Product Monograph

Including Patient Medication Information

PrIDENOS™

Denosumab injection

120 mg/1.7 mL solution for subcutaneous injection

Single-use Vial

Professed Standard

RANK Ligand Inhibitor

(Bone Metabolism Regulator)

Apotex Inc.
150 Signet Drive
Toronto, Ontario
M9L 1T9

Date of Authorization:
March 11, 2026

Control Number: 283188

Recent Major Label Changes

Not applicable	

Table of Contents

Certain sections or subsections that are not applicable at the time of preparation of the most recent authorized product monograph are not listed.

Part 1: Healthcare Professional Information

IDENOS™ (denosumab injection) is a biosimilar biologic drug (biosimilar) to XGEVA® (denosumab injection). A biosimilar is a biologic drug that was granted authorization based on a demonstration of similarity to a version previously authorized in Canada, known as the reference biologic drug.

1 Indications

Indications have been granted on the basis of similarity between IDENOS and the reference biologic drug XGEVA®.

IDENOS (denosumab injection) is indicated for:

- reducing the risk of developing skeletal-related events in patients with multiple myeloma and in patients with bone metastases from breast cancer, prostate cancer, non-small cell lung cancer, and other solid tumours.
- treatment of adults and skeletally mature adolescents with giant cell tumour of bone that is unresectable or where surgical resection is likely to result in severe morbidity (see 14 Clinical Trials).
- treatment of hypercalcemia of malignancy that is refractory to intravenous bisphosphonate (see 14 Clinical Trials).

1.1 Pediatrics

Pediatrics (< 18 years of age): The safety and efficacy of denosumab have not been studied in pediatric populations other than skeletally mature adolescents (aged 13-17 years) with giant cell tumour of bone (GCTB).
IDENOS is not indicated for use in pediatric patients other than skeletally mature adolescents with GCTB (see 7.1.3 Pediatrics).

1.2 Geriatrics

Geriatrics (≥ 65 years of age): Of the total number of patients in the pivotal clinical studies in patients with advanced cancer, 1271 patients (44.4%) treated with denosumab, were ≥ 65 years old. Of the total number of patients in the pivotal clinical study in patients with multiple myeloma, 387 patients (45.1%) treated with denosumab, were > 65 years old. No overall differences in safety or efficacy were observed between older and younger patients.

2 Contraindications

- Patients who are hypersensitive to this drug or to any ingredient in the formulation or component of the container. For a complete listing, see 6 Dosage Forms, Strengths, Composition and Packaging. Anaphylactic reactions have been reported (see 7 Warnings and Precautions, Hypersensitivity and 8.5 Post-Market Adverse Reactions).
- Pre-existing hypocalcemia must be corrected prior to initiating therapy with IDENOS (see 7 Warnings and Precautions, Endocrine and Metabolism, Hypocalcemia).

3 Serious Warnings and Precautions Box

Osteonecrosis of the jaw (ONJ) (see 7 Warnings and Precautions, Other, and 8 Adverse Reactions)

4 Dosage and Administration

4.1 Dosing Considerations

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

4.2 Recommended Dose and Dosage Adjustment

Multiple Myeloma and Bone Metastasis from Solid Tumours

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

Giant Cell Tumour of Bone

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

Hypercalcemia of Malignancy Refractory to Intravenous Bisphosphonate

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

Health Canada has not authorized an indication for pediatric use (see 1.1 Pediatrics).

4.2.1 Discontinuing Treatment

Hypercalcemia Following Treatment Discontinuation in Patients with Giant Cell Tumour of Bone and in Patients with Growing Skeletons

Clinically significant hypercalcemia requiring hospitalization and complicated by acute renal injury has been reported in denosumab-treated patients with GCTB and patients with growing skeletons weeks to months following treatment discontinuation. After treatment is discontinued, monitor patients for signs and symptoms of hypercalcemia, consider periodic assessment of serum calcium as clinically indicated, and reevaluate the patients' calcium and vitamin D supplementation requirements. Manage hypercalcemia as clinically appropriate (see 7.1.3 **Error! Reference source not found.** and 8 **Error! Reference source not found.**).

Multiple Vertebral Fractures (MVF) Following Treatment Discontinuation

Multiple vertebral fractures (MVF), not due to bone metastases, may occur following discontinuation of treatment with denosumab, particularly in patients with risk factors such as osteoporosis or prior fractures.

Advise patients not to interrupt XBRYK therapy without their physician's advice. When XBRYK treatment is discontinued, evaluate the individual patient's risk for vertebral fractures.

4.4 Administration

Prior to administration, IDENOS may be removed from the refrigerator and brought to room temperature (up to 25°C) by standing in the original carton. This generally takes 15 to 30 minutes. Do not warm IDENOS in any other way (see 11 Storage, Stability and Disposal).

Visually inspect IDENOS for particulate matter and discolouration prior to administration. IDENOS is a colourless to yellowish solution. Do not use if the solution is discoloured or cloudy or if the solution contains many particles or foreign particulate matter.

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

IDENOS is intended for use under the guidance and supervision of physicians who have fully familiarized themselves with the efficacy/safety profile of IDENOS. After an initial training in

proper subcutaneous injection technique, patients may self -inject IDENOS if a physician determines that is appropriate and with medical follow-up as necessary.

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

4.5 Missed Dose

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

5 Overdose

There is no experience with overdosage of IDENOS.

For the most recent information in the management of a suspected drug overdose, contact your regional poison control centre or Health Canada's toll-free number, 1-844 POISON-X (1-844-764-7669).

6 Dosage Forms, Strengths, Composition, and Packaging

To help ensure the traceability of biologic products, healthcare professionals should record both the brand name and the non-proprietary (active ingredient) name as well as other product-specific identifiers such as the Drug Identification Number (DIN) and the batch/lot number of the product supplied.

Table 1. Dosage Forms, Strengths, and Composition

Route of Administration	Dosage Form/ Strength/Composition	Non-Medicinal Ingredients
Subcutaneous	120 mg denosumab in 1.7 mL solution in a single-use vial	Acetic acid, polysorbate 20, sodium hydroxide, sorbitol, and water for injection (USP).

IDENOS is a sterile, preservative-free, colourless to yellowish solution formulated at pH 5.2.

IDENOS is supplied in a single-use vial containing 120 mg denosumab, 78.20 mg (4.6%) sorbitol, 1.84 mg (18 mM) acetic acid, 0.17 mg (0.01%) polysorbate 20, water for injection (USP), and sodium hydroxide to a pH of 5.2.

IDENOS is supplied in a carton containing 1 vial.

7 Warnings and Precautions

Please see 3 Serious Warnings and Precautions Box.

General

IDENOS (denosumab) contains the active ingredient denosumab. Patients being treated with IDENOS should not be treated concomitantly with other medicinal products containing denosumab.

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

Carcinogenesis and Genotoxicity

Please see 16 Non-Clinical Toxicology.

Endocrine and Metabolism

Hypocalcemia

Denosumab can cause severe symptomatic hypocalcemia and fatal cases have been reported. Signs and symptoms of severe hypocalcemia may include, for example, altered mental status, tetany, seizures and QTc prolongation. Pre-existing hypocalcemia must be corrected prior to initiating therapy with IDENOS. Monitor calcium levels, (i) prior to the initial dose of IDENOS, (ii) within two weeks after the initial dose, and (iii) if suspected symptoms of hypocalcemia occur. Administer adequate calcium and vitamin D, and magnesium, as necessary. Additional monitoring should be considered during therapy in patients with risk factors for hypocalcemia, or if otherwise indicated based on the clinical condition of the patient. Monitor levels more frequently when IDENOS is administered with other drugs that can also lower calcium levels. If hypocalcemia occurs while receiving IDENOS, additional short-term calcium supplementation and additional monitoring may be necessary (see 4 Dosage and Administration, and 8 Adverse Reactions, Hypocalcemia and 8.5 Post-Market Adverse Reactions).

An increased risk of hypocalcemia has been observed in patients with increasing degree of renal impairment. Patients with severe renal impairment (creatinine clearance less than 30 mL/min and/or receiving dialysis), are at a greater risk of developing hypocalcemia which is accompanied by an elevation in parathyroid hormone levels. Absence of calcium supplementation also plays a role in the increased risk of hypocalcemia development in patients with renal impairment. More frequent monitoring of calcium levels in these patients, within two weeks after administration of IDENOS, is especially important. If hypocalcemia occurs, administer adequate calcium, vitamin D, and magnesium, as necessary (see 7 Warnings and Precautions, Renal and 8 Adverse Reactions).

No dose adjustment is necessary in patients with renal impairment and there is no additional need for more frequent renal monitoring due to IDENOS administration (see 7 Warnings and Precautions, Renal).

Hepatic/Biliary/Pancreatic

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

Immune

Hypersensitivity

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

If an anaphylactic or other clinically significant allergic reaction occurs, initiate appropriate treatment immediately and discontinue further use of IDENOS (see 2 Contraindications and 8 Adverse Reactions).

