

## PROLIA™ Denosumab

### QUALITATIVE AND QUANTITATIVE COMPOSITION

Each pre-filled syringe contains 60 mg of denosumab in 1.0 mL solution (60 mg/mL)

Each vial contains 60 mg denosumab 1.0 mL solution (60 mg/mL)

### PHARMACEUTICAL FORM

Solution for subcutaneous injection.

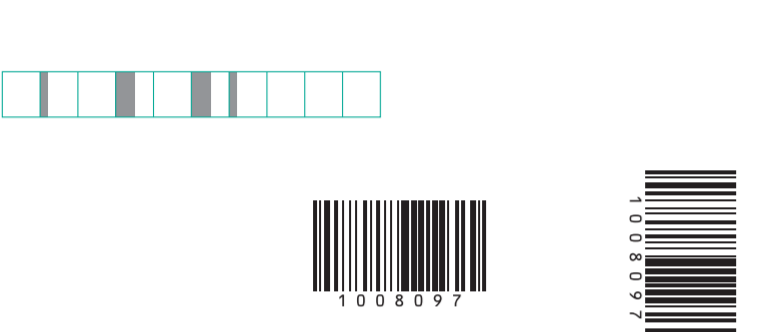
Clear, colourless to slightly yellow solution, pH 5.2 and may contain trace amounts of translucent to white proteinaceous particles.

### CLINICAL PARTICULARS

#### Indications

##### *Postmenopausal Osteoporosis*

*PROLIA* is indicated for the treatment of osteoporosis in postmenopausal women. In postmenopausal women with osteoporosis, *PROLIA* increases bone mineral density (BMD) and reduces the incidence of hip, vertebral and non-vertebral fractures.



##### *Bone Loss in Patients Undergoing Hormone Ablation for Cancer*

*PROLIA* is indicated for the treatment of bone loss in patients undergoing hormone ablation for prostate or breast cancer. In patients with prostate cancer, *PROLIA* reduces the incidence of vertebral fractures.

### Dosage and Administration

#### Administration

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

#### Dosage

The recommended dose of *PROLIA* is a single subcutaneous injection of 60 mg administered once every 6 months.

Patients should receive calcium and vitamin D supplements whilst undergoing treatment.

### Populations

#### Children

*PROLIA* is not recommended in paediatric patients as the safety and effectiveness of *PROLIA* have not been established in the paediatric age group. In animal studies, inhibition of RANK/RANK ligand (RANKL) with a construct of osteoprotegerin bound to Fc (OPG-Fc) has been coupled to inhibition of bone growth and lack of tooth eruption (see Pre-Clinical Safety Data). Therefore, treatment with denosumab may impair bone growth in children with open growth plates and may inhibit eruption of dentition.

#### Elderly

Based on the available safety and efficacy data in the elderly, no dosage adjustment is required (see Pharmacokinetics: Special patient populations).

#### Renal Impairment

Based on the available safety and efficacy data in the elderly, no dosage adjustment is required in patients with renal impairment (see Pharmacokinetics: Special patient populations).

Patients with severe renal impairment (creatinine clearance < 30 mL/min) or receiving dialysis are at greater risk of developing hypocalcaemia. Adequate intake of calcium and vitamin D is important in patients with severe renal impairment or receiving dialysis.

#### Hepatic impairment

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

### Contraindications

#### Hypocalcaemia

Clinically significant hypersensitivity to denosumab or any components of *PROLIA*.

### Warnings and Precautions

Adequate intake of calcium and vitamin D is important in all patients receiving *PROLIA*. Hypocalcaemia must be corrected by adequate intake of calcium and vitamin D before initiating therapy. Clinical monitoring of calcium levels is recommended for patients predisposed to hypocalcaemia (see Adverse Reactions).

Patients receiving *PROLIA* may develop skin infections (predominantly cellulitis) leading to hospitalisation. These events were reported more frequently in the denosumab (0.4%) versus the placebo (0.1%) groups. (see Adverse reactions). The overall incidence of skin infections was similar between the placebo and denosumab groups. Patients should be advised to seek prompt medical attention if they develop signs or symptoms of cellulitis.

