CORORA®
Denosumab

1. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each pre-filled syringe contains 60 mg of denosumab in 1 mL of solution (60 mg/mL).

2. PHARMACEUTICAL FORM

Solution for subcutaneous injection.

Clear, colourless to slightly yellow solution.

3. CLINICAL PARTICULARS

3.1 Indications

Postmenopausal Osteoporosis

Treatment of postmenopausal women with osteoporosis at high risk for fracture, defined as a history of osteoporotic fracture, or multiple risk factors for fracture; or patients who have failed or are intolerant to other available osteoporosis therapy, and T-score Lumbar Spine, femur or radius ≤ -2.5.

Bone Loss in Patients Undergoing Hormone Ablation for Prostate Cancer

CORORA is indicated as a treatment of bone remodelling in men at high risk for fracture after receiving androgen deprivation therapy for non-metastatic prostate cancer. In these patients CORORA also reduces the incidence of vertebral fractures.

3.2 Dosage and Administration

Administration

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

Dosage

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

Patients should receive calcium 1,000 mg daily and at least 400 IU vitamin D daily whilst undergoing treatment.

Populations

Children
CORORA is not recommended in paediatric patients as the safety and effectiveness of CORORA 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.

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 CORORA have not been studied in patients with hepatic impairment.

3.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed (see List of Excipients).

Hypocalcaemia (see Warnings and Precautions).

3.4 Warnings and Precautions

Calcium and vitamin D supplementation

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

Precautions for use

Hypocalcaemia
It is important to identify patients at risk for hypocalcaemia. Hypocalcaemia must be corrected by adequate intake of calcium and vitamin D before initiating therapy. Clinical monitoring of calcium levels is recommended before each dose and, in patients predisposed to hypocalcaemia within two weeks after the initial dose. If any patient presents with suspected symptoms of

hypocalcaemia during treatment (see Adverse Reactions for symptoms) calcium levels should be measured. Patients should be encouraged to report symptoms indicative of hypocalcaemia.

In the post-marketing setting, severe symptomatic hypocalcaemia (including fatal cases) has been reported (see Adverse Reactions), with most cases occurring in the first weeks of initiating therapy, but it can occur later.

Concomitant glucocorticoid treatment is an additional risk factor for hypocalcaemia.

Renal impairment
Patients with severe renal impairment (creatinine clearance < 30 mL/min) or receiving dialysis are at greater risk of developing hypocalcaemia. The risks of developing hypocalcaemia and accompanying parathyroid hormone elevations increase with increasing degree of renal impairment. Adequate intake of calcium, vitamin D and regular monitoring of calcium is especially important in these patients, see above.

Skin infections
Patients receiving denosumab may develop skin infections (predominantly cellulitis) leading to hospitalisation (see Adverse Reactions). Patients should be advised to seek prompt medical attention if they develop signs or symptoms of cellulitis.

Osteonecrosis of the jaw (ONJ)
ONJ has been reported rarely in patients receiving CORORA for osteoporosis (see Adverse Reactions).

The start of treatment/new treatment course should be delayed in patients with unhealed open soft tissue lesions in the mouth. A dental examination with preventive dentistry and an individual benefit-risk assessment is recommended prior to treatment with denosumab in patients with concomitant risk factors.

The following risk factors should be considered when evaluating a patient's risk of developing ONJ:

- potency of the medicinal product that inhibits bone resorption (higher risk for highly potent compounds), route of administration (higher risk for parenteral administration) and cumulative dose of bone resorption therapy.
- cancer, co-morbid conditions (e.g. anaemia, coagulopathies, infection), smoking.
- concomitant therapies: corticosteroids, chemotherapy, angiogenesis inhibitors, radiotherapy to head and neck.
- poor oral hygiene, periodontal disease, poorly fitting dentures, history of dental disease, invasive dental procedures e.g. tooth extractions.

All patients should be encouraged to maintain good oral hygiene, receive routine dental check-ups, and immediately report any oral symptoms such as dental mobility, pain or swelling or non-healing of sores or discharge during treatment with denosumab. While on treatment, invasive dental procedures should be performed only after careful consideration and be avoided in close proximity to denosumab administration.

The management plan of the patients who develop ONJ should be set up in close collaboration between the treating physician and a dentist or oral surgeon with expertise in ONJ. Temporary interruption of treatment should be considered until the condition resolves and contributing risk factors are mitigated where possible.

Atypical fractures of the femur
Atypical femoral fractures have been reported in patients receiving denosumab (see Adverse Reactions). Atypical femoral fractures may occur with little or no trauma in the subtrochanteric and diaphyseal regions of the femur. Specific radiographic findings characterise these events. Atypical femoral fractures have also been reported in patients with certain co-morbid conditions (e.g. vitamin D deficiency, rheumatoid arthritis, hypophosphatasia) and with use of certain medicinal products (e.g. bisphosphonates, glucocorticoids, proton pump inhibitors). These events have also occurred without antiresorptive therapy. Similar fractures reported in association with bisphosphonates are often bilateral; therefore, the contralateral femur should be examined in denosumab-treated patients who have sustained a femoral shaft fracture. Discontinuation of denosumab therapy in patients suspected to have an atypical femur fracture should be considered pending evaluation of the patient based on an individual benefit-risk assessment. During denosumab 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.

Long-term antiresorptive treatment
Long-term antiresorptive treatment (including both denosumab and bisphosphonates) may contribute to an increased risk for adverse outcomes such as osteonecrosis of the jaw and atypical femur fractures due to significant suppression of bone remodelling.

Concomitant treatment with other denosumab-containing medicinal products
Patients being treated with denosumab should not be treated concomitantly with other denosumab-containing medicinal products (for prevention of skeletal related events in adults with bone metastases from solid tumours).

Warnings for excipients
This medicine contains 47 mg sorbitol in each mL of solution. The additive effect of concomitantly administered products containing sorbitol (or fructose) and dietary intake of sorbitol (or fructose) should be taken into account.

This medicinal product contains less than 1 mmol sodium (23 mg) per 60 mg that is to say essentially ‘sodium-free’.

3.5 Interactions

In an interaction study, denosumab did not affect the pharmacokinetics of midazolam, which is metabolised by cytochrome P450 3A4 (CYP3A4). This indicates that denosumab should not alter the pharmacokinetics of medicinal products metabolised by CYP3A4.

There are no clinical data on the co-administration of denosumab and hormone replacement therapy (oestrogen), however the potential for a pharmacodynamic interaction is considered to be low.

In postmenopausal women with osteoporosis the pharmacokinetics and pharmacodynamics of denosumab were not altered by previous alendronate therapy, based on data from a transition study (alendronate to denosumab).

3.6 Pregnancy and Lactation

Pregnancy

There are no or limited amount of data from the use of denosumab in pregnant women. Studies in animals have shown reproductive toxicity (see Pre-Clinical Safety Data).

