anticipated date on which ~745 subjects experienced an initial on-study skeletal-related event.

The efficacy of XGEVA for the treatment of patients with advanced malignancies involving bone was demonstrated by three pivotal phase 3, international, randomized, double blind, active controlled studies compared with zoledronic acid: Study 1 in 2046 adults with advanced breast cancer and bone metastases; Study 2 in 1776 adults with other solid tumours [including non small cell lung cancer (NSCLC), renal cell cancer, colorectal cancer, small cell lung cancer, bladder cancer, head and neck cancer, GI/genitourinary cancer and others, excluding breast cancer and prostate cancer] and bone metastases or multiple myeloma; and Study 3 in 1901 men with castrate-resistant prostate cancer and bone metastases.

Patients received either 120 mg XGEVA SC every 4 weeks or 4 mg zoledronic acid (dose-adjusted for reduced renal function) IV every 4 weeks. No dosage adjustments were necessary in patients receiving XGEVA. In accordance with the zoledronic acid prescribing information, patients with creatinine clearance < 30 mL/min were excluded. Daily supplements of ≥ 500 mg calcium and ≥ 400 IU of vitamin D were strongly recommended, unless hypercalcemia was present.

In each study, the primary outcome measure was to demonstrate non-inferiority of time to first on study skeletal-related event (SRE) as compared to zoledronic acid. The secondary outcome measures were superiority of time to first on-study SRE and superiority of time to first and subsequent SRE; testing for the secondary outcome measures occurred if the primary outcome measure was statistically significant. An SRE is defined as any of the following: pathologic fracture, radiation therapy to bone, surgery to bone or spinal cord compression.

Study results

XGEVA reduced the risk of developing (delayed time to) first SRE and multiple (first and subsequent) SREs in patients with advanced malignancies involving bone. Efficacy results are provided in Table .

Table 6. Efficacy Results for XGEVA Compared to Zoledronic Acid in Patients with Advanced Malignancies Involving Bone

	Study 1 Advanced Breast Cancer		Study 2 Advanced Cancer (Other Solid Tumours and Multiple Myeloma)		Study 3 Advanced Prostate Cancer	
	XGEVA	Zoledronic Acid	XGEVA	Zoledronic Acid	XGEVA	Zoledronic Acid
N	1026	1020	886	890	950	951
First On-Study Skeletal Related Event (SRE)						
Number and Proportion of Subjects with 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 (months)	NR	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)	
Non-inferiority P-value	<0.0001		0.0007		0.0002	
Superiority P-value †	0.0101		0.0619		0.0085	
First and Subsequent SRE *						
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 †	0.0012		0.1447		0.0085	

NR = not reached
Superiority testing performed only after denosumab demonstrated to be noninferior to zoledronic acid within trial.
*Accounts for all skeletal events over time; only events occurring ≥ 21 days after the previous event are counted.
†P-values, adjusted for multiplicity, are presented for Studies 1, 2 and 3.

Overall survival and disease progression in all three studies were comparable in patients with advanced cancer between XGEVA and zoledronic acid treatment groups (see Table). In Study 2, mortality was higher with XGEVA in a subgroup analysis of patients with multiple myeloma [hazard ratio (95% CI) of 2.26 (1.13, 4.50); n = 180].

Table 7. Summary of Exploratory Tumour Outcomes

	XGEVA vs Zoledronic acid Hazard Ratio					
	Study 1		Study 2		Study 3	
Endpoint	Pt Est	95% CI*	Pt Est	95% CI*	Pt Est	95% CI*
Overall survival	0.95	0.81, 1.11	0.95	0.83, 1.08	1.03	0.91, 1.17
Time to disease progression excluding death	1.00	0.89, 1.11	1.00	0.89, 1.12	1.06	0.95, 1.18

Pt Est = point estimate
CI = confidence interval
*Not adjusted for multiplicity

Giant Cell Tumour of Bone

Study demographics and trial design

Table 8. Summary of Patient Demographics for Clinical Studies in Patients with Giant Cell Tumour of Bone

Study #	Trial design	Dosage, route of administration	Study subjects (n = number)	Mean age (Range)*	Gender (Female:Male) %*
Study 4	Phase 2, open-label, multicenter	XGEVA 120 mg SC Q4W with a loading dose on study days 8 and 15 of the first month of therapy	Adult subjects with GCTB (n = 37)	34 (19, 63)	(54:46)
Study 5	Phase 2, open-label, multicenter	XGEVA 120 mg SC Q4W with a loading dose on study days 8 and 15 of the first month of therapy	Adult subjects with GCTB (n = 272) And Skeletally Mature Adolescents with GCTB (n = 10)	36 (13, 83)	(58:42)

*Pooled data

The safety and efficacy of XGEVA was studied in two Phase 2 open-label, single arm trials (Studies 4 and 5) that enrolled 305 patients with GCTB that was either unresectable or for which surgery was associated with severe morbidity.

