DNOCLAST®
Denosumab
120 mg/1.7mL Solution for Injection

1. NAME OF THE MEDICINAL PRODUCT

DNOCLAST® 120 mg solution for injection

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each vial contains 120 mg of denosumab in 1.7 mL of solution (70 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 78 mg sorbitol in each 1.7 mL of solution.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for injection (injection).

Clear, colourless to yellowish solution and may contain trace amounts of translucent to white proteinaceous particles.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

DNOCLAST® is indicated in for reducing the risk of skeletal related events (e.g pathological fracture, radiation to bone, spinal cord compression or surgery to bone) in adults patient with bone metastases from solid tumors.

4.2 Posology and method of administration

DNOCLAST® should be administered under the responsibility of a healthcare professional.

Posology

The recommended dose of DNOCLAST® is 120 mg administered as a subcutaneous injection once every 4 weeks into the thigh, abdomen or upper arm. Supplementation of at least 500 mg calcium and 400 IU vitamin D daily is required in all patients whilst undergoing treatment.

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

Populations

Renal impairment
No dose adjustment is required in patients with renal impairment (see section 4.4 for recommendations relating to monitoring of calcium, 4.8 and 5.2).

In clinical studies of patients with varying degrees of renal function (including severe renal impairment [creatinine clearance < 30 mL/min] or receiving dialysis), there was a greater risk of developing hypocalcaemia with increasing degree of renal impairment and in the absence of calcium supplementation. Monitoring calcium levels and adequate intake of calcium and vitamin D is important in patients with severe renal impairment or receiving dialysis (see section 4.4)

Hepatic impairment
The safety and efficacy of denosumab have not been studied in patients with hepatic impairment (see section 5.2).

Elderly (age ≥ 65)
No dose adjustment is required in elderly patients (see section 5.2).

Paediatric population
The safety and efficacy of denosumab have not been established in paediatric patients . 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 section 5.3). Therefore, treatment with denosumab may impair bone growth in children with open growth plates and may inhibit eruption of dentition. dults.

Method of administration

For subcutaneous use.

For instructions for use, handling and disposal see section 6.6.

4.3 Contraindications

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

Severe, untreated hypocalcaemia (see section 4.4).

Unhealed lesions from dental or oral surgery.

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

Supplementation with calcium and vitamin D is required in all patients unless hypercalcaemia is present (see section 4.2).

Hypocalcaemia

Pre-existing hypocalcaemia must be corrected prior to initiating therapy with denosumab. Hypocalcaemia can occur at any time during therapy with denosumab. Monitoring of calcium levels should be conducted (i) prior to the initial dose of denosumab, (ii) within two weeks after the initial dose, (iii) if suspected symptoms of hypocalcaemia occur (see section 4.8 for symptoms). Additional monitoring of calcium level should be considered during therapy in patients with risk factors for hypocalcaemia, or if otherwise indicated based on the clinical condition of the patient.

Patients should be encouraged to report symptoms indicative of hypocalcaemia. If hypocalcaemia occurs while receiving denosumab, additional calcium supplementation and additional monitoring may be necessary.

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 can occur later.

Renal impairment

Patients with severe renal impairment (creatinine clearance < 30 mL/min) or receiving dialysis are at greater risk of developing hypocalcaemia. The risk of developing hypocalcaemia and accompanying elevations in parathyroid hormone increases with increasing degree of renal impairment. Regular monitoring of calcium levels is especially important in these patients.

Osteonecrosis of the jaw (ONJ)

ONJ has been reported commonly in patients receiving denosumab (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.

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, pre-existing 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 denosumab treatment should be considered until the condition resolves and contributing risk factors are mitigated where possible.

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 5 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.

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 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 pharmaceutical agents (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.

Hypercalcaemia following treatment discontinuation in patients with growing skeletons

After treatment is discontinued, monitor patients for signs and symptoms of hypercalcaemia, consider periodic assessment of serum calcium and re-evaluate the patient's calcium and vitamin D supplementation requirements (see section 4.8).

Denosumab is not recommended in patients with growing skeletons (see section 4.2). Clinically significant hypercalcaemia has also been reported in this patient group weeks to months following treatment discontinuation.

Skin Infections Leading to Hospitalisation (predominantly cellulitis)

In clinical trials in patients with advanced malignancies involving bone, skin infections leading to hospitalization (predominantly cellulitis) were reported (see section 4.8). Patients should be advised to seek prompt medical attention if they develop signs or symptoms of cellulitis.

Others

Patients being treated with denosumab should not be treated concomitantly with other denosumab containing medicinal products (for osteoporosis indications).

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

Excipients

This medicinal product contains 0.17 mg of polysorbate 20 (E432) in each vial. Polysorbates may cause allergic reactions. In this context, patients with known allergies should be considered.

This medicine contains 78 mg sorbitol in each 1.7 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 120 mg that is to say essentially 'sodium-free'.

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

No interaction studies have been performed.

In clinical trials, denosumab has been administered in combination with standard anti-cancer treatment and in subjects previously receiving bisphosphonates. There were no clinically-relevant alterations in trough serum concentration and pharmacodynamics of denosumab (creatinine adjusted urinary N-telopeptide, uNTx/Cr) by concomitant chemotherapy and/or hormone therapy or by previous intravenous bisphosphonate exposure.

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).

DNOCLAST® 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. A risk to the newborns/infants cannot be excluded. Knockout mouse studies suggest absence of RANKL during pregnancy may interfere with maturation of the mammary gland leading to impaired lactation post-partum (see section 5.3). A decision must be made on whether to abstain from breast-feeding or to abstain from DNOCLAST® therapy taking into account the benefit of breast-feeding to the newborn/infant and the benefit of therapy for 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

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

4.8 Undesirable effects

Summary of the safety profile

Overall safety profile is consistent in all approved indications for denosumab.

Hypocalcaemia has very commonly been reported following denosumab administration, mostly within the first 2 weeks. Hypocalcaemia can be severe and symptomatic (see section 4.8 - description of selected adverse reactions). The decreases in serum calcium were generally appropriately managed by calcium and vitamin D supplementation. The most common adverse reactions with denosumab are musculoskeletal pain. Cases of osteonecrosis of the jaw (see sections 4.4 and section 4.8 - description of selected adverse reactions) have been commonly observed in patients taking denosumab.