CORORA is not recommended for use in pregnant women and women of child-bearing potential not using contraception. Women should be advised not to become pregnant during and for at least 5 months after treatment with CORORA. Any effects of CORORA are likely to be greater during the second and third trimesters of pregnancy since monoclonal antibodies are transported across the placenta in a linear fashion as pregnancy progresses, with the largest amount transferred during the third trimester.

Breast-feeding

It is unknown whether denosumab is excreted in human milk. In genetically engineered mice in which RANKL has been turned off by gene removal (a “knockout mouse”), studies suggest absence of RANKL (the target of denosumab see Pharmacodynamics) during pregnancy may interfere with maturation of the mammary gland leading to impaired lactation post-partum (see Pre-Clinical Safety Data). A decision on whether to abstain from breast-feeding or to abstain from therapy with CORORA should be made, taking into account the benefit of breast-feeding to the newborn/infant and the benefit of CORORA therapy to the woman.

3.7 Effects on Ability to Drive and Use Machines

CORORA has no or negligible influence on the ability to drive and use machines.

3.8 Adverse Reactions

Summary of the safety profile

The most common side effects with denosumab (seen in more than one patient in ten) are musculoskeletal pain and pain in the extremity. Uncommon cases of cellulitis, rare cases of hypocalcaemia, hypersensitivity, osteonecrosis of the jaw and atypical femoral fractures (see Warnings and Precautions and Adverse Reactions - description of selected adverse reactions) have been observed in patients taking denosumab.

Tabulated list of adverse reactions

The data in table 1 below describe adverse reactions reported from phase II and III clinical trials in patients with osteoporosis and breast or prostate cancer patients receiving hormone ablation; and/or spontaneous reporting.

The following convention has been used for the classification of the adverse reactions (see table 1): very common (≥ 1/10), common (≥ 1/100 to < 1/10), uncommon (≥ 1/1,000 to < 1/100), rare (≥ 1/10,000 to < 1/1,000), very rare (< 1/10,000) and not known (cannot be estimated from the available data). Within each frequency grouping and system organ class, adverse reactions are presented in order of decreasing seriousness.

Table 1. Adverse reactions reported in patients with osteoporosis and breast or prostate cancer patients receiving hormone ablation

MedDRA system organ class	**Frequency category**	**Adverse reactions**
Infections and infestations	Common	Urinary tract infection
	Common	Upper respiratory tract infection
	Uncommon	Diverticulitis[1]
	Uncommon	Cellulitis[1]
	Uncommon	Ear infection
Immune system disorders	Rare	Drug hypersensitivity[1]
	Rare	Anaphylactic reaction[1]
Metabolism and nutrition disorders	Rare	Hypocalcaemia[1]
Nervous system disorders	Common	Sciatica
Gastrointestinal disorders	Common	Constipation
	Common	Abdominal discomfort
Skin and subcutaneous tissue disorders	Common	Rash
	Common	Eczema
	Common	Alopecia
	Uncommon	Lichenoid drug eruptions[1]
	Very rare	Hypersensitivity vasculitis
	Not known	Drug reaction with eosinophilia and systemic symptoms (DRESS) syndrome
Musculoskeletal and connective tissue disorders	Very common	Pain in extremity
	Very common	Musculoskeletal pain[1]
	Rare	Osteonecrosis of the jaw[1]
	Rare	Atypical femoral fractures[1]

[1] See Description of selected adverse reactions.

In a pooled analysis of data from all phase II and phase III placebo-controlled studies, influenza-like illness was reported with a crude incidence rate of 1.2% for denosumab and 0.7% for placebo. Although this imbalance was identified via a pooled analysis, it was not identified via a stratified analysis.

Description of selected adverse reactions

Hypocalcaemia
In two phase III placebo-controlled clinical trials in postmenopausal women with osteoporosis, approximately 0.05% (2 out of 4,050) of patients had declines of serum calcium levels (less than 1.88 mmol/L) following CORORA administration. Declines of serum calcium levels (less than 1.88 mmol/L) were not reported in either the two phase III placebo-controlled clinical trials in patients receiving hormone ablation or the phase III placebo-controlled clinical trial in men with osteoporosis.

In the post-marketing setting, rare cases of severe symptomatic hypocalcaemia have been reported predominantly in patients at increased risk of hypocalcaemia receiving denosumab, with most cases occurring in the first weeks of initiating therapy. Examples of the clinical manifestations of severe symptomatic hypocalcaemia have included QT interval prolongation, tetany, seizures and altered mental status (see Warnings and Precautions). Symptoms of hypocalcaemia in denosumab clinical studies included paraesthesias or muscle stiffness, twitching, spasms and muscle cramps.

Skin infections
In phase III placebo-controlled clinical trials, the overall incidence of skin infections was similar in the placebo and the denosumab groups: in postmenopausal women with osteoporosis (placebo [1.2%, 50 out of 4,041] versus CORORA [1.5%, 59 out of 4,050]); in men with osteoporosis (placebo [0.8%, 1 out of 120] versus CORORA [0%, 0 out of 120]); in breast or prostate cancer patients receiving hormone ablation (placebo [1.7%, 14 out of 845] versus CORORA [1.4%, 12 out of 860]). Skin infections leading to hospitalisation were reported in 0.1% (3 out of 4,041) of postmenopausal women with osteoporosis receiving placebo versus 0.4% (16 out of 4,050) of women receiving CORORA. These cases were predominantly cellulitis. Skin infections reported as serious adverse reactions were similar in the placebo (0.6%, 5 out of 845) and the CORORA (0.6%, 5 out of 860) groups in the breast and prostate cancer studies.

Osteonecrosis of the jaw
ONJ has been reported rarely, in 16 patients, in clinical trials in osteoporosis and in breast or prostate cancer patients receiving hormone ablation including a total of 23,148 patients (see Warnings and Precautions). Thirteen of these ONJ cases occurred in postmenopausal women with osteoporosis during the phase III clinical trial extension following treatment with denosumab for up to 10 years. Incidence of ONJ was 0.04% at 3 years, 0.06% at 5 years and 0.44% at 10 years of denosumab treatment. The risk of ONJ increased with duration of exposure to denosumab.

Atypical fractures of the femur
In the osteoporosis clinical trial program, atypical femoral fractures were reported rarely in patients treated with denosumab (see Warnings and Precautions).

Diverticulitis
In a single phase III placebo-controlled clinical trial in patients with prostate cancer receiving androgen deprivation therapy (ADT) an imbalance in diverticulitis adverse events was observed (1.2% denosumab, 0% placebo). The incidence of diverticulitis was comparable between

treatment groups in postmenopausal women or men with osteoporosis and in women undergoing aromatase inhibitor therapy for non-metastatic breast cancer.