Monitoring and Laboratory Tests

Monitor calcium levels, (i) prior to the initial dose of IDENOS, (ii) within two weeks after the initial dose, and (iii) if suspected symptoms of hypocalcemia occur. Additional monitoring should be considered during therapy in patients with risk factors for hypocalcemia, or if otherwise indicated

based on the clinical condition of the patient. Calcium levels should be monitored more frequently when IDENOS is administered with other drugs that can also lower calcium levels (See 7 Warnings and Precautions, Endocrine and Metabolism, Hypocalcemia).

Musculoskeletal

Osteonecrosis of the Jaw (ONJ)

ONJ has been reported in patients treated with denosumab or bisphosphonates, another class of anti-resorptive agents. ONJ can manifest as jaw pain, osteomyelitis, osteitis, bone erosion, tooth or periodontal infection, toothache, gingival ulceration, or gingival erosion. Persistent pain or slow healing of the mouth or jaw after dental surgery may also be manifestations of ONJ.

In clinical trials, the incidence of ONJ was higher with longer duration of exposure (see 8 Adverse Reactions). ONJ has also been diagnosed after treatment with denosumab with the majority of cases occurring within 5 months after the last dose.

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

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

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

Patients who are suspected of having or who develop ONJ while on IDENOS should receive care by a dentist or an oral surgeon. In these patients, extensive dental surgery to treat ONJ may exacerbate the condition. In patients who develop ONJ during treatment with IDENOS, a temporary interruption of treatment should be considered based on individual benefit-risk assessment until the condition resolves.

Atypical Femoral Fractures

Atypical femoral fracture has been reported with denosumab. 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 IDENOS 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.

Renal

Two clinical trials were conducted in subjects without cancer and with varying degrees of renal function. In one study, subjects (N = 55) with varying degrees of renal function (ranging from normal through end-stage renal disease requiring dialysis) received a single 60 mg subcutaneous dose of denosumab. In a second study, patients (N = 32) with severe renal impairment (creatinine clearance less than 30 mL/minute and/or on dialysis) were given two 120 mg subcutaneous doses of denosumab. In both studies, there was a greater risk of developing hypocalcemia with increasing degree of renal impairment, and in the absence of, or inadequate calcium supplementation. The development of hypocalcemia in patients with severe renal impairment (creatinine clearance less than 30 mL/min and/or receiving dialysis) was accompanied by an elevation in parathyroid hormone levels.

No dose adjustment is necessary in patients with renal impairment and there is no additional need for more frequent renal monitoring due to IDENOS administration. Adequate intake of calcium and vitamin D is important in patients with severe renal impairment or receiving dialysis (see 7 Warnings and Precautions, 8 Adverse Reactions, and 10 Clinical Pharmacology).

Skin

Skin Infections

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

7.1 Special Populations

7.1.1 Pregnancy

The safety and efficacy of denosumab in pregnant women have not been established. IDENOS is not recommended for use in pregnant women.

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

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

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

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

postpartum (see 16 Non-Clinical Toxicology).

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

7.1.2 Breastfeeding

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

Maternal exposure to denosumab during pregnancy may impair mammary gland development and lactation based on animal studies in pregnant mice lacking the RANK/RANKL signaling pathway which showed altered maturation of the maternal mammary gland, leading to impaired lactation postpartum (see 16 Non-Clinical Toxicology).

7.1.3 Pediatrics

Pediatrics (< 18 years of age): The safety and efficacy of denosumab have not been established in pediatric patients other than skeletally mature adolescents (aged 13-17 years) with GCTB.

IDENOS is not recommended for use in pediatric patients other than skeletally mature adolescents with GCTB. Clinically significant hypercalcemia after treatment discontinuation has been reported in the post-marketing setting in pediatric patients with growing skeletons who received denosumab for GCTB or for other unauthorized uses (see 7 Warnings and Precautions).

Denosumab was studied in a phase 2 open-label trial that enrolled a subset of adolescent patients (10 at interim analysis and 28 at final analysis; aged 13-17 years) with GCTB who had reached skeletal maturity defined by at least 1 mature long bone (eg, closed epiphyseal growth plate of the humerus) and body weight ≥ 45 kg (see 1 Indications and 14 Clinical Trials). The adverse reaction profile appeared similar in skeletally mature adolescents and adults.

Treatment with IDENOS may impair bone growth in children with open growth plates and may inhibit eruption of dentition. In neonatal rats, inhibition of RANKL (target of denosumab therapy) with a construct of osteoprotegerin bound to Fc (OPG-Fc) at doses ≤ 10 mg/kg was associated with inhibition of bone growth and tooth eruption. Adolescent monkeys dosed with denosumab at 15 times (50 mg/kg dose) and 2.8 times (10 mg/kg dose) the area under the curve (AUC) exposure in adult humans dosed at 120 mg subcutaneously every 4 weeks had abnormal growth plates, considered to be consistent with the pharmacological activity of denosumab. In neonatal cynomolgus monkeys exposed in utero to denosumab at 50 mg/kg, there was increased postnatal mortality; skeletal abnormalities resulting from impaired bone resorption during rapid growth, reduced bone strength and treatment-related bone fractures; reduced hematopoiesis; tooth malalignment and dental dysplasia (in the absence of adverse effects on tooth eruption); absence of peripheral lymph nodes; and decreased neonatal growth. Following a recovery period from birth out to 6 months of age, findings still observed were mildly reduced bone length (femoral, vertebral, jaw), reduced cortical thickness with associated reduced strength; extramedullary hematopoiesis; dental dysplasia; and the absence or decreased size of some lymph nodes. One infant had minimal to moderate mineralization in multiple tissues (see 16 Non-Clinical Toxicology).

7.1.4 Geriatrics

Geriatrics (≥ 65 years of age): Of the total number of patients in the pivotal clinical studies in patients with advanced cancer, 1271 patients (44.4%) treated with denosumab were ≥ 65 years old. Of the total number of patients in the pivotal clinical study in patients with multiple myeloma, 387 patients (45.1%) treated with denosumab, were > 65 years old. No overall differences in safety or efficacy were observed between older and younger patients.

8 Adverse Reactions

8.1 Adverse Reaction Overview

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

- Hypocalcemia (see 7 Warnings and Precautions, Endocrine and Metabolism, Hypocalcemia)
- Osteonecrosis of the jaw (see 7 Warnings and Precautions, Other, Osteonecrosis of the Jaw (ONJ))
- Multiple vertebral fractures following treatment discontinuation (see 7 Warnings and Precautions, Other, Multiple Vertebral Fractures (MVF) Following Treatment Discontinuation)

The most common adverse reactions in patients with bone metastasis from solid tumours receiving denosumab (per-patient incidence ≥ 10%) were dyspnea and musculoskeletal pain.

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

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

The most common adverse reactions in patients with multiple myeloma (per-patient incidence ≥ 10%) was hypocalcemia.

The most common serious adverse reactions in patients with multiple myeloma (per-patient incidence ≥ 1%) was osteonecrosis of jaw.

The most common adverse reactions resulting in discontinuation of denosumab in patients with multiple myeloma (per-patient incidence ≥ 1%) was osteonecrosis of the jaw.

In the initial integrated analysis (final analysis of Study 5 [20040215] and interim analysis of Study 6 [20062004]), the most common adverse reactions in patients with GCTB receiving denosumab (per-patient incidence ≥ 5%) were musculoskeletal pain, and hypophosphatemia. In the final integrated analysis (final analyses of both Studies 5 and 6), the following additional common adverse reactions were observed (per-patient incidence ≥ 5%): osteonecrosis of the jaw, hypocalcemia, and dyspnea.

In both the initial integrated analysis (final analysis of Study 5 and interim analysis of Study 6) and final integrated analysis (final analyses of both Studies 5 and 6), the most common serious adverse reaction in patients with GCTB receiving denosumab was osteonecrosis of the jaw.

In both the initial integrated analysis (final analysis of Study 5 and interim analysis of Study 6) and final integrated analysis (final analyses of both Studies 5 and 6), the most common adverse reaction in patients with GCTB receiving denosumab resulting in discontinuation of denosumab was osteonecrosis of the jaw.

8.2 Clinical Trial Adverse Reactions

Clinical trials are conducted under very specific conditions. Therefore, the frequencies of adverse

reactions observed in the clinical trials; may not reflect frequencies observed in clinical practice and should not be compared to frequencies reported in clinical trials of another drug.

An **adverse reaction** is an unintended event, reasonably associated with the use of a drug, whereas **adverse events** do not necessarily have a causal relationship to the drug. Although most data presented in this section reflect adverse reactions, some data include information on specific adverse events.