Tabulated list of adverse reactions

The following convention has been used for the classification of the adverse reactions based on incidence rates in four phase III, two phase II clinical studies and post-marketing experience (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 availabledata). 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 advanced malignancies involving bone

MedDRA system organ class	**Frequency category**	**Adverse reactions**
Neoplasms benign, malignant and unspecified (including cysts and polyps)	Common	New primary malignancy[1]
Immune system disorders	Rare Rare	Drug hypersensitivity[1] Anaphylactic reaction[1]
Metabolism and nutrition disorder	Very common	Hypocalcaemia[1,2]
	Common	Hypophosphataemia
Respiratory, thoracic and mediastinal disorders	Very Common	Dyspnoea
Gastrointestinal disorders	Very Common Common	Diarrhoea Tooth extraction
Skin and subcutaneous tissue disorders	Common Uncommon	Hyperhidrosis Lichenoid drug eruptions[1]
Musculoskeletal and connective tissue disorders	Very common Common Uncommon Not Known	Musculoskeletal pain[1] Osteonecrosis of the jaw[1] Atypical femoral fractures[1] Osteonecrosis of the external auditory canal[3,4]

[1]See section Description of selected adverse reactions.
[2]See section Other special populations
[3]See section 4.4
[4]Class effect

Description of selected adverse reactions

Hypocalcaemia
A higher incidence of hypocalcaemia among subjects treated with denosumab compared to zoledronic acid has been observed in SRE prevention clinical trials.

The highest incidence of hypocalcaemia was observed in a phase III trial in patients with multiple myeloma. Hypocalcaemia was reported in 16.9% of patients treated with denosumab and 12.4% of patients treated with zoledronic acid. A grade 3 decrease in serum calcium levels was experienced in 1.4% of patients treated with denosumab and 0.6% of patients treated with zoledronic acid. A grade 4 decrease in serum calcium levels was experienced in 0.4% of patients treated with denosumab and 0.1% of patients treated with zoledronic acid.

In three phase III active-controlled clinical trials in patients with advanced malignancies involving bone, hypocalcaemia was reported in 9.6% of patients treated with denosumab and 5.0% of patients treated with zoledronic acid.

A grade 3 decrease in serum calcium levels was experienced in 2.5% of patients treated with denosumab and 1.2% of patients treated with zoledronic acid. A grade 4 decrease in serum calcium levels was experienced in 0.6% of patients treated with denosumab and 0.2% of patients treated with zoledronic acid (see section 4.4).

In the post-marketing setting, severe symptomatic hypocalcaemia (including fatal cases) has been reported, with most cases occurring in the first weeks of initiating therapy. Examples of clinical manifestations of severe symptomatic hypocalcaemia have included QT interval prolongation, tetany, seizures and altered mental status (including coma) (see section 4.4). Symptoms of hypocalcaemia in clinical studies included paraesthesias or muscle stiffness, twitching, spasms and muscle cramps.

Osteonecrosis of the jaw (ONJ)
In clinical trials, the incidence of ONJ was higher with longer duration of exposure; ONJ has also been diagnosed after stopping treatment with denosumab with the majority of cases occurring within 5 months after the last dose. Patients with prior history of ONJ or osteomyelitis of the jaw, an active dental or jaw condition requiring oral surgery, non-healed dental/oral surgery, or any planned invasive dental procedure were excluded from the clinical trials.

A higher incidence of ONJ among subjects treated with denosumab compared to zoledronic acid has been observed in SRE prevention clinical trials. The highest incidence of ONJ was observed in a phase III trial in patients with multiple myeloma. In the double-blind treatment phase of this trial, ONJ was confirmed in 5.9% of patients treated with denosumab (median exposure of 19.4 months; range 1 – 52) and in 3.2% of patients treated with zoledronic acid. At the completion of the double-blind treatment phase of this trial, the patient-year adjusted incidence of confirmed ONJ in the denosumab group (median exposure of 19.4 months; range 1 - 52), was 2.0 per 100 patient-years during the first year of treatment, 5.0 in the second year, and 4.5 thereafter. The median time to ONJ was 18.7 months (range: 1 - 44).

In the primary treatment phases of three phase III active-controlled clinical trials in patients with advanced malignancies involving bone, ONJ was confirmed in 1.8% of patients treated with denosumab (median exposure of 12.0 months; range: 0.1 – 40.5) and 1.3% of patients treated with zoledronic acid. Clinical characteristics of these cases were similar between treatment groups. Among subjects with confirmed ONJ, most (81% in both treatment groups) had a history of tooth extraction, poor oral hygiene, and/or use of a dental appliance. Most subjects were receiving or had received chemotherapy.

The trials in patients with breast or prostate cancer included an denosumab extension treatment phase (median overall exposure of 14.9 months; range: 0.1 – 67.2). ONJ was confirmed in 6.9% of patients with breast cancer and prostate cancer during the extension treatment phase.

The patient-year adjusted overall incidence of confirmed ONJ was 1.1 per 100 patient-years during the first year of treatment, 3.7 in the second year and 4.6 thereafter. The median time to ONJ was 20.6 months (range: 4 - 53).

A non-randomised, retrospective, observational study in 2,877 patients with cancer treated with denosumab or zoledronic acid in Sweden, Denmark, and Norway showed that 5-year incidence proportions of medically confirmed ONJ were 5.7% (95% CI: 4.4, 7.3; median follow up time of 20 months [range 0.2-60]) in a cohort of patients receiving denosumab and 1.4% (95% CI: 0.8, 2.3; median follow up time of 13 months [range 0.1-60]) in a separate cohort of patients receiving zoledronic acid. Five-year incidence proportion of ONJ in patients switching from zoledronic acid to denosumab was 6.6% (95% CI: 4.2, 10.0; median follow up time of 13 months [range 0.2-60]).

