RESYNIV®

Denosumab

60 mg/mL Solution for Injection

1. NAME OF THE MEDICINAL PRODUCT

RESYNIV® 60 mg solution for injection in pre-filled syringe

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

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

Denosumab is a human monoclonal IgG2 antibody produced in a mammalian cell line (Chinese hamster ovary cells) by recombinant DNA technology.

Excipient with known effect
This medicine contains 46 mg sorbitol in each mL of solution.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for injection (injection).

Colourless to yellowish liquid.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Postmenopausal Osteoporosis

Treatment of osteoporosis in postmenopausal women at high risk for fractures, 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

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

DISETUJUI OLEH BPOM : 23 JULI 2026 ID : EREG10034612400183

4.2 Posology and method of administration

Posology

The recommended dose is 60 mg RESYNIV® administered as a single subcutaneous injection once every 6 months into the thigh, abdomen or upper arm.

Patients must be adequately supplemented with calcium 1,000 mg daily and at least 400 IU vitamin D daily whilst undergoing treatment (see section 4.4).

Patients treated with RESYNIV® should be given the package leaflet and the patient reminder card.

Populations

Elderly (age ≥ 65)
No dose adjustment is required in elderly patients.

Renal impairment
No dose adjustment is required in patients with renal impairment (see section 4.4 for recommendations relating to monitoring of calcium).

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 denosumab have not been studied in patients with hepatic impairment (see section 5.2).

Paediatric population
RESYNIV is should not be used in children aged < 18 years because of safety concerns of serious hypercalcaemia, and potential inhibition of bone growth and lack of tooth eruption (see Warnings and Precautions and Pre-Clinical Safety Data).

Method of administration

For subcutaneous use.

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

The instructions for use, handling and disposal are given in section 6.6.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

Hypocalcaemia (see section 4.4).

4.4 Special warnings and precautions for use

Traceability

In order to improve the traceability of biological medicinal products, the name and the batch number of the administered product should be clearly recorded.

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 section 4.8 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 section 4.8), 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 section 4.8). 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 denosumab for osteoporosis (see section 4.8).

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.

DISETUJUI OLEH BPOM : 23 JULI 2026 ID : EREG10034612400183

- 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 section 4.8). Atypical femoral fractures may occur with little or no trauma in the subtrochanteric and diaphysealregions 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 benefitrisk 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 (see section 4.2).

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

Hypercalcaemia in paediatric patients
RESYNIV® should not be used in paediatric patients (age < 18). Serious hypercalcaemia has been reported. Some clinical trial cases were complicated by acute renal injury.

Osteonecrosis of the external auditory canal
Osteonecrosis of the external auditory canal has been reported with denosumab. Possible risk factors for osteonecrosis of the external auditory canal include steroid use and chemotherapy and/or local risk factors such as infection or trauma. The possibility of osteonecrosis of the external auditory canal should be considered in patients receiving denosumab who present with ear symptoms including chronic ear infections.

DISETUJUI OLEH BPOM : 23 JULI 2026 ID : EREG10034612400183

Excipients
This medicine contains 46 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'.

4. 5 Interaction with other medicinal products and other forms of interaction

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).

4.6 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 section 5.3).

RESYNIV 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 denosumab. Any effects of denosumab 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 section 5.1) during pregnancy may interfere with maturation of the mammary gland leading to impaired lactation post-partum (see section 5.3). A decision on whether to abstain from breast-feeding or to abstain from therapy with RESYNIV should be made, taking into account the benefit of breast-feeding to the newborn/infant and the benefit of denosumab therapy to the woman.

Fertility

No data are available on the effect of denosumab on human fertility. Animal studies do not indicate direct or indirect harmful effects with respect to fertility (see section 5.3).

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

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 sections 4.4 and 4.8 - 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 Common Uncommon Uncommon Uncommon	Urinary tract infection Upper respiratory tract infection Diverticulitis[1] Cellulitis[1] Ear infection
Immune system disorders	Rare Rare	Drug hypersensitivity[1] Anaphylactic reaction[1]
Metabolism and nutrition disorder	Rare	Hypocalcaemia[1]
Nervous system disorders	Common	Sciatica
Gastrointestinal disorders	Common Common	Constipation Abdominal discomfort
Skin and subcutaneous tissue disorders	Common Common Common Uncommon Very rare Not known	Rash Eczema Alopecia Lichenoid drug eruptions[1] Hypersensitivity vasculitis Drug reaction with eosinophilia and systemic symptoms (DRESS) syndrome
Musculoskeletal and connective tissue disorders	Very common Very common Rare Rare Not Known	Pain in extremity Musculoskeletal pain[1] Osteonecrosis of the jaw[1] Atypical femoral fractures[1] Osteonecrosis of the external auditory canal[2]

[1]See section Description of selected adverse reactions.
[2]See section 4.4.

DISETUJUI OLEH BPOM : 23 JULI 2026 ID : EREG10034612400183

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 denosumab 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 section 4.4). 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 denosumab [1.5%, 59 out of 4,050]); in men with osteoporosis (placebo [0.8%, 1 out of 120] versus denosumab [0%, 0 out of 120]); in breast or prostate cancer patients receiving hormone ablation (placebo [1.7%, 14 out of 845] versus denosumab [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 denosumab. 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 denosumab (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 section 4.4). 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.

The risk of ONJ has also been assessed in a retrospective cohort study among 76,192 postmenopausal women newly initiating treatment with CORORA. The incidence of ONJ was 0.32% (95% confidence interval [CI]: 0.26, 0.39) among patients using denosumab up to 3 years and 0.51% (95% CI: 0.39, 0.65) among patients using denosumab up to 5 years of follow-up.