Drug-related hypersensitivity reactions
In the post-marketing setting, rare events of drug-related hypersensitivity, including rash, urticaria, facial swelling, erythema, and anaphylactic reactions have been reported in patients receiving CORORA.

Musculoskeletal pain
Musculoskeletal pain, including severe cases, has been reported in patients receiving CORORA in the post-marketing setting. In clinical trials, musculoskeletal pain was very common in both denosumab and placebo groups. Musculoskeletal pain leading to discontinuation of study treatment was uncommon.

Lichenoid drug eruptions
Lichenoid drug eruptions (e.g. lichen planus-like reactions) have been reported in patients in the post-marketing setting.

Other special populations

Renal impairment
In clinical studies, patients with severe renal impairment (creatinine clearance < 30 mL/min) or receiving dialysis were at greater risk of developing hypocalcaemia in the absence of calcium supplementation. Adequate intake of calcium and vitamin D is important in patients with severe renal impairment or receiving dialysis (see Warnings and Precautions).

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit-risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions.

3.9 Overdose

There is no experience with overdose in clinical studies. Denosumab has been administered in clinical studies using doses up to 180 mg every 4 weeks (cumulative doses up to 1,080 mg over 6 months), and no additional adverse reactions were observed.

4. PHARMACOLOGICAL PROPERTIES

4.1 Pharmacodynamics

Pharmacotherapeutic group: Drugs for treatment of bone diseases – Other drugs affecting bone structure and mineralisation, ATC code: M05BX04

Mechanism of action

Denosumab is a human monoclonal antibody (IgG2) that targets and binds with high affinity and specificity to RANKL, preventing activation of its receptor, RANK, on the surface of osteoclast precursors and osteoclasts. Prevention of the RANKL/RANK interaction inhibits osteoclast formation, function, and survival, thereby decreasing bone resorption in cortical and trabecular bone.

Pharmacodynamic effects

CORORA treatment rapidly reduced the rate of bone turnover, reaching a nadir for the bone resorption marker serum type 1 C-telopeptides (CTX) (85% reduction) by 3 days, with reductions maintained over the 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 CORORA's effects on bone remodelling once serum levels diminish. These effects were sustained with continued treatment. Bone turnover markers generally reached pre-treatment levels within 9 months after the last dose. Upon re-initiation, reductions in CTX by denosumab were similar to those observed in patients initiating primary denosumab treatment.

Immunogenicity

In clinical studies, neutralising antibodies have not been observed for denosumab. Using a sensitive immunoassay < 1% of patients treated with denosumab for up to 5 years tested positive for non neutralising binding antibodies with no evidence of altered pharmacokinetics, toxicity, or clinical response.

4.2 Pharmacokinetics

Absorption

Following subcutaneous administration of a 1.0 mg/kg dose, which approximates the approved 60 mg dose, exposure based on AUC was 78% as compared to intravenous administration at the same dose level. For a 60 mg subcutaneous dose, maximum serum denosumab concentrations (C_{max}) of 6 mcg/mL (range 1-17 mcg/mL) occurred in 10 days (range 2-28 days).

Biotransformation

Denosumab is composed solely of amino acids and carbohydrates as native immunoglobulin and is unlikely to be eliminated via hepatic metabolic mechanisms. Its metabolism and elimination are expected to follow the immunoglobulin clearance pathways, resulting in degradation to small peptides and individual amino acids.

Elimination

After C_{max}, 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 (53%) of patients had no measurable amounts of denosumab detected at 6 months post-dose.

No accumulation or change in denosumab pharmacokinetics with time was observed upon subcutaneous multiple-dosing of 60 mg once every 6 months. Denosumab pharmacokinetics were not affected by the formation of binding antibodies to denosumab and were similar in men and women. Age (28-87 years), race and disease state (low bone mass or osteoporosis; prostate or breast cancer) do not appear to significantly affect the pharmacokinetics of denosumab.

A trend was observed between higher body weight and lower exposure based on AUC and C_{max}. However, the trend is not considered clinically important, since pharmacodynamic effects based on bone turnover markers and BMD increases were consistent across a wide range of body weight.

Linearity/non-linearity

In dose ranging studies, denosumab exhibited non-linear, dose-dependent pharmacokinetics, with lower clearance at higher doses or concentrations, but approximately dose-proportional increases in exposures for doses of 60 mg and greater.

Special Patient Populations
Renal impairment

In a study of 55 patients with varying degrees of renal function, including patients on dialysis, the degree of renal impairment had no effect on the pharmacokinetics of denosumab.

Hepatic impairment

No specific study in patients with hepatic impairment was performed. In general, monoclonal antibodies are not eliminated via hepatic metabolic mechanisms. The pharmacokinetics of denosumab is not expected to be affected by hepatic impairment.

Paediatric population

The pharmacokinetic profile in paediatric populations has not been assessed.

4.3 Clinical Studies

Clinical efficacy and safety in postmenopausal women with osteoporosis

Efficacy and safety of denosumab administered once every 6 months for 3 years were investigated in postmenopausal women (7,808 women aged 60-91 years, of which 23.6% had prevalent vertebral fractures) with baseline bone mineral density (BMD) T-scores at the lumbar spine or total hip between –2.5 and –4.0 and a mean absolute 10-year fracture probability of 18.60% (deciles: 7.9-32.4%) for major osteoporotic fracture and 7.22% (deciles: 1.4-14.9%) for hip fracture. Women with other diseases or on therapies that may affect bone were excluded from this study. Women received calcium (at least 1,000 mg) and vitamin D (at least 400 IU) supplementation daily.

Effect on vertebral fractures
CORORA significantly reduced the risk of new vertebral fractures at 1, 2 and 3 years ($p < 0.0001$) (see table 2).

Table 2. The effect of CORORA on the risk of new vertebral fractures

	Proportion of women with fracture (%)		Absolute risk reduction (%) (95% CI)	Relative risk reduction (%) (95% CI)
	Placebo n = 3,906	CORORA n = 3,902		
0-1 year	2.2	0.9	1.4 (0.8, 1.9)	61 (42, 74)**
0-2 years	5.0	1.4	3.5 (2.7, 4.3)	71 (61, 79)**
0-3 years	7.2	2.3	4.8 (3.9, 5.8)	68 (59, 74)*

*p < 0.0001, **p < 0.0001 – exploratory analysis

Effect on hip fractures
CORORA demonstrated a 40% relative reduction (0.5% absolute risk reduction) in the risk of hip fracture over 3 years ($p < 0.05$). The incidence of hip fracture was 1.2% in the placebo group compared to 0.7% in the CORORA group at 3 years.

In a post-hoc analysis in women > 75 years, a 62% relative risk reduction was observed with CORORA (1.4% absolute risk reduction, $p < 0.01$).

Effect on all clinical fractures
CORORA significantly reduced fractures across all fracture types/groups (see table 3).