Cases of osteonecrosis of the jaw (ONJ) were reported predominantly in patients with advanced cancer receiving 120 mg every 4 weeks. ONJ was reported rarely in patients with osteoporosis receiving 60 mg every 6 months (see Adverse Reactions).

*PROLIA* contains the same active ingredient (denosumab) found in *XGEVA™*. Patients receiving *PROLIA* should not receive *XGEVA*.

Atypical femoral fractures have been reported in patients receiving *PROLIA*. Atypical femoral fractures may occur with little or no trauma in the subtrochanteric and diaphyseal regions of the femur and may be bilateral. Specific radiographic findings characterise these events.

Atypical femoral fractures have also been reported in patients with certain comorbid conditions (e.g. vitamin D deficiency, rheumatoid arthritis, hypophosphatasia), and with use of certain pharmaceutical agents (e.g. bisphosphonates, glucocorticoids, proton pump inhibitors). These events have also occurred without antiresorptive therapy. During *PROLIA*

treatment, patients should be advised to report new or unusual thigh, hip, or groin pain. Patients presenting with such symptoms should be evaluated for an incomplete femoral fracture, and the contralateral femur should also be examined.

### Interactions

*PROLIA* (60 mg subcutaneously) did not affect the pharmacokinetics of midazolam, which is metabolized by cytochrome P450 3A4 (CYP3A4), indicating that it should not affect the pharmacokinetics of drugs metabolized by this enzyme (see Pharmacokinetics).

### Pregnancy and Lactation

#### Pregnancy

There is no adequate data in pregnant women. *PROLIA* is not recommended for use in pregnant women.

At AUC exposures up to 100-fold higher than the human exposure (60 mg every 6 months), denosumab showed no evidence of impaired fertility in cynomolgus monkeys (see Pre-clinical Safety Data).

In a study of cynomolgus monkeys dosed with denosumab during the period equivalent to the first trimester at AUC exposures up to 99-fold higher than the human dose (60 mg every 6 months), there was no evidence of maternal or foetal harm. In this study, foetal lymph nodes were not examined.

In another study of cynomolgus monkeys dosed with denosumab throughout pregnancy at AUC exposures 119-fold higher than the human dose (60 mg every 6 months), there were increased stillbirths and postnatal mortality; abnormal bone growth resulting in reduced bone strength, reduced haematopoiesis, and tooth malalignment; absence of peripheral lymph nodes; and decreased neonatal growth. There was no evidence of maternal harm prior to labour; adverse maternal effects occurred infrequently during labour. Maternal mammary gland development was normal.

Studies in knockout mice suggest absence of RANKL could interfere with maturation of the maternal mammary gland leading to impaired lactation post-partum.

*Women who become pregnant during PROLIA treatment are encouraged to enrol in Amgen’s Pregnancy Surveillance Program. Patients or their physicians should contact their local GSK representative to enrol.*

#### Lactation

It is not known if denosumab is excreted in human milk. Because denosumab has the potential to cause adverse reactions in breast-feeding infants, a decision should be made whether to discontinue breast-feeding or discontinue the medicinal product.

### Effects on Ability to Drive and Use Machines

No studies on the effect on the ability to drive or use heavy machinery have been performed in patients receiving denosumab.

### Adverse Reactions

#### Clinical Trial Data

Adverse reactions are listed below by MedDRA body system organ class and by frequency. The frequency categories based on one year event rates used are:

Very common	≥ 1 in 10
Common	≥ 1 in 100 and < 1 in 10
Uncommon	≥ 1 in 1,000 and < 1 in 100
Rare	≥ 1 in 10,000 and < 1 in 1,000
Very Rare	< 1/10,000

Within each frequency grouping and system organ class, undesirable effects are presented in order of decreasing seriousness

MedDRA system organ class	Frequency category	Undesirable effect
Infections and infestations	Uncommon	Cellulitis
Metabolism and nutrition disorders	Rare	Hypocalcaemia <sup>1</sup>
Eye disorders	Common	Cataracts <sup>2</sup>
Skin and subcutaneous tissue disorders	Uncommon	Eczema <sup>3</sup>
Musculoskeletal and connective tissue disorders	Common	Pain in extremity
	Rare	Osteonecrosis of the jaw
	Very rare	Atypical femoral fracture <sup>1,4</sup>

<sup>1</sup> See Warnings and Precautions

<sup>2</sup> In men with prostate cancer receiving androgen deprivation therapy

<sup>3</sup> includes dermatitis, allergic dermatitis, atopic dermatitis and contact dermatitis.