Bone Metastasis from Solid Tumours

The safety of denosumab was evaluated in three randomized, double-blind, double-dummy trials (see 14 Clinical Trials) in which a total of 2841 patients with bone metastasis from prostate cancer, breast cancer, or other solid tumours, or lytic bony lesions from multiple myeloma received at least one dose of denosumab. In Studies 1, 2, and 3, patients were randomized to receive either 120 mg of denosumab every 4 weeks as a subcutaneous injection or 4 mg (dose adjusted for reduced renal function) of zoledronic acid every 4 weeks by intravenous (IV) infusion. Entry criteria included serum calcium (corrected) from 8 to 11.5 mg/dL (2 to 2.9 mmol/L) and creatinine clearance 30 mL/min or greater. Patients who had received IV bisphosphonates were excluded, as were patients with prior history of ONJ or osteomyelitis of the jaw, an active dental or jaw condition requiring oral surgery, non-healed dental/oral surgery, or any planned invasive dental procedure. During the study, serum chemistries including calcium and phosphorus were monitored every 4 weeks. Calcium and vitamin D supplementation was recommended but not required.

The median duration of exposure to denosumab was 12 months (range: 0.1 – 41) and median duration on-study was 13 months (range: 0.1 – 41). Of patients who received denosumab, 46% were female. Eighty-five percent were White, 5% Hispanic/Latino, 6% Asian, and 3% Black. The median age was 63 years (range: 18 – 93). Seventy-five percent of patients who received denosumab received concomitant chemotherapy.

The adverse reactions occurring during the studies were generally of a type and frequency expected in patients with cancer and bone metastases, many of whom were undergoing antineoplastic therapy. Table 2 describes adverse reactions occurring in ≥ 1% of patients in these studies.

Table 2. Adverse Reactions Occurring in ≥ 1% Subject Incidence in Either Treatment Group (Primary Advanced Cancer Safety Analysis Set) (Studies 1, 2 and 3 Integrated Analysis)

System organ class Preferred term	Denosumab 120 mg Q4W (n = 2841) (%)	Zoledronic Acid 4 mg Q4W (n = 2836) (%)
Metabolism and nutrition disorders		
Hypocalcemia	265 (9.3)	134 (4.7)
Hypophosphatemia	61 (2.1)	32 (1.1)
Musculoskeletal and connective tissue disorders		
Musculoskeletal pain	357 (12.6)	385 (13.6)
Respiratory, thoracic and mediastinal disorders		
Dyspnea	585 (20.6)	507 (17.9)
Adjudicated positive osteonecrosis of the jaw [a]	52 (1.8)	37 (1.3)

N = Number of subjects who received ≥ 1 active dose of investigational product (IP)
n = Number of subjects reporting ≥ 1 event
[a] Adverse reactions by preferred term are summarized, except for adjudicated positive osteonecrosis of the jaw.
Includes only treatment-emergent events which is defined as all events started after first dose of IP.
Preferred terms are coded using MedDRA version 12.1.

Multiple Myeloma

In Study 4, denosumab was evaluated in an international, randomized (1:1), double blind, active controlled study comparing denosumab with zoledronic acid in patients with newly diagnosed multiple myeloma (see 14 Clinical Trials). In this study, 1718 multiple myeloma patients with at least 1 bone lesion were randomized to receive 120 mg denosumab subcutaneously every 4 weeks or 4 mg zoledronic acid intravenously (IV) every 4 weeks (dose adjusted for renal impairment and patients with creatinine clearance less than 30 mL/min were excluded based on zoledronic acid prescribing information).

The number of patients across both study arms with ISS stage I, stage II, and stage III at diagnosis were 32.4%, 38.2%, and 29.3%, respectively. In the denosumab group, 46% were female, 82% were White, 12% Asian, and 4% Black. The median age was 63 years (range: 29 - 91). The median duration of exposure to denosumab was 16 months (range: 1 – 50) and median duration on study was 17 months (range: 0 – 49). The median number of doses administered was 16 for denosumab and 15 for zoledronic acid.

Table 3 describes adverse reactions occurring in ≥ 1% of patients in this study.

Table 3. Adverse Reactions Occurring in ≥ 1% Subject Incidence in Either Treatment Group (Multiple Myeloma Safety Analysis Set) (Study 4 Primary Analysis)

System organ class Preferred term	Denosumab 120 mg Q4W (n = 850) (%)	Zoledronic Acid 4 mg Q4W (n = 852) (%)
Metabolism and nutrition disorders		
Hypocalcemia	139 (16.4)	101 (11.9)
Hypophosphatemia	54 (6.4)	43 (5.0)
Musculoskeletal and connective tissue disorders		
Musculoskeletal pain	64 (7.5)	67 (7.9)
Respiratory, thoracic and mediastinal disorders		
Dyspnea	72 (8.5)	89 (10.4)
Adjudicated positive osteonecrosis of the jaw [a]	35 (4.1)	24 (2.8)

N = Number of subjects who received ≥ 1 active dose of investigational product (IP)
n = Number of subjects reporting ≥ 1 event
[a] Adverse reactions by preferred term are summarized in the table, except for adjudicated positive atypical femur fracture and adjudicated positive osteonecrosis of the jaw.
Includes only treatment-emergent events (defined as events occurred from the first dose of IP to 30 days after the last dose of IP, or end of treatment phase visit, whichever is longer), except for adjudicated positive osteonecrosis of the jaw where all events started after first dose of IP are included.
Preferred terms are coded using MedDRA version 19.0.

Giant Cell Tumour of Bone

The safety of denosumab was evaluated in two phase 2 open-label, single arm studies (Studies 5 and 6) (see 14 Clinical Trials) in which patients (n=304 at initial integrated analysis and n=548 at final integrated analysis) with GCTB received at least 1 dose of denosumab. Patients received 120 mg denosumab subcutaneously every 4 weeks with a loading dose of 120 mg on days 8 and 15. In the initial integrated analysis (final analysis of Study 5 and interim analysis of Study 6), of the 304 patients who received denosumab, 147 patients were treated with denosumab for ≥ 1 year, 46 patients for ≥ 2 years, and 15 patients for ≥ 3 years. The median number of doses received was 14 (range: 1 to 60 doses) and the median number of months on study was 11 (range: 0 to 54 months).

Fifty-eight percent of the enrolled subjects were women. The majority of subjects were white (80.3%). The median (range) age was 33 (13 to 83) years; 10 subjects were skeletally mature adolescents (aged 13 to 17 years).

At the final integrated analysis of both Studies 5 and 6, of the 548 patients who received denosumab, 467 patients were treated with denosumab for ≥ 1 year, 323 patients for ≥ 2 years, and 255 patients for ≥ 3 years. The median number of doses received was 33 (range: 4 to 138 doses) and the median number of months on study was 60 (range: 0 to 140 months) in the final integrated analysis.

Fifty-seven percent of the enrolled subjects were women. The majority of subjects were white (81.9%). The median (range) age was 33 (13 to 83) years; 28 subjects were skeletally mature adolescents (aged 13 to 17 years).

Table 4 describes adverse reactions at initial integrated analysis (final analysis of Study 5 and interim analysis of Study 6) occurring in ≥ 1% of patients in these studies.

Table 4. Adverse Reactions Occurring in ≥ 1% Subject Incidence (Giant Cell Tumour of Bone Safety Analysis Set, Treatment Analysis Phase) (Studies 5 and 6 Initial Integrated Analysis)

System organ class Preferred term	**Denosumab 120 mg Q4W (n = 304) (%)**
Metabolism and nutrition disorders	
Hypophosphatemia	17 (5.6)
Hypocalcemia	13 (4.3)
Musculoskeletal and connective tissue disorders	
Musculoskeletal pain	26 (8.6)
Respiratory, thoracic and mediastinal disorders	
Dyspnea	11 (3.6)
Adjudicated positive osteonecrosis of the jaw [a]	4 (1.3)

N = Number of subjects who received ≥ 1 active dose of investigational product (IP)
n = Number of subjects reporting ≥ 1 event
[a] Adverse reactions by preferred term are summarized in the table, except for adjudicated positive osteonecrosis of the jaw.
Includes only treatment-emergent events which is defined as all events started after first dose of IP, except hypercalcaemia. For hypercalcemia events, includes all adverse events which occurred after 30 days following last dose of denosumab in the initial treatment phase.
Subjects who rolled over from 20040215 to 20062004 or who discontinued 20040215 and re-entered 20062004 are counted only once and their analysis period will start from study 20040215 and end at study 20062004.
Preferred terms are coded using MedDRA version 14.1.

In the final analysis of Study 6, of the 526 subjects who received ≥ 1 dose of denosumab, the most common treatment-emergent adverse reactions were musculoskeletal pain (12.7%), hypophosphatemia (12.4%), osteonecrosis of the jaw (6.7%), and hypocalcemia (6.5 %). The most common treatment-emergent serious adverse reaction was osteonecrosis of the jaw (3.8%). In addition, the following treatment-emergent adverse events of interest were also observed, musculoskeletal pain (68.4%), infections (53.4%), adverse events potentially associated with hypersensitivity (20.2%), vascular disorders (10.3%) and cardiac disorders (6.1%). The incidence of treatment-emergent fatal adverse events was 2.1% (11 of 526 subjects) with three deaths being considered by investigators as being related to denosumab (0.6%; bone sarcoma, rhabdomyosarcoma and sarcoma). The incidence of treatment-emergent adverse events leading to treatment phase discontinuation was 9.9% (52 of 526 patients).