Atypical fractures of the femur
In the osteoporosis clinical trial program, atypical femoral fractures were reported rarely in patients treated with denosumab (see section 4.4).

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,

DISETUJUI OLEH BPOM : 23 JULI 2026 ID : EREG10034612400183

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 denosumab.

Musculoskeletal pain
Musculoskeletal pain, including severe cases, has been reported in patients receiving denosumab 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

Paediatric population
Denosumab should not be used in paediatric patients (age < 18). Serious hypercalcaemia has been reported. Some clinical trial cases were complicated by acute renal injury.

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 section 4.4)

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 via .email to pv.indonesia@abbott.com and/or via:

Pusat Farmakovigilans/MESO Nasional
Direktorat Pengawasan Keamanan, Mutu, dan Ekspor Impor Obat, Narkotika, Psikotropika, Prekursor, dan Zat Adiktif
Badan Pengawas Obat dan Makanan (BPOM) RI
Jl. Percetakan Negara No.23, Jakarta Pusat, 10560, Indonesia
Email: pv-center@pom.go.id
Situs web: https://e-meso.pom.go.id

4.9 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.

5. PHARMACOLOGIC PROPERTIES

5.1 Pharmacodynamic Properties

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

RESYNIV® is a biosimilar medicinal product. Detailed information is available on the website of the European Medicines Agency http://www.ema.europa.eu.

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

[Study performed by originator Prolia/Corora]

Denosumab 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 denosumab'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.

5.2 Pharmacokinetic Properties

[Study performed by originator Prolia/Corora]

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.

DISETUJUI OLEH BPOM : 23 JULI 2026 ID : EREG10034612400183

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.

5.3 Clinical Studies

[Study performed by originator Prolia/Corora]

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

DISETUJUI OLEH BPOM : 23 JULI 2026 ID : EREG10034612400183

Table 2. The effect of denosumab 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	Denosumab 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
Denosumab 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 denosumab group at 3 years.

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

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

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

	Proportion of women with fracture (%)[+]		Absolute risk reduction (%) (95% CI)	Relative risk reduction (%) (95% Cl)
	Placebo n = 3,906	Denosumab 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)**
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, denosumab 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 denosumab over 3 years were consistent regardless of the 10-year baseline fracture risk.

Effect on bone mineral density
Denosumab significantly increased BMD at all clinical sites measured, versus 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,

DISETUJUI OLEH BPOM : 23 JULI 2026 ID : EREG10034612400183

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 denosumab, 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 denosumab is required to maintain the effect of the medicinal product. Re-initiation of denosumab resulted in gains in BMD similar to those when denosumab was first administered.

Open-label extension study in the treatment of postmenopausal osteoporosis
A total of 4,550 women (2,343 denosumab & 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 denosumab. All women in the extension study were to receive denosumab 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 denosumab 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 denosumab. 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 denosumab. 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 denosumab, 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 denosumab 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.

Denosumab 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.

Denosumab 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 denosumab 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. Denosumab 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 $p < 0.0001$).

[Study performed by Mabxience on Resyniv]

Phase III study MB09-C-01-19

The primary objective of the phase III study MB09-C-01-19 was to compare the efficacy of MB09 and EU-Prolia® (referred to as Prolia® along this overview) in women with postmenopausal osteoporosis. However, as secondary objective, the study included the comparison of the following PK endpoints, during the Main Treatment period the AUC from time zero to 6 months (AUC0-6 months), Cmax following the first dose, and trough concentrations (Ctrough) at Month 6 and Month 12 were evaluated. During the Transition Period, AUC0-6 months and Cmax following the third dose at Month 12 and the Ctrough of serum denosumab at Transition Period Month 6 were evaluated.

The full title of the study is “A randomised, double-blind, parallel, multicentre, multinational study to compare the efficacy, pharmacokinetics, pharmacodynamics, safety and immunogenicity of MB09 (proposed denosumab biosimilar) versus Prolia® (EU-sourced) in postmenopausal women with osteoporosis (SIMBA Study)”

Eligible postmenopausal women with osteoporosis received three single doses of study treatment (one subcutaneous injection [one 60 mg PFS at 60 mg/mL]): the first and second dose during the Main Treatment Period on Day 1 and at Month 6; and the third dose during the Transition Period at Month 12, after all efficacy and safety assessments had been performed. Following this treatment schedule, patients were randomised to:

• MB09-MB09 arm (Arm 1): treatment with MB09 on Day 1, at Month 6 and at Month 12.

• Prolia-MB09 arm (Arm 2): treatment with EU-Prolia® on Day 1 and at Month 6, and MB09 at Month 12.

• Prolia®-Prolia® arm (Arm 3): treatment with EU-Prolia® on Day 1, at Month 6 and at Month 12.

The maximum study duration for a subject was approximately 19 months: 28 days for screening, the Main Treatment Period of 12 months, and the Transition Period of 6 months.

The study was conducted in 62 sites in Europe and Latin America. In Europe, the study was conducted in Bulgaria, Estonia, Georgia, Hungary, Latvia, Poland, and Serbia. In Latin America, the study was conducted in Mexico.