Study 4 enrolled 37 adult patients with histologically confirmed unresectable or recurrent GCTB and the main outcome measure of the trial was response rate based on histological or radiographic evidence.

Study 5 enrolled 282 adults and 10 skeletally mature adolescents (aged 13-17 years) with GCTB. The main outcome measure was to evaluate the safety profile of XGEVA. Efficacy was assessed by evaluation of time to disease progression in subjects with unresectable GCTB and by

evaluation of the proportion of subjects who do not require surgery in the subjects with resectable GCTB.

A retrospective independent review of radiographic imaging data from 190 of 305 patients enrolled in Studies 4 and 5 was performed. Patients were evaluated using modified Response Evaluation Criteria in Solid Tumours (RECIST 1.1) to evaluate tumour burden based on computed tomography (CT)/magnetic resonance imaging (MRI).

Study results

An objective response by RECIST 1.1 was observed in 47 of 187 (25%) evaluable patients (95% CI: 19, 32), including 2 of 6 (33%) evaluable adolescent patients. All responses were partial responses. The median time to response was 3 months (range: 1.5 to 20.9 months). The median duration of response was not estimable as only three patients experienced disease progression following an objective response. The median follow-up duration for evaluable patients was 13 months (range: 2 to 49 months).

Hypercalcemia Of Malignancy Refractory To Intravenous Bisphosphonate

Study demographics and design

The safety and efficacy of XGEVA was studied in a Phase 2 open-label, single-arm trial (Study 6) that enrolled 33 patients with hypercalcemia of malignancy (with or without bone metastases) refractory to treatment with intravenous bisphosphonate. In this study, refractory hypercalcemia of malignancy was defined as an albumin-corrected serum calcium (CSC) of >12.5 mg/dL (3.1 mmol/L) despite treatment with intravenous bisphosphonate in the last 7-30 days. Patients receiving dialysis for renal failure or who had treatment with thiazides, calcitonin, mithromycin, or gallium nitrate within their window of expected therapeutic effect prior to the date of screening corrected serum calcium (CSC) were excluded. Twenty-six (79%) patients had advanced solid tumors and 7 (21%) patients had advanced hematologic malignancies. Twenty-five patients (76%) had poor performance status (Eastern Cooperative Oncology Group [ECOG] ≥ 2) at baseline. Metastatic disease was present in 30 (91%) patients and metastatic bone disease in 13 (39%) patients at baseline. Three (9%) patients had non-metastatic disease, 2 with myeloma and 1 with non-Hodgkin's lymphoma.

At the time of enrollment, the median serum calcium level was 13.7 mg/dL (3.42 mmol/L). During the study, serum calcium was collected every few days in the first month, weekly during the second month, and monthly thereafter.

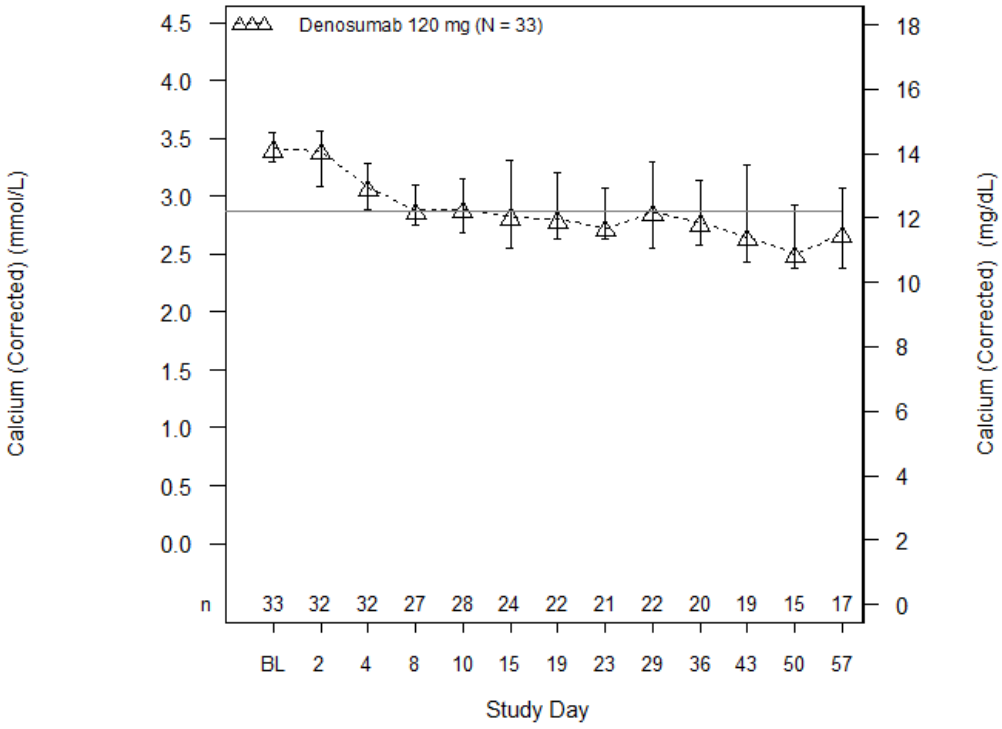
The primary outcome measure was the proportion of patients achieving a response, defined as CSC ≤ 11.5 mg/dL (2.9 mmol/L), within 10 days after XGEVA administration. Additional secondary outcomes were assessed and are presented in Table 9.