<sup>4</sup> In the osteoporosis clinical trial program, atypical femoral fractures were reported in patients treated with *PROLIA*.

### Postmarketing Data

#### Hypersensitivity Reactions

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

#### Severe Hypocalcaemia

Severe symptomatic hypocalcaemia has been reported in patients at increased risk of hypocalcaemia receiving *PROLIA*.

#### Overdose

No data from clinical trials are available regarding overdose of *PROLIA*.

Denosumab has been administered in clinical studies using doses up to 180 mg every 4 weeks (cumulative doses up to 1080 mg over 6 months).

### PHARMACOLOGICAL PROPERTIES

#### Pharmacodynamics

Mechanism of ActionDenosumab is a human monoclonal antibody (IgG2) that targets and binds with high affinity and specificity to RANKL preventing RANKL from activating its only receptor, RANK, on the surface of osteoclasts and their precursors, independent of bone surface. Prevention of the RANKL/RANK interaction inhibits osteoclast formation, function, and survival. Denosumab therefore reduces bone resorption and increases bone mass and strength in both cortical and trabecular bone.

#### Pharmacodynamic effects

In clinical studies, treatment with 60 mg of denosumab resulted in rapid reduction in the bone resorption marker serum type 1 C-telopeptides (CTX) within 6 hours of subcutaneous administration (by approximately 70%) with reductions of approximately 85% occurring by 3 days. CTX reductions were maintained over the 6-months dosing interval. At the end of each dosing interval, CTX reductions were partially attenuated from maximal reduction of ≥ 87% to approximately ≥ 45% (range 45-80%), reflecting the reversibility of denosumab’s effects on bone remodelling once serum levels diminish. These effects were sustained with continued treatment. Consistent with the physiological coupling of bone formation and resorption in skeletal remodelling, reductions in bone formation markers (e.g. bone specific alkaline phosphatase [BSAP] and serum N-terminal propeptide of type I collagen [P1NP]) were observed beginning 1 month after the first dose of denosumab.

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

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

#### Immunogenicity

Denosumab is a human monoclonal antibody; as with all therapeutic proteins, there is a theoretical potential for immunogenicity. More than 13,000 patients were screened for binding antibodies using a sensitive electrochemiluminescent bridging immunoassay. Less than 1% of patients treated with denosumab for up to 5 years tested positive (including pre-existing, transient and developing antibodies). The patients that tested positive for binding antibodies were further evaluated for neutralising antibodies using a chemiluminescent cell-based *in vitro* biological assay and none of them tested positive. No evidence of altered pharmacokinetic profile, toxicity profile, or clinical response was associated with binding antibody development.

### PHARMACOKINETICS

Following subcutaneous administration, denosumab displayed non-linear pharmacokinetics with dose over a wide dose range, and dose-proportional increases in exposure for doses of 60 mg (or 1 mg/kg) and higher.

### Absorption

Following a 60 mg subcutaneous dose of denosumab, bioavailability was 61% and maximum serum denosumab concentrations (C<sub>max</sub>) of 6 µg/mL (range 1-17 µg/mL) occurred in 10 days (range 2-28 days). After C<sub>max</sub> serum levels declined with a half-life of 26 days (range 6-52 days) over a period of 3 months (range 1.5-4.5 months). Fifty-three percent of patients had no measurable amounts of denosumab detected at 6 months post-dose.

### Distribution

No accumulation or change in denosumab pharmacokinetics with time was observed upon multiple-dosing of 60 mg subcutaneously once every 6 months.

### Metabolism

Denosumab is composed solely of amino acids and carbohydrates as native immunoglobulin. Based on nonclinical data, denosumab metabolism is expected to follow the immunoglobulin clearance pathways, resulting in degradation to small peptides and individual amino acids.

