PRODUCT MONOGRAPH

[Pr]Prolia®

(denosumab)

60 mg/mL solution for injection
Prefilled Syringe or Vial[†]

Professed Standard

RANK Ligand Inhibitor
(Bone Metabolism Regulator)

Physicians should become fully familiarized with the efficacy/safety profile of PROLIA and the full content of the Product Monograph prior to prescribing the drug.

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Date of Authorization:
August 13, 2013

Submission Control No: 158891

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[Pr]Prolia®

(denosumab)

PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	Clinically Relevant Nonmedicinal Ingredients
Subcutaneous	Solution for injection / 60 mg denosumab in 1 mL solution in a single use prefilled syringe	Single use prefilled syringe: sorbitol, acetate, polysorbate 20, water for injection (USP) and sodium hydroxide.
	60 mg denosumab in 1 mL solution in a single use vial†	Single use vial†: sorbitol, acetate, water for injection (USP) and sodium hydroxide.
		For a complete listing see Dosage Forms, Composition and Packaging section.

† 60 mg/1.0mL single use vial is not available in Canada.

DESCRIPTION

PROLIA (denosumab) is a human IgG2 monoclonal antibody with affinity and specificity for human RANK ligand (RANKL) that inhibits RANKL from activating its receptor, RANK, on the surface of osteoclasts and their precursors. Prevention of RANKL-RANK interaction inhibits osteoclast formation, function and survival, thereby decreasing bone resorption. Denosumab has an approximate molecular weight of 147 kDa and is produced in genetically engineered mammalian (Chinese Hamster Ovary) cells.

PROLIA is supplied as a single use, sterile, preservative-free, clear, colourless to slightly yellow solution formulated at pH 5.2. PROLIA is supplied in either a 60 mg/mL prefilled syringe (PFS) or a 60 mg/mL vial† presentation with a 1.0 mL volume and intended for delivery by subcutaneous injection.

INDICATIONS AND CLINICAL USE

Postmenopausal Osteoporosis

PROLIA (denosumab) is indicated for the treatment of postmenopausal women with osteoporosis at high risk for fracture, defined as a history of osteoporotic fracture, or multiple risk factors for fracture; or patients who have failed or are intolerant to other available osteoporosis therapy. In postmenopausal women with osteoporosis, PROLIA reduces the incidence of vertebral, nonvertebral and hip fractures (see **CLINICAL TRIALS**).

Treatment to Increase Bone Mass in Men with Osteoporosis at High Risk for Fracture

PROLIA is indicated as a treatment to increase bone mass in men with osteoporosis at high risk for fracture, defined as a history of osteoporotic fracture, or multiple risk factors for fracture; or patients who have failed or are intolerant to other available osteoporosis therapy (see **CLINICAL TRIALS**).

Geriatrics (≥ 65 years of age)

The majority of patients treated with PROLIA in the postmenopausal osteoporosis (PMO) clinical trial were ≥ 65 years old (see **WARNINGS AND PRECAUTIONS, Special Populations, Geriatrics**).

Of the patients in the osteoporosis study in men, 133 patients (55%) were ≥ 65 years old, while 39 patients (16%) were ≥ 75 years old.

Pediatrics

The safety and efficacy of PROLIA have not been studied in pediatric populations. PROLIA is not indicated for use in pediatric patients (see **WARNINGS AND PRECAUTIONS, Special Populations, Pediatrics**).

CONTRAINDICATIONS

- Patients who are hypersensitive to the drug or any component of the product. For a complete listing, see the **DOSAGE FORMS, COMPOSITION AND PACKAGING** section of the product monograph. Anaphylactic reactions have been reported (see **ADVERSE REACTIONS, Postmarket Adverse Drug Reactions**).
- Hypocalcemia

WARNINGS AND PRECAUTIONS

General

Adequate intake of calcium and vitamin D is important in all patients.

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

Endocrine and Metabolism

Hypocalcemia

Hypocalcemia must be corrected by adequate intake of calcium and vitamin D prior to initiating therapy with PROLIA. Other disorders affecting mineral metabolism (such as vitamin D deficiency) should be treated. In patients predisposed to hypocalcemia (eg, history of hypoparathyroidism, thyroid surgery, parathyroid surgery, malabsorption syndromes, excision of small intestine, severe renal impairment [creatinine clearance < 30 mL/min] or receiving dialysis), clinical monitoring of calcium levels is recommended (see **Monitoring and Laboratory Tests**). Patients should be advised to report to their physicians any symptoms of hypocalcemia, such as paresthesias or muscle spasms (see **ADVERSE REACTIONS, Hypocalcemia**).

Infections

In a 3-year clinical trial in women with postmenopausal osteoporosis, serious infections leading to hospitalization were reported more frequently in the PROLIA group (4.1%) than in the placebo group (3.4%). Skin infections leading to hospitalization were reported more frequently in the PROLIA (0.4%) versus the placebo (< 0.1%) groups. These cases were predominantly cellulitis. As well, infections of the abdomen, urinary tract, and ear, were more frequent in patients treated with PROLIA. Endocarditis was also reported more frequently in PROLIA-treated patients (< 0.1% PROLIA group; 0% placebo group). The incidence of opportunistic infections was balanced between PROLIA and placebo groups and the overall incidence of skin infections was similar between the PROLIA (1.5%) and placebo (1.2%) groups. Patients should be advised to seek prompt medical attention if they develop signs or symptoms of severe infection, including cellulitis and erysipelas (see **ADVERSE REACTIONS, Infections**).

Patients on concomitant immunosuppressant agents or with impaired immune systems may be at increased risk for serious infections. Consider the benefit-risk profile in such patients before treating with PROLIA. In patients who develop serious infections while on PROLIA, prescribers should assess the need for continued PROLIA therapy.

Dermatologic

In a large, 3-year clinical trial of over 7800 women with postmenopausal osteoporosis, epidermal and dermal adverse events such as dermatitis, eczema, and rashes occurred at a significantly higher rate in the PROLIA (10.8%) group compared to the placebo (8.2%) group. Most of these events were not specific to the injection site. Consider discontinuing PROLIA if severe symptoms develop (see **ADVERSE REACTIONS, Dermatologic**).

Osteonecrosis of the Jaw (ONJ)

Osteonecrosis of the jaw (ONJ) has been reported in patients treated with denosumab or bisphosphonates, another class of anti-resorptive agents. Most cases have been in cancer patients; however some have occurred in patients with osteoporosis. ONJ has been reported in clinical studies in patients receiving denosumab at a dose of 60 mg every 6 months for osteoporosis. There have been reports of ONJ in clinical studies in patients with advanced cancer treated with denosumab at the studied dose of 120 mg administered every 4 weeks.

Known risk factors for ONJ include a diagnosis of cancer with bone lesions, concomitant therapies (eg, chemotherapy, antiangiogenic biologics, corticosteroids, radiotherapy to head and neck), poor oral hygiene, dental extractions, and co-morbid disorders (eg, pre-existing dental disease, anemia, coagulopathy, infection).

A dental examination with appropriate preventative dentistry should be considered prior to treatment with PROLIA in patients with risk factors for ONJ such as invasive dental procedures (eg, tooth extraction, dental implants, oral surgery), diagnosis of cancer, concomitant therapies (eg, chemotherapy, corticosteroids) poor oral hygiene, and co-morbid disorders (eg, periodontal and/or other pre-existing dental disease, anemia, coagulopathy, infection, ill-fitting dentures).

Good oral hygiene practices should be maintained during treatment with PROLIA. If ONJ occurs during treatment with PROLIA, use clinical judgment and guide the management plan of each patient based on individual benefit/risk evaluation (see **ADVERSE REACTIONS, Osteonecrosis of the Jaw (ONJ)**.

Atypical Femoral Fractures

Atypical femoral fractures have been reported in patients receiving PROLIA. 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 arthritis, hypophosphatasia) and with use of certain pharmaceutical agents (eg, bisphosphonates, glucocorticoids, proton pump inhibitors). These events have also occurred without antiresorptive therapy. During PROLIA 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.

Suppression of Bone Turnover

In clinical trials in women with postmenopausal osteoporosis, treatment with PROLIA resulted in significant suppression of bone remodeling as evidenced by markers of bone turnover and bone histomorphometry. The significance of these findings and the effect of long-term treatment with PROLIA are unknown. Monitor patients for osteonecrosis of the jaw, atypical fractures, and delayed fracture healing (see **ADVERSE REACTIONS, Fracture Healing, Osteonecrosis of the Jaw (ONJ); ACTION AND CLINICAL PHARMACOLOGY, Pharmacodynamics; CLINICAL TRIALS, Bone Histology and Histomorphometry**).

Malignancies

See **Clinical Trial Adverse Drug Reactions**.

Special Populations

Pregnant Women

There have been no studies in pregnant women.

PROLIA is indicated only for women who are postmenopausal (see also **Pediatrics** below*)* and is not recommended for women who could become pregnant. Women who become pregnant during PROLIA treatment are encouraged to enrol in Amgen's Pregnancy Surveillance Program. Patients or their physicians should call 1-866-51-AMGEN (1-866-512-6436) to enrol.

Developmental toxicity studies have been performed in cynomolgus monkeys at AUC exposures of up to 100-fold higher than the human exposure. No evidence of impaired fertility was observed.

In a study of cynomolgus monkeys dosed with denosumab during the period equivalent to the first trimester at AUC exposures up to 99-fold higher than the human dose (60 mg every 6 months), 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 post-natal 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.

Studies in mice suggest absence of RANKL during pregnancy may interfere with maturation of the mammary gland leading to impaired lactation postpartum.

Nursing Women

PROLIA is not recommended for use in nursing women (see also **Pediatrics** below*).* It is not known whether PROLIA is excreted into human milk. Because PROLIA has the potential to cause adverse reactions in nursing infants, a decision should be made whether to discontinue nursing or discontinue the drug. Women who are nursing during PROLIA treatment are encouraged to enrol in Amgen's Lactation Surveillance Program. Patients or their physicians should call 1-866-51-AMGEN (1-866-512-6436) to enrol.

Males

PROLIA may cause fetal harm*.*

The extent to which PROLIA is present in seminal fluid is unknown. There is a potential for fetal exposure to PROLIA when a man treated with PROLIA has unprotected sexual intercourse with a pregnant partner. The risk of fetal harm is likely to be low. Advise men being treated with PROLIA of this potential risk to a partner who could become pregnant.

Pediatrics

The safety and effectiveness of PROLIA in pediatric patients have not been studied.

PROLIA is not recommended in pediatric patients. Adolescent primates (cynomolgus monkeys) dosed with denosumab at 27 and 150 times (10 and 50 mg/kg dose) the clinical exposure based on AUC had abnormal growth plates. In neonatal rats, inhibition of RANKL (target of denosumab therapy) with a construct of osteoprotegerin bound to Fc (OPG-Fc) at high doses was associated with inhibition of bone growth and tooth eruption. Therefore, treatment with PROLIA may inhibit bone growth in children with open growth plates and may inhibit eruption of dentition. In neonatal cynomolgus monkeys exposed in utero to denosumab at 50 mg/kg, there was increased post-natal 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, Animal Toxicology**).

Geriatrics (≥ 65 years of age)

Females

In the PMO clinical trial, 94.7% of the patients who received PROLIA were ≥ 65 years old and 31.6% were ≥ 75 years old. No overall differences in safety or efficacy were observed between patients ≥ 65 years old and patients ≥ 75 years old. Other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

Males

In the male osteoporosis trial, no overall differences in efficacy were observed in patients ≥ 65 years of age (N = 133) who received PROLIA, compared with younger patients. However, greater sensitivity of some older individuals cannot be ruled out.

There were 133 patients (55%) ≥ 65 years of age, of whom 39 patients (16%) were ≥ 75 years. The incidence of adverse events (AEs) in patients ≥ 65 and ≥ 75 years of age were 107 events in 50 patients (73.5%) and 30 events in 14 patients (70.0%) in the PROLIA group vs. 124 events in 43 patients (67.2%) and 45 events in 12 patients (63.2%) in the placebo group, respectively; the incidence of serious adverse events (SAEs) were 14 events in 10 patients (14.7%) and 5 events in 4 patients (20.0%) in the PROLIA group vs. 8 events in 6 patients (9.4%) and 1 event in 1 patient (5.3%) in the placebo group, respectively. The incidence of AEs in patients < 65 years of age were 61 events in 36 patients (69.2%) in the PROLIA group vs. 100 events in 41 patients (73.2%) in the placebo group; the incidence of SAEs in patients < 65 years of age were 2 events in 1 patient (1.9%) in the PROLIA group vs. 5 events in 4 patients (7.1%) in the placebo group.

For men with sexual partners who could become pregnant, see also **Special Populations, Pregnant Women**.

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 of denosumab; thus, dose adjustment for renal impairment is not necessary.

In clinical studies, patients with severe renal impairment (creatinine clearance < 30 mL/min) or receiving dialysis were at greater risk of developing hypocalcemia. Adequate intake of calcium and vitamin D is important in patients with severe renal impairment or receiving dialysis (see **WARNINGS AND PRECAUTIONS, Hypocalcemia**).