Patients received XGEVA subcutaneously every 4 weeks with additional 120 mg doses on days 8 and 15 of the first month of therapy.

Study results

Based on Kaplan-Meier estimates, 59% of patients met the primary end point by day 10 and 73.9% by day 57, responding to XGEVA treatment with CSC levels ≤ 11.5 mg/dL..

Figure 1: Corrected serum calcium by visit (median and interquartile range)



N = Number of patients who received at least 1 dose of denosumab; n = Number of patients who had no missing data at baseline and the timepoint of interest

Table 9: Efficacy in Patients with Hypercalcemia of Malignancy Refractory to Bisphosphonate Therapy

	N = 33	Kaplan-Meier Estimates by Visit (95% CI[a])
All Responders (CSC ≤ 11.5 mg/dL) by Day 10	21	59.0% (41.5%, 74.5%)
All Responders by Day 57	23	73.9% (56.7%, 86.2%)
Complete Responders (CSC ≤ 10.8 mg/dL) by Day 10	12	34.3% (19.3%, 52.7%)
All Complete Responders by Day 57	21	75.2% (56.3%, 88.4%)

N = Number of subjects who received ≥ 1 investigational product and have a screening serum calcium corrected by albumin (from local lab) > 12.5 mg/dL (3.1 mmol/L)
KM = Kaplan-Meier
[a]Confidence interval is calculated using bootstrap method.

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).

DETAILED PHARMACOLOGY

Animal Pharmacology

Denosumab has been shown to be a potent inhibitor of bone resorption in monkeys via inhibition of RANKL. Adolescent monkeys dosed with denosumab at 15 times (50 mg/kg dose) and 2.8 times (10 mg/kg dose) the area under the curve (AUC) exposure in adult humans dosed at 120 mg subcutaneously every 4 weeks had abnormal growth plates, considered to be consistent with the pharmacological activity of denosumab. Tissue distribution studies indicated that denosumab does not bind to tissues known for expression of other members of the TNF superfamily, including TNF-related apoptosis-inducing ligand (TRAIL).

Since 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, such as OPG-Fc and RANK-Fc, were used to evaluate the pharmacodynamic properties of denosumab in rodent models. In mouse bone metastasis models of human prostate cancer, NSCLC, and estrogen receptor (ER) positive and negative breast cancer, OPG-Fc reduced osteolytic, osteoblastic, and osteolytic/osteoblastic lesions, delayed formation of de novo bone metastasis, and reduced skeletal tumour growth. When OPG-Fc was combined with hormonal therapy (tamoxifen) or chemotherapy (docetaxel) in these models, there was additive inhibition of skeletal tumour growth in breast, prostate or lung cancer respectively. In a mouse model of mammary tumour induction, RANK-Fc delayed tumour formation.

The role of osteoclast-mediated hypercalcemia was evaluated in 2 murine models of humoral hypercalcemia of malignancy through the use of osteoprotegerin (OPG), an endogenous decoy receptor that binds and neutralizes RANKL. In one model, mice were inoculated with syngeneic colon adenocarcinoma cells, and in the other mice were injected with high-dose parathyroid hormone-related protein (PTHrP) (0.5 mg/kg, SC, twice per day). In both models, a single injection of OPG caused more rapid reversal of established hypercalcemia and longer lasting suppression of hypercalcemia than high-dose bisphosphonates.

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 (see **WARNINGS AND PRECAUTIONS, Special Populations, Pediatrics**).

Clinical Pharmacology

Pharmacodynamics

In a phase 2 study of patients with breast cancer and bone metastases who had not previously received IV bisphosphonate therapy, SC doses of XGEVA 120 mg every 4 weeks caused a rapid reduction in markers of bone resorption (uNTX/creatinine and serum CTx) with a median reduction of 82% for uNTX/Cr within 1 week. Reductions in bone turnover markers were maintained, with median uNTX/Cr reductions of 74% to 82% from weeks 2 to 25 of continued 120 mg every 4 weeks dosing. In phase 3 clinical studies of patients with advanced cancer who had not previously received IV bisphosphonate therapy, median reductions of approximately 80% in uNTx/Cr from baseline after 3 months of treatment were observed across 2075 XGEVA-treated advanced cancer patients (breast, prostate, multiple myeloma or other solid tumours).

Similarly, in a phase 2 study of patients with solid tumours and bone metastases (including patients with multiple myeloma and bone disease) who were receiving IV bisphosphonate therapy, yet had uNTX/Cr levels > 50 nM/mM, SC dosing of XGEVA administered either every 4 weeks or every 12 weeks caused an approximate 80% reduction in uNTX/creatinine from baseline after 3 and 6 months of treatment.