### Elimination

Denosumab is composed solely of amino acids and carbohydrates as native immunoglobulin and is not expected to be eliminated via hepatic metabolic mechanisms (e.g. cytochrome p450 (CYP) enzymes) Based on nonclinical data, its elimination is expected to follow the immunoglobulin clearance pathways, resulting in degradation to small peptides and individual amino acids.

### Drug Interactions

In a study of 17 postmenopausal women with osteoporosis, midazolam (2 mg oral) was administered two weeks after a single dose of denosumab (60 mg subcutaneously), which corresponds to time of maximal pharmacodynamic effects of denosumab. Denosumab did not affect the pharmacokinetics of midazolam, which is metabolized by cytochrome P450 3A4 (CYP3A4). This indicates that denosumab should not alter the PK of drugs metabolized by CYP3A4.

### Special Patient Populations

#### Elderly (greater than or equal to 65 years of age)

Age was not found to be a significant factor on denosumab pharmacokinetics in a population pharmacokinetic analysis of patients ranging in age from 28 to 87 years of age.

#### Children and Adolescents (up to 18 years of age)

No pharmacokinetic data are available in paediatric patients.

### Race

The pharmacokinetics of denosumab were not affected by race in post-menopausal women or in breast cancer patients undergoing hormone ablation.

### Renal Impairment

In a study of 55 patients with varying degrees of renal function, including patients on dialysis, the degree of renal impairment had no effect on the pharmacokinetics and pharmacodynamics of denosumab; therefore dose adjustment for renal impairment is not necessary.

### Hepatic Impairment

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

### CLINICAL STUDIES

#### Treatment of Postmenopausal Osteoporosis

The efficacy and safety of denosumab in the treatment of postmenopausal osteoporosis was demonstrated in FREEDOM, a 3-year, randomised, double-blind, placebo-controlled, multinational study that demonstrated that denosumab was effective compared to placebo in reducing new vertebral, non-vertebral and hip fractures in post-menopausal women with osteoporosis.

7,808 women aged 60-91 years were enrolled of which 23.6% had prevalent vertebral fractures. Women were randomised to receive subcutaneous injections of either placebo (n = 3,906) or denosumab 60 mg (n = 3,902) once every 6 months. Women received calcium (at least 1,000 mg) and vitamin D (at least 400 IU) supplementation daily. The primary efficacy variable was the incidence of new vertebral fractures. Secondary efficacy variables included the incidence of non-vertebral fractures and hip fractures, assessed at 3 years.

Denosumab significantly reduced the risk of new vertebral, nonvertebral, and hip fractures compared with placebo. All 3 efficacy fracture endpoints achieved the statistical significance level based on the pre-specified sequential testing scheme.

#### Effect on vertebral fractures

Denosumab significantly reduced the risk of new vertebral fractures (primary endpoint) by 68% (risk ratio: 0.32; p<0.0001) over 3 years. The 3-year fracture rates for new vertebral fractures were 7.2% in the placebo group and 2.3% in the *PROLIA* group (unadjusted absolute risk reduction of 4.8%) Reductions were also observed over 1 year (61% relative risk reduction; 1.4% unadjusted absolute risk reduction) and 2 years (71% relative risk reduction; 3.5% unadjusted absolute risk reduction) (all p < 0.0001).

Denosumab also reduced the risk of other prespecified categories of fractures, including new and worsening vertebral fractures (67% relative risk reduction, 4.8% unadjusted absolute risk reduction), multiple new vertebral fractures (61% relative risk reduction, 1.0% unadjusted absolute risk reduction), clinical vertebral fractures (69% relative risk reduction, 1.8% unadjusted absolute risk reduction) over 3 years..

The reductions in the risk of new vertebral fractures by denosumab over 3 years were consistent and significant regardless of 10-year major osteoporotic baseline fracture risk as assessed by FRAX® (WHO’s Fracture Risk Assessment Tool algorithm) and whether or not women had a prevalent vertebral fracture or history of a non-vertebral fracture, and regardless of baseline age, BMD, bone turnover level and prior use of a medicinal product for osteoporosis.

In postmenopausal women with osteoporosis over the age of 75, denosumab reduced the incidence of new vertebral (64%), and non-vertebral (16%) fractures.