Hepatic Impairment

The safety and efficacy of PROLIA have not been studied in patients with hepatic impairment.

Monitoring and Laboratory Tests

In patients with a history of hypocalcemia, or signs and symptoms of hypocalcemia or predisposed to hypocalcemia (eg, history of hypoparathyroidism, thyroid surgery, parathyroid surgery, malabsorption syndromes, excision of small intestine, severe renal impairment [creatinine clearance < 30 mL/min] or receiving dialysis), clinical monitoring of calcium levels is recommended (see **WARNINGS AND PRECAUTIONS, Renal Impairment**).

Information to be Provided to the Patient

Patients must be adequately supplemented with calcium and vitamin D. All patients should be instructed on the importance of calcium and vitamin D supplementation in maintaining serum calcium levels. Patients should be advised to seek prompt medical attention if they develop signs or symptoms of hypocalcemia (eg, paresthesias or muscle spasms) (see **PART III: CONSUMER INFORMATION**).

Patients should be advised to seek prompt medical attention if they develop signs or symptoms of cellulitis.

Patients should be aware of the most commonly associated side effects of PROLIA therapy.

If a dose of PROLIA is missed, the injection should be administered as soon as convenient. Thereafter, injections should be scheduled every 6 months from the date of the last injection.

Latex Sensitivity Allergies

The patient or caregiver should be informed that the needle cap on the single use prefilled syringe contains dry natural rubber (a derivative of latex), which should not be handled by persons with a known sensitivity to latex.

ADVERSE REACTIONS

Adverse Drug Reaction Overview

A total of 8091 women (4050 PROLIA vs. 4041 placebo) were enrolled in placebo-controlled studies of women with postmenopausal osteoporosis or low bone mass (Study 1 and Study 2), and a total of 242 men (121 PROLIA vs. 121 placebo) were enrolled in a placebo-controlled study of men with osteoporosis (Study 5).

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.

Treatment of Postmenopausal Osteoporosis

The safety of PROLIA was assessed in clinical studies of up to 5 years in duration.

The safety of PROLIA in the treatment of postmenopausal osteoporosis was assessed in a large, 3-year, randomized, double-blind, placebo-controlled, multinational study of 7808 postmenopausal women aged 60 to 91 years with osteoporosis (Study 1). A total of 3876 women received placebo and 3886 women received PROLIA administered once every 6 months as a single 60 mg subcutaneous (SC) dose. All women received calcium (at least 1000 mg) and vitamin D (at least 400 IU) supplementation per day. The incidence of adverse events was 93% in both treatment groups (n = 3605 in the PROLIA group and 3607 in the placebo group). The 3 most common adverse events overall were back pain (1347 [34.7%] PROLIA, 1340 [34.6%] placebo), arthralgia (784 [20.2%] PROLIA, 782 [20.2%] placebo), and hypertension (614

[15.8%] PROLIA, 636 [16.4%] placebo). The most common adverse events (> 5% and more common than placebo) were back pain (1347 [34.7%] PROLIA, 1340 [34.6%] placebo), pain in extremity (453 [11.7%] PROLIA, 430 [11.1%] placebo), hypercholesterolemia (280 [7.2%] PROLIA, 236 [6.1%] placebo), musculoskeletal pain (297 [7.6%] PROLIA, 291 [7.5%] placebo) and cystitis (228 [5.9%] PROLIA, 225 [5.8%] placebo). The incidence of serious adverse events was 25.8% (n = 1004) in the PROLIA group and 25.1% (n = 972) in the placebo group. The 3 most common serious adverse events were osteoarthritis (63 [1.6%] PROLIA, 79 [2.0%] placebo), atrial fibrillation (36 [0.9%] PROLIA, 33 [0.9%] placebo), and pneumonia (34 [0.9%] PROLIA, 36 [0.9%] placebo). Deaths occurred in 70 subjects (1.8%) in the denosumab group and 90 subjects (2.3%) in the placebo group. Adverse events leading to treatment discontinuation occurred in 192 (4.9%) women in the PROLIA group and 202 (5.2%) women in the placebo group. The 3 most common adverse events leading to treatment discontinuation were breast cancer (including patients with a history of breast cancer) (20 [0.5%] PROLIA, 10 [0.3%] placebo), back pain (6 [0.2%] PROLIA, 10 [0.3%] placebo), and constipation (6 [0.2%] PROLIA, 6 [0.2%] placebo). Cardiac disorders leading to discontinuation were reported in 14 patients (0.4%) in the PROLIA group and 3 patients (< 0.1%) in the placebo group.

Adverse events reported in ≥ 1% of postmenopausal women with osteoporosis are shown in Table 1.

Table 1. Adverse Events Occurring in ≥ 1% of Patients with Postmenopausal Osteoporosis

SYSTEM ORGAN CLASS Preferred Term	PROLIA (N = 3886) n (%)	Placebo (N = 3876) n (%)
BLOOD AND LYMPHATIC SYSTEM DISORDERS		
Anemia	129 (3.3)	107 (2.8)
CARDIAC DISORDERS		
Angina pectoris	101 (2.6)	87 (2.2)
Atrial fibrillation	79 (2.0)	77 (2.0)
Palpitations	59 (1.5)	59 (1.5)
Cardiac failure	53 (1.4)	38 (1.0)
Arrhythmia	41 (1.1)	41 (1.1)
EAR AND LABYRINTH DISORDERS		
Vertigo	195 (5.0)	187 (4.8)
Tinnitus	35 (0.9)	55 (1.4)
ENDOCRINE DISORDERS		
Hypothyroidism	62 (1.6)	59 (1.5)
EYE DISORDERS		
Cataract	229 (5.9)	253 (6.5)
Glaucoma	59 (1.5)	64 (1.7)
Conjunctivitis	48 (1.2)	59 (1.5)
GASTROINTESTINAL DISORDERS		
Constipation	355 (9.1)	361 (9.3)
Diarrhea	228 (5.9)	236 (6.1)
Dyspepsia	178 (4.6)	212 (5.5)
Nausea	178 (4.6)	193 (5.0)
Abdominal pain	146 (3.8)	149 (3.8)
Abdominal pain upper	129 (3.3)	111 (2.9)
Gastritis	99 (2.5)	109 (2.8)
Vomiting	91 (2.3)	93 (2.4)
Flatulence	84 (2.2)	53 (1.4)
Gastrooesophageal reflux disease	80 (2.1)	66 (1.7)
Hemorrhoids	55 (1.4)	50 (1.3)
Hiatus hernia	49 (1.3)	56 (1.4)
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS		
Edema peripheral	189 (4.9)	155 (4.0)
Fatigue	115 (3.0)	127 (3.3)
Asthenia	90 (2.3)	73 (1.9)
Noncardiac chest pain	84 (2.2)	90 (2.3)
Pain	47 (1.2)	55 (1.4)
Pyrexia	45 (1.2)	40 (1.0)
HEPATOBILIARY DISORDERS		
Cholelithiasis	52 (1.3)	69 (1.8)

Table 1. Adverse Events Occurring in ≥ 1% of Patients with Postmenopausal Osteoporosis

SYSTEM ORGAN CLASS Preferred Term	PROLIA (N = 3886) n (%)	Placebo (N = 3876) n (%)
INFECTIONS AND INFESTATIONS		
Nasopharyngitis	563 (14.5)	600 (15.5)
Influenza	331 (8.5)	335 (8.6)
Bronchitis	301 (7.7)	301 (7.8)
Urinary tract infection	245 (6.3)	253 (6.5)
Cystitis	228 (5.9)	225 (5.8)
Upper respiratory tract infection	190 (4.9)	167 (4.3)
Pneumonia	152 (3.9)	150 (3.9)
Sinusitis	101 (2.6)	121 (3.1)
Pharyngitis	91 (2.3)	78 (2.0)
Gastroenteritis	81 (2.1)	94 (2.4)
Herpes zoster	79 (2.0)	72 (1.9)
Lower respiratory tract infection	69 (1.8)	86 (2.2)
Viral infection	66 (1.7)	72 (1.9)
Rhinitis	63 (1.6)	84 (2.2)
Respiratory tract infection	55 (1.4)	69 (1.8)
Ear infection	43 (1.1)	21 (0.5)
Tooth infection	26 (0.7)	41 (1.1)
INJURY, POISONING AND PROCEDURAL COMPLICATIONS		
Fall	205 (5.3)	250 (6.4)
Contusion	162 (4.2)	192 (5.0)
Radius fracture	104 (2.7)	116 (3.0)
Joint sprain	60 (1.5)	65 (1.7)
Procedural pain	57 (1.5)	54 (1.4)
Humerus fracture	42 (1.1)	49 (1.3)
Rib fracture	40 (1.0)	33 (0.9)
Ulna fracture	37 (1.0)	39 (1.0)
Foot fracture	34 (0.9)	39 (1.0)
Lumbar vertebral fracture	25 (0.6)	72 (1.9)
Thoracic vertebral fracture	22 (0.6)	53 (1.4)
INVESTIGATIONS		
Weight decreased	41 (1.1)	49 (1.3)
METABOLISM AND NUTRITION DISORDERS		
Hypercholesterolemia	280 (7.2)	236 (6.1)
Diabetes mellitus	62 (1.6)	58 (1.5)
Hyperlipidemia	45 (1.2)	35 (0.9)
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS		
Back pain	1347 (34.7)	1340 (34.6)
Arthralgia	784 (20.2)	782 (20.2)
Pain in extremity	453 (11.7)	430 (11.1)
Osteoarthritis	436 (11.2)	442 (11.4)
Musculoskeletal pain	297 (7.6)	291 (7.5)
Muscle spasms	167 (4.3)	182 (4.7)
Bone pain	142 (3.7)	117 (3.0)

Table 1. Adverse Events Occurring in ≥ 1% of Patients with Postmenopausal Osteoporosis

SYSTEM ORGAN CLASS Preferred Term	PROLIA (N = 3886) n (%)	Placebo (N = 3876) n (%)
Neck pain	129 (3.3)	136 (3.5)
Myalgia	114 (2.9)	94 (2.4)
Spinal osteoarthritis	82 (2.1)	64 (1.7)
Musculoskeletal chest pain	61 (1.6)	63 (1.6)
Tendonitis	56 (1.4)	47 (1.2)
Joint swelling	55 (1.4)	66 (1.7)
Arthritis	48 (1.2)	53 (1.4)
NERVOUS SYSTEM DISORDERS		
Headache	237 (6.1)	258 (6.7)
Dizziness	217 (5.6)	218 (5.6)
Sciatica	178 (4.6)	149 (3.8)
Syncope	67 (1.7)	71 (1.8)
Paraesthesia	63 (1.6)	56 (1.4)
Memory impairment	52 (1.3)	37 (1.0)
PSYCHIATRIC DISORDERS		
Depression	213 (5.5)	221 (5.7)
Insomnia	126 (3.2)	122 (3.1)
Anxiety	123 (3.2)	123 (3.2)
RENAL AND URINARY DISORDERS		
Urinary incontinence	39 (1.0)	40 (1.0)
Renal cyst	23 (0.6)	39 (1.0)
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS		
Cough	224 (5.8)	238 (6.1)
Dyspnea	93 (2.4)	105 (2.7)
Asthma	66 (1.7)	65 (1.7)
Pharyngolaryngeal pain	52 (1.3)	67 (1.7)
Chronic obstructive pulmonary disease	38 (1.0)	39 (1.0)
SKIN AND SUBCUTANEOUS TISSUE DISORDERS		
Rash	96 (2.5)	79 (2.0)
Pruritus	87 (2.2)	82 (2.1)
Eczema	50 (1.3)	25 (0.6)
Alopecia	31 (0.8)	41 (1.1)
VASCULAR DISORDERS		
Hypertension	614 (15.8)	636 (16.4)
Varicose vein	58 (1.5)	60 (1.5)
Hematoma	38 (1.0)	51 (1.3)

N = Number of subjects who received ≥ 1 dose of investigational product
n = Number of subjects reporting ≥ 1 event
Includes only treatment-emergent adverse events

Less Common Clinical Trial Adverse Reactions* (< 1%)

MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS: *Arthralgia, Muscle spasms, Pain in extremity, Bone pain, Myalgia, Musculoskeletal stiffness, Musculoskeletal pain, Osteoarthritis, Neck pain, Exostosis, Joint swelling, Muscle fatigue, Limb discomfort, Tendonitis, Joint stiffness, Muscular weakness, Nodule on extremity, Fistula, Groin pain, Joint ankylosis, Limb deformity, Muscle hemorrhage, Rheumatoid arthritis, Spinal deformity, Spondylitis, Polymyalgia rheumatica, Sensation of heaviness, Arthritis, Bone callus excessive, Foot deformity, Muscle atrophy, Osteitis, Renal rickets, Resorption bone increased, Synovitis, Tendon pain, Tenosynovitis*