Pharmacokinetics

Denosumab pharmacokinetic parameters were not affected by the formation of binding antibodies to denosumab.

At the level of the administered dose, the pharmacokinetics of denosumab do not appear to be affected by gender, age (18 – 87 years), race, body weight (36 to 174 kg), or disease state.

TOXICOLOGY

Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenicity

Since denosumab is highly species-specific and is not active in rodents, traditional rodent cancer bioassays could not be performed. RANKL inhibition (the target of denosumab) has been studied in a wide range of short-term animal models of cancer and shown no carcinogenic potential. Additionally, RANKL inhibition has shown no evidence of immunosuppression in a wide range of animal models.

Mutagenicity

The genotoxic potential of denosumab has not been evaluated. Denosumab is a recombinant protein made up entirely of naturally-occurring amino acids and contains no inorganic or synthetic organic linkers or other non-protein portions. Therefore, it is unlikely that denosumab or any of its derived fragments would react with DNA or other chromosomal material.

Impairment of Fertility

Denosumab had no effect on female fertility or male reproductive organs in monkeys at exposures that were 9.5- to 16-fold higher than the human exposure for 120 mg SC administered once every 4 weeks.

Table 10. Summary of Preclinical Toxicity and Reproductive Studies with Denosumab

Type of Study	Species and strain	Number per sex per group	Route of Administration	Dose (mg/kg) and dosing regimen	Study Duration	Treatment related findings	NOAEL (mg/kg)
Repeated-dose Toxicity	Cynomolgus monkey	6	Subcutaneous or Intravenous	Once weekly: 0, 0.1, 1.0, & 10.0 (SC); 10.0 (IV)	1-month dosing with 3 months recovery	Consistent with the pharmacological action of denosumab, there were rapid and marked decreases in circulating markers of bone turnover at all doses. Correlating with these changes, there was increased bone mineral density in males dosed at 1 and 10 mg/kg. With the exception of bone mineral density which tended to be maintained, these changes were recovered or recovering following 3 treatment free months. There were no treatment related effects on organ weights or histopathology findings.	10 (SC and IV)
	Cynomolgus monkey	8	Subcutaneous	Once monthly: 0, 1, 10, 50	6 and 12 months with 3 months recovery	Consistent with the pharmacological action of denosumab, there were rapid and marked decreases in circulating markers of bone turnover at 10 and 50 mg/kg. Correlating to these changes, there was increased bone mineral density, bone mineral content, cortical area and thickness, and bone strength parameters in males dosed at 50 mg/kg, and females dosed at 10 and 50 mg/kg. In addition, there was enlargement of the growth plates, decreased osteoblasts and osteoclasts, and decreased chondroclasis at 10 and 50 mg/kg. These changes were recovered or recovering following 3 treatment free months. There were no treatment related changes in opthalmoscopy, cardiovascular physiology, sperm motility and morphology, circulating immunoglobulins and lymphocyte subsets, or organ weights.	50
Female Fertility	Cynomolgus monkey	6 Females	Subcutaneous	Once weekly: 0, 2.5, 5, 12.5	Over 2 menstrual cycles before mating and for 4 weeks after mating	No treatment related effects on cyclicity, circulating reproductive hormones, mating success.	12.5

Table 10. Summary of Preclinical Toxicity and Reproductive Studies with Denosumab

Type of Study	Species and strain	Number per sex per group	Route of Administration	Dose (mg/kg) and dosing regimen	Study Duration	Treatment related findings	NOAEL (mg/kg)
Embryo-fetal Development	Cynomolgus monkey	16 Females	Subcutaneous	Once weekly: 0, 2.5, 5, 12.5	Gestation days 20-50	No treatment related effects on mother or embryonic development were observed. Peripheral lymph nodes were not evaluated.	12.5
Enhanced pre- and post-natal development	Cynomolgus monkey	29 Females	Subcutaneous	Once monthly: 0, 50	Gestation days 20 -22 to birth	There were increased fetal losses during gestation, increased stillbirths and post-natal mortality (see Table). Treatment-related findings in the offspring included decreased body weight gain and decreased neonatal growth; skeletal abnormalities resulting from impaired bone resorption during rapid growth, including bones at the base of the skull resulting in altered cranial shape and exophthalmos, reduced bone strength and treatment-related bone fractures; reduced hematopoiesis; decreased serum levels of bone resorption and bone formation biomarkers; tooth malalignment and dental dysplasia (in the absence of adverse effects on tooth eruption); infections; and absence of peripheral lymph nodes. Following a recovery period from birth out to 6 months of age, findings still observed were mildly reduced bone length (femoral, vertebral, jaw); reduced cortical thickness with associated reduced strength; extramedullary hematopoiesis; dental dysplasia; and the absence of decreased size of some lymph nodes. One infant had minimal to moderate mineralization in multiple tissues. The initially lower growth rates returned to, but never exceeded the growth rate in the control group, and hence, the infants exposed to denosumab remained smaller than control infants, as measured by body weight and morphometric measurements. For the denosumab-treated maternal animals, there was a decrease in serum levels of bone resorption and formation biomarkers, and serum alkaline phosphatase levels; recovery was evident by the end of the treatment-free period. Maternal mammary gland development was normal.	A NOAEL was not identified.