Hypercalcemia of Malignancy Refractory to Intravenous Bisphosphonate

The safety of denosumab was evaluated in an open-label, single-arm trial (Study 7) in which 33 patients were enrolled with hypercalcemia of malignancy (with or without bone metastases) refractory to treatment with intravenous bisphosphonate. Patients received denosumab subcutaneously every 4 weeks with additional 120 mg doses on Days 8 and 15 of the first month of therapy.

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

The adverse reaction profile of denosumab in patients with hypercalcemia of malignancy was similar to that reported in Studies 1, 2, 3, 5, and 6 (Table 5). The most common adverse reactions (≥ 10%) were dyspnea (9 patients, 27%) and hypophosphatemia (4 patients, 12.1%). The patient incidence of fatal adverse events was 78.8%. The most frequently reported serious adverse reaction was dyspnea (3 subjects, 9%). No adverse reactions leading to discontinuation were reported as related to denosumab treatment.

Table 5. Adverse Reactions Occurring in ≥ 1% Subject Incidence (Hypercalcemia of Malignancy Safety Analysis Set) (Study 7 Safety Follow-up Analysis Data)

System organ class Preferred term	**Denosumab 120 mg Q4W (n = 33) (%)**
Metabolism and nutrition disorders	
Hypophosphatemia	4 (12.1)
Hypocalcemia	3 (9.1)

Musculoskeletal and connective tissue disorders	
Musculoskeletal pain	2 (6.1)
Respiratory, thoracic and mediastinal disorders	
Dyspnea	9 (27.3)

N = Number of subjects who received ≥ 1 active dose of investigational product (IP)
n = Number of subjects reporting ≥ 1 event
Adverse reactions by preferred term are summarized in the table.
Includes only treatment-emergent events which is defined as all events started after first dose of IP.
Preferred terms are coded using MedDRA version 16.0.

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

Hypocalcemia

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

Severe hypocalcemia (corrected serum calcium less than 7 mg/dL or less than 1.75 mmol/L) occurred in 3.1% of patients treated with denosumab and 1.3% of patients treated with zoledronic acid. Of patients who experienced severe hypocalcemia, 33% experienced 2 or more episodes of severe hypocalcemia and 16% experienced 3 or more episodes (see 7 Warnings and Precautions, Endocrine and Metabolism, Hypocalcemia).

Initially in clinical trials in patients with GCTB, moderate hypocalcemia (corrected serum calcium less than 8 to 7 mg/dL or less than 2 to 1.75 mmol/L) occurred in 2.6% of patients treated with denosumab. At the final integrated analysis of clinical trials in patients with GCTB, moderate hypocalcemia (as defined above) occurred in 4.4% of patients treated with denosumab.

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

In one study, subjects (N = 55) with varying degrees of renal function (ranging from normal through end-stage renal disease requiring dialysis) received a single 60 mg subcutaneous dose of denosumab. Hypocalcemia was observed in 8 subjects (15%), 1 (2%) of whom was symptomatic. Two subjects (4%) each experienced an adverse event of hypocalcemia that was classified as serious. Both subjects had severe chronic kidney disease (CKD) and were enrolled before the protocol required supplementation of calcium and vitamin D.

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

intact PTH (iPTH) values were 6.1 pmol/L (1.06 pmol/L, 13.2 pmol/L) and 16.3 pmol/L (0.3 pmol/L, 37.0 pg/mL) in the severe CKD and CKD on dialysis groups, respectively. At end of study (Day 113), median (range) iPTH values were 7.1 pmol/L (0.85 pmol/L, 372.2 pmol/L) and 31.5 pmol/L (1.3 pmol/L, 136.1 pmol/mL) in the severe CKD and CKD on dialysis groups, respectively. The median percent change from baseline to end of study (Day 113) was 15.0% in the severe CKD group and 107.5% in the CKD on dialysis group. The median (range) maximal elevation of PTH was 19.4 pmol/L (2.8 pmol/L, 372.2 pmol/L) in the severe CKD group and 64.2 pmol/L (1.3 pmol/L, 396.1 pmol/L) in the CKD on dialysis group. The median (range) % change of the maximal elevation of PTH values from baseline was 164.8% (28.2%, 2729.0%) in the severe CKD group and 256.1% (46.8%, 1681.9%) in the CKD on dialysis group. The median (range) time to reach maximal elevation of PTH was 22.5 days (3 days, 115 days) in the severe CKD group and 64.0 days (6 days, 115 days) in the CKD dialysis group. The median duration (range) of the elevation (20% above baseline) of PTH was 41.0 days (3.0 days, 112.0 days) in the severe CKD group and 79.5 days (11.0 days, 216.0 days) in the CKD on dialysis group.

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

Osteonecrosis of the Jaw (ONJ)

In clinical trials in patients with advanced cancer, ONJ was confirmed in 1.8% of patients in the denosumab group (median exposure of 12.0 months; range 0.1 – 40.5) and 1.3% of patients in the zoledronic acid group (see 7 Warnings and Precautions). Fifty-eight percent of subjects in the denosumab group and 65% of subjects in the zoledronic acid group had a prior or concurrent tooth extraction, 42% of subjects in the denosumab group and 27% of subjects in the zoledronic acid group had used a denture or other dental appliance, and 31% of subjects in the denosumab group and 32% of subjects in the zoledronic acid group had poor oral hygiene.

The trials in patients with breast or prostate cancer included a denosumab extension treatment phase (median overall exposure of 14.9 months; range 0.1 – 67.2) (see 14 Clinical Trials).For patients who were randomized to denosumab and continued on denosumab in the open label extension phase, the patient-year adjusted incidence of confirmed ONJ was 1.1 per 100 patient-years during the first year of treatment, 3.7 in the second year, and 4.6 thereafter. The median time to ONJ was 20.6 months (range: 4 – 53) (see 7 Warnings and Precautions).

In a phase 3 double-blind, active-controlled clinical trial in patients with newly diagnosed multiple myeloma, ONJ was confirmed in 4.1% of patients in the denosumab group (median exposure of 15.8 months; range 1 – 49.8) and 2.8% of patients in the zoledronic acid group. At the completion of the double-blind treatment phase of this trial, the patient-year adjusted incidence of confirmed ONJ in the denosumab group (median exposure of 19.4 months; range 1 – 52) was 2.0 per 100 patient-years during the first year of treatment, 5.0 in the second year, and 4.5 thereafter. The median time to ONJ was 18.7 months (range: 1 - 44) (see 7 Warnings and Precautions).

In clinical trials in patients with GCTB, at initial integrated analysis (final analysis of Study 5 and interim analysis of Study 6), ONJ was confirmed in 4 of 304 (1.3%) patients who received denosumab. The median time to ONJ was 16 months (range: 13 to 20 months).

A final analysis of a phase 2 open-label clinical trial (Study 6) in patients with GCTB demonstrated that ONJ was confirmed in 36 of 526 (6.8%) patients (median number of 34 doses; range 4 – 116). Of these 36 cases, 26 (4.9%) were reported as serious adverse events by investigators. At the completion of the trial, median time on trial including safety follow-up phase was 60.9 months (range: 0 – 112.6). The patient-year adjusted incidence of confirmed ONJ was 1.5 per 100 patient-years overall (0.2 per 100 patient-years during the first year of

treatment, 1.5 in the second year, 1.8 in the third year, 2.1 in the fourth year, 1.4 in the fifth year, and 2.2 thereafter). The median time to ONJ was 41 months (range: 11 – 96) (see 7 Warnings and Precautions).

Atypical Femoral Fractures (AFF)

In the clinical trial program, atypical femoral fracture has been reported uncommonly in patients treated with denosumab 120 mg and the risk increased with longer duration of treatment. Events have occurred during treatment and up to 9 months after treatment was discontinued.

Malignancies

In a pooled safety analysis of clinical trials in cancer patients with bone metastases, the overall incidence of new primary malignancies was 0.99% (28 out of 2841 patients) in the denosumab group and 0.63% (18 out of 2836 patients) in the zoledronic acid group. In the breast cancer trial, the incidence was 0.5 % in both denosumab (5/1020 patients) and zoledronic acid groups (5/1013 patients). In other solid tumours or multiple myeloma, the incidence was 0.6% (5/878 patients) and 0.3% (3/878 patients) in the denosumab and zoledronic acid groups, respectively. In the prostate cancer trial, the incidence was 1.9% (18/943 patients) in the denosumab group and 1.1% (10/945 patients) in the zoledronic acid group. In the final analysis of the GCTB trial (Study 6), the incidence of malignancy was 3.8% (20/526 patients, all adults).

8.3 Less Common Clinical Trial Adverse Reactions

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

Immune System Disorders: drug hypersensitivity

Less Common Clinical Trial Adverse Reactions (< 1%) in Patients with Multiple Myeloma by System Organ Class

Immune System Disorders: drug hypersensitivity

8.4 Abnormal Laboratory Findings: Hematologic, Clinical Chemistry, and Other Quantitative Data

Clinical Trial Findings

In clinical trials in cancer patients with bone metastases, a grade 3 decrease in serum calcium levels was experienced in 2.5% of patients treated with denosumab and 1.2% of patients treated with zoledronic acid. A grade 4 decrease in serum calcium levels was experienced in 0.6% of patients treated with denosumab and 0.2% of patients treated with zoledronic acid (see 7 Warnings and Precautions, Renal). In studies, the development of hypocalcemia in patients with severe renal impairment (creatinine clearance less than 30 mL/min and/or receiving dialysis) was accompanied by an elevation in parathyroid hormone levels.