Patient population, stratification and inclusion/exclusion criteria:

The main inclusion criteria included postmenopausal status (defined as at least 12 consecutive months of amenorrhea prior to date of screening with a follicle-stimulating hormone level of ≥30 mIU/mL or surgical menopause [bilateral oophorectomy with or without hysterectomy] ≥12 months prior to the screening visit when follicle-stimulating hormone is not required), age ≥55 and ≤80 years at screening, body weight ≥50 kg and ≤99.9 kg, a body mass index (BMI) of ≤30 kg/m2 at screening, absolute BMD consistent with Tscore ≤ -2.5 and ≥ -4 at the lumbar spine or total hip as measured by dual-energy X-ray absorptiometry (DXA) during the Screening Period, at least two intact, nonfractured vertebrae in the L1 to L4 region and at least one hip joint is evaluable by DXA, and an adequate organ function.

Exclusion criteria included previous exposure to denosumab or any other monoclonal antibody or fusion protein containing IgG or other biologic agent targeting IgG, history and/or presence of one severe or more than two moderate vertebral fractures or hip fracture, recent long bone fracture (within 6 months), history and/or presence of bone metastases, bone disease, or metabolic disease other than osteoporosis, malignancy within the 5 years before enrolment (except cervical carcinoma in situ or basal cell carcinoma, which are not prohibitive), intravenous bisphosphonate, strontium or fluoride administered for osteoporosis within 5 years of screening, or oral bisphosphonates ≥12 months cumulative use prior to screening.

The randomisation was stratified by baseline BMD T-score at the lumbar spine (≤ -3.0 and > -3.0 standard deviation [SD]), BMI (<25 and ≥25 kg/m2), age at study entry (≥55 to <68 years versus ≥68 to ≤80 years) and prior bisphosphonate medication use at study entry (prior use of bisphosphonates versus no prior bisphosphonate use).

Efficacy endpoints

Primary efficacy endpoint

To demonstrate equivalent efficacy of MB09 to Prolia®, the percentage change from baseline (%CfB) in lumbar spine BMD after 52 weeks was compared. The choice of this primary endpoint was endorsed by the CHMP during the scientific advice procedure (EMA/CHMP/SAWP/25066/2020; clarification letter EMA/133427/2020).

The primary objective of study MB09-C-01-19 was to demonstrate equivalent efficacy of MB09 to Prolia® in postmenopausal women with osteoporosis in terms of difference in means in %CfB in lumbar spine BMD at Month 12.

At Month 12, the difference in LS means (95% CI) in %CfB in lumbar spine BMD between MB09 and Prolia® was entirely contained within the predefined margin of [-1.45, 1.45] for acceptance of equivalence, so MB09 can be considered therapeutically equivalent to Prolia®. The results of the sensitivity analysis using MMRM (after MI for the missing lumbar spine BMD values at Month 12) supported the main analysis. The equivalence conclusion was robust with equivalence limits still met when imputed %CfB values were worsened by 6 across both groups or in the MB09 group only.

DISETUJUI OLEH BPOM : 23 JULI 2026 ID : EREG10034612400183

Furthermore, a large magnitude of change (≥4.5) in imputed %CfB in lumbar spine BMD was required in MB09 and Prolia® in opposite directions to tip the results towards nonequivalence. Supplementary analysis using log transformed lumbar spine BMD as a ratio of baseline BMD showed that the geometric mean ratio (95% CI) of lumbar spine BMD between MB09 and Prolia® indicated a similar treatment effect of MB09 and Prolia® on lumbar spine BMD at Month 12.

Subgroup analysis by age at study entry, baseline lumbar spine BMD T-score, BMI, prior bisphosphonate use, region, body weight, or smoking status showed that the LS mean differences in %CfB in lumbar spine BMD between MB09 and Prolia® at Month 12 were small and consistent with the overall estimate, with the lower limit of 95% CI above -1.45 for most subgroups.

Supportive estimand 1b was defined as the difference in means (MB09-Prolia®) in the %CfB in lumbar spine BMD 12 months in postmenopausal women with osteoporosis treated with subcutaneous denosumab injections every 6 months, irrespective of whether subjects discontinued treatment for any reason, had errors or deviations in dosing, or took any prohibited therapies or other osteoporosis medications. Estimation was via multiple imputation and ANCOVA on FAS. Since the retrieved dropout rate was low, a treatment failure penalty was applied to the imputed values at Month 12 for those subjects who received only one dose of study treatment to center the distribution of each subject's %CfB values around their baseline level. The resulting difference in LS means which was also entirely contained within the predefined margin of [-1.45, 1.45] for acceptance of equivalence, supporting the conclusion that MB09 can be considered therapeutically equivalent to Prolia® irrespective of failed eligibility criteria and whether subjects discontinued treatment for any reason, had errors or deviations in dosing, or took any prohibited therapies or other osteoporosis medications. This equivalence was additionally supported by the tipping point sensitivity analysis of %CfB-TF in lumbar spine BMD and supplementary analyses using ANCOVA without MI.

The key secondary objectives of the study were to compare the efficacy of MB09 to Prolia® in terms of lumbar spine BMD at Month 6 and hip and femur neck BMD at Month 6 and Month 12. Results of the main analysis (MMRM in mFAS) of %CfB in BMD between MB09 and Prolia for estimands 2a to 4a (assuming that all women received two denosumab doses without any errors or deviations in dosing and without receipt of any prohibited therapies or other osteoporosis medications), showed that all the 95% CIs were within -1 to 1 providing evidence that MB09 was similar to Prolia®.

Supplementary analysis using log transformed lumbar spine BMD as a ratio of baseline BMD for estimand 2a showed that the geometric mean ratio (95% CI) of lumbar spine BMD between MB09 and Prolia® indicated a similar treatment effect of MB09 and Prolia® on lumbar spine BMD at Month 6.