Table 10. Summary of Preclinical Toxicity and Reproductive Studies with Denosumab

Type of Study	Species and strain	Number per sex per group	Route of Administration	Dose (mg/kg) and dosing regimen	Study Duration	Treatment related findings	NOAEL (mg/kg)
						At birth out to 1 month of age, infants had measureable blood levels of denosumab (22-621% of the maternal levels). Only one infant had measureable concentrations of denosumab on BD91, and no infants had measurable concentrations on BD180. Generally, the effects observed in mothers and infants were consistent with the pharmacological action of denosumab.	
Safety Pharmacology	Cynomolgus monkey	3 Males	Subcutaneous	Single dose: 0, 0.3, 3, 30	7 Days	No treatment related effects on heart rate, blood pressure, electrical activity of the heart, or respiratory rate were observed.	30
	Sprague Dawley weanling rats	71 male and 67 female	Subcutaneous	Rat OPG-Fc: 1, 10 mg/kg/week Murine RANK-Fc: 10 mg/kg/week	6 weeks	Increased bone volume, density and strength. Increased cancellous bone with reduced osteoclast number. Reduced long bone growth with altered growth plate morphology and increased thickness. Impaired tooth eruption and tooth root formation.	N/A
		10 males and 3-10 females	Subcutaneous	Rat OPG-Fc: 3, 10 mg/kg/week	6 weeks	Changes seen at the 10 mg/kg/week were similar to those in the previous study. Effects were less at the 3 mg/kg/week.	N/A
		10-11 males and 9-10 females	Subcutaneous	Rat OPG-Fc: 1, 3, 10 mg/kg/week	6 weeks with 10 weeks recovery	Effects were partially reversible when OPG-Fc was discontinued	N/A
Other Studies – Tissue Cross-reactivity	Cynomolgus monkey, rat, rabbit	N/A	*In Vitro*	5 or 25 mcg/mL	N/A	Staining of lymphoid tissue in rabbit and cynomolgus monkey and staining of chondrocytes in rat were observed.	N/A
	Cynomolgus monkey, human	N/A	*In Vitro*	1 or 10 mcg/mL	N/A	Staining of lymphoid tissue in monkey, but no staining in human tissue was observed.	N/A

Table 10. Summary of Preclinical Toxicity and Reproductive Studies with Denosumab

Type of Study	Species and strain	Number per sex per group	Route of Administration	Dose (mg/kg) and dosing regimen	Study Duration	Treatment related findings	NOAEL (mg/kg)
	Human	N/A	*In Vitro*	1 or 10 mcg/mL	N/A	Staining of lymphoid tissue was observed.	N/A

N/A = not applicable

Table 11. Total Fetal Losses[c], all Groups

Dose (mg/kg)	Total No. Pregnant Females; Infants Born (M/F)	Gestation Day (GD) of Fetal Loss	% Fetal Loss by Dose Level			
			Full Gestation	First Trimester (GD20 to GD50)	Third Trimester Total (≥GD100)	Third Trimester Stillbirths (≥GD140)
0	29; 22 (13/9)	GDs 32, 32, 33, 104, 152, 157, 170	24.1% (7/29)	10.3% (3/29)	13.8% (4/29)	10.3% (3/29)
50	29; 16 (7/9)	GDs 31, 32, 33, 33, 46, 88[a], 132, 151, 156[a], 157, 158, 160, 168	40.7% (11/27) 44.8%** (13/29)	17.2% (5/29)	22.2% (6/27) 24.1%** (7/29)	18.5% (5/27) 20.7%** (6/29)
Historical Control Data[b] Range			24.8% (33/133) (6.7 to 38.9%)	6.8% (9/133) (0 to 11.8%)	15.8% (21/133) (0 to 28.6%)	9.0% (12/133) (0 to 16.7%)

[a] Two adult females were excluded from fetal loss calculations except for first trimester because each had an anti-drug antibody (ADA) response beginning at GD76 with subsequent decrease in pharmacologic effect (bone biomarkers) prior to fetal loss; results indicated by a double asterisk (**) include these ADA-positive adult females.
[b] Based on 8 enhanced PPND studies conducted at the Testing Facility from 2008 to 2010.
[c] Fetal losses occurring prior to GD140 were considered abortions; those occurring on or after GD140 were considered stillbirths.

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PART III: CONSUMER INFORMATION

PrXGEVA®
(denosumab)

pronounced ex-jee-va

This section is part III of a three-part "Product Monograph" published when XGEVA (denosumab) was approved for sale in Canada and is designed specifically for consumers. This section is a summary and will not tell you everything about XGEVA. Contact your doctor or pharmacist if you have any questions about the drug.

ABOUT THIS MEDICATION

What the medication is used for

- XGEVA is used for reducing the risk of developing cancer-related complications like broken bones and/or bone pain that need surgery or radiation.