Table 3. The effect of CORORA on the risk of clinical fractures over 3 years

	Proportion of women with fracture (%)+		Absolute risk reduction (%) (95% CI)	Relative risk reduction (%) (95% CI)
	Placebo n = 3,906	CORORA n = 3,902		
Any clinical fracture[1]	10.2	7.2	2.9 (1.6, 4.2)	30 (19, 41)***
Clinical vertebral fracture	2.6	0.8	1.8 (1.2, 2.4)	69 (53, 80)***
Non-vertebral fracture[2]	8.0	6.5	1.5 (0.3, 2.7)	20 (5, 33)**

	Proportion of women with fracture (%)[+]		Absolute risk reduction (%) (95% CI)	Relative risk reduction (%) (95% CI)
	Placebo n = 3,906	CORORA n = 3,902		
Major non-vertebral fracture[3]	6.4	5.2	1.2 (0.1, 2.2)	20 (3, 34)*
Major osteoporotic fracture[4]	8.0	5.3	2.7 (1.6, 3.9)	35 (22, 45)***

*p ≤ 0.05; **p = 0.0106 *(secondary endpoint included in multiplicity adjustment)*, ***p ≤ 0.0001

[+] Event rates based on Kaplan-Meier estimates at 3 years.

[1] Includes clinical vertebral fractures and non-vertebral fractures.

[2] Excludes those of the vertebrae, skull, facial, mandible, metacarpus, and finger and toe phalanges.

[3] Includes pelvis, distal femur, proximal tibia, ribs, proximal humerus, forearm, and hip.

[4] Includes clinical vertebral, hip, forearm, and humerus fractures, as defined by the WHO.

In women with baseline femoral neck BMD ≤ -2.5, CORORA reduced the risk of non-vertebral fracture (35% relative risk reduction, 4.1% absolute risk reduction, p < 0.001, exploratory analysis).

The reduction in the incidence of new vertebral fractures, hip fractures and non-vertebral fractures by CORORA over 3 years were consistent regardless of the 10-year baseline fracture risk.

Effect on bone mineral density

CORORA significantly increased BMD at all clinical sites measured, versus placebo at 1, 2 and 3 years. CORORA 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 (all p < 0.0001).

In clinical studies examining the effects of discontinuation of CORORA, BMD returned to approximately pre-treatment levels and remained above placebo within 18 months of the last dose. These data indicate that continued treatment with CORORA is required to maintain the effect of the medicinal product. Re-initiation of CORORA resulted in gains in BMD similar to those when CORORA was first administered.

Open-label extension study in the treatment of postmenopausal osteoporosis

A total of 4,550 women (2,343 CORORA & 2,207 placebo) who missed no more than one dose of investigational product in the pivotal study described above and completed the month 36 study visit agreed to enrol in a 7-year, multinational, multicentre, open-label, single-arm extension study to evaluate the long-term safety and efficacy of CORORA. All women in the extension study were to receive CORORA 60 mg every 6 months, as well as daily calcium (at least 1 g) and vitamin D (at least 400 IU). A total of 2,626 subjects (58% of the women included in the extension study i.e. 34% of the women included in the pivotal study) completed the extension study.

In patients treated with CORORA for up to 10 years, BMD increased from the pivotal study baseline by 21.7% at the lumbar spine, 9.2% at the total hip, 9.0% at the femoral neck, 13.0% at the trochanter and 2.8% at the distal 1/3 radius. The mean lumbar spine BMD T-score at the end of the study was -1.3 in patients treated for 10 years.

Fracture incidence was evaluated as a safety endpoint but efficacy in fracture prevention cannot be estimated due to high number of discontinuations and open-label design. The cumulative incidence of new vertebral and non-vertebral fractures were approximately 6.8% and 13.1% respectively, in patients who remained on denosumab treatment for 10 years (n = 1,278). Patients who did not complete the study for any reason had higher on-treatment fracture rates.

Thirteen adjudicated cases of osteonecrosis of the jaw (ONJ) and two adjudicated cases of atypical fractures of the femur occurred during the extension study.

Bone histology in postmenopausal women and men with osteoporosis

Bone histology was evaluated in 62 postmenopausal women with osteoporosis or with low bone mass who were either naïve to osteoporosis therapies or had transitioned from previous alendronate therapy following 1-3 years treatment with CORORA. Fifty nine women participated in the bone biopsy sub-study at month 24 (n = 41) and/or month 84 (n = 22) of the extension study in postmenopausal women with osteoporosis. Bone histology was also evaluated in 17 men with osteoporosis following 1 year treatment with CORORA. Bone biopsy results showed bone of normal architecture and quality with no evidence of mineralisation defects, woven bone or marrow fibrosis. Histomorphometry findings in the extension study in postmenopausal women with osteoporosis showed that the antiresorptive effects of CORORA, as measured by activation frequency and bone formation rates, were maintained over time.

Clinical efficacy and safety in patients with bone loss associated with androgen deprivation

Efficacy and safety of CORORA once every 6 months for 3 years were investigated in men with histologically confirmed non-metastatic prostate cancer receiving ADT (1,468 men aged 48-97 years) who were at increased risk of fracture (defined as > 70 years, or < 70 years with a BMD T-score at the lumbar spine, total hip, or femoral neck < -1.0 or a history of an osteoporotic fracture.) All men received calcium (at least 1,000 mg) and vitamin D (at least 400 IU) supplementation daily.

CORORA significantly increased BMD at all clinical sites measured, relative to treatment with placebo at 3 years: 7.9% at the lumbar spine, 5.7% at the total hip, 4.9% at the femoral neck, 6.9% at the hip trochanter, 6.9% at the distal 1/3 radius and 4.7% at the total body (all $p < 0.0001$). In a prospectively planned exploratory analysis, significant increases in BMD were observed at the lumbar spine, total hip, femoral neck and the hip trochanter 1 month after the initial dose.

CORORA demonstrated a significant relative risk reduction of new vertebral fractures: 85% (1.6% absolute risk reduction) at 1 year, 69% (2.2% absolute risk reduction) at 2 years and 62% (2.4% absolute risk reduction) at 3 years (all $p < 0.01$).

Clinical efficacy and safety in patients with bone loss associated with adjuvant aromatase inhibitor therapy

Efficacy and safety of CORORA once every 6 months for 2 years were investigated in women with non-metastatic breast cancer (252 women aged 35-84 years) and baseline BMD T-scores between -1.0 to -2.5 at the lumbar spine, total hip or femoral neck. All 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, fracture efficacy was not evaluated. CORORA significantly increased BMD at all clinical sites measured, relative to treatment with placebo at 2 years: 7.6% at lumbar spine, 4.7% at total hip, 3.6% at femoral neck, 5.9% at hip trochanter, 6.1% at distal 1/3 radius and 4.2% at total body (all $p < 0.0001$).