Skin Infections (predominantly cellulitis) Leading to Hospitalisation

In three phase III active-controlled clinical trials patients with advanced malignancies involving bone, skin infections leading to hospitalisation (predominantly cellulitis) were reported more frequently in patients receiving Denosumab (0.9%) compared with zoledronic acid (0.7%). In postmenopausal women with osteoporosis, skin infections leading to hospitalisastion were reported for 0.4% women receiving Denosumab 60 mg every 6 months and for 0.1% women receiving placebo (see section 4.4)

Drug related hypersensitivity reactions
In the post-marketing setting, events of hypersensitivity, including rare events of anaphylactic reactions, have been reported in patients receiving denosumab.

Atypical fractures of the femur
In the clinical trial programme, atypical femoral fractures have been reported uncommonly in patients treated with denosumab and the risk increased with longer duration of treatment. Events have occurred during treatment and up to 9 months after treatment was discontinued (see section 4.4).

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

New primary malignancy
In the primary double blind treatment phases of four phase III active-controlled clinical trials in patients with advanced malignancies involving bone, new primary malignancy was reported in 54/3691 (1.5%) of patients treated with denosumab (median exposure of 13.8 months; range: 1.0–51.7) and 33/3688 (0.9%) of patients treated with zoledronic acid (median exposure of 12.9 months; range: 1.0-50.8).
The cumulative incidence at one year was 1.1 % for denosumab and 0.6 % for zoledronic acid, respectively.
No treatment-related pattern in individual cancers or cancer groupings was apparent.

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

Paediatric population

Denosumab is not recommended in paediatric patients as the safety and effectiveness of Denosumab have not been established in the paediatric age group. Clinically significant hypercalcaemia after treatment discontinuation has been reported in the post-marketing setting in paediatric patients (see section 4.4)

Other special populations

Renal impairment
In a clinical study of patients without advanced cancer with severe renal impairment (creatinine clearance < 30 mL/min) or receiving dialysis, there was a greater risk of developing hypocalcaemia in the absence of calcium supplementation. The risk of developing hypocalcaemia during denosumab treatment is greater with increasing degree of renal impairment. In a clinical study in patients without advanced cancer, 19% of patients with severe renal impairment (creatinine clearance < 30 mL/min) and 63% of patients receiving dialysis developed hypocalcaemia despite calcium supplementation. The overall incidence of clinically significant hypocalcaemia was 9%.

Accompanying increases in parathyroid hormone have also been observed in patients receiving denosumab with severe renal impairment or receiving dialysis. Monitoring of calcium levels and adequate intake of calcium and vitamin D is especially important in patients with renal impairment (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 and 120 mg weekly for 3 weeks.

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

Mechanism of action

RANKL exists as a transmembrane or soluble protein. RANKL is essential for the formation, function and survival of osteoclasts, the sole cell type responsible for bone resorption. Increased osteoclast activity, stimulated by RANKL, is a key mediator of bone destruction in metastatic bone disease and multiple myeloma. Denosumab is a human monoclonal antibody (IgG2) that targets and binds with high affinity and specificity to RANKL, preventing the RANKL/RANK interaction from occurring and resulting in reduced osteoclast numbers and function, thereby decreasing bone resorption and cancerinduced bone destruction.

Pharmacodynamic effects

[Study performed by originator Xgeva]

In phase II clinical studies of patients with advanced malignancies involving bone, subcutaneous (SC) dosing of denosumab administered either every 4 weeks (Q4W) or every 12 weeks resulted in a rapid reduction in markers of bone resorption (uNTx/Cr, serum CTx), with median reductions of approximately 80% for uNTx/Cr occurring within 1 week regardless of prior bisphosphonate therapy or baseline uNTx/Cr level. In phase III clinical trials of patients with advanced malignancies involving bone, median uNTx/Cr reductions of approximately 80% were maintained through 49 weeks of denosumab treatment (120 mg every Q4W).

Immunogenicity

Anti-denosumab antibodies may develop during denosumab treatment. No apparent correlation of antibody development with pharmacokinetics, clinical response or adverse event has been observed.

Clinical efficacy and safety in patients with bone metastases from solid tumours

Efficacy and safety of 120 mg denosumab SC every 4 weeks or 4 mg zoledronic acid (dose-adjusted for reduced renal function) IV every 4 weeks were compared in three randomised, double-blind, active-controlled studies, in IV-bisphosphonate naïve patients with advanced malignancies involving bone: adults with breast cancer (study 1), other solid tumours or multiple myeloma (study 2), and castrate-resistant prostate cancer (study 3). Within these active-controlled clinical trials, safety was evaluated in 5,931 patients. Patients with prior history of ONJ or osteomyelitis of the jaw, an active dental or jaw condition requiring oral surgery, non-healed dental/oral surgery, or any planned invasive dental procedure, were not eligible for inclusion in these studies. The primary and secondary endpoints evaluated the occurrence of one or more skeletal related events (SREs). In studies demonstrating superiority of denosumab to zoledronic acid, patients were offered open-label denosumab in a pre-specified 2-year extension treatment phase. An SRE was defined as any of the following: pathologic fracture (vertebral or non-vertebral), radiation therapy to bone (including the use of radioisotopes), surgery to bone, or spinal cord compression.

Denosumab reduced the risk of developing a SRE, and developing multiple SREs (first and subsequent) in patients with bone metastases from solid tumours (see table 2).

