

PRODUCT MONOGRAPH

PrXGEVA[®]
(denosumab)

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

Professed Standard

RANK Ligand Inhibitor
(Bone Metabolism Regulator)

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Table of Contents

PART I: HEALTH PROFESSIONAL INFORMATION.....	3
SUMMARY PRODUCT INFORMATION	3
DESCRIPTION.....	3
INDICATIONS AND CLINICAL USE.....	3
CONTRAINDICATIONS	4
WARNINGS AND PRECAUTIONS.....	4
ADVERSE REACTIONS.....	7
DRUG INTERACTIONS	18
DOSAGE AND ADMINISTRATION	18
OVERDOSAGE	19
ACTION AND CLINICAL PHARMACOLOGY	19
STORAGE AND STABILITY.....	21
DOSAGE FORMS, COMPOSITION AND PACKAGING	21
PART II: SCIENTIFIC INFORMATION	22
PHARMACEUTICAL INFORMATION.....	22
CLINICAL TRIALS.....	22
DETAILED PHARMACOLOGY	25
TOXICOLOGY	26
REFERENCES	30
PART III: CONSUMER INFORMATION.....	32

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 <i>For a complete listing see Dosage Forms, Composition and Packaging section.</i>

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**).

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. XGEVA is not indicated for use in pediatric patients (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.

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 receive PROLIA.

Endocrine and Metabolism

Hypocalcemia

XGEVA can cause severe hypocalcemia. Pre-existing hypocalcemia must be corrected prior to initiating therapy with XGEVA. Monitor calcium levels and administer calcium, magnesium, and vitamin D as necessary. Monitor levels more frequently when XGEVA is administered with other drugs that can also lower calcium levels. If hypocalcemia occurs while receiving XGEVA, additional short-term calcium supplementation may be necessary (see **DOSAGE AND ADMINISTRATION, and ADVERSE REACTIONS**).

Based on clinical trials using a lower dose of denosumab, patients with a creatinine clearance less than 30 mL/min or receiving dialysis are at a greater risk of hypocalcemia compared to patients with normal renal function. The risk of hypocalcemia at the recommended dosing schedule of 120 mg every 4 weeks has not been evaluated in patients with a creatinine clearance less than 30 mL/min or receiving dialysis (see **Special Populations – Renal Impairment**).

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.

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, 2.2% of patients receiving XGEVA developed ONJ (see **ADVERSE REACTIONS**).

An oral exam should be performed by the prescriber prior to initiation of XGEVA treatment and a dental examination with appropriate preventive dentistry should be considered prior to treatment with XGEVA. Good oral hygiene practices should be maintained during treatment with XGEVA. While on treatment, patients should avoid invasive dental procedures. 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.

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.

In an embryofetal developmental study, cynomolgus monkeys received subcutaneous denosumab weekly during organogenesis at AUC exposures up to 9.1-fold higher than exposures for the recommended human dose of 120 mg every 4 weeks [corresponding to a 6.5-fold higher dose based on body weight (mg/kg)]. No evidence of maternal toxicity or fetal harm was observed. However, this study only assessed fetal toxicity during the first trimester, and fetal lymph nodes were not examined. Potential adverse developmental effects resulting from exposures during the second and third trimesters have not been assessed in animals.

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 who become pregnant during XGEVA treatment are encouraged to enroll in Amgen’s Pregnancy Surveillance Program. Patients or their physicians should call 1-866-51-AMGEN (1-866-512-6436) to enroll.

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**).

Women who are nursing during XGEVA treatment are encouraged to enroll in Amgen's Lactation Surveillance Program. Patients or their physicians should call 1-866-51-AMGEN (1-866-512-6436) to enroll.

Pediatrics

XGEVA is not recommended for use in pediatric patients. The safety and effectiveness of XGEVA in pediatric patients have not been established.

Treatment with XGEVA may impair bone growth in children with open growth plates and may inhibit eruption of dentition. In neonatal rats, inhibition of RANKL (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 2.7 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 (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

Patients with severe renal impairment (creatinine clearance < 30 mL/min or on dialysis) were excluded from pivotal clinical studies (see **CLINICAL TRIALS**).

Based on clinical trials using a lower dose of denosumab, patients with a creatinine clearance less than 30 mL/min or receiving dialysis are at greater risk of severe hypocalcemia compared to patients with normal renal function.

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

Calcium levels should be monitored as necessary while receiving XGEVA. Calcium levels should be monitored more frequently when XGEVA is administered with other drugs that can also lower calcium levels.

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 receiving XGEVA (per-patient incidence greater than or equal to 25%) were fatigue/asthenia, hypophosphatemia, and nausea (see Table 1).

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

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

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.

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 $\geq 1\%$ of patients in these studies.