4.4 Pre-Clinical Safety Data

In single and repeated dose toxicity studies in cynomolgus monkeys, denosumab doses resulting in 100 to 150 times greater systemic exposure than the recommended human dose had no impact on cardiovascular physiology, male or female fertility, or produced specific target organ toxicity.

Standard tests to investigate the genotoxicity potential of denosumab have not been evaluated, since such tests are not relevant for this molecule. However, due to its character it is unlikely that denosumab has any potential for genotoxicity.

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

In pre-clinical studies conducted in knockout mice lacking RANK or RANKL, impairment of lymph node formation was observed in the foetus. An absence of lactation due to inhibition of mammary gland maturation (lobulo-alveolar gland development during pregnancy) was also observed in knockout mice lacking RANK or RANKL.

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. A no observed adverse effect level for reproductive effects was not established. Following a 6 month period after birth, bone related changes showed recovery and there was no effect on tooth eruption. However, the effects on lymph nodes and tooth malalignment persisted, and minimal to moderate mineralisation in multiple tissues was seen in one animal (relation to treatment uncertain). There was no evidence of maternal harm prior to labour; adverse maternal effects occurred infrequently during labour. Maternal mammary gland development was normal.

In pre-clinical bone quality studies in monkeys on long-term denosumab treatment, decreases in bone turnover were associated with improvement in bone strength and normal bone histology. Calcium levels were transiently decreased and parathyroid hormone levels transiently increased in ovariectomised monkeys treated with denosumab.

In male mice genetically engineered to express huRANKL (knock-in mice), which were subjected to a transcortical fracture, denosumab delayed the removal of cartilage and remodelling of the fracture callus compared to control, but biomechanical strength was not adversely affected.

Knockout mice (see Pregnancy and Lactation) lacking RANK or RANKL exhibited decreased body weight, reduced bone growth and lack of tooth eruption. In neonatal rats, inhibition of RANKL (target of denosumab therapy) with high doses of a construct of osteoprotegerin bound to Fc (OPG-Fc) was associated with inhibition of bone growth and tooth eruption. These changes were partially reversible in this model when dosing with RANKL inhibitors was discontinued. Adolescent primates dosed with denosumab at 27 and 150 times (10 and 50 mg/kg dose) the clinical exposure had abnormal growth plates. Therefore, treatment with denosumab may impair bone growth in children with open growth plates and may inhibit eruption of dentition.

5. PHARMACEUTICAL PARTICULARS

5.1 List of Excipients

Glacial acetic acid*,
Sodium hydroxide (for pH adjustment)*
Sorbitol
Polysorbate 20
Water for Injection.
*Acetate buffer is formed by mixing acetic acid with sodium hydroxide.

5.2 Incompatibilities

In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products.

5.3 Shelf Life

36 months.

5.4 Special Precautions for Storage

Store in a refrigerator (2°C – 8°C).

Do not freeze.

Keep the pre-filled syringe in the outer carton in order to protect from direct light.

Do not shake.

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

5.5 Nature and Contents of Container

CORORA is a sterile and preservative-free product.

Syringe

Single use pre-filled syringe with stainless steel 27 gauge needle.

Pack size of one, presented in blistered (pre-filled syringe with a needle guard).

5.6 Instructions for Use/Handling

Before administration, the CORORA solution should be inspected for particulate matter and discolouration. The solution should not be used if cloudy or discoloured.

Do not shake.

To avoid discomfort at the site of injection, allow the pre-filled syringe to reach room temperature (up to 25°C) before injecting and inject slowly. Inject the entire contents of the pre-filled syringe. Dispose of any medicinal product remaining in the pre-filled syringe. Instruction for self-administration by subcutaneous injection is included in the package leaflet.

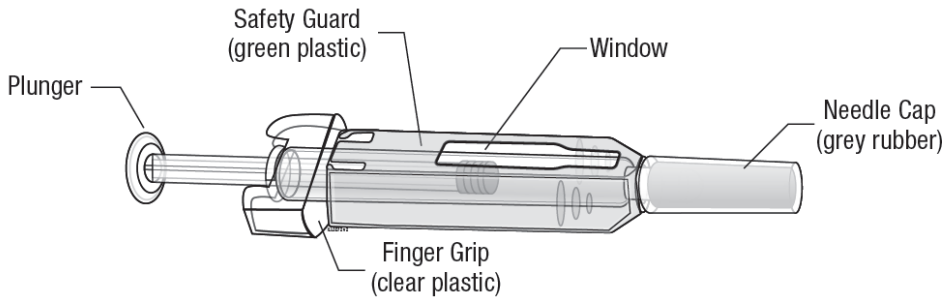
Any unused product or waste material should be disposed of in accordance with local requirements.

Not all presentations are available in every country.

INSTRUCTIONS FOR INJECTING WITH THE CORORA PRE-FILLED SYRINGE WITH A MANUAL NEEDLE GUARD

IMPORTANT: In order to minimize accidental needlesticks, the CORORA single use pre-filled syringe will have a green safety guard; manually activate the safety guard after the injection is given.

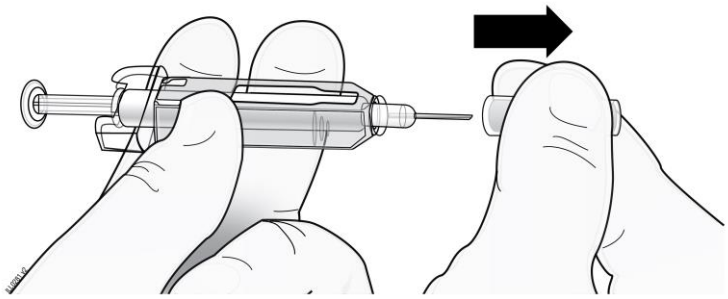
DO NOT slide the green safety guard forward over the needle before administering the injection; it will lock in place and prevent injection.



Activate the green safety guard (slide over the needle) after the injection.

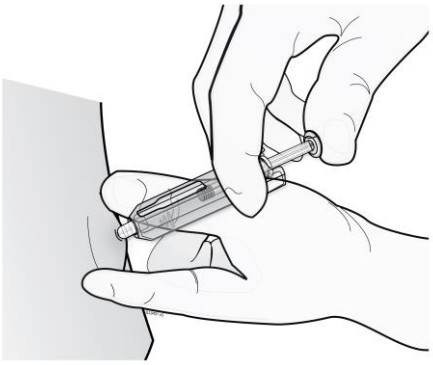
Step 1: Remove Grey Needle Cap

Remove needle cap.



Step 2: Administer Injection

Insert needle and inject all the liquid.