  XGEVA is not used for reducing the risk of developing cancer-related complications in patients with multiple myeloma.

- XGEVA is used to treat giant cell tumor of bone, which cannot be treated by surgery or where surgery is not the best option in adults and adolescents (aged 13-17 years) whose bones have stopped growing.
- XGEVA is used to reduce high levels of calcium in the blood in cancer patients (hypercalcemia of malignancy) after other drugs called bisphosphonates did not work.

How it works

XGEVA works differently than other medications used to treat cancer patients whose disease has spread to their bones. It works as a RANK Ligand (RANKL) inhibitor. RANKL is a protein that promotes the breakdown of bone. XGEVA blocks RANKL to stop the breakdown of bone. This action strengthens your bones by increasing bone mass and lowers the chance of the cancer causing problems with your bones, such as fractures or severe pain requiring radiation treatment.

XGEVA reduces the amount of calcium in the blood by reducing the breakdown of bones. In patients with hypercalcemia of malignancy, the breakdown of bones can cause too much calcium in the blood.

When it should not be used

You should not be given XGEVA if:

- you are allergic to denosumab or any other ingredient of XGEVA. Allergic reactions (eg, rash, hives, or in rare cases, swelling of the face, lips, tongue, throat, or trouble breathing) have been reported.
- you have hypocalcemia (low calcium levels in the blood), until your doctor corrects this condition.

What the medicinal ingredient is

The medicinal ingredient in XGEVA is denosumab.

What the important nonmedicinal ingredients are

The other ingredients are sorbitol, acetate, water for injection and sodium hydroxide.

What dosage forms it comes in

XGEVA is a liquid for injection, with enough liquid in it for one shot. Each vial delivers 120 mg of denosumab. XGEVA is supplied in a carton containing 1 vial.

WARNINGS AND PRECAUTIONS

What important information do I need to know about taking XGEVA?

XGEVA contains the same medicine as another drug called PROLIA, but at a different dose. If you are being treated with XGEVA, you should not be taking PROLIA or vice versa.

Hypocalcemia (low calcium levels in the blood)

XGEVA may lower levels of calcium in your blood. In the postmarketing setting, cases of low blood calcium with severe symptoms, including death, have been reported. If you have low blood calcium before you start receiving XGEVA, it may get worse during treatment. Your low blood calcium must be treated before you receive XGEVA. Most people with low calcium levels do not have symptoms, but some people may have symptoms. When the calcium levels in your blood go down, your body tries to correct the calcium levels by increasing the amount of a hormone made by your parathyroid glands (parathyroid hormone) in your blood. Call your doctor right away if you have symptoms of low blood calcium such as:

- Spasms, twitches, or cramps in your muscles.
- Numbness or tingling in fingers, toes or around the mouth.

Conditions which increase the risk of low blood calcium:

- If you cannot take daily calcium and/or vitamin D.
- If you have severe kidney disease or are on dialysis.

Your doctor will tell you to take calcium and vitamin D to help prevent low calcium levels in your blood while you take XGEVA, unless your blood calcium is high. Take calcium and vitamin D as your doctor tells you to.

Osteonecrosis of the Jaw (sore in mouth involving gums or jaw bones)

Severe jaw bone problems may happen when you take XGEVA. Your doctor should examine your mouth before you start XGEVA. Your doctor may tell you to see your dentist before you start XGEVA. It is important for you to practice good mouth care such as brushing and flossing your teeth regularly during treatment with XGEVA.

Tell your doctor immediately about any dental symptoms, including pain or unusual feeling in your teeth or gums, or any dental infections. If possible, you should not undergo tooth extraction or other dental procedures (excluding regular dental cleaning) while you are receiving treatment with XGEVA without talking to your doctor first.

If you do need dental work, tell your dentist that you are receiving XGEVA and tell your doctor that you are having dental work done.

Unusual Thigh Bone Fractures

Unusual fracture in the thigh bone may occur with some medicines, including XGEVA. Contact your doctor if you experience new or unusual pain in your hip, groin, or thigh.

High Calcium Levels in the Blood after Stopping Treatment with XGEVA

Some patients, who are still growing during treatment with XGEVA, have developed high calcium levels in the blood weeks to months after stopping treatment.

Your doctor will monitor you for signs and symptoms of high levels of calcium, after you stop receiving XGEVA.

Skin Infections

Tell your doctor promptly if you develop a swollen, red area on your skin that feels hot and tender with symptoms of fever (cellulitis) while taking XGEVA.

Pregnancy or Breast-Feeding

XGEVA is not recommended for use in women who are pregnant or plan to become pregnant and nursing mothers. XGEVA may interfere with normal bone and tooth development in fetuses and nursing babies, and may interfere with breastfeeding.

XGEVA is not intended for use in pregnant women. You should not be given XGEVA if you are pregnant. A highly effective method of birth control should be used when taking XGEVA, or for at least 5 months after the last dose of XGEVA.