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

In the clinical trials in patients with GCTB (final analysis of Study 5 and interim analysis of Study 6), the subject incidence of grade 2 corrected serum calcium decreases was 2.6%, while no grade 3 or grade 4 incidences were observed. In the same integrated analysis, Common Terminology Criteria for Adverse Events (CTCAE) grade 3 low phosphorus values were

observed for 29 patients (9.5%).

In the final integrated analysis of both Studies 5 and 6, the subject incidence of grade 2, 3 and 4 corrected serum calcium decreases were 4.4%, 0.2% and 0.4%, respectively. CTCAE grade 3 low phosphorus values were observed for 108 patients (19.7%).

8.5 Post-Market Adverse Reactions

In the post-marketing experience, the following have been reported in patients receiving denosumab:

- Severe symptomatic hypocalcemia, including fatal cases
- Hypersensitivity, including anaphylactic reactions
- Musculoskeletal pain, including severe cases
- Lichenoid drug eruptions (eg, lichen planus-like reactions)
- Alopecia

9 Drug Interactions

9.2 Drug Interactions Overview

No formal drug interaction studies have been conducted with denosumab.

9.3 Drug-Behavioural Interactions

The interaction of denosumab with individual behavioural risks (e.g. cigarette smoking, cannabis use, and/or alcohol consumption) has not been studied.

9.4 Drug-Drug Interactions

Interactions with other drugs have not been established.

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

9.5 Drug-Food Interactions

Interactions with food have not been established.

9.6 Drug-Herb Interactions

Interactions with herbal products have not been established.

9.7 Drug-Laboratory Test Interactions

Interactions with laboratory tests have not been established.

10 Clinical Pharmacology

10.1 Mechanism of Action

Denosumab is a fully human IgG2 monoclonal antibody with high affinity and specificity for human RANK Ligand (RANKL). Denosumab binds to RANK Ligand (RANKL), a transmembrane or soluble protein essential for the formation, function, and survival of osteoclasts, the cells responsible for bone resorption. Binding of denosumab to RANKL inhibits RANKL from activating its only 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 and interrupting cancer-induced bone destruction.

Multiple Myeloma and Bone Metastasis from Solid Tumours

Denosumab prevents RANKL from activating its receptor, RANK, on the surface of osteoclasts and their precursors. Increased osteoclast activity, stimulated by RANKL, is a key mediator of bone disease in metastatic tumours and multiple myeloma. Prevention of the RANKL/RANK interaction inhibits osteoclast formation, function, and survival, thereby decreasing bone resorption and interrupting cancer-induced bone destruction.

Giant Cell Tumour of Bone

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

Hypercalcemia of Malignancy Refractory to Intravenous Bisphosphonates

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

Animal Pharmacology

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

Since the biological activity of denosumab in animals is specific to nonhuman primates, evaluation of genetically engineered (knockout) mice or use of other biological inhibitors of the RANK/RANKL pathway, such as OPG-Fc and RANK-Fc, were used to evaluate the pharmacodynamic properties of denosumab in rodent models. In mouse bone metastasis models of human prostate cancer, NSCLC, and estrogen receptor (ER) positive and negative breast cancer, OPG-Fc reduced osteolytic, osteoblastic, and osteolytic/osteoblastic lesions, delayed formation of de novo bone metastasis, and reduced skeletal tumour growth. When OPG-Fc was combined with hormonal therapy (tamoxifen) or chemotherapy (docetaxel) in these

models, there was additive inhibition of skeletal tumour growth in breast, prostate or lung cancer respectively. In a mouse model of mammary tumour induction, RANK-Fc delayed tumour formation.

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

RANK/RANKL knockout mice exhibited absence of lymph node formation, as well as an absence of lactation due to inhibition of mammary gland maturation (lobulo-alveolar gland development during pregnancy). Neonatal RANK/RANKL knockout mice exhibited reduced bone growth and lack of tooth eruption. A corroborative study in 2-week-old rats given the RANKL inhibitor OPG-Fc also showed reduced bone growth, altered growth plates and impaired tooth eruption. These changes were partially reversible in this model when dosing with the RANKL inhibitors was discontinued (see 7.1.3 Pediatrics).

10.2 Pharmacodynamics

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

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

In a phase 3 study of patients with newly diagnosed multiple myeloma who received SC doses of denosumab 120 mg every 4 weeks (Q4W), median reductions in uNTx/Cr of approximately 75% were observed by week 5. Reductions in bone turnover markers were maintained, with median reductions of 74% to 79% for uNTx/Cr from weeks 9 to 49 of continued 120 mg Q4W dosing.

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

10.3 Pharmacokinetics

Following SC administration, bioavailability was 62% based on a population PK analysis. Relative AUC exposure ratios for SC vs. IV dosing were 78% and 75% for doses of 1.0 and 3.0 mg/kg in postmenopausal women. Denosumab displayed non-linear pharmacokinetics with dose over a wide dose range, but approximately dose-proportional increases in exposure for

doses of 60 mg (or 1 mg/kg) and higher (for example, 3.8- to 4.0-fold increases in mean C_{max} and AUC values for a 3-fold increase in dose from 60 to 180 mg). In subjects with advanced cancer, who received multiple SC doses of 120 mg every 4 weeks an approximate 2.5-fold accumulation in serum denosumab $AUC_{(0\text{-tau})}$ exposures was observed and steady-state was achieved on or after 6 doses. These results indicate that denosumab pharmacokinetics does not change with time or multiple dosing. In subjects with multiple myeloma who received 120 mg every 4 weeks, median trough levels varied by less than 8% between months 6 and 12. In subjects with GCTB who received 120 mg every 4 weeks with a loading dose on days 8 and 15, steady-state levels were achieved within the first month of treatment. Between weeks 9 and 49, median trough levels varied by less than 9%. At steady-state in these subjects, the mean serum trough concentration was 20.6 mcg/mL (range, 0.456 to 56.9 mcg/mL). In patients who discontinued 120 mg every 4 weeks dosing, the mean half-life was 28 days (range 14 to 55 days).

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

Special populations and conditions

- **Pediatrics**

  The pharmacokinetics of denosumab has not been established in pediatric patients other than skeletally mature adolescents (aged 13-17 years) with GCTB.

  In skeletally-mature adolescents (13 – 17 years of age; N = 10) with GCTB, the pharmacokinetics of denosumab were similar to those observed in adult subjects with GCTB (N = 15).

- **Geriatrics**

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

- **Sex**

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

- **Ethnic origin**

  The pharmacokinetics of denosumab was not affected by race.

- **Hepatic insufficiency**

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

- **Renal insufficiency**

  Two clinical trials were conducted in patients without cancer and with varying degrees of renal function. In one study, patients (N = 55) with varying degrees of renal function (ranging from normal through end-stage renal disease requiring dialysis) received a single 60 mg subcutaneous dose of denosumab. Hypocalcemia was observed in 8 subjects (15%), 1 (2%) of whom was symptomatic. Two patients (4%) each experienced an adverse reaction of hypocalcemia that was classified as serious. Both patients had severe chronic kidney disease (CKD) and were enrolled before the protocol required

supplementation of calcium and vitamin D.

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

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

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

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

10.4 Immunogenicity

All therapeutic proteins have the potential for immunogenicity.

The detection of antibody formation is highly dependent on the sensitivity and specificity of the assay. Additionally, the observed incidence of antibody (including neutralizing antibody) positivity in an assay may be influenced by several factors including assay methodology, sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, comparison of incidence of antibodies in the studies described below with the incidences of antibodies in other studies or to other products may be misleading.

In clinical studies, neutralizing antibodies have not been observed for denosumab in advanced cancer patients or GCTB patients. Using an electrochemiluminescent bridging immunoassay, less than 1% of patients treated with denosumab for up to 3 years tested positive for binding antibodies (including pre-existing, transient, and developing antibodies). None of the patients tested positive for neutralizing antibodies as assessed using a chemiluminescent cell-based in vitro biological assay. There was no evidence of altered pharmacokinetic profile, toxicity profile, or clinical response associated with binding antibody development.

11 Storage, Stability, and Disposal

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

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

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

Protect IDENOS from direct light and heat.

Avoid vigorous shaking of IDENOS.

Part 2: Scientific Information

13 Pharmaceutical Information

Drug Substance

Non-proprietary name of the drug substance(s): denosumab

Molecular formula and molecular mass: 147 kDa

Structure (for biologics): Denosumab is a fully human IgG2 monoclonal antibody heterotetramer consisting of two heavy chains of the gamma 2 subclass (447 amino acids per chain) and two light chains of the kappa subclass (215 amino acids per chain)

Product Characteristics:

Denosumab is produced in genetically engineered mammalian (Chinese hamster ovary) cells.