Table 2. Efficacy results in patients with advanced malignancies involving bone

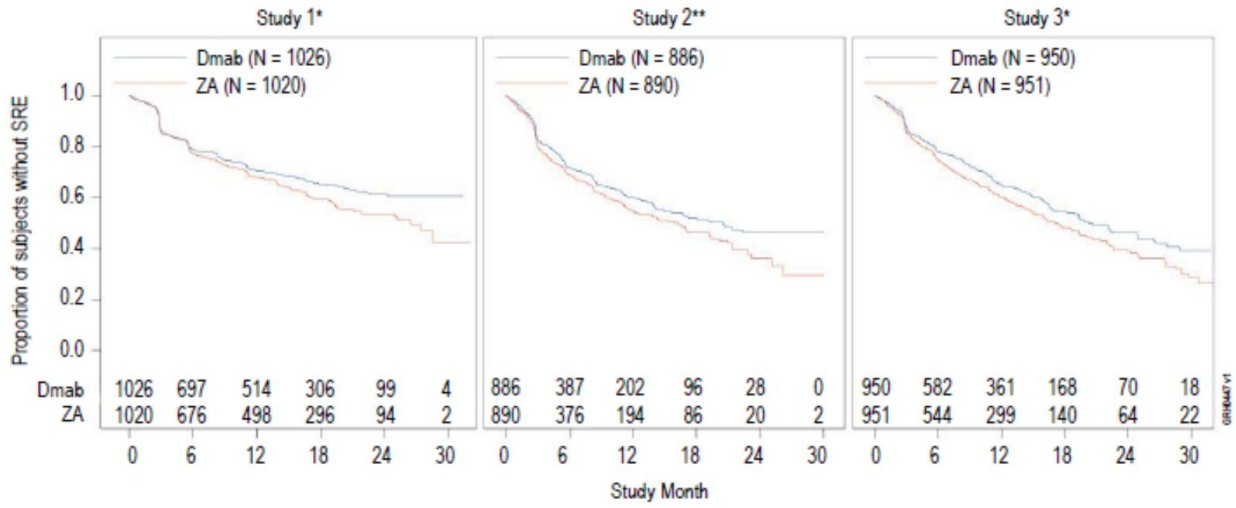
	Study 1 breast cancer		**Study 2 other solid tumours** or multiple myeloma**		**Study 3 prostate cancer**		**Combined advanced cancer**	
	denosumab	zoledronic acid	denosumab	zoledronic acid	denosumab	zoledronic acid	denosumab	zoledronic acid
N	1,026	1,020	886	890	950	951	2,862	2,861
First SRE								
Median time (months)	NR	26.4	20.6	16.3	20.7	17.1	27.6	19.4
Difference in median time (months)	NA		4.2		3.5		8.2	

HR (95% CI) / RRR (%)	0.82 (0.71, 0.95) / 18		0.84 (0.71, 0.98) / 16		0.82 (0.71, 0.95) / 18		0.83 (0.76, 0.90) / 17	
Non-inferiority / Superiority p-values	< 0.0001† / 0.0101†		0.0007† / 0.0619†		0.0002† / 0.0085†		< 0.0001 / < 0.0001	
Proportion of subjects (%)	30.7	36.5	31.4	36.3	35.9	40.6	32.6	37.8
First and subsequent SRE*								
Mean number/ patient	0.46	0.60	0.44	0.49	0.52	0.61	0.48	0.57
Rate ratio (95% CI) / RRR (%)	0.77 (0.66, 0.89) / 23		0.90 (0.77, 1.04) / 10		0.82 (0.71, 0.94) / 18		0.82 (0.75, 0.89) / 18	
Superiority p-value	0.0012†		0.1447†		0.0085†		< 0.0001	
SMR per Year	0.45	0.58	0.86	1.04	0.79	0.83	0.69	0.81
First SRE or HCM								
Median time (months)	NR	25.2	19.0	14.4	20.3	17.1	26.6	19.4
HR (95% CI) / RRR (%)	0.82 (0.70, 0.95) / 18		0.83 (0.71, 0.97) / 17		0.83 (0.72, 0.96) / 17		0.83 (0.76, 0.90) / 17	
Superiority p-value	0.0074		0.0215		0.0134		< 0.0001	
First radiation to bone								
Median time (months)	NR	NR	NR	NR	NR	28.6	NR	33.2
HR (95% CI) / RRR (%)	0.74 (0.59, 0.94) / 26		0.78 (0.63, 0.97) / 22		0.78 (0.66, 0.94) / 22		0.77 (0.69, 0.87) / 23	
Superiority p-value	0.0121		0.0256		0.0071		< 0.0001	

NR = not reached; NA = not available; HCM = hypercalcaemia of malignancy; SMR = skeletal morbidity rate; HR = Hazard Ratio; RRR = Relative Risk Reduction †Adjusted p-values are presented for studies 1, 2 and 3 (first SRE and first and subsequent SRE endpoints); *Accounts for all skeletal events over time; only events occurring ≥ 21 days after the previous event are counted.

** Including NSCLC, renal cell cancer, colorectal cancer, small cell lung cancer, bladder cancer, head and neck cancer, GI/genitourinary cancer and others, excluding breast and prostate cancer.

Figure 1. Kaplan-Meier plots of time to first on-study SRE



Dmab = Denosumab 120 mg Q4W
ZA = Zolendronic Acid 4 mg Q4W
N = Number of subjects randomised
*= Statistically significant for superiority; **= Statistically significant for non-inferiority

Disease progression and overall survival with bone metastases from solid tumours

Disease progression was similar between denosumab and zoledronic acid in all three studies and in the pre-specified analysis of all three studies combined.

In studies 1, 2 and 3, overall survival was balanced between denosumab and zoledronic acid in patients with advanced malignancies involving bone: patients with breast cancer (hazard ratio and 95% CI was 0.95 [0.81, 1.11]), patients with prostate cancer (hazard ratio and 95% CI was 1.03 [0.91, 1.17]), and patients with other solid tumours or multiple myeloma (hazard ratio and 95% CI was 0.95 [0.83, 1.08]). A post-hoc analysis in study 2 (patients with other solid tumours or multiple myeloma) examined overall survival for the 3 tumour types used for stratification (non-small cell lung cancer, multiple myeloma, and other). Overall survival was longer for denosumab in non-small cell lung cancer (hazard ratio [95% 13 CI] of 0.79 [0.65, 0.95]; n = 702) and longer for zoledronic acid in multiple myeloma (hazard ratio [95% CI] of 2.26 [1.13, 4.50]; n = 180) and similar between denosumab and zoledronic acid in other tumour types (hazard ratio [95% CI] of 1.08 (0.90, 1.30); n = 894). This study did not control for prognostic factors and anti-neoplastic treatments. In a combined pre-specified analysis from studies 1, 2 and 3, overall survival was similar between denosumab and zoledronic acid (hazard ratio and 95% CI 0.99 [0.91, 1.07]).