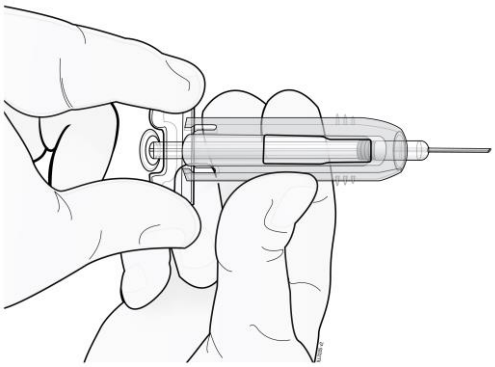


DO NOT put grey needle cap back on needle.

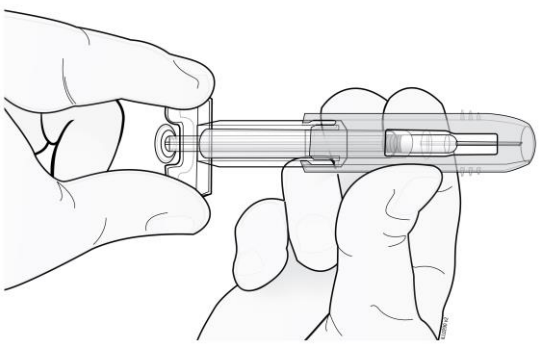
Step 3: Immediately Slide Green Safety Guard Over Needle

With the **needle pointing away from you…**
Hold the pre-filled syringe by the clear plastic finger grip with one hand. Then, with the other hand, grasp the green safety guard by its base and gently slide it towards the needle until the green safety guard locks securely in place and/or you hear a "click". **DO NOT** grip the green safety guard too firmly – it will move easily if you hold and slide it gently.

Hold clear finger grip.



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



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

HARUS DENGAN RESEP DOKTER

Pada proses pembuatannya bersinggungan dengan bahan bersumber babi

Box, 1 pre-filled syringe @ 60 mg/mL Reg No. XXXXXXXXXXXXXXX

Manufactured by:
Amgen Manufacturing Limited
State Road 31, Km 24.6,
Juncos, Puerto Rico 00777, USA

Registered by:
PT. Tunggal Idaman Abdi
Jl. Jend. Ahmad Yani No. 7
Jakarta 13230, Indonesia

Date of revision: June 2023

Version No.: IDPROPI05

AMGEN®

Informasi Produk untuk Pasien

CORORA® 60 mg Larutan untuk injeksi
denosumab

Baca isi leaflet ini dengan seksama sebelum Anda mulai menggunakan obat ini karena leaflet ini mengandung informasi yang penting bagi Anda.
- Simpan leaflet ini. Anda mungkin perlu membacanya lagi.
- Jika Anda memiliki pertanyaan lebih lanjut, tanyakan kepada dokter atau apoteker Anda.
- Obat ini diresepkan hanya untuk Anda. Jangan diberikan kepada orang lain. Hal tersebut dapat membahayakan orang tersebut walaupun gejala yang ditimbulkan sama dengan Anda.
- Jika Anda mengalami efek samping, bicarakan dengan dokter atau apoteker Anda. Termasuk efek samping yang mungkin tidak tercantum dalam leaflet ini (lihat bagian 4).

Apa saja yang ada pada leaflet ini

1. Apakah CORORA itu dan apa kegunaannya
2. Apa yang perlu Anda ketahui sebelum Anda menggunakan CORORA
3. Bagaimana cara penggunaan CORORA
4. Kemungkinan efek samping
5. Bagaimana cara penyimpanan CORORA
6. Isi kemasan dan informasi lainnya

1. Apakah CORORA itu dan apa kegunaannya

Apakah CORORA dan bagaimana cara kerjanya

CORORA mengandung denosumab, protein (antibodi monoklonal) yang menghambat kerja protein lain, untuk mengobati pengeroposan tulang dan osteoporosis. Perawatan dengan CORORA membuat tulang lebih kuat dan kecil kemungkinannya untuk patah.

Tulang merupakan jaringan hidup dan diperbarui sepanjang waktu. Estrogen membantu menjaga kesehatan tulang. Setelah menopause, kadar estrogen menurun yang dapat menyebabkan tulang menjadi tipis dan rapuh. Hal ini dapat menyebabkan kondisi yang disebut osteoporosis. Banyak penderita osteoporosis yang tidak menunjukkan gejala, namun tetap berisiko mengalami patah tulang, terutama pada tulang belakang, pinggul, dan pergelangan tangan.

Operasi atau obat-obatan yang menghentikan produksi estrogen atau testosteron yang digunakan untuk mengobati pasien dengan kanker payudara atau prostat juga dapat menyebabkan pengeroposan tulang. Tulang menjadi lebih lemah dan mudah patah.

Apa kegunaan CORORA

Osteoporosis pascamenopause
Pengobatan wanita pascamenopause dengan osteoporosis dengan risiko tinggi patah tulang, didefinisikan sebagai riwayat patah tulang osteoporosis, atau beberapa faktor risiko patah tulang; atau pasien yang gagal atau tidak toleran terhadap terapi osteoporosis lain yang tersedia, dan T-score Lumbar Spine, femur atau radius ≤ -2,5.

Pengeroposan Tulang pada Pasien yang Menjalani Ablasi Hormon untuk Kanker Prostat
CORORA diindikasikan sebagai pengobatan remodeling tulang pada pria yang berisiko tinggi untuk patah tulang setelah menerima terapi deprivasi androgen untuk kanker prostat non-metastasis. Pada pasien ini CORORA juga mengurangi kejadian patah tulang belakang.

Tanyakan kepada dokter Anda jika Anda memiliki pertanyaan tentang mengapa obat ini diresepkan untuk Anda.

2. Apa yang perlu Anda ketahui sebelum Anda menggunakan CORORA

Jangan menggunakan CORORA

- jika Anda memiliki kadar kalsium rendah dalam darah (hipokalsemia).
- jika Anda alergi terhadap denosumab atau bahan lain dari obat ini (tercantum di bagian 6).

Peringatan dan perhatian

Bicaralah dengan dokter atau apoteker Anda sebelum menggunakan CORORA.

Saat dirawat dengan CORORA, Anda mungkin mengalami infeksi kulit dengan gejala seperti area kulit yang bengkak dan merah, paling sering di kaki bagian bawah, yang terasa panas dan nyeri (selulitis), dan mungkin dengan gejala demam. Harap beri tahu dokter Anda segera jika Anda mengalami gejala-gejala ini.

Anda juga harus mengonsumsi suplemen kalsium dan vitamin D saat menjalani perawatan dengan CORORA. Dokter Anda akan membicarakan hal ini dengan Anda.

Anda mungkin memiliki kadar kalsium yang rendah dalam darah Anda saat menerima CORORA. Harap beri tahu dokter Anda segera jika Anda melihat salah satu dari gejala berikut: kejang, kedutan, atau kram pada otot Anda, dan/atau mati rasa atau kesemutan

di jari tangan, jari kaki, atau di sekitar mulut Anda, dan/atau kejang, kebingungan, atau kehilangan kesadaran.