GASTROINTESTINAL DISORDERS: *Nausea, Constipation, Diarrhea, Vomiting, Abdominal pain, Flatulence, Abdominal pain upper, Dry mouth, Gastritis, Dyspepsia, Stomach discomfort, Abdominal distension, Abdominal discomfort, Abdominal pain lower, Coeliac disease, Faecalith, Frequent bowel movements, Gastric ulcer, Gastritis erosive, Gastrooesophageal reflux disease, Gingivitis, Glossodynia, Hemorrhoids, Irritable bowel syndrome, Oral cavity fistula, Pancreatitis, Pancreatitis acute, Rectal hemorrhage, Aphthous stomatitis, Change of bowel habit, Enterocolitis, Gastroduodenitis, Gastrointestinal hemorrhage, Lip swelling, Melaena, Oesophageal spasm, Rectal prolapse, Reflux oesophagitis, Tongue ulceration*

INFECTIONS AND INFESTATIONS: *Nasopharyngitis, Respiratory tract infection, Upper respiratory tract infection, Influenza, Urinary tract infection, Rhinitis, Lower respiratory tract infection, Pneumonia, Bronchitis, Cystitis, Sinusitis, Herpes zoster, Oral herpes, Pharyngitis, Herpes virus infection, Tinea pedis, Viral infection, Chlamydial infection, Eczema infected, Gastroenteritis viral, Herpes ophthalmic, Laryngitis, Liver abscess, Lung infection, Viremia, Borrelia infection, Chronic sinusitis, Diverticulitis, Furuncle, Genital infection fungal, Gingival infection, Hematoma infection, Helicobacter infection, Herpes simplex, Sialoadenitis, Tracheitis*

NERVOUS SYSTEM DISORDERS: *Headache, Dizziness, Paraesthesia, Lethargy, Somnolence, Hypoaesthesia, Ischemic stroke, Dysgeusia, Sciatica, Tremor, Parosmia, Syncope, Transient ischemic attack, Disturbance in attention, Epilepsy, Freezing phenomenon, Global amnesia, Guillain-Barre syndrome, Head discomfort, Hemicephalalgia, Hypotonia, Poor quality sleep, Trigeminal neuralgia, Hypersomnia, Loss of consciousness, Memory impairment, Ageusia, Amnesia, Anosmia, Dyskinesia, Formication, Intercostal neuralgia, Migraine, Muscle contractions involuntary, Neuritis cranial, Parkinson's disease, Parkinsonism, Restless legs syndrome*

GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS: *Asthenia, Fatigue, Injection site pain, Edema peripheral, Injection site erythema, Pain, Influenza like illness, Injection site irritation, Feeling hot, Malaise, Injection site bruising, Injection site reaction, Injection site hematoma, Injection site rash, Pyrexia, Noncardiac chest pain, Peripheral coldness, Chills, Injection site warmth, Chest discomfort, Feeling cold, Gait disturbance, Hernia, Impaired healing, Injection site discomfort, Injection site mass, Injection site swelling, Irritability, Injection site pruritus, Fat tissue increased, Injection site scab, Thirst*

SKIN AND SUBCUTANEOUS TISSUE DISORDERS: *Pruritus, Rash, Alopecia, Hyperhidrosis, Eczema, Dermatitis allergic, Erythema, Dry skin, Rash macular, Rash pruritic, Onychomadesis, Ecchymosis, Pruritus generalised, Dermatitis, Rosacea, Subcutaneous nodule, Blister, Dermatitis atopic, Hair growth abnormal, Heat rash, Hyperkeratosis, Lichen planus, Nail disorder, Psoriasis, Rash generalised, Skin exfoliation, Skin warm, Urticaria, Acne, Night sweats, Pigmentation disorder, Purpura, Rash maculo-papular, Skin lesion, Skin nodule, Skin wrinkling, Swelling face, Vasculitic rash*

VASCULAR DISORDERS: *Hypertension, Hot flush, Aortic calcification, Deep vein thrombosis, Flushing, Hematoma, Varicose vein, Arteriosclerosis, Aortic stenosis, Orthostatic hypotension, Peripheral ischemia, Vasculitis, Hypotension, Thrombophlebitis, Hypertensive crisis, Venous thrombosis*

RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS: *Cough, Pharyngolaryngeal pain, Dyspnea, Dysphonia, Nasal congestion, Epistaxis, Rhinorrhea, Pulmonary embolism, Asthma, Dyspnea exertional, Nocturnal dyspnea, Sinus congestion, Sneezing, Vasomotor rhinitis, Acute pulmonary edema, Nasal dryness, Pleurisy, Productive cough, Rhinitis allergic*

CARDIAC DISORDERS: *Palpitations, Angina pectoris, Cardiac failure, Arrhythmia, Acute myocardial infarction, Extrasystoles, Ventricular extrasystoles, Atrial fibrillation, Myocardial infarction, Cardiac failure chronic, Coronary artery disease, Hypertensive cardiomyopathy, Ischemic cardiomyopathy, Supraventricular extrasystoles, Tachycardia, Mitral valve incompetence, Tachyarrhythmia*

EYE DISORDERS: *Cataract, Glaucoma, Conjunctivitis allergic, Dry eye, Ocular discomfort, Eyelid pain, Lacrimation increased, Visual disturbance, Vitreous disorder, Conjunctivitis, Eye pain, Arteriosclerotic retinopathy, Blepharitis, Blepharospasm, Eyelids pruritus, Lacrimal gland enlargement, Photophobia, Vision blurred, Vitreous hemorrhage*

EAR AND LABYRINTH DISORDERS: *Vertigo, Ear pain, Ear discomfort, Tinnitus, Cerumen impaction, Ear congestion, Ear disorder, Otosalpingitis, Tympanic membrane perforation*

NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS): *Breast cancer, Ovarian cancer, Basal cell carcinoma, Benign neoplasm of thyroid gland, Benign soft tissue neoplasm, Cerebellar tumour, Cervix carcinoma, Lipoma, Multiple myeloma, Uterine leiomyoma, Benign breast neoplasm, Acral lentiginous melanoma stage unspecified, Adenocarcinoma, Benign bone neoplasm, Benign neoplasm, Bladder neoplasm, Colon cancer, Diffuse large B-cell lymphoma recurrent, Hemangioma, Hemangioma of liver, Lipoma of breast, Melanocytic naevus*

BLOOD AND LYMPHATIC SYSTEM DISORDERS: *Eosinophilia, Leukopenia, Thrombocytopenia, Anemia, Leukocytosis, Lymphadenopathy, Lymphocytosis, Neutrophilia, Pancytopenia, Neutropenia, Bone marrow failure, Lymphopenia*

INVESTIGATIONS: *Weight decreased, Blood pressure increased, Alanine aminotransferase increased, Coagulation time shortened, Red blood cell sedimentation rate increased, Blood chloride decreased, Blood sodium decreased, Weight increased, Cardiac murmur, Aspartate aminotransferase increased, Hemoglobin decreased, International normalised ratio increased, Platelet count decreased, Red blood cell count decreased, Rheumatoid factor positive*

METABOLISM AND NUTRITION DISORDERS: *Hypercalcemia, Anorexia, Hypercholesterolemia, Decreased appetite, Diabetes mellitus, Glucose tolerance impaired, Hypomagnesemia*

PSYCHIATRIC DISORDERS: *Depression, Depressed mood, Insomnia, Apathy, Dysthymic disorder, Sleep disorder, Restlessness*

RENAL AND URINARY DISORDERS: *Dysuria, Hematuria, Nephrolithiasis, Acute prerenal failure, Polyuria, Urge incontinence, Urine abnormality, Pollakiuria, Nephrosclerosis, Nocturia, Proteinuria, Renal impairment, Urine odour abnormal*

REPRODUCTIVE SYSTEM AND BREAST DISORDERS: *Breast pain, Vulvovaginal pruritus, Breast disorder, Vaginal hemorrhage, Breast discomfort, Vulvovaginal dryness, Breast mass, Fibrocystic breast disease, Breast necrosis, Breast tenderness, Vulvovaginal burning sensation*

ENDOCRINE DISORDERS: *Goitre, Hyperthyroidism, Hypothyroidism, Hyperparathyroidism*

INJURY, POISONING AND PROCEDURAL COMPLICATIONS: *Thoracic vertebral fracture, Clavicle fracture, Femoral neck fracture, Post procedural hemorrhage, Lumbar vertebral fracture, Fall, Anastomotic ulcer hemorrhage, Contusion, Humerus fracture, Ilium fracture, Joint dislocation, Joint sprain, Post concussion syndrome, Radius fracture, Scratch*

HEPATOBILIARY DISORDERS: *Liver disorder, Hepatic cyst, Cholecystitis, Cholelithiasis*

IMMUNE SYSTEM DISORDERS: *Hypersensitivity, Drug hypersensitivity*

CONGENITAL, FAMILIAL AND GENETIC DISORDERS: *Familial tremor*

SURGICAL AND MEDICAL PROCEDURES: *Fistula repair*

****Terms designated by investigators as related to study drugs***

Hypocalcemia

In postmenopausal women with osteoporosis in Study 1, declines of serum calcium concentrations to less than the normal range were reported in 15 (0.4%) women in the placebo group and 63 (1.6%) women in the PROLIA group. Declines of serum calcium concentrations to < 7.5 mg/dL (< 1.88 mmol/L) were reported in 2 (< 0.1%) women in the placebo group and 1 (< 0.1%) in the PROLIA group. In clinical studies, subjects with impaired renal function were more likely to have greater reductions in serum calcium levels compared to subjects with normal renal function. In a study of 55 patients with varying degrees of renal function who did not receive calcium and vitamin D supplementation, symptomatic hypocalcemia or serum calcium levels < 7.5 mg/dL was observed in 5 subjects, including no subjects in the normal renal function group, 10% (1 out of 10) of subjects in the CrCL 50 to 80 mL/min group, 29% (2 out of 7) of subjects in the CrCL < 30 mL/min group, and 29% (2 out of 7) of subjects in the hemodialysis group (see **WARNINGS AND PRECAUTIONS**).

Infections

Receptor activator of nuclear factor kappa-B ligand (RANKL) is expressed on activated T and B lymphocytes and in lymph nodes. Therefore, a RANKL inhibitor such as PROLIA may increase the risk of infection. In the clinical study of 7808 postmenopausal women with osteoporosis, the incidence of infections resulting in death was 6 (0.2%) in both placebo and PROLIA treatment groups. The incidence of nonfatal serious infections was 3.3% (n = 128) in the placebo group and 4.0% (n = 154) in the PROLIA group. Hospitalizations due to serious infections in the abdomen 28 (0.7%) placebo vs. 36 (0.9%) PROLIA, urinary tract 20 (0.5%) placebo vs. 29 (0.7%) PROLIA, and ear 0 (0.0%) placebo vs. 5 (0.1%) PROLIA were reported. Endocarditis was reported in 0 (0.0%) placebo patients and 3 (0.1%) patients receiving PROLIA.

Overall skin infections leading to hospitalization were reported more frequently in patients treated with PROLIA (2 [< 0.1%] placebo vs. 15 [0.4%] PROLIA) among women with postmenopausal osteoporosis in Study 1. These events were predominantly comprised of erysipelas (0 [0%] placebo and 7 [0.2%] PROLIA) and cellulitis (1 [< 0.1%] placebo and 6 [0.2%] PROLIA) (see **WARNINGS AND PRECAUTIONS**).

The overall incidence of infections was similar between the PROLIA and placebo groups (2055 [52.9%] PROLIA, 2108 [54.4%] placebo). The incidence of specific infection types was as follows: urinary tract infections (245 [6.3%] PROLIA, 253 [6.5%] placebo), upper respiratory infections (190 [4.9%] PROLIA, 167 [4.3%] placebo), ear infections (43 [1.1%] PROLIA, 21 [0.5%] placebo), and diverticulitis (28 [0.7%] PROLIA, 22 [0.6%] placebo).

There was no imbalance in the reporting of opportunistic infections (4 [0.1%] PROLIA, 3 [0.1%] placebo).

Dermatologic

A significantly higher number of patients treated with PROLIA developed epidermal and dermal adverse events (such as dermatitis, eczema, and rashes), with these events reported in 8.2% (n = 316) of placebo and 10.8% (n = 421) of PROLIA group (p < 0.0001). Most of these events were not specific to the injection site (see **WARNINGS AND PRECAUTIONS, Dermatologic**).

Osteonecrosis of the Jaw (ONJ)

ONJ has been reported rarely in the open-label osteoporosis clinical trial program in patients treated with PROLIA (see **WARNINGS AND PRECAUTIONS**).

Atypical Femoral Fracture

In the osteoporosis clinical trial program, atypical femoral fractures were reported in patients treated with PROLIA (see **WARNINGS AND PRECAUTIONS**).