The ANCOVA on FAS of %CfB in BMD estimated estimands 2b, 3b, and 4b irrespective of discontinuation of treatment for any reason, errors or deviation in dosing, and whether any prohibited therapies or other osteoporosis medications were taken; this included all subjects and data records irrespective of failed eligibility criteria, receipt of prohibited medications, or receipt of both doses. Results were similar to estimations of estimands 2a, 3a, and 4a, respectively and thus, supported the conclusion of equivalence of MB09 to Prolia® with all 95% CIs falling within -1 to 1.

Subgroup analyses by age at study entry, baseline lumbar spine BMD T-score, BMI, prior bisphosphonate use, region, body weight, or smoking status showed that the LS mean differences in %CfB in lumbar spine BMD between MB09 and Prolia® at Month 6 were small and consistent with the overall estimate.

Overall, MB09 was therapeutically equivalent to Prolia based on %CfB in lumbar spine BMD at Month 12. The treatment effects of MB09 on lumbar spine BMD at Month 6 and hip and femur neck BMD at Months 6 and 12 were also similar to Prolia®.

DISETUJUI OLEH BPOM : 23 JULI 2026 ID : EREG10034612400183

Pharmacokinetic Results:

Main Treatment Period

Following SC administration of MB09 and Prolia, mean serum denosumab concentrations were highest at Day 11 and declined slowly through Month 6 (Day 182). The mean serum denosumab concentrations versus time profiles were similar for both treatment groups. Following SC administration of MB09, the geometric mean Cmax was 5960 ng/mL and was similar to the geometric mean Cmax of Prolia (5700 ng/mL) in the Main Treatment Period.

The total serum exposure over the 6-month dosing interval (AUC0-6 months) for MB09 as geometric mean was 360,000 day*ng/mL and was similar to the geometric mean AUC0-6 months of denosumab following administration of Prolia (337,000 day*ng/mL). The 6-month and 12-month Ctrough for MB09 were similar to Prolia.

Following SC administration of MB09, systemic exposure (Cmax and AUC0-6 months) was equivalent to that observed following SC administration of Prolia with the 95% CI of the geometric LS mean ratios falling within the acceptance limits (80.00%, 125.00%) in all instances.

Transition/Safety Follow-up Period

Following SC administration of MB09 (MB09-MB09 arm) in the Transition Period, the geometric mean Cmax was 5840 ng/mL and was similar to the geometric mean Cmax of Prolia (Prolia-Prolia arm) (5630 ng/mL). The total serum exposure over the 6-month dosing interval (AUC0-6 months) for MB09 as geometric mean was 360,000 day*ng/mL and was similar to the geometric mean AUC0-6 months of denosumab following administration of Prolia (353,000 day*ng/mL). The 6-month Ctrough for MB09 was similar to Prolia.

Following SC administration of MB09 (Prolia-MB09 arm) in the Transition Period, the geometric mean Cmax was 5800 ng/mL and was similar to the geometric mean Cmax of Prolia (Prolia-Prolia arm) (5630 ng/mL). The total serum exposure over the 6-month dosing interval (AUC0-6 months) for MB09 as geometric mean was 350,000 day*ng/mL and was similar to the geometric mean AUC0-6 months of denosumab following administration of Prolia (353,000 day*ng/mL). The 6-month Ctrough for MB09 was similar to Prolia.

Following SC administration of MB09 in the Transition Period, systemic exposure (Cmax and AUC0-6 months) was equivalent to that observed following SC administration of Prolia irrespective of the treatment during the Main Treatment Period, with the 95% CIs of the geometric LS mean ratios falling within the acceptance limits (80.00%, 125.00%) in all instances.

Pharmacodynamic Results:

Main Treatment Period

Baseline levels of sCTX were comparable across both treatment groups. Profiles of sCTX and %CfB (%inhibition) of sCTX were comparable across both treatment groups. Following SC administration of MB09 or Prolia, sCTX concentrations decreased rapidly and remained suppressed for the remainder of the sampling period with mean %CfB values, representing %inhibition, ranging from 70.1% to 89.3% for MB09 and 70.5% to 89.5% for Prolia. The mean %CfB was 75.7% at Month 6 and 70.1% at Month 12 for MB09 and 75.3% at Month 6 and 70.5% at Month 12 for Prolia. Imax was 91.0% for MB09 and 91.5% for Prolia. AUEC0-6 months and AUIC0-6 months were also comparable for both the treatment groups with

DISETUJUI OLEH BPOM : 23 JULI 2026 ID : EREG10034612400183

the 95% CIs of the geometric LS mean ratios of the AUEC0-6 months and AUIC0-6 months falling within the acceptance limits (80.00%, 125.00%).

Transition/Safety Follow-up Period

Profiles of sCTX and %CfB (%inhibition) of sCTX were comparable across all treatment arms in the Transition Period. Following SC administration of MB09 or Prolia in the Transition Period, sCTX concentrations decreased rapidly and remained suppressed through Transition Period Month 3. Profiles for all treatment arms trended to return to Transition Period baseline levels at Month 6, however were still lower than baseline prior to the Main Treatment Period. Imax was 91.4% and 91.2% for MB09 (MB09 in the Main Treatment Period and Prolia in the Main Treatment Period, respectively) and 90.9% for Prolia (Prolia-Prolia arm). AUEC0-6 months and AUIC0-6 months were also comparable for all the treatment arms.

Safety Results:

Main Treatment Period

Safety results of the Main Treatment Period were summarised by MB09 (277 subjects) and Prolia (278 subjects) groups for comparison. The MB09 group included subjects from Arm 1 (MB09-MB09) and the Prolia group pooled subjects from Arm 2 (Prolia-MB09) and Arm 3 (Prolia-Prolia) per study treatment received in the Main Treatment Period.