Beri tahu dokter Anda jika Anda pernah atau pernah memiliki masalah ginjal yang parah, gagal ginjal atau membutuhkan dialisis atau sedang mengonsumsi obat-obatan yang disebut glukokortikoid (seperti prednisolon atau deksametason), yang dapat meningkatkan risiko Anda mendapatkan kalsium darah rendah jika Anda tidak mengonsumsi kalsium suplemen.

Masalah dengan mulut, gigi, atau rahang Anda

Efek samping yang disebut osteonekrosis rahang (ONJ) (kerusakan tulang di rahang) jarang dilaporkan (dapat mempengaruhi hingga 1 dari 1.000 orang) pada pasien yang menerima CORORA untuk osteoporosis. Risiko ONJ meningkat pada pasien yang dirawat dalam waktu lama (dapat mempengaruhi hingga 1 dari 200 orang jika dirawat selama 10 tahun). ONJ juga dapat terjadi setelah menghentikan pengobatan. Penting untuk mencoba mencegah berkembangnya ONJ karena ini mungkin merupakan kondisi yang menyakitkan yang sulit untuk diobati. Untuk mengurangi risiko pengembangan ONJ, lakukan tindakan pencegahan berikut:

Sebelum menerima perawatan, beri tahu dokter atau perawat Anda (profesional perawatan kesehatan) jika Anda:

- memiliki masalah dengan mulut atau gigi Anda seperti kesehatan gigi yang buruk, penyakit gusi, atau pencabutan gigi yang direncanakan.
- tidak mendapatkan perawatan gigi rutin atau sudah lama tidak melakukan pemeriksaan gigi.
- adalah perokok (karena hal ini dapat meningkatkan risiko masalah gigi).
- sebelumnya telah diobati dengan bifosfonat (digunakan untuk mengobati atau mencegah gangguan tulang).
- sedang mengonsumsi obat-obatan yang disebut kortikosteroid (seperti prednisolon atau deksametason).
- Memiliki penyakit kanker.

Dokter Anda mungkin meminta Anda untuk menjalani pemeriksaan gigi sebelum memulai perawatan dengan CORORA.

Saat dirawat, Anda harus menjaga kebersihan mulut dan menjalani pemeriksaan gigi rutin. Jika Anda memakai gigi palsu, Anda harus memastikannya pas. Jika Anda sedang menjalani perawatan gigi atau akan menjalani operasi gigi (misalnya pencabutan gigi),

beri tahu dokter Anda tentang perawatan gigi Anda dan beri tahu dokter gigi Anda bahwa Anda sedang dirawat dengan CORORA.

Hubungi dokter dan dokter gigi Anda segera jika Anda mengalami masalah dengan mulut atau gigi Anda seperti gigi goyang, nyeri atau bengkak, atau luka yang tidak sembuh-sembuh atau keluar cairan, karena ini bisa menjadi tanda ONJ.

Patah tulang paha yang tidak biasa
Beberapa orang mengalami patah tulang yang tidak biasa di tulang paha mereka saat dirawat dengan CORORA. Hubungi dokter Anda jika Anda mengalami nyeri baru atau tidak biasa di pinggul, selangkangan, atau paha Anda.

Anak-anak dan remaja

CORORA tidak dianjurkan untuk anak-anak dan remaja di bawah usia 18 tahun. Penggunaan CORORA pada anak-anak dan remaja belum diteliti.

Obat – obatan lain dan CORORA

Beritahu dokter atau apoteker Anda jika Anda sedang mengonsumsi, baru saja mengonsumsi atau mungkin sedang mengonsumsi obat lain. Sangat penting bagi Anda untuk memberitahu dokter Anda jika Anda sedang dirawat dengan obat lain yang mengandung denosumab.

Anda tidak boleh mengonsumsi CORORA bersamaan dengan obat lain yang mengandung denosumab.

Kehamilan dan menyusui

CORORA belum diuji pada wanita hamil. Penting untuk memberitahu dokter Anda jika Anda sedang hamil; kemungkinan hamil; atau berencana untuk hamil. CORORA tidak dianjurkan untuk digunakan jika Anda sedang hamil. Wanita yang berpotensi melahirkan anak harus menggunakan metode kontrasepsi yang efektif saat dirawat dengan CORORA dan setidaknya 5 bulan setelah menghentikan pengobatan dengan CORORA.

Jika Anda hamil selama pengobatan dengan CORORA atau kurang dari 5 bulan setelah menghentikan pengobatan dengan CORORA, mohon informasikan kepada dokter Anda.

Tidak diketahui apakah CORORA diekskresikan dalam ASI. Penting untuk memberitahu dokter Anda jika Anda sedang menyusui atau berencana untuk melakukannya. Dokter Anda kemudian akan membantu Anda memutuskan apakah Anda akan berhenti

menyusui, atau berhenti mengonsumsi CORORA, dengan mempertimbangkan manfaat menyusui bagi bayi dan manfaat CORORA bagi ibu.

Jika Anda menyusui selama perawatan CORORA, harap beritahu dokter Anda.

Mintalah saran dari dokter atau apoteker Anda sebelum minum obat apa pun.

Mengemudi dan menjalankan mesin

CORORA tidak memiliki atau dapat diabaikan pengaruhnya pada kemampuan mengemudi dan menggunakan mesin.

CORORA mengandung sorbitol

Obat ini mengandung 47 mg sorbitol dalam setiap mL larutan.

CORORA mengandung natrium

Obat ini mengandung kurang dari 1 mmol natrium (23 mg) per 60 mg, dengan kata lain dapat dikatakan 'bebas natrium'.

3. Bagaimana cara penggunaan CORORA

Dosis yang dianjurkan adalah satu pre-filled syringe 60 mg diberikan setiap 6 bulan sekali, dalam suntikan tunggal di bawah kulit (subkutan). Tempat terbaik untuk menyuntik adalah bagian atas paha dan perut. Pengasuh Anda juga dapat menyuntikkannya pada area luar lengan atas Anda. Silakan berkonsultasi dengan dokter Anda untuk tanggal injeksi berikutnya. Setiap kemasan CORORA berisi kartu pengingat, yang dapat dikeluarkan dari karton dan digunakan untuk mencatat tanggal injeksi berikutnya.

Anda juga harus mengonsumsi suplemen kalsium dan vitamin D saat menjalani perawatan dengan CORORA. Dokter Anda akan membicarakan hal ini dengan Anda.

Dokter Anda akan memutuskan akan lebih baik, Anda atau pengasuh Anda yang akan menyuntikkan CORORA. Dokter atau penyedia layanan kesehatan Anda akan menunjukkan kepada Anda atau pengasuh Anda cara menggunakan CORORA.

Jangan dikocok.