Cardiovascular Disorders

The incidence of positively adjudicated cardiovascular serious adverse events was 186 (4.8%) PROLIA and 178 (4.6%) placebo, with a hazard ratio (95% confidence interval) of 1.02 (0.83, 1.25). Adjudicated cardiovascular events were further sub-categorized as follows: cardiovascular death, acute coronary syndrome, stroke/transient ischemic attack, congestive heart failure, other vascular event, and arrhythmia. The incidence of these subcategories was 23 (0.6%) PROLIA and 31 (0.8%) placebo for cardiovascular death, 47 (1.2%) PROLIA and 39 (1.0%) placebo for acute coronary syndrome, 56 (1.4%) PROLIA and 54 (1.4%) placebo for stroke/transient ischemic attack, 27 (0.7%) PROLIA and 22 (0.6%) placebo for congestive heart failure, 31 (0.8%) PROLIA and 30 (0.8%) placebo for other vascular event, and 52 (1.3%) PROLIA and 45 (1.2%) placebo for arrhythmia.

Fracture Healing

Delayed fracture healing of nonvertebral fractures was reported in 2 out of 303 (0.7%) subjects in the PROLIA group (3 out of 386 [0.8%] nonvertebral fractures) and 2 out of 364 (0.5%) subjects in the placebo group (2 out of 465 [0.4%] nonvertebral fractures). In addition, nonunion of nonvertebral fractures was reported in 0 out of 303 (0%) subjects in the PROLIA group (0 out of 386 [0%] nonvertebral fractures) and 1 out of 364 (0.3%) subjects in the placebo group (1 out of 465 [0.2%] nonvertebral fractures). For fractures that occurred near the final study closure, additional follow-up after study closure identified 2 additional subjects in the placebo group and 0 in the PROLIA group with delayed fracture healing. Of the subjects with a distal radius fracture, 1 out of 104 (1.0%) subjects in the PROLIA group (1 out of 106 [0.9%] distal radius fractures) and 0 out of 116 (0%) subjects in the placebo group (0 out of 118 [0%] distal radius fractures) had delayed fracture healing.

Malignancies

The overall incidence of new malignancies was 188 (4.8%) in the PROLIA and 166 (4.3%) in the placebo groups. The most common malignancies (≥ 0.2%) included: breast cancer (28 [0.7%] PROLIA, 26 [0.7%] placebo), colon cancer (11 [0.3%] PROLIA, 8 [0.2%] placebo), lung neoplasm malignant (9 [0.2%] PROLIA, 9 [0.2%] placebo), gastric cancer (7 [0.2%] PROLIA, 3 [0.1%] placebo), pancreatic carcinoma (7 [0.2%] PROLIA, 3 [0.1%] placebo), squamous cell carcinoma of skin (6 [0.2%] PROLIA, 8 [0.2%] placebo), and recurrent breast cancer (6 [0.2%] PROLIA, 2 [0.1%] placebo). Other malignancies reported include: thyroid cancer (2 [0.1%] PROLIA, 0 [0%] placebo), carcinoid of the stomach (1 [< 0.1%] PROLIA, 0 [0%] placebo), uterine cancer (3 [0.1%] PROLIA, 1 [< 0.1%] placebo), ovarian cancer metastatic (2 [0.1%] PROLIA, 0 [0%] placebo), ovarian epithelial cancer (2 [0.1%] PROLIA, 0 [0%] placebo), vulval

cancer (2 [0.1%] PROLIA, 0 [0%] placebo), and lentigo maligna stage unspecified (3 [0.1%] PROLIA, 0 [0%] placebo). A causal relationship to drug exposure has not been established.

Hypersensitivity Reactions

The incidence of adverse drug reactions potentially associated with hypersensitivity was 50 (1.3%) in the PROLIA group and 50 (1.3%) in the placebo group. The most common adverse event potentially associated with hypersensitivity was urticaria (27 [0.7%] PROLIA, 27 [0.7%] placebo).

Pancreatitis

Pancreatitis was reported in 4 patients (0.1%) in the placebo and 8 patients (0.2%) in the PROLIA groups. Of these reports, one patient in the placebo group and all 8 patients in the PROLIA group had serious events including 2 deaths in the PROLIA group. Several patients had a prior history of pancreatitis or a confounding event (eg, gallstones). The time from product administration to event occurrence was variable.

Laboratory Abnormalities

The most frequent laboratory abnormalities were changes in serum calcium with compensatory physiological changes in serum phosphorus. The median percent change from baseline (interquartile range) at month 1 for serum calcium was -2.1% (-5.2% to 1.0%) for PROLIA and 1.0% (-2.0% to 3.2%) for placebo. The median percent change from baseline (interquartile range) at month 1 for serum phosphorus was -8.3% (-15.8% to 0%) for PROLIA and 0% (-5.6% to 8.3%) for placebo. Alkaline phosphatase was also reduced, by month 6, which reflects reduced osteoclast activity in bone, with a decrease from baseline of 25% in PROLIA subjects compared to 3% to 8% in placebo subjects.

Serum phosphorous levels were between 2.0 and 2.5 mg/dL in 2.0% (n = 82) of patients in the placebo group and 7.0% (n = 263) of patients in the denosumab group. Decrease in platelet levels to between 50,000/mm^3 and 75,000/mm^3 was reported at 0.2% (n = 7) in the placebo group and 0.4% (n = 14) in the denosumab group, and decrease in platelet levels to < 25,000/mm^3 was reported at < 0.1% (n = 2) in the placebo group and at 0.1% (n = 4) in the denosumab group. Increase in asparate aminotransferase (AST) levels to between 1.0 and 2.5 x the upper limit of normal (ULN) was reported at 5.0% (n = 206) in the placebo group and 7.0% (n = 264) in the denosumab group, and increase in alanine aminotransferase levels (ALT) to between 2.5 and 5.0 x ULN were reported at 0.5% (n = 21) in the placebo group and 1.0% (n = 37) in the denosumab group. Increase in total bilirubin value to between 3.0 and 10.0 x ULN was reported at 0.0% (n = 0) in the placebo group and 0.1% (n = 5) in the denosumab group.

Long Term Safety in Postmenopausal Osteoporosis

A total of 4550 patients who completed Study 1 (N = 7808) enrolled into a 7-year, multinational, multicenter, open label, single-arm extension study to evaluate the long-term safety and efficacy of PROLIA. All patients in the extension study receive PROLIA every 6 months as a single 60 mg SC dose, as well as daily calcium (1 g) and vitamin D (at least 400 IU).

Based on data from the first 2 years of the extension study for patients who received PROLIA in Study 1 and continued on therapy (years 4 and 5 of PROLIA treatment; N = 2343), the overall

subject incidence rates or adverse events and serious adverse events reported (event rates per 100 patient-years) were similar to that observed in the initial 3 years of Study 1. For patients who crossed over to PROLIA from placebo in Study 1 (N = 2206), the overall subject incidence rates of adverse events and serious adverse events reported (event rates per 100 patient-years) were also similar to that observed in the first 3 years of Study 1. Two cases of osteonecrosis of the jaw were observed during the first 2 years of the extension study; both resolved.

A summary of the safety results are provided in the following Table.

Table 2. Subject-year-adjusted Adverse Events Rates (per 100 Patient-years)

	Placebo	PROLIA		
	Study 1 Years 1-3 N = 3883 (Subject-year = 10738.8) Rate (Events)	**Study 1 Years 1-3 N = 3879 (Subject-year = 10805.6) Rate (Events)**	**Cross-Over Extension Years 1-2 N = 2206 (Subject-year = 4236.1) Rate (Events)**	**Long-Term Extension Years 4-5 N = 2343 (Subject-year = 4502.0) Rate (Events)**
All Adverse Events (AE)	237.3 (25482)	235.1 (25406)	187.8 (7956)	179.8 (8094)
Most Common AEs				
Arthralgia	10.2 (1099)	10.3 (1115)	7.0 (295)	7.5 (339)
Back Pain	19.1 (2052)	19.0 (2053)	7.2 (305)	6.8 (305)
Hypertension	6.7 (723)	6.5 (701)	5.6 (239)	6.0 (271)
Nasopharyngitis	7.4 (799)	7.1 (762)	5.3 (225)	4.8 (216)
Osteoarthritis	5.5 (587)	4.8 (519)	4.3 (183)	4.5 (203)
Pain in extremity	5.2 (555)	5.6 (600)	3.5 (148)	3.3 (149)
Serious Adverse Events	16.4 (1758)	17.3 (1870)	17.2 (729)	15.3 (690)
Deaths	0.9 (92)	0.7 (72)	0.8 (33)	0.6 (26)
Clinically Significant AEs				
Hypocalcemia	<0.1 (3)	0 (0)	0.1 (5)	<0.1 (1)
Osteonecrosis of the Jaw	0 (0)	0 (0)	<0.1 (2)	0 (0)
Serious Infections	1.4 (155)	1.8 (194)	1.9 (79)	1.4 (65)
Infections	40.2 (4318)	39.8 (4304)	34.7 (1468)	33.3 (1500)
Malignancies	1.8 (197)	2.0 (219)	1.8 (76)	2.1 (95)
Delayed Fracture Healing	<0.1 (5)	<0.1 (2)	<0.1 (1)	0 (0)
Pancreatitis	<0.1 (3)	<0.1 (9)	<0.1 (1)	<0.1 (1)
Eczema	0.7 (77)	1.3 (139)	1.1 (45)	1.1 (50)
Hypersensitivity	0.9 (92)	0.9 (101)	1.0 (41)	0.8 (38)

Subject-year = Total subject-years of follow-up, including time through the end of study date; Events = Number of events; Rate = Event rate per 100 patient-years ([events / Patient-year] * 100)
N = Number of patients who received ≥ 1 dose of investigational product. Treatment groups are based on the original randomized assignments in the 20030216 study.
Multiple occurrences of the same event for a subject are counted as multiple events. Includes only treatment-emergent adverse events.

Other Studies in Postmenopausal Women

The safety of PROLIA was assessed in a 2-year, randomized, double-blind, placebo-controlled, multinational study of 332 postmenopausal women aged 43 to 83 years with low bone mass (Study 2). A total of 165 women received placebo and 164 women received PROLIA administered once every 6 months as a single 60 mg SC dose. All women received calcium (at least 1000 mg) and vitamin D (at least 400 IU) supplementation per day. The incidence of adverse events was 156 (95%) in the PROLIA group and 157 (95%) in the placebo group. The incidence of serious adverse events was 11% (n = 18) in the PROLIA group and 6% (n = 9) in the placebo group. No subject died during the study. The 3 most common adverse events were arthralgia (26% (n = 43) PROLIA vs. 26% (n = 42) placebo), nasopharyngitis (22% (n = 36) PROLIA vs. 19% (n = 32) placebo), and back pain (20% (n = 33) PROLIA vs. 21% (n = 34) placebo).

Two randomized, double-blind, active-controlled studies (Study 3 and Study 4) assessed the safety of PROLIA compared with alendronate. In Study 3, a total of 1179 postmenopausal women with low bone mass who were treatment naive (593 randomized to PROLIA 60 mg SC once every 6 months, 586 randomized to alendronate tablets 70 mg once weekly) received investigational product and were evaluated for safety. All women received daily supplemental calcium (at least 1000 mg) and vitamin D (at least 400 IU). The incidence of adverse events was 81% (n = 480) in the PROLIA group and 82% (n = 482) in the alendronate group. The incidence of serious adverse events was 6% (n = 34) in the PROLIA group and 6% (n = 37) in the alendronate group. One subject in each treatment group died during the study. The 3 most frequent adverse events were arthralgia (13% (n = 75) PROLIA vs. 10% (n = 56) alendronate), nasopharyngitis (8% (n = 45) PROLIA vs. 7% (n = 43) alendronate), and back pain (7% (n = 42) PROLIA vs. 10% (n = 56) alendronate).

In Study 4, a total of 502 postmenopausal women with low bone mass who were being treated with alendronate for a median duration of 3 years (253 PROLIA 60 mg SC every 6 months, 249 alendronate tablets 70 mg once weekly) received investigational product and were evaluated for safety. All women received daily supplemental calcium (at least 1000 mg) and vitamin D (at least 400 IU). The incidence of adverse events was 78% (n = 197) in the PROLIA group and 79% (n = 196) in the alendronate group. The incidence of serious adverse events was 6% (n = 15) in the PROLIA group and 6% (n = 16) in the alendronate group. One subject in the PROLIA treatment group died during the study. The 3 most frequent adverse events were nasopharyngitis (13% (n = 34) PROLIA vs. 11% (n = 27) alendronate), back pain (11% (n = 27) PROLIA vs. 12% (n = 29) alendronate), and arthralgia (6% (n = 15) PROLIA vs. 10% (n = 26) alendronate).

The safety profile of denosumab in women with postmenopausal osteoporosis was consistent with results in these 3 studies among women with postmenopausal bone loss. No notable differences were observed between those women who had received prior osteoporosis therapy versus those who had not received prior osteoporosis therapy (ie, alendronate).

Immunogenicity in Postmenopausal Women

Denosumab is a human monoclonal antibody. As with all therapeutic proteins, there is potential for immunogenicity with PROLIA. More than 13000 patients were screened for binding antibodies using a sensitive electrochemiluminescent bridging immunoassay. Less than 1% (55

out of 8113) of patients treated with PROLIA for up to 5 years tested positive for antibodies (including pre-existing, transient, and developing antibodies). The patients that tested positive for binding antibodies were further evaluated for neutralizing antibodies using a chemiluminescent cell-based *in vitro* biological assay and none of them tested positive. No evidence of altered pharmacokinetic profile, toxicity profile, or clinical response was associated with binding antibody development.