Effect on pain

The time to pain improvement (i.e. ≥ 2-point decrease from baseline in BPI-SF worst pain score) was similar for denosumab and zoledronic acid in each study and the integrated analyses. In a post-hoc analysis of the combined dataset, the median time to worsening pain (> 4-point worst pain score) in patients with mild or no pain at baseline was delayed for denosumab compared to zoledronic acid (198 versus 143 days) (p = 0.0002).

Clinical efficacy in patients with multiple myeloma

Denosumab was evaluated in an international, randomised (1:1), double-blind, active-controlled study comparing denosumab with zoledronic acid in patients with newly diagnosed multiple myeloma, study 4. In this study, 1,718 multiple myeloma patients with at least one bone lesion were randomised to receive

120 mg denosumab subcutaneously every 4 weeks (Q4W) or 4 mg zoledronic acid intravenously (IV) every 4 weeks (dose-adjusted for renal function). The primary outcome measure was demonstration of non-inferiority of time to first on study skeletal related event (SRE) as compared to zoledronic acid.
Secondary outcome measures included superiority of time to first SRE, superiority of time to first and subsequent SRE, and overall survival. An SRE was defined as any of the following: pathologic fracture (vertebral or non-vertebral), radiation therapy to bone (including the use of radioisotopes), surgery to bone, or spinal cord compression.
Across both study arms, 54.5% of patients intended to undergo autologous PBSC transplantation, 95.8% patients utilised/planned to utilise a novel anti-myeloma agent (novel therapies include bortezomib, lenalidomide, or thalidomide) in first-line therapy, and 60.7% of patients had a previous SRE. The number of patients across both study arms with ISS stage I, stage II, and stage III at diagnosis were 32.4%, 38.2%, and 29.3%, respectively.
The median number of doses administered was 16 for denosumab and 15 for zoledronic acid.
Efficacy results from study 4 are presented in figure 2 and table 3.

Figure 2. Kaplan-Meier plot for time to first on-study SRE in patients with newly diagnosed multiple myeloma

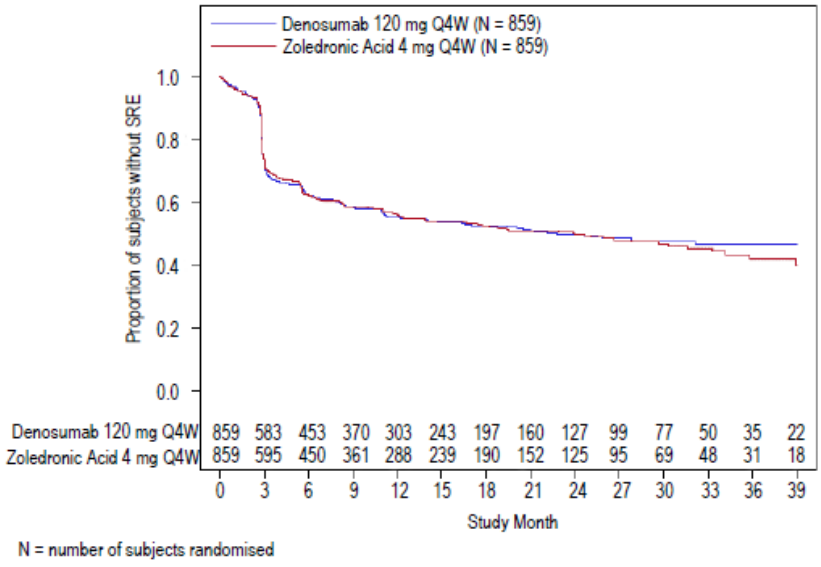


Table 3. Efficacy results for denosumab compared to zoledronic acid in patients with newly diagnosed multiple myeloma

	Denosumab (N = 859)	Zoledronic Acid (N = 859)
First SRE		
Number of patients who had SREs (%)	376 (43.8)	383 (44.6)
Median time to SRE (months)	22.8 (14.7, NE)	23.98 (16.56, 33.31)
Hazard ratio (95% CI)	0.98 (0.85, 1.14)	
First and subsequent SRE		
Mean number of events/patient	0.66	0.66
Rate ratio (95% CI)	1.01 (0.89, 1.15)	
Skeletal morbidity rate per year	0.61	0.62
First SRE or HCM		
Median time (months)	22.14 (14.26, NE)	21.32 (13.86, 29.7)
Hazard ratio (95% CI)	0.98 (0.85, 1.12)	
First radiation to bone		
Hazard ratio (95% CI)	0.78 (0.53, 1.14)	
Overall survival		
Hazard ratio (95% CI)	0.90 (0.70, 1.16)	

NE = not estimable
HCM = hypercalcaemia of malignancy

[Study performed by Mabxience on Dnoclast]

Pharmacokinetics

Phase I study MB09-A-01-19:

The primary objective of this study, "*A randomised, double-blind, three-arm, single dose, parallel study to compare the pharmacokinetics, pharmacodynamics, safety and immunogenicity profile of MB09 (proposed denosumab biosimilar) and EU-/US-sourced Xgeva® in healthy male volunteers*", was to assess the bioequivalence of single subcutaneous (SC) doses in healthy subjects of MB09 *versus* EU-sourced Xgeva®, MB09 *versus* US-sourced Xgeva® and between EU- and US-Xgeva®.

A total of 257 subjects were enrolled, of whom 255 (99.2%) (85 in the MB09 arm, 86 in the EU-Xgeva® arm and 86 in the US-Xgeva® arm) were randomised and received the study treatment, a single 35 mg dose of MB09, EU-Xgeva® or US-Xgeva® by SC injection.

The PK population from the MB09 and EU- or US-Xgeva® treatment arms consisted of all subjects who received the study treatment, who did not have major protocol deviations, and had sufficient data to calculate primary PK endpoints (255 subjects, 85 per arm). A statistical analysis of the primary PK parameters (AUC0-last and Cmax) derived from measurements of denosumab serum concentrations in the MB09, EU-, and US-Xgeva® treatment arms in the PK population is shown in Table below.