14 Clinical Trials

14.1 Clinical Trials by Indication

Bone Metastasis from Solid Tumours

Table 6. Summary of Patient Demographics for Clinical Trials in Patients with Advanced Malignancies Involving Bone

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

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

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

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

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

Study results

Denosumab reduced the risk of developing (delayed time to) first SRE and multiple (first and subsequent) SREs in patients with advanced malignancies involving bone. Efficacy results are provided in Table 7.

Table 7. Efficacy Results for Denosumab Compared to Zoledronic Acid in Patients with Advanced Malignancies Involving Bone

	Study 1 Advanced Breast Cancer		Study 2 Advanced Cancer (Other Solid Tumours and Multiple Myeloma)		Study 3 Advanced Prostate Cancer	
	Denosumab	Zoledronic Acid	Denosumab	Zoledronic Acid	Denosumab	Zoledronic Acid
N	**1026**	**1020**	**886**	**890**	**950**	**951**
First On-Study Skeletal Related Event (SRE)						
Number and Proportion of Subjects with SREs (%)	315 (30.7)	372 (36.5)	278 (31.4)	323 (36.3)	341 (35.9)	386 (40.6)
Components of First SRE						
Radiation to Bone	82 (8.0)	119 (11.7)	119 (13.4)	144 (16.2)	177 (18.6)	203 (21.3)
Pathological Fracture	212 (20.7)	238 (23.3)	122 (13.8)	139 (15.6)	137 (14.4)	143 (15.0)
Surgery to	12 (1.2)	8 (0.8)	13 (1.5)	19 (2.1)	1 (0.1)	4 (0.4)

Bone						
Spinal Cord Compression	9 (0.9)	7 (0.7)	24 (2.7)	21 (2.4)	26 (2.7)	36 (3.8)
Median Time (months)	NR	26.4	20.5	16.3	20.7	17.1
Hazard Ratio (95% CI)	0.82 (0.71, 0.95)		0.84 (0.71, 0.98)		0.82 (0.71, 0.95)	
Non-inferiority P-value	<0.0001		0.0007		0.0002	
Superiority P-value †	0.0101		0.0619		0.0085	
First and Subsequent SRE *						
Mean Number/Patient	0.46	0.60	0.44	0.49	0.52	0.61
Rate Ratio (95% CI)	0.77 (0.66, 0.89)		0.90 (0.77, 1.04)		0.82 (0.71, 0.94)	
Superiority P-value†	0.0012		0.1447		0.0085	

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

Overall survival and disease progression in all three studies were comparable in patients with advanced cancer between denosumab and zoledronic acid treatment groups (see Table 8). In Study 2, mortality was higher with denosumab in a subgroup analysis of patients with multiple myeloma [hazard ratio (95% CI) of 2.26 (1.13, 4.50); n = 180].

Table 8. Summary of Exploratory Tumour Outcomes

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

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

Multiple Myeloma

In Study 4, denosumab was evaluated in an international, randomized (1:1), double-blind, active-controlled study comparing denosumab with zoledronic acid in patients with newly diagnosed multiple myeloma.

In this study, 1718 multiple myeloma patients with at least 1 bone lesion were randomized to receive 120 mg denosumab subcutaneously every 4 weeks or 4 mg zoledronic acid intravenously (IV) every 4 weeks (dose adjusted for renal impairment and patients with creatinine clearance less than 30 mL/min were excluded based on zoledronic acid prescribing information). Randomization was stratified by intent to undergo autologous peripheral blood stem cell (PBSC) transplantation (yes or no), the anti-myeloma agent being utilized/planned to be utilized in first- line therapy [novel therapy-based or non-novel therapy-based (novel therapies include bortezomib, lenalidomide, or thalidomide)], stage at diagnosis (International Staging System I or II or III), previous SRE (yes or no), and region (Japan or other countries). The primary outcome measure was demonstration of non-inferiority of time to first skeletal-related event (SRE) as compared to zoledronic acid. Secondary outcome measures included superiority of time to first SRE, superiority of time to first and subsequent SRE, and overall survival. An SRE was defined as any of the following: pathologic fracture (vertebral or non-vertebral), radiation therapy to bone (including the use of radioisotopes), surgery to bone, or spinal cord compression.

Across both study arms, 54.5% of patients intended to undergo autologous PBSC transplantation, 95.8% patients utilized/planned to utilize a novel anti-myeloma agent in first-line therapy, and 60.7% of patients had a previous SRE. The number of patients across both study arms with ISS stage I, stage II, and stage III at diagnosis were 32.4%, 38.2%, and 29.3%, respectively.

Median age was 63 years (range: 29 – 91), 82% of patients were White, 12% Asian, 4% Black, and 46% of patients were women. The median number of doses administered was 16 for denosumab and 15 for zoledronic acid.

Study Results

In patients with newly diagnosed multiple myeloma, denosumab was non-inferior to zoledronic acid in delaying the time to first SRE following randomization (Table 9).

Table 9. Efficacy Results for Denosumab Compared to Zoledronic Acid in Patients with Newly Diagnosed Multiple Myeloma

	Denosumab (N = 859)	Zoledronic Acid (N = 859)
First SRE		
Number of Patients who had SREs (%)	376 (43.8)	383 (44.6)
Median Time to SRE (months) (95% CI)	22.83 (14.72, NE)	23.98 (16.56, 33.31)
Hazard Ratio[a] (95% CI)	0.98 (0.85, 1.14)	
Non-inferiority p-value[a]	0.010	
Components of First SRE		
Radiation to Bone	47 (5.5)	62 (7.2)
Pathological Fracture	342 (39.8)	338 (39.3)
Surgery to Bone	37 (4.3)	48 (5.6)
Spinal Cord Compression	6 (0.7)	4 (0.5)

[a]Based on a Cox proportional hazards model stratified by randomization stratification factors

The hazard ratio between denosumab and zoledronic acid treatment groups and 95% CI for overall survival (OS) was 0.90 (0.70, 1.16).

Giant Cell Tumour of Bone

Table 10. Summary of Patient Demographics for Clinical Trials in Patients with Giant Cell Tumour of Bone (GCTB)

Study #	Study design	Dosage, route of administration	Study subjects (n = number)	Mean age (Range)[a]	Sex (Female:Male) %[a]
Study 5	Phase 2, open-label, multicenter	Denosumab 120 mg SC Q4W with a loading dose on study days 8 and 15 of the first month of therapy	Adult subjects with GCTB (n = 37)	34 (19, 63)	(54:46)
Study 6 (interim analysis)	Phase 2, open-label, multicenter	Denosumab 120 mg SC Q4W with a loading dose on study days 8 and 15 of the first month of therapy	Adult subjects with GCTB (n = 272) And Skeletally Mature Adolescents with GCTB (n = 10)	36 (13, 83)	(58:42)

[a] Pooled data

The safety and efficacy of denosumab was studied in two phase 2 open-label, single arm trials (Studies 5 and 6) that enrolled patients with GCTB that was either unresectable or for which surgery was associated with severe morbidity.

Study 5 enrolled 37 adult patients with histologically confirmed unresectable or recurrent GCTB and the main outcome measure of the trial was response rate based on histological or radiographic evidence.

At the interim analysis, Study 6 enrolled 282 adults, and 10 skeletally mature adolescents (aged 13-17 years) with GCTB. By the end of the study, Study 6 had enrolled 507 adults and 28 skeletally mature adolescents (aged 13-17 years) with GCTB. The main outcome measure was to evaluate the safety profile of denosumab. Efficacy was assessed by evaluation of time to disease progression in subjects with unresectable GCTB and by evaluation of the proportion of subjects who do not require surgery in the subjects with resectable GCTB.

A retrospective independent review of radiographic imaging data from 190 of 305 patients enrolled in Studies 5 and 6 was performed. Patients were evaluated using modified Response Evaluation Criteria in Solid Tumours (RECIST 1.1) to evaluate tumour burden based on computed tomography (CT)/magnetic resonance imaging (MRI).

Study Results

Overall, in the retrospective interim analysis, an objective response by RECIST 1.1 was observed in 47 of 187 (25.1%) evaluable patients (95% CI: 19.1, 32.0), including 2 of 6 (33.3%) evaluable adolescent patients. All responses were partial responses. The median

time to response was 3 months (range: 1.5 to 20.9 months). The median duration of response was not estimable as only three patients experienced disease progression following an objective response. The median follow-up duration for evaluable patients was 13 months (range: 2 to 49 months).

Hypercalcemia of Malignancy Refractory to Intravenous Bisphosphonate

The safety and efficacy of denosumab was studied in a phase 2 open-label, single-arm trial (Study 7) that enrolled 33 patients with hypercalcemia of malignancy (with or without bone metastases) refractory to treatment with intravenous bisphosphonate. In this study, refractory hypercalcemia of malignancy was defined as an albumin-corrected serum calcium (CSC) of >12.5 mg/dL (3.1 mmol/L) despite treatment with intravenous bisphosphonate in the last 7 -30 days. Patients receiving dialysis for renal failure or who had treatment with thiazides, calcitonin, mithramycin, or gallium nitrate within their window of expected therapeutic effect prior to the date of screening corrected serum calcium (CSC) were excluded. Twenty-six (79%) patients had advanced solid tumours and 7 (21%) patients had advanced hematologic malignancies.