The detection of antibody formation is dependent on the sensitivity and specificity of the assay. The observed incidence of antibody positivity in an assay may be influenced by factors such as sample handling, concomitant medications, and underlying disease. For these reasons, comparison of antibodies to denosumab with the incidence of antibodies to other products may be misleading.

Treatment to Increase Bone Mass in Men with Osteoporosis at High Risk for Fracture

The safety of PROLIA in the treatment of men with osteoporosis was assessed in a randomized, double-blind, placebo-controlled study; a 1 year double-blind phase followed by a 1 year open-label extension.

During the double-blind phase, a total of 242 men (121 PROLIA, 121 placebo) were enrolled; a total of 120 men were exposed to placebo and 120 men were exposed to PROLIA administered subcutaneously once every 6 months as a single 60 mg dose. All men were instructed to take at least 1000 mg of calcium and 800 IU of vitamin D supplementation per day.

The most common adverse reactions (≥ 5% and more common than placebo) reported in men with osteoporosis were: back pain (10 [8.3%] PROLIA, 8 [6.7%] placebo), arthralgia (8 [6.7%] PROLIA, 7 [5.8%] placebo), and nasopharyngitis (8 [6.7%] PROLIA, 7 [5.8%] placebo).

There were 2 deaths during the clinical trial: 1 (0.8%, acute myocardial infarction) in the PROLIA group and 1 (0.8%, basilar artery thrombosis) in the placebo group.

There were 16 serious adverse events (SAEs) in 11 patients (9.2%) in the PROLIA group: 6 cardiovascular (2 arterial thrombosis limb, 2 myocardial infarction, 1 peripheral ischaemia, 1 vascular pseudoaneurysm), 3 prostate cancer, and one each of: chest pain, acute pancreatitis, cholecystitis, injury, post procedural complication, road traffic accident, spinal column stenosis (severity: 3 moderate, 12 severe, and 1 fatal). In the placebo group, there were 13 SAEs in 10 patients (8.3%): 3 cardiovascular (peripheral ischaemia, atrial fibrillation, basilar artery thrombosis)**,** 3 musculoskeletal (ligament rupture, meniscus lesion, osteoarthritis), 2 ophthalmic (retinal detachment, vitreous haemorrhage), and one each of: pancreatitis, pneumonia, prostatic adenoma, skull malformation, and cerebral haemorrhage (severity: 2 mild, 8 moderate, 2 severe, and 1 fatal).

The number (percentage) of patients who discontinued the investigational product or withdrew from the study due to adverse events was 4 patients (3.3%) with 4 events for the PROLIA group (prostate cancer, myocardial infarction, upper respiratory tract infections, and road traffic accident), vs. 0 for the placebo group.

Adverse events reported in ≥ 1% of PROLIA-treated or placebo-treated patients are shown in Table 3.

Table 3. Adverse Events Occurring in ≥ 1% of Men with Osteoporosis (First 12 Months Analysis)

SYSTEM ORGAN CLASS Preferred Term	Prolia (N = 120) n (%)	Placebo (N = 120) n (%)
CARDIAC DISORDERS		
Angina pectoris	2 (1.7)	0 (0.0)
Arrhythmia	2 (1.7)	0 (0.0)
Atrial fibrillation	0 (0.0)	2 (1.7)
EYE DISORDERS		
Cataract	2 (1.7)	3 (2.5)
Conjunctivitis	0 (0.0)	2 (1.7)
GASTROINTESTINAL DISORDERS		
Diarrhoea	2 (1.7)	3 (2.5)
Flatulence	2 (1.7)	0 (0.0)
Gastrooesophageal reflux disease	1 (0.8)	2 (1.7)
Constipation	0 (0.0)	7 (5.8)
Abdominal pain upper	0 (0.0)	3 (2.5)
Dyspepsia	0 (0.0)	2 (1.7)
Gastric polyps	0 (0.0)	2 (1.7)
Inguinal hernia	0 (0.0)	2 (1.7)
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS		
Chest pain	2 (1.7)	1 (0.8)
Fatigue	1 (0.8)	2 (1.7)
INFECTIONS AND INFESTATIONS		
Nasopharyngitis	8 (6.7)	7 (5.8)
Sinusitis	2 (1.7)	1 (0.8)
Tooth infection	2 (1.7)	1 (0.8)
Upper respiratory tract infection	2 (1.7)	1 (0.8)
Influenza	1 (0.8)	4 (3.3)
Pneumonia	0 (0.0)	2 (1.7)
INJURY, POISONING AND PROCEDURAL COMPLICATIONS		
Fall	2 (1.7)	2 (1.7)
Contusion	2 (1.7)	0 (0.0)
Post procedural haematoma	1 (0.8)	2 (1.7)
Procedural pain	0 (0.0)	3 (2.5)
Arthropod bite	0 (0.0)	2 (1.7)
INVESTIGATIONS		
Weight decreased	0 (0.0)	2 (1.7)
METABOLISM AND NUTRITION DISORDERS		
Hypercholesterolaemia	3 (2.5)	0 (0.0)
Hyperglycaemia	0 (0.0)	2 (1.7)
Hyponatraemia	0 (0.0)	2 (1.7)

Table 3. Adverse Events Occurring in ≥ 1% of Men with Osteoporosis (First 12 Months Analysis)

SYSTEM ORGAN CLASS Preferred Term	Prolia (N = 120) n (%)	Placebo (N = 120) n (%)
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS		
Back pain	10 (8.3)	8 (6.7)
Arthralgia	8 (6.7)	7 (5.8)
Osteoarthritis	4 (3.3)	2 (1.7)
Muscle spasms	3 (2.5)	0 (0.0)
Myalgia	2 (1.7)	5 (4.2)
Pain in extremity	2 (1.7)	3 (2.5)
Bone pain	2 (1.7)	0 (0.0)
Musculoskeletal pain	1 (0.8)	4 (3.3)
Musculoskeletal chest pain	1 (0.8)	2 (1.7)
Musculoskeletal stiffness	0 (0.0)	2 (1.7)
Spinal osteoarthritis	0 (0.0)	2 (1.7)
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCLUDING CYSTS AND POLYPS)		
Prostate cancer[a]	3 (2.5)	0 (0.0)
Prostatic adenoma	1 (0.8)	2 (1.7)
NERVOUS SYSTEM DISORDERS		
Dizziness	2 (1.7)	2 (1.7)
Headache	1 (0.8)	5 (4.2)
RENAL AND URINARY DISORDERS		
Renal cyst	0 (0.0)	2 (1.7)
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS		
Cough	1 (0.8)	3 (2.5)
Asthma	0 (0.0)	2 (1.7)
SKIN AND SUBCUTANEOUS TISSUE DISORDERS		
Rash	1 (0.8)	2 (1.7)
VASCULAR DISORDERS		
Arterial thrombosis limb	2 (1.7)	0 (0.0)
Hypertension	1 (0.8)	5 (4.2)

N = Number of subjects who received ≥ 1 dose of investigational product
n = Number of subjects reporting ≥ 1 event
Includes only treatment-emergent adverse events
[a] 2 of the prostate cancer cases were diagnosed within the first month of the patients receiving PROLIA

Osteonecrosis of the Jaw

No cases of osteonecrosis of the jaw (ONJ) were reported.

New Malignancies

New malignancies were reported in 4 patients (3.3%; 3 prostate cancers, 1 basal cell carcinoma) in the PROLIA group and 0 in the placebo group.

Cardiac Disorders

There were 6 patients (5.0%) with cardiac AEs (2 angina pectoris, 2 myocardial infarction and 2 arrhythmia) in the PROLIA group, and 3 patients (2.5%, 2 atrial fibrillation and 1 palpitations) in the placebo group. There were 2 patients (1.7%) with serious cardiac AEs (2 myocardial infarction) in the PROLIA group, and 1 (0.8%, atrial fibrillation) in the placebo group.

Fracture

Clinical fractures were confirmed for 1 patient (0.8%) in the PROLIA group and 2 patients (1.7%) in the placebo group; new morphometric vertebral fractures were confirmed in no patients in the PROLIA group and 1 patient (0.8%) in the placebo group.

Laboratory Abnormalities

PROLIA administration was associated with decreases in serum calcium. At day 15, median change from baseline in albumin-adjusted serum calcium was -1.1% in the PROLIA group and 0.0% in the placebo group. No decrease in median serum calcium was observed at months 6 and 12. No patients had Grade 3 or 4 low serum calcium values during the study.

PROLIA administration also was associated with decreases in serum phosphorus. Median change from baseline in phosphorus was (PROLIA, placebo) -6.0%, 2.9% at day 15; -4.7%, 0.0% at month 6; and 0.0%, 0.0% at month 12. No patients had Grade 3 or 4 low serum phosphorus values during the study.

Postmarket Adverse Drug Reactions

Hypersensitivity Reactions

Hypersensitivity reactions including rash, urticaria, facial swelling, erythema, and anaphylactic reactions have been reported in patients receiving PROLIA.

Severe Hypocalcemia

Severe symptomatic hypocalcemia has been reported in patients at increased risk of hypocalcemia receiving PROLIA. Symptoms of severe hypocalcemia may include tetany and convulsions. Healthcare Professionals should follow standard medical care guidelines for the treatment of signs and symptoms associated with severe hypocalcemia. See **WARNINGS AND PRECAUTIONS, Hypocalcemia** for further information on monitoring hypocalcemia.

DRUG INTERACTIONS

Overview

No formal drug interaction studies have been conducted with PROLIA.

Drug-Drug Interactions

Interactions with other drugs have not been established.

The pharmacokinetics and pharmacodynamics of PROLIA were similar in postmenopausal women with osteoporosis transitioning from alendronate therapy compared to those who had not received prior alendronate therapy.

Drug-Food Interactions

Interactions with food have not been established.

Drug-Herb Interactions

Interactions with herbal products have not been established.

Drug-Laboratory Interactions

Interactions with laboratory tests have not been established.

DOSAGE AND ADMINISTRATION

Dosing Considerations

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

Patients must be adequately supplemented with calcium and vitamin D at the recommended doses[a].

PROLIA is indicated for the treatment of osteoporosis in postmenopausal women at high risk for fracture, defined as a history of osteoporotic fracture, or multiple risk factors for fracture; or patients who have failed or are intolerant to other available osteoporosis therapy. In postmenopausal women with osteoporosis, PROLIA reduces the incidence of vertebral, nonvertebral and hip fractures.

PROLIA is also indicated as a treatment to increase bone mass in men with osteoporosis at high risk for fracture. The high risk for fracture is defined as a history of osteoporotic fracture, or multiple risk factors for fracture; or patients who have failed or are intolerant to other available osteoporosis therapy.

[a]2010 clinical practice guidelines for the diagnosis and management of osteoporosis in Canada: summary

Recommended Dose

The recommended dose of PROLIA (denosumab) is a single SC injection of 60 mg, once every 6 months.

Administration

Administration of PROLIA should be performed by an individual who has been adequately trained in injection techniques.

Parenteral drug products should be inspected visually for particulate matter and discolouration prior to administration, whenever solution and container permit. PROLIA 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 cloudy.

Prior to administration, PROLIA may be allowed to reach room temperature (up to 25°C) in the original container.

Administer PROLIA via SC 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 with PROLIA.

ACTION AND CLINICAL PHARMACOLOGY

Mechanism of Action

PROLIA is a RANK ligand (RANKL) inhibitor. RANKL exists as a transmembrane or soluble protein. RANK ligand is essential for the formation, function and survival of osteoclasts, the sole cell type responsible for bone resorption. Osteoclasts play an important role in bone loss associated with osteoporosis. Denosumab targets and binds with high affinity and specificity to RANKL, preventing RANKL from activating its only receptor, RANK, on the surface of osteoclasts and their precursors, independent of bone surface. Prevention of RANKL-RANK interaction inhibits osteoclast formation, function and survival, thereby decreasing bone resorption and increasing bone mass and strength in both cortical and trabecular bone throughout the skeleton.

Pharmacodynamics

In clinical studies, treatment with 60 mg of PROLIA resulted in rapid reduction in the bone resorption marker serum type 1 C-telopeptide (CTX) within 6 hours of SC administration by approximately 70%, with reductions of approximately 85% occurring by 3 days. CTX levels were below the limit of assay quantitation (0.049 ng/mL) in 39 to 68% of subjects 1 to 3 months after dosing of PROLIA. CTX reductions were maintained over the 6-month dosing interval. At the end of each dosing interval, CTX reductions were partially attenuated from maximal reduction of ≥ 87% to ≥ 45% (range 45% to 80%), as serum denosumab levels diminished, reflecting the reversibility of the effects of PROLIA on bone remodelling. These effects were maintained with continued treatment. Consistent with the physiological coupling of bone

formation and resorption in skeletal remodeling, subsequent reductions in bone formation markers were observed beginning 1 month after the first dose of PROLIA.