It is not known whether XGEVA is excreted into human milk.

Use in Children

XGEVA is not recommended for anyone under 18 years of age except for adolescents with giant cell tumor of bone whose bones have stopped growing. The use of XGEVA has not been studied in children and adolescents with other cancers that have spread to bone.

INTERACTIONS WITH THIS MEDICATION

Before starting XGEVA, tell your doctor about all the medicines you take, including prescription and non-prescription drugs, vitamins and herbal supplements.

Interactions between XGEVA and other drugs have not been studied.

PROPER USE OF THIS MEDICATION

XGEVA is administered as a single injection under the skin (subcutaneous) once every four weeks. You should not inject XGEVA into the muscle (intramuscular), into your veins (intravenous) or between the layers of the skin (intradermal). The injection can be in your upper arm, upper thigh, or abdomen. The injection should be administered under the supervision of your doctor who is familiar with this drug. You may be able to give yourself XGEVA injections only if you have been trained in giving the injection and your doctor thinks you are capable of doing it correctly and if your doctor follows up with you as necessary.

Before injection, remove the vial from the refrigerator and allow it to reach room temperature (up to 25°C) in the original container. This will make the injection more comfortable. Do not shake. See instructions for injection.

Keep all medicines, including XGEVA, away from children.

Do not share XGEVA product with others, even if they have a similar disease.

Usual dose

The usual dose of XGEVA is 120 mg administered once every 4 weeks. If you are being treated for giant cell tumor of bone or hypercalcemia of malignancy, you will receive an additional dose 1 week and 2 weeks after the first dose in the first month of treatment only.

You should also take supplements of calcium and vitamin D as instructed by your doctor.

Overdose

In case of drug overdose, contact a health care practitioner, hospital emergency department or regional Poison Control Centre immediately, even if there are no symptoms.

Missed Dose

If you miss a dose you should try to receive that dose as soon as you can. In order for XGEVA to work properly, XGEVA needs to be given every 4 weeks. Continue to schedule your doses every four weeks.

INSTRUCTIONS FOR INJECTION

IMPORTANT: TO HELP AVOID CONTAMINATION AND POSSIBLE INFECTION DUE TO INJECTION, PLEASE READ AND FOLLOW THESE INSTRUCTIONS CAREFULLY.

How to prepare for XGEVA injection

XGEVA is available as a liquid in vials. When you receive your XGEVA, always check to see that:

- The name XGEVA appears on the package and vial label.
- The expiration date on the vial label has not passed. **Do not use a vial after the date on the label.**
- The XGEVA liquid in the vial is clear, colourless to slightly yellow.

Only use disposable syringes and needles. Use the syringes only once and dispose of them as instructed by your doctor or nurse.

Setting up for an injection

1. Find a clean flat working surface, such as a table.
2. Remove the vial of XGEVA from the refrigerator. Allow XGEVA to reach room temperature (this takes about 15 to 30 minutes). Vials should be used only once. DO NOT SHAKE THE VIAL. Shaking may damage the XGEVA. If the vial has been shaken vigorously, the solution may appear foamy and it should not be used.
3. Assemble the supplies you will need for an injection:

- XGEVA vial and sterile disposable syringe and a 27-gauge needle.
- Two alcohol swabs and one cotton ball or gauze pad.
- Puncture-proof disposal container.

4. Clean your work surface thoroughly and wash your hands with soap and warm water.

Selecting and preparing the injection site

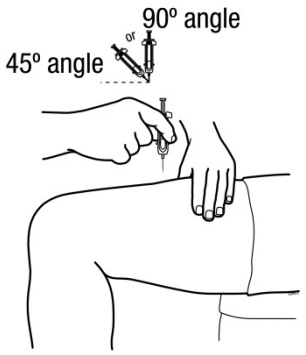
1. Choose an injection site. The recommended injection sites for XGEVA are:
   - The outer area of your upper arms.
   - The abdomen, except for the two-inch (5 cm) area around your navel.
   - The top of your thighs.

How to prepare the dose of XGEVA in vials

1. Take the cap off the vial. Clean the stopper with an alcohol swab.
2. Check the package containing the syringe. If the package has been opened or damaged, do not use that syringe. Dispose of that syringe in the puncture-proof disposal container. If the syringe package is undamaged, open the package and remove the syringe.
3. Keep the vial on your flat working surface and insert the needle straight down through the rubber stopper. Do not put the needle through the rubber stopper more than once.
4. Push the plunger of the syringe down and inject the air from the syringe into the vial of XGEVA. Keeping the needle inside the vial, turn the vial upside down. Make sure that the tip of the needle is in the XGEVA liquid.
5. Keeping the vial upside down, slowly pull back on the plunger to fill the syringe with XGEVA liquid. Withdraw the entire content of the vial.
6. Keeping the needle in the vial, turn the syringe needle up and check for air bubbles in the syringe. If there are air bubbles, gently tap the syringe with your fingers until the air bubbles rise to the top of the syringe. Then slowly push the plunger up to force the air bubbles out of the syringe.
7. Remove the syringe from the vial but **do not lay it down** or let the needle touch anything.