#### Effect on all clinical fractures

Denosumab significantly decreased the risk of non-vertebral fractures (secondary endpoint) by 20% (hazard ratio: 0.80; p = 0.0106) over 3 years. Three-year non-vertebral fracture rates were 8.0% in the placebo group to 6.5% in the denosumab group (unadjusted absolute risk reduction of 1.5%).

Denosumab also reduced the risk of clinical (30% relative risk reduction, 2.9% unadjusted absolute risk reduction), major non-vertebral (20% relative risk reduction, 1.2% unadjusted absolute risk reduction), and major osteoporotic fractures (35% relative risk reduction, 2.7% unadjusted absolute risk reduction) over 3 years.

In women with baseline femoral neck BMD T-score ≤ -2.5, denosumab reduced the incidence of non-vertebral fractures (35% relative risk reduction, 4.1% unadjusted absolute risk reduction, p < 0.001) over 3 years. Reductions in non-vertebral fractures were observed regardless of baseline 10-year probability of a major osteoporotic fracture as assessed by FRAX®.

#### Effect on hip fractures

Denosumab significantly decreased the risk of hip fractures (secondary endpoint) by 40% (hazard ratio: 0.60; p = 0.0362) over 3 years. Three-year hip fracture rates were 1.2% in the placebo group and 0.7% in the denosumab group (unadjusted absolute risk reduction of 0.5%). The reductions in the risk of hip fractures over 3 years were consistent and significant regardless of baseline 10-year probability of a hip fracture as assessed by FRAX®.

In women with high fracture risk as defined above by baseline age, BMD and prevalent vertebral fracture, a 48% relative risk reduction was observed with denosumab (1.1% unadjusted absolute risk reduction).

In a post-hoc analysis in postmenopausal women with osteoporosis over the age of 75 denosumab reduced the incidence of hip fractures (62%).

#### Effect on bone mineral density (BMD)

Denosumab significantly increased BMD at all clinical sites measured, relative to treatment with placebo at 1, 2 and 3 years. Denosumab increased BMD by 9.2% at the lumbar spine, 6.0% at the total hip, 4.8% at the femoral neck, 7.9% at the hip trochanter, 3.5% at the distal 1/3 radius and 4.1% at the total body over 3 years. Increases in BMD at lumbar spine, total hip and hip trochanter were observed as early as 1 month after the initial dose. Denosumab increased lumbar spine BMD from baseline in 96% of postmenopausal women at 3 years. Consistent effects on BMD were observed at the lumbar spine regardless of baseline age, race, weight/BMI, BMD and bone turnover level.

#### Bone Histology

Histology assessments showed bone of normal architecture and quality, as well as the expected decrease in bone turnover relative to placebo treatment. There was no evidence of mineralisation defects, woven bone or marrow fibrosis.

### Open-label Extension Study in the Treatment of Postmenopausal Osteoporosis

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

Based on data from the first 2 years of the extension study for patients who received denosumab in the FREEDOM study and continued on therapy (years 4 and 5 of denosumab treatment), the overall subject incidence rates of adverse events and serious adverse events reported were similar to that observed in the initial 3 years of the FREEDOM study.

For patients who crossed over to denosumab from placebo in the FREEDOM study , the overall subject incidence rates of adverse events and serious adverse events reported also similar to the first 3 years of the FREEDOM study. Two cases of ONJ were observed; both resolved.

Denosumab treatment maintained a low incidence of new vertebral and non-vertebral fractures in years 4 and 5 (2.8% of patients had at least one new vertebral fracture by month 24, 2.5% of patients had a nonvertebral fracture).

Denosumab treatment continued to increase BMD at the lumbar spine (3.3%), total hip (1.3%), femoral neck (1.2%) and trochanter (1.8%) in years 4 and 5. Percent increase in BMD from the original FREEDOM study baseline (ie, after 5 years of treatment) in the long-term group was 13.8% at the lumbar spine, 7.0% at the total hip, 6.2% at the femoral neck and 9.7% at the trochanter.