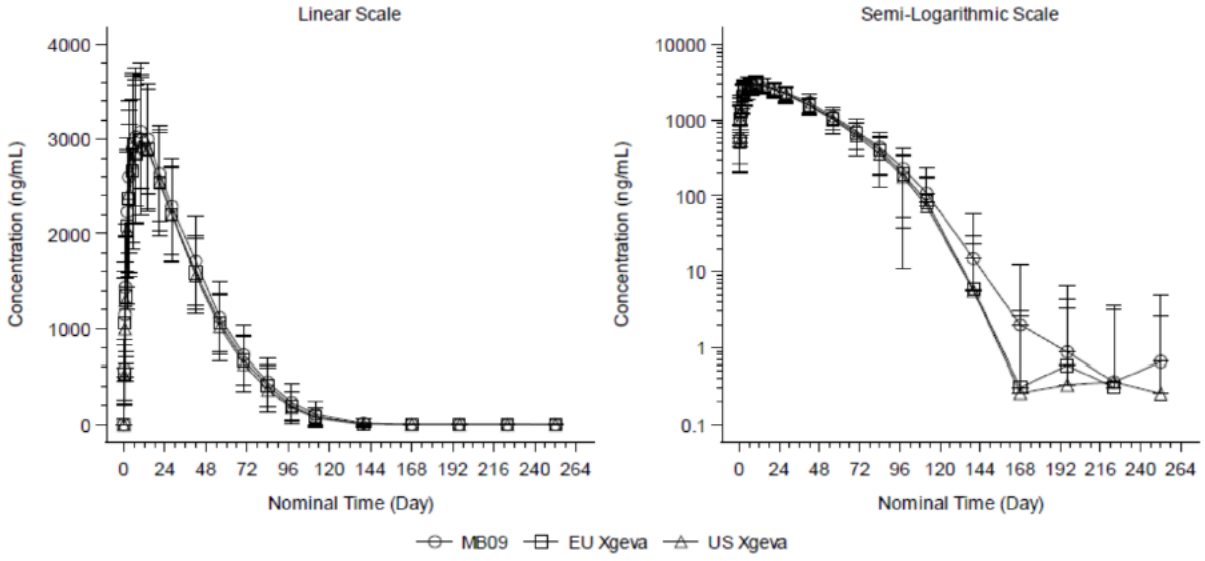
Statistical comparison of PK parameters for MB09 and Xgeva® PK populations in study MB09-A-01-19

PK parameter (unit)	Treatment	Geometric LS means (n)	Comparison	%Ratio	90% CI of the %Ratio
AUC0-last (day*ng/mL)	MB09	150,000 (85)	MB09 / EU-Xgeva	105.93	(99.54, 112.73)
	EU-Xgeva	142,000 (85)	MB09 / US-Xgeva	108.87	(102.30, 115.86)
	US-Xgeva	138,000 (85)	EU-Xgeva / US-Xgeva	102.77	(96.58, 109.37)
Cmax (ng/mL)	MB09	3,290 (85)	MB09 / EU-Xgeva	105.13	(98.86, 111.80)
	EU-Xgeva	3,130 (85)	MB09 / US-Xgeva	104.75	(98.50, 111.40)
	US-Xgeva	3,140 (85)	EU-Xgeva / US-Xgeva	99.64	(93.69, 105.96)

Abbreviations: AUC0-last, area under concentration-time curve from time 0 to the last quantifiable concentration; CI, confidence interval; Cmax, maximum observed serum concentration; LS, least squares; n, number of subjects with evaluable values; %Ratio, ratio of geometric LS means.

The mean serum concentrations of denosumab are shown in Figure. Following single SC doses of MB09, EU-Xgeva® or US-Xgeva®, mean serum concentrations of denosumab increased steadily after dosing until approximately 10 days post-dose, before declining in a mono-exponential manner. Mean serum concentrations were measurable up to the end of study (Day 253) for the MB09 and US-Xgeva® arms and up to Day 225 for the EU-Xgeva® arm.

. Mean serum concentration profiles of denosumab in study MB09-A-01-19 (PK population).



Following a single SC dose of MB09, EU-Xgeva® or US-Xgeva®, systemic exposure to denosumab (AUC0-last, and Cmax) was equivalent across all treatment arms; the 90% CIs around the geometric least square (LS) mean ratio lay within the predefined acceptance limits (80.00%, 125.00%) for the three pairwise comparisons, hence PK equivalence was concluded.

Serum secondary PK parameters of denosumab in study MB09-A-01-19 (PK population)

PK Parameter (unit)	MB09 (N=85)	EU-sourced Xgeva (N=85)	US-sourced Xgeva (N=85)
AUC0-99 (day*ng/mL)	143,000 (25.3)	136,000 (23.1)	133,000 (26.3)
AUC0-∞ (day*ng /mL)	147,000 (26.9)	139,000 (24.3)	136,000 (27.4)
Tmax (day)	10.00 (1.95 – 43.04)	9.99 (2.97 – 28.02)	9.95 (3.02 – 27.99)
t1/2 (days)	12.5 (38.6)	12.4 (37.6)	12.1 (37.2)
CL/F (L/day)	0.238 (26.9)	0.251 (24.3)	0.258 (27.4)
Vz/F (L)	4.28 (34.2)	4.48 (33.0)	4.48 (35.1)

Values are presented as geometric mean (geometric CV%) except for T_{max}, as median (minimum – maximum).

Abbreviations: AUC_{0-99}, area under concentration-time curve from time 0 to Day 99 post-dose; $AUC_{0-\infty}$, area under concentration-time curve from time 0 extrapolated to infinity; CL/F, apparent total body clearance following extravascular administration; CV, coefficient of variation; N, number of subjects in treatment; $t_{1/2}$, terminal phase half-life; T_{max}, time to reach maximum observed serum concentration; Vz/F, apparent volume of distribution during the terminal phase following extravascular administration.

Following single SC doses of MB09, EU- or US-Xgeva®, Cmax of denosumab were attained (Tmax) approximately 10 days post-dose for all treatment arms (median estimates). Thereafter, serum concentrations of denosumab declined with comparable apparent terminal half-lives (t1/2), with geometric mean t1/2 ranging from 12.1 to 12.5 days across all treatment arms.