The overall incidence of TEAEs in both treatment groups was similar (161 subjects [58.1%] in the MB09 group and 150 subjects [54.0%] in the Prolia group). The TEAEs in most subjects were Grade 1 (90 subjects [16.2%]) or Grade 2 (188 subjects [33.9%]) in severity. Grade 3 TEAEs were reported in 33 subjects (5.9%). No Grade 4 or Grade 5 TEAEs were reported during the Main Treatment Period. The most common TEAEs by PT (incidence ≥2.0%) included (MB09 versus Prolia) upper respiratory tract infection (7.2% versus 7.2%), arthralgia (5.4% versus 5.4%), COVID-19 (5.1% versus 5.4%), blood parathyroid hormone (PTH) increased (4.0% versus 1.4%), hypertension (3.6% versus 2.2%), nasopharyngitis (3.6% versus 8.3%), osteoarthritis (3.2% versus 3.6%), urinary tract infection (3.2% versus 3.2%), diarrhoea (2.5% versus 1.4%), hypothyroidism (2.2% versus 2.2%), back pain (2.2% versus 2.5%), and contusion (2.2% versus 1.8%). Overall, the incidence of TEAEs was similar in both the treatment groups.

Study treatment-related TEAEs were reported in 41 subjects (14.8%) in the MB09 group and 24 subjects (8.6%) in the Prolia group and most commonly included blood PTH increased (2.5%) and urinary tract infection (1.1%); other study treatment-related TEAEs included blood calcium decreased (0.9%), hypocalcaemia (0.5%), adjusted calcium decreased (0.4%), and cystitis (0.4%). Of the TEAEs related to the study treatment, most were Grade 1 or Grade 2 in severity.

The incidence of serious TEAEs was low (32 subjects [5.8%]: 19 subjects [6.9%] in the MB09 group and 13 subjects [4.7%] in the Prolia group). Serious TEAEs were most frequently reported in the SOCs of musculoskeletal and connective tissue disorders (mostly fractures), gastrointestinal disorders, and hepatobiliary disorders. All serious TEAEs were reported in 1 subject, except fracture-related TEAEs (4 subjects: 1 subject with hip fracture in each of the MB09 and Prolia groups; 1 subject with ulna fracture in the MB09 group, and 1 subject with ankle fracture in the Prolia group) and cholelithiasis (2 subjects: 1 subject in each of the MB09 and Prolia groups). Most serious TEAEs were classified as Grade 3 (26 subjects [4.7 %]). The Grade 3 serious TEAEs of osteonecrosis of jaw (1 subject in the MB09 group) and migraine (1 subject in the Prolia group) were considered related to the study treatment. No deaths were reported in the Main Treatment Period. The incidence of TEAEs that led to discontinuation of study treatment was also

DISETUJUI OLEH BPOM : 23 JULI 2026 ID : EREG10034612400183

low (4 subjects [0.7%]: 2 subjects with gingivitis, 1 subject with osteonecrosis of jaw, and 1 subject with renal cancer metastatic, all in the MB09 group).

Treatment-emergent AESIs were reported in 155 subjects (27.9%): 80 subjects (28.9%) in the MB09 group and 75 subjects (27.0%) in the Prolia group. The AESIs in most subjects were Grade 1 (7.7%) or Grade 2 (19.6%) in severity. Serious AESIs were reported in 4 subjects, of which serious AESIs in 3 subjects were Grade 3 in severity and included pulmonary tuberculosis, osteonecrosis of jaw, and psoriasis, each reported in 1 subject in the MB09 group. New fractures were reported in a total of 16 subjects (2.9%): 10 subjects (3.6%) in the MB09 group and 6 subjects (2.2%) in the Prolia group.

Shifts were noted for most clinical laboratory parameters but were not considered to be of potential clinical concern. Treatment-emergent AEs related to changes in clinical laboratory parameters, vital signs, and electrocardiograms (ECGs) were reported in few subjects. Of these, only a few TEAEs were considered related to the study treatment including blood PTH increased (2.5%), blood calcium decreased (0.9%), hypocalcaemia (0.5%), adjusted calcium decreased (0.4%), alanine aminotransferase increased (0.2%), aspartate aminotransferase increased (0.2%), gamma-glutamyl transferase increased (0.2%), blood albumin decreased (0.2%), and hyperuricaemia (0.2%); the overall incidence was similar in both the treatment groups.

Transition Period

The safety of the subjects who transitioned from Prolia to MB09 treatment was assessed by summarising their safety results in the Transition Period and comparing them with those who received Prolia treatment throughout. Thus, Transition Period safety results were summarized for the SAF-TP by Prolia-MB09 (130 subjects) and Prolia-Prolia (123 subjects) arms.

The overall incidence of TEAEs in the Prolia-MB09 and Prolia-Prolia arms was similar (36 subjects [27.7%] and 36 subjects [29.3%], respectively). Majority of the TEAEs were Grade 1 (19 subjects [7.5%]) or Grade 2 (51 subjects [20.2%]) in severity. There was no greater tendency for more TEAEs or more severe TEAEs in the transitioning arm (Prolia-MB09) and specifically, 9 subjects (6.9%) in this arm had Grade 1 and 27 subjects (20.8%) had Grade 2 TEAEs that started during the Transition Period. Two Grade 3 TEAEs were reported in 2 subjects (1.6%) in the Prolia-Prolia arm following the third dose of Prolia in the Transition Period. No Grade 4 or Grade 5 TEAEs were reported during the Transition Period in the Prolia-MB09 and Prolia-Prolia arms. Of note, one Grade 4 TEAE of pneumonia haemophilus that later worsened in severity leading to the subject's death (Grade 5 TEAE of pneumonia) was reported during the Transition Period in the MB09-MB09 arm, which was considered unrelated to the study treatment.