Bone turnover markers (bone resorption and formation markers) generally reached pre-treatment levels within 9 months after the last 60 mg SC dose. Upon re-initiation, the degree of inhibition of CTX by PROLIA was similar to that observed in patients initiating PROLIA treatment.

In a clinical study of postmenopausal women with low bone mass (N = 504) who were previously treated with alendronate for a median duration of 3 years, those transitioning to receive PROLIA experienced additional reductions in serum CTX, compared with women who remained on alendronate. In this study, the changes in serum calcium were similar between the 2 groups.

Pharmacokinetics

In dose ranging studies, denosumab exhibited nonlinear, dose-dependent pharmacokinetics for doses between 0.01 mg/kg to 3.0 mg/kg inclusive. Clearance or apparent clearance (mL/hr/kg) was higher at lower doses and had a linear inverse relationship with dose on a log-log plot. Exposures (SC dosing) based on area under the serum denosumab concentration-time curve (AUC) increased greater than dose-proportionally from 0.01 to 1 mg/kg (700-fold for the 100-fold increase in dose), but approximately dose-proportionally from 1 to 3 mg/kg (3.9-fold for the 3-fold increase in dose).

Figure 1. Individual Serum Denosumab Concentration-Time Profiles Following Single Dose SC Administration at 1.0 mg/kg to Healthy Postmenopausal Women

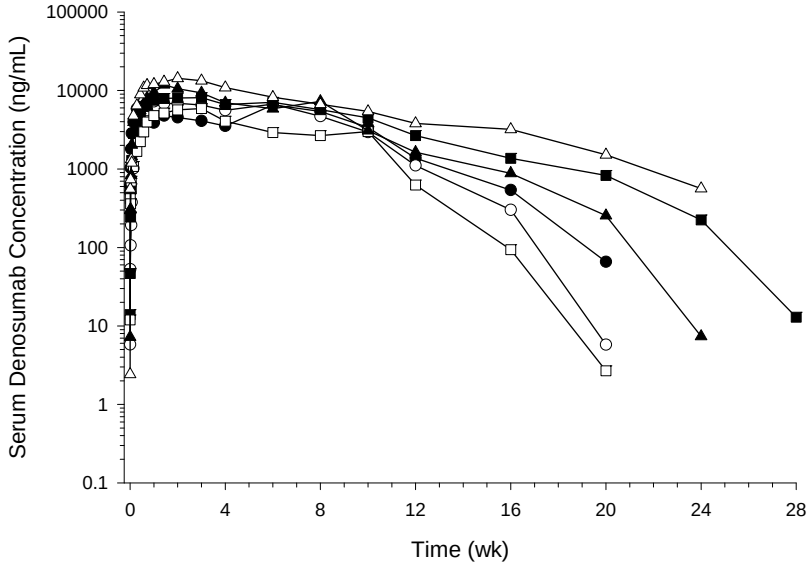

Table 4. Mean (SD) Denosumab Pharmacokinetic Parameters Following Single Dose SC Administration of 1.0 mg/kg Denosumab to Healthy Postmenopausal Women (N = 6)

T_{max} (days)	C_{max} (μg/mL)	$AUC_{0\text{-}inf}$ (μg x day/mL)	CL/F (mL/hr)	MRT (days)	$t_{1/2}$ (days)	$t_{1/2,z}$ (days)
17.5 (7 - 42)	8.99 (3.34)	538 (224)	6.61 (2.93)	44.2 (6.96)	30.2 (7.04)	8.00 (0.975)

SD = standard deviation; C_{max} = Maximum observed concentration; T_{max} = time of C_{max} (range reported instead of SD); $AUC_{0\text{-}inf}$ = Area under the serum concentration-time curve from pre-dose to infinity; CL/F = apparent clearance; MRT = mean residence time; $t_{1/2}$ = half-life following C_{max}; $t_{1/2,z}$ = terminal-phase half-life

Table 5. Mean (SD) Denosumab Pharmacokinetic Parameters Following SC Administration of 60 mg Denosumab Every 6 Months to Postmenopausal Women with Low BMD (n = 32-46)*

Dose	T_{max} (days)	C_{max} (μg/mL)	$AUC_{0\text{-}tau}$ (μg x day/mL)	CL/F (mL/hr)	MRT (days)	$t_{1/2}$ (days)	C_{min} (μg/mL)
1st	26 (2.9 - 32)	7.93 (2.95)	503 (239)	6.71 (5.00)	44.2 (9.48)	25.4 (8.47)	0.137 (0.334)
2nd	29 (1.9 - 42)	6.94 (3.18)	448 (239)	7.50 (5.04)	45.0 (9.99)	27.1 (8.99)	0.132 (0.334)

SD = standard deviation; C_{max} = Maximum observed concentration; T_{max} = time of C_{max} (range reported instead of SD); $AUC_{0\text{-}tau}$ = area under the serum denosumab concentration-time curve over the dosing interval; CL/F = apparent clearance; MRT = mean residence time; $t_{1/2}$ = half-life following C_{max}; C_{min} = trough serum denosumab concentration

*1st dose: n = 46 for T_{max}, C_{max}, $AUC_{0\text{-}tau}$, CL/F, & MRT; n = 32 for $t_{1/2}$; n = 38 for C_{min}

*2nd dose: n = 44 for T_{max}, C_{max}, $AUC_{0\text{-}tau}$, CL/F, & MRT; n = 33 for $t_{1/2}$; n = 39 for C_{min}

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 (28 to 87 years), race, or disease state.

Special Populations

Geriatrics

The pharmacokinetics of denosumab were not affected by age.

Pediatrics

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

Race

The pharmacokinetics of denosumab were not affected by race in post-menopausal women.

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 of denosumab; thus, dose adjustment for renal impairment is not necessary.

STORAGE AND STABILITY

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

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

Protect PROLIA from light and do not expose to temperatures above 25°C.

Avoid vigorous shaking of PROLIA.

Do not use PROLIA beyond the expiry date stamped on the label.

DOSAGE FORMS, COMPOSITION AND PACKAGING

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

PROLIA is supplied in a single use prefilled syringe with a safety guard, or in a single use vial[†].

Each 1.0 mL single use prefilled syringe of PROLIA contains 60 mg denosumab, 4.7% sorbitol, 17 mM acetate, 0.01% polysorbate 20, water for injection (USP), and sodium hydroxide to a pH of 5.2.

Each 1.0 mL single use vial[†] of PROLIA contains 60 mg denosumab, 4.7% sorbitol, 17 mM acetate, water for injection (USP), and sodium hydroxide to a pH of 5.2.

PROLIA is supplied in a dispensing pack containing one prefilled syringe or one vial[†].

[†] 60 mg/1.0mL single use vial is not available in Canada.

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

Drug Substance

Proper name: denosumab

Molecular mass: 147 kDa (approximate)

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).

Physicochemical Properties: Prolia® (denosumab) is a clear, colourless to slightly yellow solution. The solution may contain trace amounts of translucent to white proteinaceous particles.

CLINICAL TRIALS

Treatment of Osteoporosis in Postmenopausal Women

Study Demographics and Design [Study 1 (FREEDOM)]

In postmenopausal women with osteoporosis, the safety and efficacy of PROLIA (denosumab) were assessed in a randomized double-blind controlled study.

Study #	Trial Design	Dosage , route of administration and duration	Study patients (n)	Mean age (range) (yrs)
Study 1 (FREEDOM)	Phase 3, randomized, double-blind, placebo-controlled	PROLIA 60 mg or placebo SC injection every 6 months for 3 years	7808 patients with osteoporosis (PROLIA: 3902 Placebo: 3906)	72 (60, 91)

The efficacy and safety of PROLIA administered once every 6 months for 3 years were investigated in postmenopausal women (7,808 women aged 60-91 years, of which 23.6% had prevalent vertebral fractures) with baseline bone mineral density (BMD) T-scores at the lumbar spine or total hip between –2.5 and –4.0 and a mean absolute 10-year fracture probability of 18.60% (deciles: 7.9-32.4%) for major osteoporotic fracture and 7.22% (deciles: 1.4-14.9%) for hip fracture. Women with other diseases or on therapies that may affect bone (such as rheumatoid arthritis, osteogenesis imperfecta, and Paget's disease) were excluded from this study. Women were randomized to receive SC injections of either placebo (n = 3906) or PROLIA 60 mg (n = 3902) once every 6 months. Women received calcium (at least 1,000 mg) and vitamin D (at least 400 IU) supplementation daily. The primary efficacy variable was the incidence of new vertebral fractures over 3 years. Secondary efficacy variables included the incidence of non-vertebral fracture and hip fracture, assessed over 3 years. The study was

powered to detect a 45% reduction in the incidence of new vertebral fractures, a 40% decrease in the risk of non-vertebral fractures and a 40% decrease in the risk of hip fractures.

Effects on Fracture Incidence

New Vertebral Fractures

PROLIA, when taken with calcium and vitamin D and compared with calcium and vitamin D alone, significantly reduced the incidence of new vertebral fractures over 36 months from 7.2% in the placebo group to 2.3% in the PROLIA group ($p < 0.0001$). The absolute reduction in risk of vertebral fractures was 4.8% and the relative reduction was 68% (Table 6). The number needed to treat (NNT) over the three years to prevent 1 new vertebral fracture was 20.7 (95% CI: 17.3, 25.8).

Table 6. The Effect of PROLIA on Vertebral Fracture Incidence over 3 Years

	Proportion of Women with Fracture (%)		Absolute Risk Reduction (%) (95% CI)	Relative Risk Reduction (%) (95% CI)
	Placebo N = 3691 (%)	PROLIA N = 3702 (%)		
0 - 1 Year	2.2	0.9	1.4 (0.8, 1.9)	61 (42, 74)*
0 - 2 Years	5.0	1.4	3.5 (2.7, 4.3)	71 (61,79)*
0 - 3 Years	7.2	2.3	4.8 (3.9, 5.8)	68 (59, 74)*

*p< 0.0001

In the long-term, open-label extension of Study 1, in women who received PROLIA in Study 1 and continued on therapy (years 4 and 5 of PROLIA treatment), PROLIA treatment maintained a low incidence of new vertebral fractures in years 4 and 5 (59 [2.8%] women had at least one new vertebral fracture and 14 [0.6%] women had a clinical vertebral fracture by year 2 of the extension study).

Among women who crossed over to PROLIA from placebo in Study 1, 34 (1.7%) had at least one new vertebral fracture and 3 (0.1%) had a clinical vertebral fracture by year 2 of the extension study.

Hip Fractures

The incidence of hip fracture was 1.2% for placebo-treated women compared to 0.7% for PROLIA-treated women. The observed absolute reduction in the risk of hip fracture at 3 years was 0.3%, with a 95% CI across the zero (-0.1%, 0.7%), and the relative risk reduction was 40% (95% CI: 0.37, 0.97; $p = 0.0362$).

Non-vertebral Fractures

The incidence of non-vertebral fracture was 8.0% for placebo-treated women, compared with 6.5% for PROLIA-treated women. The observed absolute reduction in risk of non-vertebral fractures over 3 years was 1.5% (0.3, 2.7) and the relative risk reduction was 20% (95% CI: 5, 33%; $p = 0.0106$).

The incidences of nonvertebral fractures at other locations were as follows: distal femur (3 [< 0.1%] placebo, 0 [0%] PROLIA), forearm (120 [3.1%] placebo, 103 [2.6%] PROLIA), wrist

(107 [2.7%] placebo, 90 [2.3%] PROLIA), humerus (45 [1.2%] placebo, 38 [1.0%] PROLIA), proximal humerus (41 [1.0%] placebo, 30 [0.8%] PROLIA), clavicle/rib (25 [0.6%] placebo, 34 [0.9%] PROLIA), proximal tibia (5 [0.1%] placebo, 3 [< 0.1%] PROLIA), and pelvic (13 [0.3%] placebo, 10 [0.3%] PROLIA).

Among women who received PROLIA for 3 years in Study 1 and continued on therapy in the long-term, open-label extension, PROLIA treatment maintained a low incidence of nonvertebral fractures in years 4 and 5 (32 [1.4%] during year 4 and 25 [1.1%] during year 5). The most common sites for nonvertebral fractures during the long-term, open-label extension of Study 1 were wrist (n = 21), rib (n = 9), hip (n = 7), and ankle (n = 7) (with n = number of affected women).

Among women who crossed over to PROLIA from placebo in Study 1, 52 subjects (2.4%) had a nonvertebral fracture during year 4, and 35 subjects (1.7%) had a nonvertebral fracture during year 5. The most common sites for nonvertebral fractures in the cross-over group during the first 2 years in the extension were wrist (n = 30), hip (n = 14), ankle (n = 13), and foot (n = 9).

Effect on Bone Mineral Density (BMD)

Treatment with PROLIA significantly increased BMD at all clinical sites measured at 1, 2, and 3 years. PROLIA increased lumbar spine BMD by 8.8%, total hip BMD by 6.4%, femoral neck BMD by 5.2%, and hip trochanter BMD by 8.3% over 3 years (all $p < 0.0001$).