A non-parametric assessment of Tmax indicated that there was no statistical difference in the time to attain maximum serum concentrations of denosumab between all the three treatment groups.

The secondary PK parameters determined were all similar in the MB09, EU- and US-Xgeva® arms of the study. Therefore, the PK profiles of MB09 and Xgeva® were considered to be comparable.

In conclusion, the study results show that MB09 and Xgeva® display a similar PK profile. Of note, no differences were observed between the US-RMP and the EU-RMP, demonstrating biosimilarity in terms of PK between the differently sourced RMPs.

Pharmacodynamics

Studies MB09-A-01-19 included as a secondary objective comparative PD evaluation between MB09 and the RMP by means of changes in serum C-terminal telopeptide of Type 1 collagen (sCTX) levels. A justification on the use of sCTX as a validate marker is provided in Section 2.7.2.1. Moreover, use of sCTX as a PD endpoint was endorsed by the CHMP during the scientific advice procedure (EMA/CHMP/SAWP/25066/2020; clarification letter EMA/133427/2020).

Several PD parameters were estimated for sCTX using absolute serum concentration values or percent change from baseline (%CfB) values. The following parameters were calculated as PD endpoints for the similarity assessment between MB09 and the RMP: area under the effect *versus* time curve (AUEC) and area under the % inhibition curve (AUIC) of sCTX.

Following MB09, percent change from baseline sCTX levels to day 253 (AUIC0-253) were comparable for all three treatment groups, with just a 2% to 4% difference observed.

Furthermore, for the three pairwise comparisons, the 90% CIs around the geometric LS mean ratios lay within the predefined acceptance limits (80.00%, 125.00%)

Statistical analysis of sCTX PD parameters (AUIC0-253; PD population)

PD Parameter (unit)	Treatment	Geometric LS Means (n)	Comparison	%Ratio	90% CI of the %Ratio
$AUIC_{0-253}$ (day*%)	MB09	18,700 (85)	MB09 / EU Xgeva	103.68	(99.30, 108.24)
	EU-Xgeva	18,000 (85)	MB09 / US Xgeva	101.69	(97.42, 106.15)
	US-Xgeva	18,400 (85)	EU Xgeva / US Xgeva	98.08	(93.95, 102.41)

Abbreviations: $AUIC_{0-253}$, area under the % inhibition curve from time 0 to Day 253 (using %CfB data); CfB, change from baseline; CI, confidence interval; n, number of subjects with evaluable values; %Ratio, ratio of geometric LS means; sCTX, serum C-terminal telopeptide of Type 1 collagen; LS, least squares.

Note: An ANCOVA model was fitted to the natural log transformed PD parameters with treatment and stratification factor (body weight) as fixed effects. For AUEC, the logged pre-dose sCTX concentration (i.e., baseline) was also fitted as a covariate.

In conclusion, percent of change from baseline sCTX levels (AUIC0-253) was comparable for all three treatment groups, hence PD equivalence was concluded based on change from baseline sCTX data.Of note, no differences were observed between the US-RMP and the EU-RMP, demonstrating biosimilarity in terms of PD between the differently sourced RMPs.

Immunogenicity

Comparisons of MB09 and RMP immunogenicity were among the secondary objectives of studies MB09-A-01-19 (healthy volunteers). The validated assays were used for the detection of anti-drug antibodies (ADAs) and neutralising antibodies (NAb) against denosumab.

ADA assay results were positive in 1 (1.2%) subject at Day 169 in MB09 arm. In EU-Xgeva® arm ADA assay results were positive in 1 (1.2%) subject at Days 11, 99, 169, 225, and 253 and in 2 (2.4%) subjects at Day 43. In US-Xgeva® arm, ADA assay results were positive in 1 (1.2%) subject at Day 11. None of the ADAs detected had neutralising capacity.

The number of subjects experiencing treatment-induced immunogenicity was very low, with only 4 of the 255 subjects included in the PK and PD populations assigned an ADA positive status: 1 in the MB09 treatment arm, 2 in the EU-Xgeva® treatment arm and 1 in the US-Xgeva® treatment arm.

As a result, no meaningful impact assessment could be performed and subjects experiencing treatment-induced immunogenicity had negligible impact on the overall study conclusions. For this reason, all PK and PD assessments were based on data from all subjects (i.e., not accounting for ADA status).

Overview of Safety:

In this phase I [MB09-A-01-19 (healthy volunteers)], double-blind, three-arm, parallel group study, which was designed to investigate and compare the PK, PD, safety and immunogenicity profile of MB09 and Xgeva® in healthy male volunteers, single 35 mg SC doses of MB09 and EU- and US-approved Xgeva® were safe and generally well tolerated.

No subjects discontinued due to an adverse event (AE) in either the MB09 or EU-Xgeva® treatment arms (85 subjects/arm). Except a TEAE of adjustment disorder, which was recovering/resolving, all reported treatment-emergent adverse events (TEAEs) resolved by the end of the study.

There was no statistically significant difference between any study treatment arm with respect to the number of subjects reported with at least a TEAE ($p > 0.05$), as determined by Fisher Exact test and adjusted

according to Bonferroni correction method; 18 of 85 subjects (21.2%) with 29 events and 28 of 85 subjects (32.9%) with 40 events reported TEAEs in the MB09 and EU-Xgeva® arms, respectively. The most commonly reported TEAEs were blood creatine phosphokinase (CPK) increased (17 [6.7%] subjects), nasopharyngitis (7 [2.7%] subjects) and blood triglycerides increased (5 [2%] subjects).

Four TEAEs reported in 3 (1.2%) subjects were considered as possibly related to the study treatment by the investigator. Of these, one was a Grade 1 headache in the MB09 arm, 2 were Grade 1 arthralgia episodes in the EU-Xgeva® arm and a Grade 2 rash papular (US-sourced Xgeva® arm), which all resolved without treatment.