The most common TEAEs by PT (overall incidence ≥1.0%) included (Prolia-MB09 versus Prolia-Prolia, respectively) upper respiratory tract infection (3.8% versus 1.6%), COVID-19 (2.3% versus 2.4%), nasopharyngitis (1.5% versus 1.6%), bronchitis (0.8% versus 1.6%), urinary tract infection (0.8% versus 1.6%), hypertension (0.8% versus 2.4%), and obesity (0.8% versus 1.6%). Overall, the incidence of TEAEs was similar in the Prolia-MB09 and Prolia-Prolia arms. Study treatment-related TEAEs were reported in 3 subjects (2.3%) in the Prolia-MB09 arm and 5 subjects (4.1%) in the Prolia-Prolia arm and included upper respiratory tract infection and asymptomatic bacteriuria, each in 1 subject (0.8%), and dizziness and pruritus in 1 subject (0.8%) in the Prolia-MB09 arm and bronchitis and cataract in 1 subject (0.8%), myalgia, spinal pain, and asthenia in 1 subject (0.8%), and headache, alopecia, and injection site mass, each in 1 subject (0.8%) in the Prolia-Prolia arm. All TEAEs related to the study treatment were Grade 1 or Grade 2 in severity.

DISETUJUI OLEH BPOM : 23 JULI 2026 ID : EREG10034612400183

No serious TEAEs were reported in the Prolia-MB09 arm compared with 2 subjects (1.6%; 3 events) with serious TEAEs in the Prolia-Prolia arm: Grade 3 cardiac disorder in 1 subject and Grade 2 diverticulitis and thrombophlebitis in 1 subject. None of the serious TEAEs were considered related to the study treatment.

Treatment-emergent AESIs were reported in 38 subjects (15.0%), with similar incidence in the Prolia-MB09 and Prolia-Prolia arms: 17 subjects (13.1%) and 21 subjects (17.1%), respectively. The AESIs were nonserious and Grade 1 (5 subjects [2.0%]) or Grade 2 (33 subjects [13.0%]) in severity. New fractures were reported in a total of 4 subjects (1.6%): 2 subjects (1.5%) in the Prolia-MB09 arm and 2 subjects (1.6%) in the Prolia-Prolia arm.

Shifts were noted for most clinical laboratory parameters but were not considered to be of potential clinical concern. Treatment-emergent AEs related to changes in clinical laboratory parameters, vital signs, and ECGs were reported in few subjects. Of these, the TEAE of asymptomatic bacteriuria reported in 1 subject in the Prolia-MB09 arm was considered related to the study treatment.

Overall, the safety profile of the treatment arms Prolia-MB09 and Prolia-Prolia was similar with no notable difference in the incidence of TEAEs and treatment-related TEAEs after single transition from Prolia to MB09 as compared with Prolia throughout.

Throughout the Study

Safety results throughout the study were summarised by treatment arm for the SAF: MB09-MB09 (277 subjects), Prolia-MB09 (140 subjects), and Prolia-Prolia (138 subjects), with a focus on comparing the safety between subjects who received MB09 throughout and those who received Prolia throughout. These results were cumulative of the Main Treatment Period and the Transition Period. Overall, the safety profile of the treatment arms MB09-MB09 and Prolia-Prolia was similar with no notable differences in the incidence of TEAEs between subjects who received MB09 throughout and those who received Prolia throughout.

Immunogenicity Results

The incidence of TI-ADA was low: with 7 subjects detected to be ADA positive throughout the study, including 1 subject in the MB09-MB09 arm (Transition Period), 3 subjects in the Prolia-MB09 arm (Main Treatment Period), and 3 subjects in the Prolia-Prolia arm (Main Treatment Period). All the ADAs were transient. None of the ADAs detected had neutralizing capacity.

As the number of ADA-positive subjects (n=7/555) was very small compared with the ADA negative subjects (n=548/555), their impact on safety or efficacy, as assessed during the Main Treatment Period, was not meaningful and the results in the ADA-positive subjects remained similar to the overall study results.

Study MB09-C-01-19 met its objectives and successfully demonstrated the therapeutic equivalence of proposed biosimilar MB09 to the reference product EU-Prolia:

- Equivalent efficacy was demonstrated between MB09 and EU-Prolia in postmenopausal women with osteoporosis in terms of difference in means in percentage change from baseline in lumbar spine BMD at Month 12, which lay within a predefined margin. This conclusion was robust to different handling strategies for ICEs and assumptions for missing data.

DISETUJUI OLEH BPOM : 23 JULI 2026 ID : EREG10034612400183

- All secondary efficacy endpoints supported the results of the primary endpoint indicating a similar treatment effect of MB09 and Prolia on lumbar spine, hip, and femur neck BMD at Month 6 and Month 12.
- Denosumab serum exposure in terms of Cmax and, AUC0-6 months was similar between MB09 and EU-Prolia with 95% CIs of the geometric LS mean ratios falling within the acceptable limits in all instances.
- The inhibiting effect of denosumab on the PD parameter sCTX was similar to that of EU-Prolia with 95% CIs of the geometric mean ratios of the AUEC0-6 months and AUIC0-6 months falling within the acceptable limits. The inhibition was maintained in the Transition Period.
- MB09 demonstrated a safety profile similar to that of EU-Prolia in terms of nature, severity, and frequency of the TEAEs and within the expectations in the study population.
- The development of an immunogenic response was low, as expected per Prolia product information.