Twenty-five patients (76%) had poor performance status (Eastern Cooperative Oncology Group [ECOG] ≥ 2) at baseline. Metastatic disease was present in 30 (91%) patients and metastatic bone disease in 13 (39%) patients at baseline. Three (9%) patients had non-metastatic disease, 2 with myeloma and 1 with non-Hodgkin's lymphoma.

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

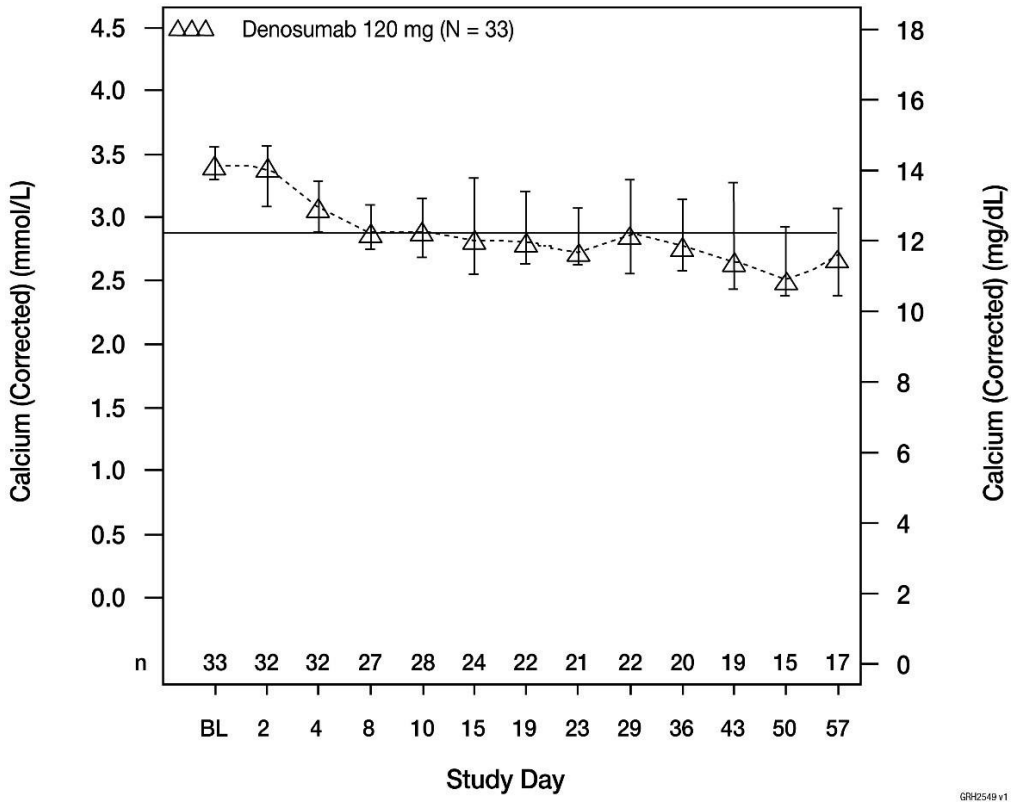
The primary outcome measure was the proportion of patients achieving a response, defined as CSC ≤ 11.5 mg/dL (2.9 mmol/L), within 10 days after denosumab administration. Additional secondary outcomes were assessed and are presented in Table 11.

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

Study Results

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

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



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

Table 11. Efficacy in Patients with Hypercalcemia of Malignancy Refractory to Bisphosphonate Therapy

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

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

Median time to response (CSC ≤ 11.5 mg/dL) was 9 days (95% CI: 8, 19), and the median duration of response was 104 days (95% CI: 7, not estimable). Median time to complete response (CSC ≤10.8 mg/dL) was 23 days (95% CI: 9, 36), and the median duration of complete response was 34 days (95% CI: 1, 134).

15 Microbiology

No microbiological information is required for this drug product.

16 Non-Clinical Toxicology

Genotoxicity

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.

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.

Reproductive and Developmental Toxicology

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

Table 12. Summary of Preclinical Toxicity and Reproductive Studies with Denosumab

Type of Study	Species and strain	Number per sex per group	Route of Administration	Dose (mg/kg) and dosing regimen	Study Duration	Treatment related findings	NOAEL (mg/kg)
Repeated-dose Toxicity	Cynomolgus monkey	6	Subcutaneous or Intravenous	Once weekly: 0, 0.1, 1.0, & 10.0 (SC); 10.0 (IV)	1-month dosing with 3 months recovery	Consistent with the pharmacological action of denosumab, there were rapid and marked decreases in circulating markers of bone turnover at all doses. Correlating with these changes, there was increased bone mineral density in males dosed at 1 and 10 mg/kg. With the exception of bone mineral density which tended to be maintained, these changes were recovered or recovering following 3 treatment free months. There were no treatment related effects on organ weights or histopathology findings.	10 (SC and IV)
	Cynomolgus monkey	8	Subcutaneous	Once monthly : 0, 1, 10, 50	6 and 12 months with 3 months recovery	Consistent with the pharmacological action of denosumab, there were rapid and marked decreases in circulating markers of bone turnover at 10 and 50 mg/kg. Correlating to these changes, there was increased bone mineral density, bone mineral content, cortical area and thickness, and bone strength parameters in males dosed at 50 mg/kg, and females dosed at 10 and 50 mg/kg. In addition, there was	50

						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.	
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 Development	Cynomolgus monkey	16 Females	Subcutaneous	Once weekly: 0, 2.5, 5, 12.5	Gestation days 20-50	No treatment related effects on mother or embryonic development were observed. Peripheral lymph nodes were not evaluated.	12.5

Enhanced pre- and post-natal development	Cynomolgus monkey	29 Females	Subcutaneous	Once monthly: 0, 50	Gestation days 20 - 22 to birth	There were increased fetal losses during gestation, increased stillbirths and post-natal mortality (see Table 12). Treatment-related findings in the offspring included decreased body weight gain and decreased neonatal growth; skeletal abnormalities resulting from impaired bone resorption during rapid growth, including bones at the base of the skull resulting in altered cranial shape and exophthalmos, reduced bone strength and treatment- related bone fractures; reduced hematopoiesis; decreased serum levels of bone resorption and bone formation biomarkers; tooth malalignment and dental dysplasia (in the absence of adverse effects on tooth eruption); infections; and absence of peripheral lymph nodes. Following a recovery period from birth out to 6 months of age, findings still observed were mildly reduced bone length (femoral, vertebral, jaw); reduced cortical thickness with associated reduced strength; extramedullary hematopoiesis; dental dysplasia; and the absence of decreased	A NOAEL was not identified.

						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 the maternal levels). Only one infant had measurable concentrations of denosumab on BD91, and no infants had measurable concentrations on BD180. Generally, the effects observed in mothers and infants were consistent with the pharmacological action of denosumab.	

Table 12. 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)
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 males and 67 females	Subcutaneous	Rat OPG-Fc: 1, 10 mg/kg/week Murine RANK-Fc: 10 mg/kg/week	6 weeks	Increased bone volume, density and strength. Increased cancellous bone with reduced osteoclast number. Reduced long bone growth with altered growth plate morphology and increased thickness. Impaired tooth eruption and tooth root formation.	N/A
		10 males and 3-10 females	Subcutaneous	Rat OPG-Fc: 3, 10 mg/kg/week	6 weeks	Changes seen at the 10 mg/kg/week were similar to those in the previous study. Effects were less at the 3 mg/kg/week.	N/A
		10-11 males and 9-10 females	Subcutaneous	Rat OPG-Fc: 1, 3, 10 mg/kg/week	6 weeks with 10 weeks recovery	Effects were partially reversible when OPG-Fc was discontinued	N/A
Other Studies – Tissue Cross-reactivity	Cynomolgus monkey, rat, rabbit	N/A	*In Vitro*	5 or 25 mcg/mL	N/A	Staining of lymphoid tissue in rabbit and cynomolgus monkey and staining of chondrocytes in rat were observed.	N/A
	Cynomolgus monkey, human	N/A	*In Vitro*	1 or 10 mcg/mL	N/A	Staining of lymphoid tissue in monkey, but no staining in human tissue was observed.	N/A
	Human	N/A	*In Vitro*	1 or 10 mcg/mL	N/A	Staining of lymphoid tissue was observed.	N/A

N/A = not applicable; NOAEL = no observed adverse effect level

Table 13. Total Fetal Losses[c], all Groups

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

[a] Two adult females were excluded from fetal loss calculations except for first trimester because each had an anti-drug antibody (ADA) response beginning at GD76 with subsequent decrease in pharmacologic effect (bone biomarkers) prior to fetal loss; results indicated by a double asteris k (**) 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

17 Supporting Product Monographs

XGEVA® (denosumab injection 120 mg/1.7 mL solution for injection), submission control 297080, Product Monograph, Amgen Canada Inc., August 11, 2025.