In the long-term, open-label extension of Study 1, in women who received PROLIA in Study 1 and continued on therapy (years 4 and 5 of PROLIA treatment), PROLIA treatment continued to increase BMD from extension baseline at the lumbar spine (3.3%), total hip (1.3%), femoral neck (1.2%) and trochanter (1.8%) in years 4 and 5. Percent increase in BMD from the original Study 1 baseline (ie, after 5 years of treatment) in the long-term group was 13.8% at the lumbar spine, 7.0% at the total hip, 6.2% at the femoral neck and 9.7% at the trochanter.

Among women who crossed over to PROLIA from placebo in Study 1, BMD gains from extension baseline were 8.0% (lumbar spine), 4.2% (total hip), 3.5% (femoral neck), and 5.6% (trochanter) after 2 years of denosumab administration.

The following Table lists BMD yearly percent changes for each group by site.

Table 7. Bone Mineral Density Yearly Percent Change by Site

	Long-term Group		**Cross-over Group**	
	Year 4	**Year 5**	**Year 4**	**Year 5**
Lumbar spine	1.7%	1.6%	5.4%	2.4%
Total hip	0.7%	0.6%	3.0%	1.1%
Femoral neck	0.9%	0.4%	2.3%	1.2%
Trochanter	1.0%	0.8%	4.1%	1.4%

Bone Histology and Histomorphometry

A total of 115 transiliac crest bone biopsy specimens were obtained from 92 postmenopausal women with osteoporosis at either month 24 and/or month 36 (53 specimens in PROLIA group, 62 specimens in placebo group). Of the biopsies obtained, 115 (100%) were adequate for

qualitative histology and 7 (6%) in the denosumab group were adequate for full quantitative histomorphometry assessment.

Qualitative histology assessments showed normal architecture and quality with no evidence of mineralization defects, woven bone, or marrow fibrosis in patients treated with PROLIA.

The presence of double tetracycline labeling in a biopsy specimen provides an indication of active bone remodeling, while the absence of tetracycline label suggests suppressed bone formation. In subjects treated with PROLIA, 35% had no tetracycline label present at the month 24 biopsy and 38% had no tetracycline label present at the month 36 biopsy, while 100% of placebo-treated patients had double label present at both time points. When compared to placebo, treatment with PROLIA resulted in virtually absent activation frequency and markedly reduced bone formation rates. However, the long-term consequences of this degree of suppression of bone remodeling are unknown.

Treatment to Increase Bone Mass in Men with Osteoporosis at High Risk for Fracture

Study Demographics and Design [Study 5 (ADAMO)]

In men with osteoporosis, the efficacy and safety of PROLIA were assessed in a randomized, double-blind, placebo-controlled study.

Study #	Trial Design	Dosage , route of administration and duration	Study patients (n)	Mean age (range) (yrs)
Study 5 (ADAMO)	Phase 3, randomized, double-blind, placebo-controlled	PROLIA 60 mg or placebo SC injection every 6 months (Q6M) (2 doses)	242 men with osteoporosis (PROLIA: 121 Placebo: 121)	65 (31, 84)

The efficacy and safety of PROLIA in increasing bone mass in men with osteoporosis was demonstrated in a 1-year, randomized, double-blind, placebo-controlled, multinational study of men with low bone mass, who had a baseline BMD T-score between –2.0 and –3.5 at the lumbar spine or femoral neck. Men with a BMD T-score between –1.0 and –3.5 at the lumbar spine or femoral neck and with history of prior fragility fracture were also enrolled. Men with other diseases (such as rheumatoid arthritis, osteogenesis imperfecta, and Paget's disease) or on therapies that may affect bone were excluded from this study.

The 242 men enrolled in the study ranged in age from 31 to 84 years and were randomized to receive SC injections of either PROLIA 60 mg (n = 121) or placebo (n = 121) once every 6 months. Patients also received at least 1000 mg calcium and at least 800 IU vitamin D supplementation daily.

Previous fractures in the PROLIA and placebo groups were: 91 events in 47 patients (38.8%) vs. 76 events in 48 patients (39.7%) for any self-reported historical fractures since age 30, 18 events in 16 patients (13.2%) vs. 21 events in 20 patients (16.5%) for self-reported historical major osteoporotic fractures, and 43 events in 30 patients (24.8%) vs. 31 events in 25 patients (20.7%) for confirmed prevalent vertebral fractures, respectively.

The primary efficacy variable was percent change in lumbar spine BMD from baseline to 1 year. Secondary efficacy variables included percent change in total hip and femoral neck BMD from baseline to 1 year.

Effects on BMD

Treatment with PROLIA statistically significantly increased BMD at 1 year: the treatment differences in BMD at 1 year were: 4.8% (+5.7% PROLIA, +0.9% placebo, $p < 0.0001$ [95% CI: 4.0%, 5.6%]) at the lumbar spine; 2.0% (+2.4% PROLIA, +0.3% placebo) at the total hip; and 2.2% (+2.1% PROLIA, 0.0% placebo) at femoral neck.

Consistent effects on BMD were observed at the lumbar spine regardless of baseline age, race, weight/body mass index (BMI), BMD, baseline testosterone levels and level of bone turnover.

The correlation between increased bone density and reduction of bone fracture in men with osteoporosis has not been established.

Bone Histology and Histomorphometry

The transiliac crest bone biopsy substudy enrolled 29/242 patients at selected study centres in Study 5 (17 specimens in PROLIA group, 12 specimens in placebo group), after 12 months of treatment. Six (6) of the samples in the PROLIA group were adequate for full quantitative histomorphometry assessment. Qualitative histology assessments showed normal architecture and quality with no evidence of mineralization defects, woven bone, or marrow fibrosis in patients treated with PROLIA.

All subjects scheduled for the biopsy were to follow a double tetracycline/demeclocycline labelling procedure prior to undergoing the biopsy. The presence of double tetracycline labeling in a biopsy specimen provides an indication of active bone remodeling, while the absence of tetracycline label suggests suppressed bone formation. In patients treated with PROLIA, 6% (n = 1) had no tetracycline label present at the month 12 biopsy, while 100% of placebo-treated patients (n = 12) had double label present. When compared to placebo, treatment with PROLIA resulted in markedly reduced bone formation rates. However, the long-term consequences of this degree of suppression of bone remodeling are unknown.

DETAILED PHARMACOLOGY

Animal Pharmacology

Denosumab is a fully human monoclonal antibody that binds to RANK ligand (RANKL) with high affinity and specificity. Denosumab blocks the interaction of RANKL with RANK, mimicking the endogenous effects of OPG. RANKL is a key mediator in the pathway required for the differentiation, survival, and activation of osteoclasts, the cells that resorb bone. Inhibition of the RANKL pathway by administration of denosumab leads to a rapid decrease in markers of bone resorption and numbers of osteoclasts.

The single- and multiple-dose pharmacokinetics of denosumab following intravenous or subcutaneous administration of denosumab were evaluated in mice, rats, and cynomolgus monkeys. Serum concentrations of denosumab were determined using a conventional sandwich enzyme-linked immunosorbent assay (ELISA) with a limit of quantification (LOQ) ranging from 0.78 to 5 ng/mL. In addition, tissue distribution (by liquid scintillation counting) and

quantitative whole body autoradiography studies were conducted in cynomolgus monkeys following a single SC dose.

In mice and rats, species in which denosumab does not bind RANKL, the intravenous pharmacokinetics of denosumab were linear over the dose range of approximately 0.1 to 10 mg/kg, with low clearance and a volume of distribution at steady-state (Vss) that indicated a lack of extensive extravascular distribution. After a single SC dose (1 mg/kg), maximum serum denosumab concentrations (C_{max}) occurred at 72 hours postdose in both species, and bioavailability was 86% in mice and 56% in rats.

Approximately 6- and 15-fold higher clearance was observed in huRANKL and knock-out mice lacking expression of the Fc neonatal receptor (FcRn), respectively, indicating important roles of RANKL and FcRn in denosumab disposition.

In cynomolgus monkeys, a species in which denosumab binds RANKL, the intravenous pharmacokinetics of denosumab were non-linear over the dose range of 0.0016 to 1 mg/kg (with approximately 16-fold higher clearance at the lowest relative to highest dose) but were approximately dose-linear between 1 and 3 mg/kg. At all doses, the Vss indicated a lack of extensive extravascular distribution. The subcutaneous pharmacokinetics of denosumab were also nonlinear in monkeys over the dose range of 0.0016 to 1 mg/kg, but were approximately dose-linear between 1 and 3 mg/kg.

Clinical Pharmacology

Pharmacodynamics

In clinical studies, treatment with 60 mg of PROLIA resulted in rapid reduction in the bone resorption marker serum type 1 C-telopeptide (CTX) within 6 hours of SC administration by approximately 70%, with reductions of approximately 85% occurring by 3 days. CTX levels were below the limit of assay quantitation (0.049 ng/mL) in 39 to 68% of subjects 1 to 3 months after dosing of PROLIA. CTX reductions were maintained over the 6-month dosing interval. At the end of each dosing interval, CTX reductions were partially attenuated from maximal reduction of ≥ 87% to ≥ 45% (range 45% to 80%), as serum denosumab levels diminished, reflecting the reversibility of the effects of PROLIA on bone remodelling. These effects were maintained with continued treatment. Consistent with the physiological coupling of bone formation and resorption in skeletal remodeling, subsequent reductions in bone formation markers were observed beginning 1 month after the first dose of PROLIA.

Bone turnover markers (bone resorption and formation markers) generally reached pre-treatment levels within 9 months after the last 60 mg SC dose. Upon re-initiation, the degree of inhibition of CTX by PROLIA was similar to that observed in patients initiating PROLIA treatment.

In a clinical study of postmenopausal women with low bone mass (N = 504) who were previously treated with alendronate for a median duration of 3 years, those transitioning to receive PROLIA experienced additional reductions in serum CTX, compared with women who remained on alendronate. In this study, the changes in serum calcium were similar between the 2 groups.

Pharmacokinetics

Denosumab pharmacokinetics 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 (28 to 87 years), race, 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 100- to 150-fold higher than the human exposure for 60 mg SC administered once every 6 months.

Animal Toxicology

Denosumab is a potent inhibitor of osteoclastic bone resorption via inhibition of RANK ligand (RANKL).

In ovariectomized monkeys, once-monthly treatment with denosumab suppressed bone turnover and caused significant gain in BMD, and strength of cancellous and cortical bone. Bone tissue was normal with no evidence of mineralization defects, accumulation of osteoid, or woven bone.

Transition from 6-month alendronate treatment to denosumab in monkeys did not cause any meaningful decreases in serum calcium and significantly increased or maintained BMD of the whole body, lumbar spine, and distal radius. Bone strength parameters at these sites were maintained or improved with transition to denosumab, relative to continuous treatment with alendronate. Bone strength and reduction in bone resorption at all skeletal sites were maintained or improved in monkeys switched from alendronate to denosumab.

Since the biological activity of denosumab in animals is specific to non-human primates, evaluation of genetically engineered ("knockout") mice or use of other biological inhibitors of the RANK/RANKL pathway, namely OPG-Fc, provided additional information on the

pharmacodynamic properties of denosumab. RANK/RANKL knockout mice exhibited impairment of lymph node formation, had an absence of lactation due to inhibition of mammary gland maturation (lobulo-alveolar gland development during pregnancy), and exhibited reduced bone growth and lack of tooth eruption. Similar phenotypic changes were seen in a corroborative study in 2-week old rats given the RANK ligand inhibitor OPG-Fc. After 10 weeks on study, these changes were partially reversible in this model when dosing with the RANKL inhibitors was discontinued. Refer to Table 8. Summary of Preclinical Toxicity and Reproductive Studies with Denosumab for details of the individual study results.

Table 8. 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 (SC) or Intravenous (IV)	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 50mg/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
Embryo-fetal	Cynomolgus	16	Subcutaneous	Once weekly:	Gestation days	No treatment related effects on mother or embryonic	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)
Development	monkey	Females		0, 2.5, 5, 12.5	20-50	development were observed. Peripheral lymph nodes were not evaluated.	
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 9). 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 or 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. At birth out to 1 month of age, infants had measurable blood levels of denosumab (22-621% of maternal levels). Only one infant had measurable concentrations of denosumab on BD91, and no infants had measurable concentrations on BD180. Generally, the effects	A NOAEL was not identified

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)
						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
	Sprague Dawley neonatal rats	51 male and 49 female	Subcutaneous	Rat OPG-Fc or ALN: 5 μL/g/week for 6 weeks followed by 10 week treatment-free period	16 weeks	Ten weeks after the discontinuation of a 6-week course of OPG-Fc administration, neonatal rats exhibited evidence of restored bone resorption and partial normalization of bone density, size, and strength. Molar eruption, which had been substantially delayed during the administration of OPG-Fc, exhibited partial recovery in some animals within 10 weeks of its discontinuation. The relative increases in bone volume, density, and strength that occurred during 6 weeks of ALN administration were generally preserved 10 weeks after its discontinuation, whereas molar eruption did not recover within this timeframe. Modest epiphyseal growth plate changes persisted 10 weeks after discontinuing high-dose OPG-Fc. Bone size, body weight, and molar root development remained significantly reduced 10 weeks after discontinuation of OPG-Fc or ALN when compared to the vehicle control group.	N/A
Other Studies – Tissue Cross-reactivity	Cynomolgus monkey, rat, rabbit	N/A	*In Vitro*	5 or 25 μg/mL	N/A	Staining of lymphoid tissue in rabbit and cynomolgus monkey and staining of chondrocytes in rat were observed.	N/A

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)
	Cynomolgus monkey, human	N/A	*In Vitro*	1 or 10 μg/mL	N/A	Staining of lymphoid tissue in monkey, but no staining in human tissue was observed.	N/A
	Human	N/A	*In Vitro*	1 or 10 μg/mL	N/A	Staining of lymphoid tissue was observed.	N/A

N/A = not applicable

Table 9. 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]			24.8% (33/133)	6.8% (9/133)	15.8% (21/133)	9.0% (12/133)
Range			(6.7 to 38.9%)	(0 to 11.8%)	(0 to 28.6%)	(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

[Pr]Prolia®
(denosumab)

pronounced PRO-lee-ah

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

Please read this information carefully before you start to take your medicine, even if you have just refilled your prescription. Some of the information may have changed. Keep this pamphlet since you may need to refer to it after starting treatment with PROLIA.