Overall, the results from data collected from all subjects who completed the 12-month Main Treatment Period of the study demonstrated that MB09 was well tolerated with acceptable safety profile and an improvement in BMD that was comparable to EU-Prolia. The PK and PD profile of MB09 was also comparable to EU-Prolia. This supports the clinical activity of MB09 in postmenopausal women with osteoporosis. The safety profile remained similar after single transition from Prolia to MB09 as compared with MB09 throughout or Prolia throughout.

5.4 Preclinical 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 preclinical 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;

DISETUJUI OLEH BPOM : 23 JULI 2026 ID : EREG10034612400183

adverse maternal effects occurred infrequently during labour. Maternal mammary gland development was normal.

In preclinical 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 section 4.6) 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.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Acetic acid, glacial*
Sodium hydroxide (for pH adjustment)*
Sorbitol (E420)
Polysorbate 20
Water for injections
* Acetate buffer is formed by mixing acetic acid with sodium hydroxide

6.2 Incompatibilities

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

6.3 Shelf life

The expiry date is 36 months.

Once removed from the refrigerator, RESYNIV® may be stored at room temperature (up to 25°C) for up to 30 days in the original container. It must be used within this 30 days period.

6.4 Special precautions for storage

Store in a refrigerator (2°C – 8°C).
Do not freeze.
Keep the container in the outer carton in order to protect from light.

DISETUJUI OLEH BPOM : 23 JULI 2026 ID : EREG10034612400183

6.5 Nature and contents of container

One mL solution in a single use pre-filled syringe made from type I glass with stainless steel 29 gauge needle, with needle guard.

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

6.6 Special precautions for disposal and other handling

- Before administration, the solution should be inspected. Do not inject the solution if it contains particles, or is 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.

(detailed see Appendix)

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

Pack Size :

Resyniv 60 mg/mL solution for injection in pre-filled syringes :
Box of 1 pre-filled syringes
Reg. No. DKIxxxxxxxxxx

HARUS DENGAN RESEP DOKTER

Marketing Authorization Holder :

PT Abbott Indonesia
Jl Raya Jakarta Bogor Km. 37
Depok Indonesia

Manufactured by:

Universal Farma S.L.
C/El Tejido, 2, Azuqueca de Henares,
19200 Guadalajara, Spanyol

Released by :

GH GENHELIX S.A.
Parque Tecnológico de León
Edificio GENHELIX C/Julia Morros, s/n
Armunia, 24009 León, Spanyol

Initial submission
L026/10/24
Date of revision : 08 Jul 2026

Abbott

DISETUJUI OLEH BPOM : 23 JULI 2026 ID : EREG10034612400183

APPENDIX

INSTRUCTION FOR USE

Read these instructions before start using Resyniv® pre-filled syringes with needle guard.

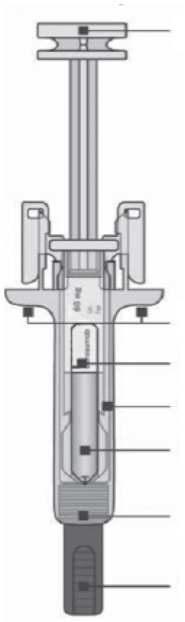
IMPORTANT INFORMATION

Important information you need to know before injecting Resyniv®:

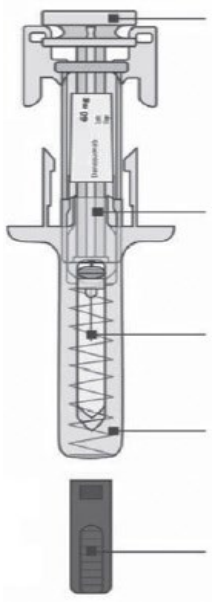
- Resyniv® is for subcutaneous injection only (inject directly under the skin).
- **Do not** open the outer box until you are ready to use this medicine.
- **Do not** remove the needle cap from the pre-filled syringe until you are ready to inject.
- **Do not** use the pre-filled syringe if it has been dropped on a hard surface.
- **Do not** attempt to activate the pre-filled syringe prior to injection.
- **Do not** attempt to remove the needle guard from the pre-filled syringe

Figure 1 shows what the pre-filled syringe with needle guard looks like before (a) and after (b) use.

a) Before use



b) After use



GET READY FOR INJECTION

1. Select injection site (Figure E)

The recommended injection site for Resyniv:

- Upper part of your thigh.
- Belly, except for a 5 cm area right around your belly button.
- Outer area of upper arm (only if someone else is giving you the injection).

Do not inject into areas where the skin is tender, bruised, red, or hard. Avoid injecting into areas with scars or stretch marks.

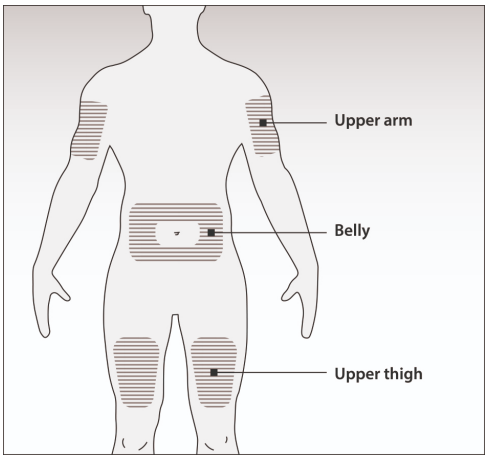


Figure E

2. Clean injection site

- Clean the injection site with an alcohol wipe **(Figure F).**
- Let the skin dry.
- Do not touch the injection site before injecting.