Patient Medication Information

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

PrIDENOS™

Denosumab injection

This Patient Medication Information is written for the person who will be taking **IDENOS**. This may be you or a person you are caring for. Read this information carefully. Keep it as you may need to read it again

This patient medication information is a summary. It will not tell you everything about this medication. If you have more questions about this medication or want more information about **IDENOS**, talk to a healthcare professional.

IDENOS is a biosimilar biologic drug (biosimilar) to the reference biologic drug XGEVA®. A biosimilar is authorized based on its similarity to a reference biologic drug that was already authorized for sale in Canada.

Serious warnings and precautions box

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

What IDENOS is used for:

- IDENOS is used for reducing the risk of developing cancer-related complications like broken bones and/or bone pain that need surgery or radiation.
- IDENOS is used for reducing the risk of developing cancer-related complications in patients with multiple myeloma. Multiple myeloma is a cancer of plasma cells (a type of white blood cell).
- IDENOS is used to treat giant cell tumour of bone, which cannot be treated by surgery or where surgery is not the best option in adults and adolescents (aged 13-17 years) whose bones have stopped growing.
- IDENOS is used to reduce high levels of calcium in the blood in cancer patients (hypercalcemia of malignancy) after other drugs called bisphosphonates did not work.

How IDENOS works:

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

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

The ingredients in IDENOS are:

Medicinal ingredients: denosumab

Non-medicinal ingredients: acetic acid, polysorbate 20, sodium hydroxide, sorbitol and water for

injection.

IDENOS comes in the following dosage form(s):

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

Do not use IDENOS if:

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

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

- IDENOS contains the medicine denosumab. If you are being treated with IDENOS, you should not be taking other medicines containing denosumab.
- Patients being treated with IDENOS should not be treated concomitantly with bisphosphonates.

To help avoid side effects and ensure proper use, talk to your healthcare professional before you take IDENOS. Talk about any health conditions or problems you may have, including:

Hypocalcemia (low calcium levels in the blood)

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

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

Conditions which increase the risk of low blood calcium:

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

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

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

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

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

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

Unusual Thigh Bone Fractures

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

High Calcium Levels in the Blood after Stopping Treatment with IDENOS

Some patients with giant cell tumour of the bone and some who are still growing during treatment with denosumab, have developed high calcium levels in the blood weeks to months after stopping treatment.

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

Risk of Broken Bones in the Spine After Stopping Treatment with IDENOS

Do not stop taking IDENOS without first talking with your doctor. After treatment with IDENOS is stopped, there may be an increased risk of having broken bones in your spine especially in people who have had a fracture or who have had osteoporosis (a condition in which bones become thin and fragile).

Skin Infections

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

Pregnancy or Breast-Feeding

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

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

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

Use in Children

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

Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.

The following may [also] interact with IDENOS:

Before starting IDENOS, tell your doctor about all the medicines you take, including prescription

and non-prescription drugs, vitamins and herbal supplements.

Interactions between denosumab and other drugs have not been studied.

How to take IDENOS:

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

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

Keep all medicines, including IDENOS, away from children.

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

INSTRUCTIONS FOR INJECTION

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

How to prepare for IDENOS injection

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

- The name IDENOS appears on the package and vial label.
- The expiration date on the vial label has not passed. **Do not use a vial after the date on the label.**
- The IDENOS liquid in the vial is colourless to yellowish.

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

Setting up for an injection

1. Find a clean flat working surface, such as a table.
2. Remove the vial of IDENOS from the refrigerator. Allow IDENOS to reach room temperature (this takes about 15 to 30 minutes). Vials should be used only once. DO NOT SHAKE THE VIAL. Shaking may damage the IDENOS. If the vial has been shaken vigorously, the solution may appear foamy and it should not be used.
3. Assemble the supplies you will need for an injection:
    - IDENOS vial and sterile disposable syringe and a 27-gauge needle.
    - Two alcohol swabs and one cotton ball or gauze pad.
    - Puncture-proof disposal container.
4. Clean your work surface thoroughly and wash your hands with soap and warm water.

Selecting and preparing the injection site

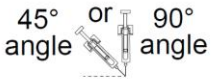
1. Choose an injection site. The recommended injection sites for IDENOS are:
   - The outer area of your upper arms (not recommended for self-injection).
   - The abdomen, except for the two-inch (5 cm) area around your navel.
   - The top of your thighs.

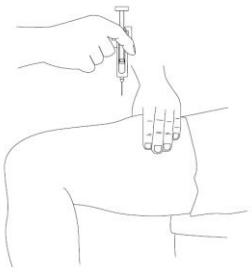
How to prepare the dose of IDENOS in vials

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

Injecting the dose of IDENOS

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





4. After the needle is inserted, let go of the skin slowly, making sure the needle stays in the skin. Inject the prescribed dose subcutaneously by pushing down on the syringe plunger,

as directed by your doctor, nurse or pharmacist.

5. When the syringe is empty, pull the needle out of the skin and place a cotton ball or gauze over the injection site and press for several seconds.
6. Use a syringe, needle and vial only once. DO NOT put the needle cover (the cap) back on the needle. Discard the vial with any remaining IDENOS liquid.

Disposal of syringes, needles and vials

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

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

Usual dose:

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

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

Overdose:

If you think you, or a person you are caring for, have taken too much IDENOS, contact a healthcare professional, hospital emergency department or regional poison control centre or Health Canada's toll-free number, 1-844 POISON-X (1-844-764-7669) immediately, even if there are no signs or symptoms.

Missed dose:

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

Possible side effects from using IDENOS:

These are not all the possible side effects you may have when taking IDENOS. If you experience any side effects not listed here, tell your healthcare professional.

- Low blood calcium (hypocalcemia)

  Symptoms of low blood calcium may include muscle spasms, twitches, cramps, numbness or tingling in fingers, toes or around the mouth
- Skin infection with swollen, red area of skin that feels hot and tender and may be accompanied by fever (cellulitis)
- Sore in mouth involving gums or jaw bones (osteonecrosis of the jaw)

- Shortness of breath (dyspnea)
- Low phosphate levels in the blood (hypophosphatemia)
- Allergic reactions (eg, rash, hives, or in rare cases, swelling of the face, lips, tongue, throat, or trouble breathing)
- Unusual thigh bone fractures (atypical femoral fracture)
- Rash that may occur on the skin or sores in the mouth (lichenoid drug eruption)
- Hair loss (alopecia)
- Pain, sometimes severe, in the muscles, joints, arms, legs or back
- High calcium levels in the blood (hypercalcemia) after stopping treatment in patients who are still growing while on treatment with IDENOS
- High calcium levels in the blood (hypercalcemia) after stopping treatment in patients with giant cell tumour of the bone
- Broken bones in your spine (multiple vertebral fractures) after stopping treatment with IDENOS

Serious side effects and what to do about them

Frequency / Side Effect[a] / Symptom	Talk to your healthcare professional		Stop taking the / this drug (if applicable) and get immediate medical help
	Only if severe	In all cases	
Very common			
Low calcium levels in the blood [muscle spasms, twitches, cramps, numbness or tingling in fingers, toes or around the mouth] (hypocalcemia)		√	
Common			
Sore in mouth involving gums or jaw bones (osteonecrosis of the jaw)		√	
Uncommon			
Skin infection (mainly cellulitis) leading to hospitalization		√	
High calcium levels in the blood (hypercalcemia) after stopping treatment in patients with giant cell tumour of bone		√	
Unusual thigh bone fractures (atypical femoral fracture)		√	
Rare			
Allergic reactions [e.g. rash, hives, or in rare cases, swelling of the face, lips, tongue, throat, or trouble breathing] (drug hypersensitivity)		√	

High calcium levels in the blood (hypercalcemia) after stopping treatment in patients who are still growing while on treatment with IDENOS		√	
Broken bones in your spine following discontinuation of IDENOS (multiple vertebral fracture)		√	

[a] Frequency reflects all adverse events

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, tell your healthcare professional.

Reporting side effects

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (canada.ca/drug-device-reporting) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

NOTE: Contact your healthcare professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

Storage:

Keep out of the reach and sight of children.

IDENOS should be stored in the refrigerator at 2°C to 8°C in the original carton to protect it from light. Do not freeze IDENOS. Do not shake IDENOS.

IDENOS may be removed from the refrigerator and allowed to reach room temperature (up to 25°C) to make the injection more comfortable.

Once removed from the refrigerator, IDENOS must not reach temperatures above 25°C and must be used within 30 days. If not used within 30 days, IDENOS should be discarded.

Do not use IDENOS 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.

If you want more information about IDENOS:

- Talk to your healthcare professional
- Find the full product monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada Drug Product Database website (Drug Product Database: Access the database); the manufacturer's website (http://www.apotex.ca/products), or by calling 1-800-667-4708, or
- Call the Victory Program at 1-888-706-4717.

This leaflet was prepared by Apotex Inc., Toronto, Ontario M9L 1T9

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