### Comparative Clinical Data vs alendronate in the Treatment of Postmenopausal Women with Low Bone Mass

In two randomised, double-blind, active-controlled studies, one in treatment-naïve women and another in women previously treated with alendronate, Denosumab showed significantly greater increases in BMD and reductions in bone turnover markers (e.g. serum CTX), compared to alendronate.

Consistently greater increases in BMD were seen at the lumbar spine, total hip, femoral neck, hip trochanter, and distal 1/3 radius in women treated with denosumab, compared to those who continued to receive alendronate therapy (all p < 0.05).

#### Clinical efficacy in the treatment of bone loss associated with hormone ablation

##### Treatment of bone loss associated with androgen deprivation

The efficacy and safety of denosumab in the treatment of bone loss associated with androgen deprivation was assessed in a 3-year randomised, double-blind, placebo-controlled, multinational study of 1,468 men with non-metastatic prostate cancer aged 48-97 years. Men less than 70 years of age also had either a BMD T-score at the lumbar spine, total hip, or femoral neck < -1.0 or a history of an osteoporotic fracture. Subjects either received subcutaneous injections of either denosumab 60 mg (n = 734) or placebo (n = 734) once every 6 months. Men received calcium (at least 1,000 mg) and vitamin D (at least 400 IU) supplementation daily.

Significant increases in BMD were observed at the lumbar spine, total hip, femoral neck and the hip trochanter as early as 1 month after the initial dose. Denosumab increased lumbar spine BMD by 7.9%, total hip BMD by 5.7%, femoral neck BMD by 4.9%, hip trochanter BMD by 6.9%, distal 1/3 radius BMD by 6.9%, and total body BMD by 4.7% over 3 years, relative to placebo (p < 0.0001). Consistent effects on BMD were observed at the lumbar spine regardless of age, race, geographical region, weight/BMI, BMD, bone turnover level; duration of androgen deprivation and presence of vertebral fracture at baseline.

Denosumab significantly decreased the risk of new vertebral fractures by 62% (hazard ratio: 0.38; p < 0.0063) over 3 years. Reductions were also observed over 1 year (85% relative risk reduction; 1.6% absolute risk reduction), and 2 years (69% relative risk reduction; 2.2% absolute risk reduction) (all p < 0.01). Denosumab also reduced the subject incidence of more than one osteoporotic fracture at any site by 72% relative to placebo over 3 years (placebo 2.5% vs. denosumab 0.7%, p = 0.0063).

##### Treatment of bone loss in women undergoing aromatase inhibitor therapy for breast cancer

The efficacy and safety of denosumab in the treatment of bone loss associated with adjuvant aromatase inhibitor therapy was assessed in a 2-year, randomised, double-blind, placebo-controlled multinational study of 252 women with non-metastatic breast cancer aged 35-84 years. Women had baseline BMD T-scores between -1.0 to -2.5 at the lumbar spine, total hip or femoral neck. Women were randomised to receive subcutaneous injections of either denosumab 60 mg (n = 127) or placebo (n = 125) once every 6 months. Women received calcium (at least 1,000 mg) and vitamin D (at least 400 IU) supplementation daily. The primary efficacy variable was percent change in lumbar spine BMD.

Denosumab significantly increased BMD at all clinical sites measured, relative to treatment with placebo at 2 years: 7.6% at the lumbar spine, 4.7% at the total hip, 3.6% at the femoral neck, 5.9% at the hip trochanter, 6.1% at the distal 1/3 radius and 4.2% at the total body. Significant increases in BMD were observed at the lumbar spine as early as 1 month after the initial dose. Consistent effects on BMD were observed at the lumbar spine regardless of baseline age, duration of aromatase inhibitor therapy, weight/BMI, prior chemotherapy, prior selective estrogen receptor modulator (SERM) use, and time since menopause.

### Pre-Clinical Safety Data

#### Carcinogenicity

The carcinogenic potential of denosumab has not been evaluated in long-term animal studies.

#### Mutagenicity

The genotoxic potential of denosumab has not been evaluated.

### Reproductive toxicology

#### Fertility

Denosumab had no effect on female fertility or male reproductive organs in monkeys at AUC exposures that were 100- to 150-fold higher than the human exposure at 60 mg administered subcutaneously once every 6 months.

#### Animal Pharmacology