3. Remove needle cap

- Carefully pull the needle cap straight off (Figure G).
- Throw away the needle cap, and do not attempt to re-cap the needle.

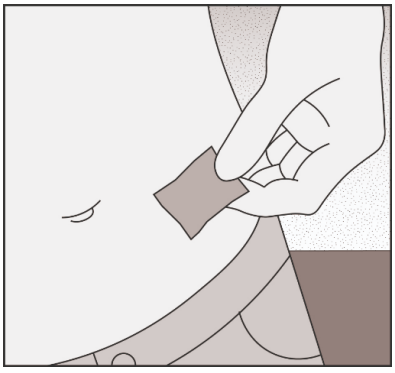


Figure F

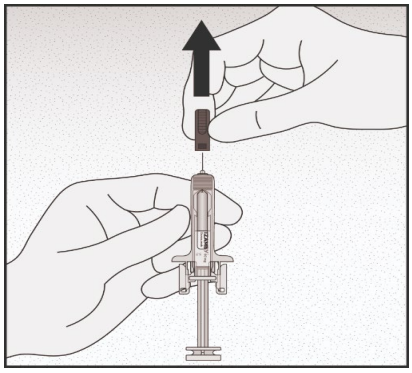


Figure G

4. Inject Resyniv®

Insert the needle

- Pinch the injection site to create a firm surface **(Figure H).** Do not touch the cleaned area of the skin.
  Note: It is important to keep the skin pinched when injecting.
- Insert the needle at 45 to 90-degree angle into the pinched skin **(Figure I).**

DISETUJUI OLEH BPOM : 23 JULI 2026 ID : EREG10034612400183

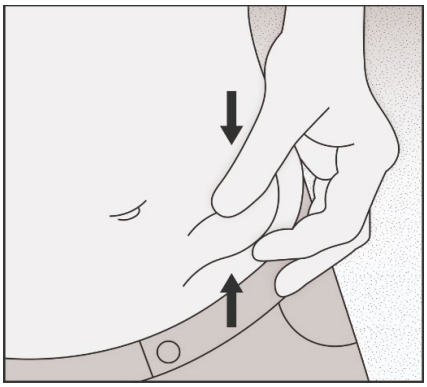


Figure H

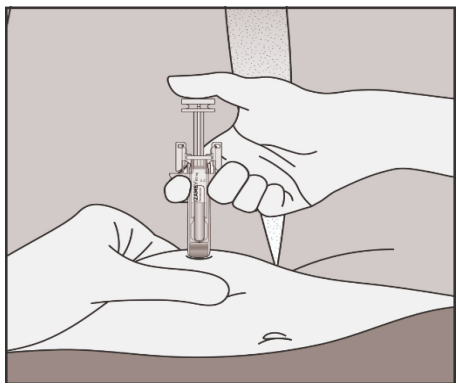


Figure I

- Slowly push the plunger all the way in until all the liquid is injected, and the syringe is empty **(Figure J).**
  Note: The plunger must be pushed all the way down to be sure the full dose has been injected and the needle guard will activate.
- Take the thumb off the plunger to allow the needle guard to cover the needle (**Figure K**).

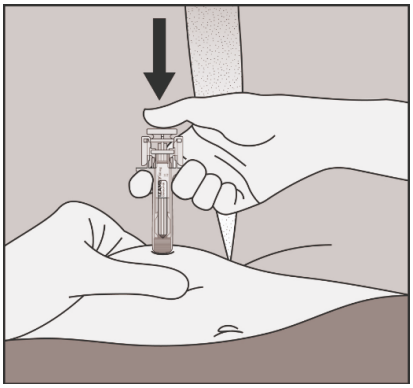


Figure J

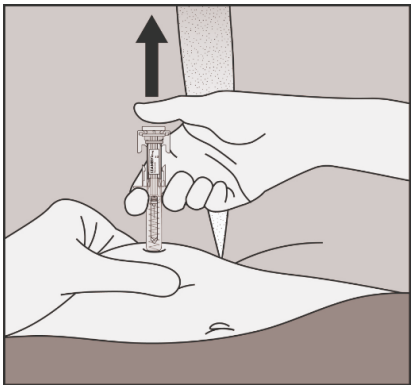


Figure K

- Then lift the syringe off the skin (**Figure L**).
- Release the pinched skin.
- Discard the used pre-filled syringe and other supplies in a sharps disposal container.
- Record the date of patient next injection on the reminder card included in the pack (**Figure M**).

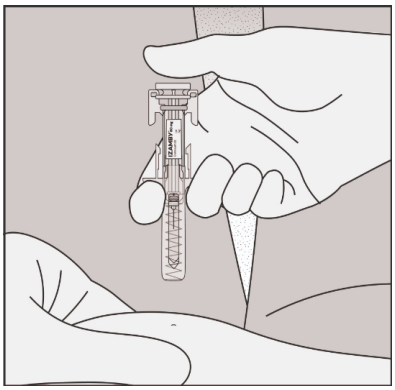


Figure L

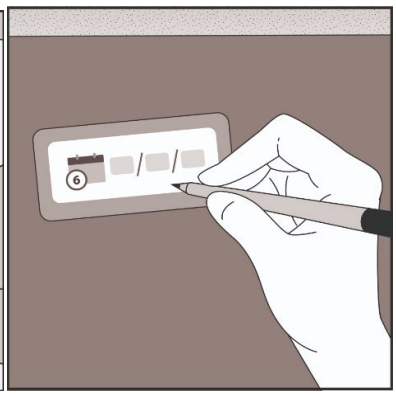


Figure M