Injecting the dose of XGEVA

1. Hold the syringe in the hand you will use to inject XGEVA. With the other hand, clean the injection site with an alcohol swab. Use a circular motion from the inside to the outside of the injection site.
2. Pinch a fold of skin at the cleaned injection site.
3. Holding the syringe like a pencil, use a quick "dart-like" motion to insert the needle either straight up and down (90-degree angle) or at a slight angle (45 degrees) into the skin.



4. After the needle is inserted, let go of the skin. Inject the prescribed dose subcutaneously as directed by your doctor, nurse or pharmacist.
5. When the syringe is empty, pull the needle out of the skin and place a cotton ball or gauze over the injection site and press for several seconds.
6. Use a syringe, needle and vial only once. DO NOT put the needle cover (the cap) back on the needle. Discard the vial with any remaining XGEVA liquid.

Disposal of syringes, needles and vials

You should always follow the instructions given by your doctor, nurse, or pharmacist on how to properly dispose of containers with used syringes, needles and vials. There may be special provincial or local laws for disposal of used needles and syringes.

- Place all used needles, needle covers, syringes, and vials (empty or unused contents) into a "Sharps" container given to you by your doctor or pharmacist or in a hard-plastic container with a screw-on cap, or a metal container with a plastic lid, labelled "used syringes." Do not use glass or clear plastic containers.
- When the container is full, tape around the cap or lid to make sure the cap or lid does not come off. **Do not throw the container in the household trash. Do not recycle.**
- **Always** keep the container out of the reach of children.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

Like all medicines, XGEVA can cause side effects, although not everybody gets them.

Possible side effects include:

- Low blood calcium (hypocalcemia).

  Symptoms of low blood calcium may include muscle spasms, twitches, cramps, numbness or tingling in fingers, toes or around the mouth.
- Skin infection with swollen, red area of skin that feels hot and tender and may be accompanied by fever (cellulitis).
- Sore in mouth involving gums or jaw bones.
- Shortness of breath (dyspnea)
- Low phosphate levels in the blood (hypophosphatemia)
- Allergic reactions (eg, rash, hives, or in rare cases, swelling of the face, lips, tongue, throat, or trouble breathing)

- Unusual thigh bone fractures
- Pain, sometimes severe, in the muscles, joints, arms, legs or back.
- High calcium levels in the blood (hypercalcemia) after stopping treatment in patients who are still growing while on treatment with XGEVA.

These are not all the possible side effects of XGEVA. Tell your doctor if you have any side effect that bothers you or that does not go away. For more information, ask your doctor or pharmacist.

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM

Symptom / effect		Talk with your doctor or pharmacist		Stop taking drug and call your doctor or pharmacist
		Only if severe	In all cases	
Common (more than 1 in 100)	Sore in mouth involving gums or jaw bones (Osteonecrosis of the jaw)		√	
	Low calcium levels in the blood (muscle spasms, twitches, cramps, numbness or tingling in fingers, toes or around the mouth)		√	
Uncommon (less than 1 in 100)	Skin infection (mainly cellulitis) leading to hospitalization		√	

This is not a complete list of side effects. For any unexpected effects while taking XGEVA, contact your doctor or pharmacist.

HOW TO STORE IT

Keep out of the reach and sight of children.

Store XGEVA in your refrigerator at 2°C to 8°C until the time of your injection. Do not freeze.

When removed from the refrigerator, XGEVA must be kept at room temperature (up to 25°C) in the original carton and must be used within 30 days.

Store in original carton in order to protect from light. Do not shake XGEVA.

Do not use XGEVA after the expiry date which is printed on the carton and label. The expiry date refers to the last day of that month.

Medicines should not be disposed of via wastewater or household waste. Ask your pharmacist how to dispose of medicines that are no longer required.

REPORTING SUSPECTED SIDE EFFECTS

You can report any suspected adverse reactions associated with the use of health products to the Canada Vigilance Program by one of the following 3 ways:

- Report online at www.healthcanada.gc.ca/medeffect
- Call toll-free at 1-866-234-2345
- Complete a Canada Vigilance Reporting Form and:
  - Fax toll-free to 1-866-678-6789, or
  - Mail to: Canada Vigilance Program
    Health Canada
    Postal Locator 0701D
    Ottawa, Ontario
    K1A 0K9

Postage paid labels, Canada Vigilance Reporting Form and the adverse reaction reporting guidelines are available on the MedEffect® Canada Web site at www.healthcanada.gc.ca/medeffect.

Note: Should you require information related to the management of side effects, contact your health professional. The Canada Vigilance Program does not provide medical advice.

MORE INFORMATION

For more information or to obtain the full product monograph, prepared for health professionals, please refer to www.xgeva.ca.

The Victory Program phone number is 1-888-706-4717.

The Amgen Canada Medical Information phone number is 1-866-502-6436.

This leaflet was prepared by Amgen Canada Inc.

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