Jika dosis CORORA terlewat

Jika dosis CORORA terlewatkan, injeksi harus diberikan sesegera mungkin. Setelah itu, suntikan harus dijadwalkan setiap 6 bulan sejak tanggal suntikan terakhir.

Jika Anda menghentikan pengobatan dengan CORORA

Untuk mendapatkan manfaat maksimal dari perawatan Anda dalam mengurangi risiko patah tulang, penting untuk menggunakan CORORA selama dokter Anda meresepkannya untuk Anda. Jangan menghentikan pengobatan Anda tanpa menghubungi dokter Anda.

4. Kemungkinan efek samping

Seperti semua obat-obatan, obat ini dapat menyebabkan efek samping, meskipun tidak semua orang mendapatkannya.

Jarang, pasien yang menerima CORORA dapat mengalami infeksi kulit (terutama selulitis). **Harap beritahu dokter Anda segera jika Anda** mengalami gejala-gejala ini saat menjalani pengobatan CORORA: bengkak, area kulit merah, paling sering di kaki bagian bawah, yang terasa panas dan nyeri, dan mungkin dengan gejala demam.

Jarang terjadi, pasien yang menerima CORORA dapat mengalami rasa sakit di mulut dan/atau rahang, pembengkakan atau luka yang tidak sembuh-sembuh di mulut atau rahang, keluar cairan, mati rasa atau rasa berat di rahang, atau gigi goyang. Ini bisa menjadi tanda kerusakan tulang di rahang (osteonekrosis). **Beritahu dokter dan dokter gigi Anda segera** jika Anda mengalami gejala seperti itu saat dirawat dengan CORORA atau setelah menghentikan perawatan.

Jarang terjadi, pasien yang menerima CORORA mungkin memiliki kadar kalsium yang rendah dalam darah (hipokalsemia). Gejalanya meliputi kejang, kedutan, atau kram pada otot Anda, dan/atau mati rasa atau kesemutan di jari tangan, jari kaki atau di sekitar mulut dan/atau kejang, kebingungan, atau kehilangan kesadaran. Jika salah satu dari gejala tersebut Anda alami, **beritahu dokter Anda segera**. Kalsium yang rendah dalam darah juga dapat menyebabkan perubahan irama jantung yang disebut pemanjangan QT yang terlihat dengan elektrokardiogram (EKG).

Fraktur tulang paha yang jarang terjadi dapat terjadi pada pasien yang menerima CORORA. **Hubungi dokter Anda** jika Anda mengalami nyeri baru atau tidak biasa di pinggul, selangkangan atau paha karena ini mungkin merupakan indikasi awal kemungkinan patah tulang paha.

Jarang terjadi, reaksi alergi dapat terjadi pada pasien yang menerima CORORA. Gejalanya meliputi pembengkakan pada wajah, bibir, lidah, tenggorokan atau bagian tubuh lainnya; ruam, gatal-gatal atau gatal-gatal pada kulit, mengi atau kesulitan bernapas. **Beritahu dokter Anda** jika Anda mengalami gejala-gejala ini saat dirawat dengan CORORA.

Efek Samping yang sangat umum (dapat mempengaruhi lebih dari 1 dari 10 orang):
- nyeri tulang, sendi, dan/atau otot yang terkadang parah,
- nyeri lengan atau kaki (nyeri yang ekstrim).

Efek Samping yang umum (dapat mempengaruhi hingga 1 dari 10 orang):
- buang air kecil yang menyakitkan, sering buang air kecil, darah dalam urin, ketidakmampuan untuk menahan urin,
- infeksi saluran pernapasan atas,
- rasa sakit, kesemutan atau mati rasa yang bergerak ke bawah kaki Anda (linu panggul),
- konstipasi,
- ketidaknyamanan perut,
- ruam,
- kulit gatal, kemerahan dan/atau kering (eksim),
- rambut rontok (alopecia).

Efek samping yang tidak umum (dapat mempengaruhi hingga 1 dari 100 orang):
- demam, muntah dan rasa tidak nyaman atau sakit di perut (divertikulitis),
- infeksi telinga,
- ruam yang mungkin terjadi pada kulit atau luka di mulut (erupsi obat lichenoid).

Efek samping yang sangat jarang (dapat mempengaruhi hingga 1 dari 10000 orang):
- reaksi alergi yang dapat merusak pembuluh darah terutama di kulit (misalnya, bintik-bintik ungu atau merah kecoklatan, gatal-gatal atau luka kulit) (vasculitis hipersensitivitas).

Pelaporan efek samping

Jika Anda mengalami efek samping, bicarakan dengan dokter atau apoteker Anda. Hal Ini termasuk efek samping yang mungkin tidak tercantum dalam leaflet ini. Dengan melaporkan efek samping Anda dapat membantu menyediakan informasi keamanan obat ini.

5. Bagaimana cara penyimpanan CORORA

Jauhkan obat ini dari jangkauan dan penglihatan anak-anak.

Jangan menggunakan obat ini setelah tanggal kadaluarsa yang tertera pada dus dan label setelah EXP.

Simpan pada lemari pendingin (2°C - 8°C).
Jangan dibekukan.
Simpan pre-filled syringe di dalam dus agar terlindung dari cahaya langsung.
Jangan dikocok.
Jika dikeluarkan dari lemari pendingin, CORORA harus disimpan pada suhu ruang yang terkontrol (Simpan pada suhu dibawah 25°C atau 30°C di dalam dus asli dan harus digunakan dalam waktu 30 hari).

Jangan membuang obat-obatan melalui air limbah atau limbah rumah tangga. Tanyakan apoteker Anda bagaimana membuang obat-obatan yang tidak lagi Anda gunakan. Langkah-langkah ini akan membantu melindungi lingkungan.

6. Isi kemasan dan informasi lainnya

Apakah kandungan CORORA

- Zat aktifnya adalah denosumab. Setiap 1 mL pre-filled syringe mengandung 60 mg denosumab (60 mg/mL).
- Bahan-bahan lainnya adalah asam asetat glasial, natrium hidroksida, sorbitol, polisorbat 20, dan air untuk injeksi.

Seperti apa CORORA dan isi kemasannya

CORORA adalah larutan injeksi jernih dan tidak berwarna hingga sedikit kuning tersedia dalam kemasan pre-filled syringe siap pakai.

Diproduksi oleh:
Amgen Manufacturing Limited
State Road 31, Km 24.6,
Juncos, Puerto Rico 00777, USA

Diregistrasi oleh:
PT. Tunggal Idaman Abdi
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Nomor Izin Edar:
XXXXXXXXXXXXXX

Leaflet direvisi terakhir pada Jun 2023.

HARUS DENGAN RESEP DOKTER

Pada proses pembuatannya bersinggungan dengan bahan bersumber babi

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DISETUJUI OLEH BPOM TANGGAL 24 APRIL 2024 REG ID : EREG100193VR12300100