Table 1. Percentage of Patients with Adverse Events \geq 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)

SYSTEM ORGAN CLASS	Denosumab (N = 2841)	Zoledronic Acid (N = 2836)
Preferred Term	n (%)	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)
HEPATOBIILIARY 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)
Respiratory tract infection	40 (1.4)	36 (1.3)
Sepsis	37 (1.3)	34 (1.2)
Pharyngitis	35 (1.2)	41 (1.4)

SYSTEM ORGAN CLASS	Denosumab	Zoledronic Acid
Preferred Term	(N = 2841)	(N = 2836)
	n (%)	n (%)
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)
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS		
Back pain	718 (25.3)	747 (26.3)
Arthralgia	570 (20.1)	632 (22.3)

SYSTEM ORGAN CLASS	Denosumab	Zoledronic Acid
Preferred Term	(N = 2841)	(N = 2836)
	n (%)	n (%)
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)
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)

SYSTEM ORGAN CLASS	Denosumab (N = 2841)	Zoledronic Acid (N = 2836)
Preferred Term	n (%)	n (%)
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)
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)

SYSTEM ORGAN CLASS	Denosumab	Zoledronic Acid
Preferred Term	(N = 2841)	(N = 2836)
	n (%)	n (%)
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%)

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, hemochezia, loose tooth, hypoesthesia oral, odynophagia, intestinal obstruction, aphthous stomatitis, gastrointestinal hemorrhage, hematemeses, 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 discoloration, 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*

HEPATOBIILIARY 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, peri-arthritis, 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, fornication, 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 discoloration, rash erythematous, eczema, nail discoloration, blister, petechiae, skin disorder, periorbital edema, dermatitis contact, skin nodule, subcutaneous nodule, skin irritation, onychoclasia, 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, photodermatitis, 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

Hypocalcemia

In clinical trials in patients with advanced cancer, 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**).

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

In a trial of 55 patients, without cancer and with varying degrees of renal impairment, who received a single dose of 60 mg denosumab and not treated with calcium and vitamin D, 8 of 17 patients with a creatinine clearance less than 30 mL/min or receiving dialysis experienced

corrected serum calcium levels less than 8.0 mg/dL as compared to 0 of 12 patients with normal renal function. The risk of hypocalcemia at the recommended dosing schedule of 120 mg every 4 weeks has not been evaluated in patients with a creatinine clearance less than 30 mL/min or receiving dialysis.

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 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.

When events occurring during the extended double-blind treatment phase of approximately 4 months in each study are included, the incidence of confirmed ONJ was 2.2% in patients who received XGEVA and 1.6% in patients who received zoledronic acid.

Malignancies

From a pooled safety analysis of 3 pivotal 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

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**).

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

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

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

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 discoloration 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.

Administration should be performed by an individual who has been trained in giving subcutaneous injections.

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

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.

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.

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). With multiple SC doses of 120 mg every 4 weeks in subjects with advanced breast cancer, 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. 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. 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

In a study of 55 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. Dose adjustment for renal impairment is not required.

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

Study demographics and trial design

Table 2. 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 3.

Table 3. 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 4). 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 4. Summary of Exploratory Tumour Outcomes

Endpoint	XGEVA vs Zoledronic acid Hazard Ratio					
	Study 1		Study 2		Study 3	
	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

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 2.7 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.

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 9.1- to 15-fold higher than the human exposure for 120 mg SC administered once every 4 weeks.

Table 5. 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 ophthalmoscopy, 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

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
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	<i>In Vitro</i>	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	<i>In Vitro</i>	1 or 10 mcg/mL	N/A	Staining of lymphoid tissue in monkey, but no staining in human tissue was observed.	N/A
	Human	N/A	<i>In Vitro</i>	1 or 10 mcg/mL	N/A	Staining of lymphoid tissue was observed.	N/A

N/A = not applicable

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PART III: CONSUMER INFORMATION

PrXGEVA®
(denosumab)

pronounced ex-jee-va

This leaflet 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 leaflet 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.

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 break down 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.

When it should not be used

You should not be given XGEVA if:

- you are allergic to denosumab or any other ingredient of XGEVA.

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 PROLIA, which is used to treat osteoporosis in women after menopause. XGEVA, which is given at a higher dose 1 time every 4 weeks, should not be used to treat this condition.

Hypocalcemia (low calcium levels in the blood)

XGEVA may lower levels of calcium in your blood. 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. 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.

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.

Pregnancy Surveillance Program: XGEVA is not intended for use in pregnant women. If you become pregnant while taking XGEVA, talk to your doctor about enrolling with Amgen's Pregnancy Surveillance Program, or call 1-866-51-AMGEN (1-866-512-6436). The purpose of this program is to collect information about women who have become pregnant while taking XGEVA.

Lactation Surveillance Program: It is not known whether XGEVA is excreted into human milk. If you are nursing while taking XGEVA, talk to your doctor about enrolling with Amgen's

Lactation Surveillance Program, or call 1-866-51-AMGEN (1-866-512-6436). The purpose of this program is to collect information about women who are nursing while taking XGEVA.

Use in Children

XGEVA is not recommended for anyone under 18 years of age. The use of XGEVA in children and adolescents has not been studied.

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. The injection can be in your upper arm, upper thigh, or abdomen. It can be given by an individual who is trained in giving subcutaneous injections.

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. 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

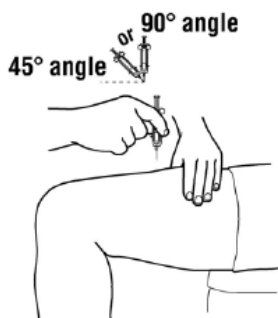
1. Take the cap off the vial. Clean the stopper with an alcohol swab.
2. Check the package containing the syringe. If the package has been opened or damaged, do not use that syringe. Dispose of that syringe in the puncture-proof disposal container. If the syringe package is undamaged, open the package 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.

- Remove the syringe from the vial but **do not lay it down** or let the needle touch anything.

Injecting the dose of XGEVA

- 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.
- Pinch a fold of skin at the cleaned injection site.
- 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.



- After the needle is inserted, let go of the skin. Inject the prescribed dose subcutaneously as directed by your doctor, nurse or pharmacist.
- 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.
- 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.

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		√	
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.

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