Remember that your physician has prescribed this medicine only for you. Never give it to anyone else.

ABOUT THIS MEDICATION

What the medication is used for:

PROLIA is used to:

- treat osteoporosis (thinning and weakening of the bone) in women after menopause who
  - have an increased risk for fractures or;
  - cannot use other osteoporosis medicines, or other osteoporosis medicines did not work well.
- increase bone mass in men with osteoporosis at high risk for fracture.

What is osteoporosis?

Bone is constantly changing. There are special cells in the body called osteoclasts whose primary function is to remove bone. There is another type of cell called osteoblasts, which are bone-forming cells. In normal bone, there is a balance between the actions of these two cells. In people with osteoporosis, this balance no longer exists. Instead, the cells that remove bone work overtime, removing bone faster than new bone can be created. The result is bone that is thinner, weaker and more likely to break. Osteoporosis may occur without any pain or other symptoms. Sometimes the first symptom of osteoporosis is a fragility fracture, a broken bone that may be caused by a minor fall, or simple activities such as lifting groceries or getting out of bed. A fragility fracture can significantly increase the risk of future fractures. Aside from prescribing PROLIA, your doctor can guide you in other ways to manage your bone health.

What it does:

PROLIA works differently than other osteoporosis medications. It is a RANK ligand inhibitor. RANK ligand is a protein which activates the cells that break down bone (osteoclasts). PROLIA blocks RANK ligand to stop the cells that break down bone. This action strengthens your bones by increasing bone mass and lowers the chance of breaking bones of the hip, spine, and nonspinal sites.

When PROLIA should not be used:

You should not use PROLIA if you:

- Are allergic to denosumab or any other ingredient of PROLIA. Allergic reactions (eg, rash, hives, or in rare cases, swelling of the face, lips, tongue, throat, or trouble breathing) have been reported.
- Have low calcium levels in your blood (hypocalcemia)
- Are a child
- Are pregnant or breast-feeding
- Do not have access to a health professional or trained injector

What the medicinal ingredient is:

The medicinal ingredient in PROLIA is denosumab.

What the important nonmedicinal ingredients are:

The other ingredients are sorbitol, acetate, polysorbate 20, water for injection and sodium hydroxide. The needle cover on the single use prefilled syringe contains dry natural rubber (latex), which should not be handled by persons allergic to this substance.

What dosage forms it comes in:

PROLIA is a liquid for injection, available in a prefilled syringe or a single use vial[†].

PROLIA is a clear, colourless to slightly yellow solution. Do not use if the solution is cloudy.

[†] 60 mg/1.0mL single use vial is not available in Canada.

WARNINGS AND PRECAUTIONS

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

PROLIA contains the same medicine as XGEVA, which is used to reduce the risk of developing cancer-related complications. PROLIA, which is given at a lower dose once every 6 months, should not be used to treat this condition.

There is an increased risk of skin infection (cellulitis) with PROLIA therapy, most commonly on the leg. See a doctor urgently if you develop swollen, red, hot or painful skin, with or without fever.

You should take calcium and vitamin D supplements as recommended by your healthcare professional.

PROLIA is recommended for women after menopause (more than one year after your last period) and for men with osteoporosis at high risk for fracture.

BEFORE you use PROLIA talk to your doctor or pharmacist if you:

- Have low blood calcium
- Cannot take daily calcium and vitamin D
- Had parathyroid or thyroid surgery (glands located in your neck)
- Have been told you have trouble absorbing minerals in your stomach or intestines (malabsorption syndrome)
- Have kidney problems or are on kidney dialysis
- Have ever had an allergic reaction to PROLIA
- Plan to have dental surgery or teeth removed
- Have a history of cancer
- Could become pregnant

Tell your doctor and pharmacist about all the medicines you take, including prescription and nonprescription drugs, vitamins, and herbal supplements, and keep an up-to-date list of all of them.

The needle cover on the single use prefilled syringe contains dry natural rubber (latex), which should not be handled by persons allergic to it.

PROLIA may interfere with normal bone and tooth development in fetuses, nursing babies, and children under 18 years of age. Children under 18 years of age should not take PROLIA.

Women who are pregnant or could become pregnant should not take PROLIA. Tell your doctor right away if you become pregnant while taking PROLIA. If you become pregnant during PROLIA treatment, you are encouraged to enrol in Amgen's Pregnancy Surveillance Program by calling 1-866-51-AMGEN (1-866-512-6436).

Nursing mothers should not take PROLIA. It may also interfere with breastfeeding. If you are nursing during PROLIA treatment, you are encouraged to enrol in Amgen's Lactation Surveillance Program by calling 1-866-51-AMGEN (1-866-512-6436).

PROLIA may lower levels of calcium in the blood. Low blood calcium should be treated before receiving PROLIA. Symptoms of low blood calcium may include muscle spasms, twitches, cramps, numbness or tingling in hands, feet or around the mouth, and weakness. Some patients may not have any symptoms of low calcium.

Tell your doctor right away if you have symptoms of infection, including:

- Fever or chills
- Skin that looks red, swollen, hot or tender to touch
- Severe abdominal pain
- Frequent or urgent need to urinate or burning feeling when you urinate

Tell your doctor if you have any of the following symptoms of skin problems that do not go away or get worse:

- Redness
- Itching
- Rash
- Dry or leathery skin
- Open, crusted or peeling skin
- Blisters

After you start PROLIA:

- Take good care of your teeth and gums, and see your dentist regularly
- If you have a history of dental problems (such as poorly fitting dentures or gum disease), see your dentist before starting PROLIA
- Tell your dentist that you are taking PROLIA, especially if you are having dental work

A dental condition called osteonecrosis of the jaw which can cause tooth and jawbone loss has been reported in patients treated with PROLIA. Tell your doctor and dentist immediately about any dental symptoms, including pain or unusual feeling in your teeth or gums, or any dental infections.

Some people have developed unusual fractures in their thigh bone. Contact your doctor if you experience new or unusual pain in your hip, groin, or thigh.

INTERACTIONS WITH THIS MEDICATION

Drug interactions between PROLIA and other drugs have not been studied.

You should discuss with your doctor any medications or vitamins or herbal products you are taking before using PROLIA.

PROPER USE OF THIS MEDICATION

PROLIA is administered as a single injection under the skin (subcutaneous) every 6 months. The injection can be in your upper arm, upper thigh, or abdomen. It can be given any time by a health professional or by a trained injector, with or without food.

Your prefilled syringe may be left outside the refrigerator to reach room temperature (up to 25°C) before injection. This will make the injection more comfortable. See instructions for injection.

Keep all medicines, including PROLIA, away from children.

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

Usual dose:

The usual dose of PROLIA is 60 mg administered once every 6 months. You should also take supplements of calcium and vitamin D.

Missed dose:

If you miss a dose you should receive your next dose as soon as convenient. Schedule your next dose 6 months from the date of your last injection.

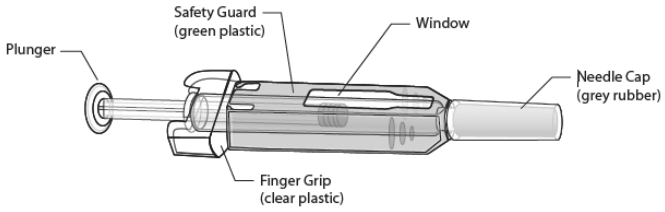
Overdose:

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

INSTRUCTIONS FOR INJECTION:

IMPORTANT: In order to minimize accidental needle sticks, the PROLIA single use prefilled syringe has a green safety guard that should be manually activated after the injection is given.

DO NOT slide the green safety guard forward over the needle before administering the injection – it will lock in place and prevent injection.

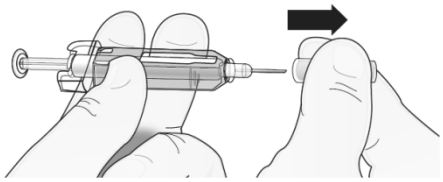


The green safety guard should be activated (slid over the needle) AFTER the injection.

The grey needle cap on the single use prefilled syringe contains dry natural rubber (a derivative of latex), which should not be handled by persons sensitive to latex.

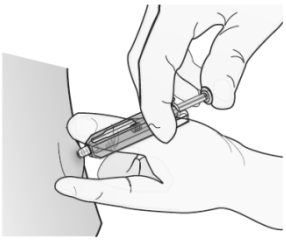
Step 1 – Remove Grey Needle Cap

Remove Needle Cap



Step 2 – Administer Injection

Insert needle and inject all the liquid



DO NOT put grey needle cap back on needle.

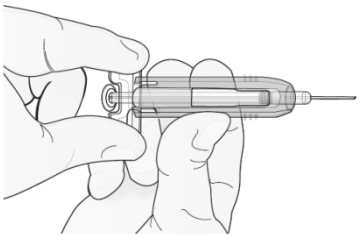
Step 3 – Immediately Slide Green Safety Guard over Needle

With the needle pointing away from you

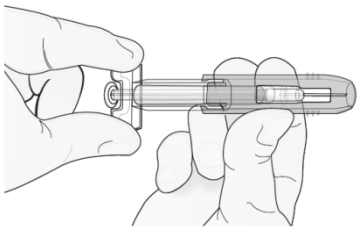
Hold the prefilled syringe by the clear plastic finger grip with one hand. Then, with the other hand, grasp the green safety guard by its base and gently slide it towards the needle until the green safety guard locks securely in place and/or you hear a 'click.'

DO NOT grip the green safety guard too firmly – it will move easily if you hold and slide it gently.

Hold clear Finger Grip



Gently slide green safety guard over needle and lock securely in place. Do not grip green safety guard too firmly when sliding over needle.



Immediately dispose of the syringe and needle cap in the nearest sharps container. DO NOT put the needle cap back on the used syringe.

For administration of PROLIA from the single use vial†, use a 27-gauge needle to withdraw and inject the 1 mL dose. Do not re-enter the vial†.

† 60 mg/1.0mL single use vial is not available in Canada.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

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

Possible side effects include:

- Pain in muscles, arms, legs or back. These side effects were also very common in patients taking placebo.
- 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.
- Allergic reactions (eg, rash, hives, or in rare cases, swelling of the face, lips, tongue, throat, or trouble breathing).
- Skin condition with itching, redness and/or dryness (eczema). Injection site reactions were uncommon.
- Skin infection with swollen, red area of skin, that feels hot and tender and may be accompanied by fever (cellulitis).
- Common cold (runny nose or sore throat)

These are not all the possible symptoms or side effects you may experience; if you are concerned about any effects you experience you should contact your doctor.

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 (≥ 1%, in 1 to 10% of patients)	Skin condition with itching, redness and/or dryness (eczema)	√		
Uncommon (≥ 0.1%, < 1%)	Skin infection (mainly cellulitis) leading to hospitalization, erysipelas (serious and rapid skin infection commonly on the face or legs)		√	
	Urinary tract infection, pancreatitis (inflamed pancreas causing severe stomach pains), and ear infection		√	
Rare (≥ 0.01%,< 0.1%)	Low calcium levels in the blood		√	
	Endocarditis (inflammation of the inner lining of the heart)		√	√
	Sore in mouth involving gums or jaw bones (Osteonecrosis of the jaw)		√	√
Very Rare (< 0.01%)	Unusual thigh bone fractures		√	

HOW TO STORE IT

Keep out of the reach and sight of children.

When prescribed PROLIA, you will likely need to fill your prescription at a pharmacy. Store PROLIA in your refrigerator at 2°C to 8°C until your injection appointment with your health professional or trained injector. Do not freeze.

When removed from the refrigerator, PROLIA 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 use PROLIA 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, contact the ProVital Support Program information line, toll-free at: 1-877-776-1002 or visit www.prolia.ca.

This leaflet was prepared by Amgen Canada Inc.

Last revised: August 13, 2013