The majority of TEAEs were of Grade 2 (30 [11.8] subjects with 44 TEAEs) and Grade 3 (19 [7.5] subjects with 26 TEAEs) in severity; 34 Grade 3 or higher TEAEs were reported in 26 (10.2%) subjects and included AEs of blood CPK increased, blood triglycerides increased, aspartate aminotransferase increased, syncope, hyperkalaemia, osteoma, and depression. None of these TEAEs were related to the study treatment.

There were no deaths during the study. In MB09 arm, 2 serious AEs (SAEs) were reported in 2 (2.4%) subjects: osteoma (Grade 3) and depression (Grade 3). The events were considered serious as they led to hospitalisation. Both SAEs resolved and were not considered as related to the study treatment by the investigator.

Overall, proposed biosimilar (MB09) demonstrated a safety profile similar to that of the RMP in terms of nature, severity, and frequency of the TEAEs. Furthermore, the safety profile of MB09 was within the expectations in the study population. Study demonstrated that MB09 was well tolerated with acceptable safety profile.

5.2 Pharmacokinetic Properties

[Study performed by originator Xgeva]

Absorption

Following subcutaneous administration, bioavailability was 62%.

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

In subjects with advanced cancer, who received multiple doses of 120 mg every 4 weeks an approximate 2-fold accumulation in serum denosumab concentrations was observed and steady-state was achieved by 6 months, consistent with time-independent pharmacokinetics. In subjects who discontinued 120 mg every 4 weeks, the mean half-life was 28 days (range 14 to 55 days).

A population pharmacokinetic analysis did not indicate clinically significant changes in the systemic exposure of denosumab at steady-state with respect to age (18 to 87 years), race/ethnicity (Blacks, Hispanics, Asians and Caucasians explored), gender or solid tumour types. Increasing body weight was associated with decreases in systemic exposure, and vice versa. The alterations were not considered

clinically-relevant, since pharmacodynamic effects based on bone turnover markers were consistent across a wide range of body weight.

Linearity/non-linearity

Denosumab displayed non-linear pharmacokinetics with dose over a wide dose range, but approximately dose-proportional increases in exposure for doses of 60 mg (or 1 mg/kg) and higher. The non-linearity is likely due to a saturable target-mediated elimination pathway of importance at low concentrations.

Special Patient Populations

Renal impairment

In studies of denosumab (60 mg, n = 55 and 120 mg, n = 32) in patients without advanced cancer but with varying degrees of renal function, including patients on dialysis, the degree of renal impairment had no effect on the pharmacokinetics of denosumab; thus dose adjustment for renal impairment is not required. There is no need for renal monitoring with denosumab dosing.

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.

Elderly

No overall differences in safety or efficacy were observed between geriatric patients and younger patients. Controlled clinical studies of denosumab in patients with advanced malignancies involving bone over age 65 revealed similar efficacy and safety in older and younger patients. No dose adjustment is required in elderly patients.

5.3 Preclinical safety data

Since the biological activity of denosumab in animals is specific to nonhuman primates, evaluation of genetically engineered (knockout) mice or use of other biological inhibitors of the RANK/RANKL pathway, such as OPG-Fc and RANK-Fc, were used to evaluate the pharmacodynamic properties of denosumab in rodent models.

In mouse bone metastasis models of oestrogen receptor positive and negative human breast cancer, prostate cancer and non-small cell lung cancer, OPG-Fc reduced osteolytic, osteoblastic, and osteolytic/osteoblastic lesions, delayed formation of de novo bone metastases, and reduced skeletal tumour growth. When OPG-Fc was combined with hormonal therapy (tamoxifen) or chemotherapy (docetaxel) in these models, there was additive inhibition of skeletal tumour growth in breast, and prostate or lung cancer respectively. In a mouse model of mammary tumour induction, RANK-Fc reduced hormone-induced proliferation in mammary epithelium and delayed tumour formation.

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 single and repeated dose toxicity studies in cynomolgus monkeys, denosumab doses resulting in 2.7 to 15 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.

In a study of cynomolgus monkeys dosed with denosumab during the period equivalent to the first trimester of pregnancy, denosumab doses resulting in 9 times greater systemic exposure than the recommended human dose did not induce maternal toxicity or foetal harm during a period equivalent to the first trimester, although foetal lymph nodes were not examined.

In another study of cynomolgus monkeys dosed with denosumab throughout pregnancy at systemic exposures 12-fold higher than the human dose, 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 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.

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.

In preclinical studies knockout mice lacking RANK or RANKL had an absence of lactation due to inhibition of mammary gland maturation (lobulo-alveolar gland development during pregnancy) and exhibited impairment of lymph node formation. Neonatal RANK/RANKL knockout mice exhibited decreased body weight, reduced bone growth, altered growth plates and lack of tooth eruption. Reduced bone growth, altered growth plates and impaired tooth eruption were also seen in studies of neonatal 18 rats administered RANKL inhibitors, and these changes were partially reversible when dosing of RANKL inhibitor was discontinued. Adolescent primates dosed with denosumab at 2.7 and 15 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 3 years.

Once removed from the refrigerator, DNOCLAST® 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 vial in the outer carton in order to protect from light.

6.5 Nature and contents of container

1.7 mL solution in a single use 2R Type I clear glass vial with a 13 mm bromobutyl stopper and an aluminium seal with a plastic flip-off cap.

Pack size of one

6.6 Special precautions for disposal and other handling

- Before administration, the solution should be inspected visually. The solution may contain trace amounts of translucent to white proteinaceous particles. Do not inject the solution if it is cloudy or discoloured.
- Do not shake.
- To avoid discomfort at the site of injection, allow the vial to reach room temperature (up to 25°C) before injecting and inject slowly.
- The entire contents of the vial should be injected.
- A 27 gauge needle is recommended for the administration of denosumab.
- The vial should not be re-entered.

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

Pack Size :
DNOCLAST® 120 mg/1.7 mL solution for injection in vial :
Box of 1 vial
Reg. No. DKIxxxxxxxxxxx

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
L025/10/24
Date of revision : 08 Jul 2026

Abbott

Selebaran kemasan: Informasi untuk pasien

Dnoclast® 120 mg Larutan untuk injeksi
Denosumab

Bacalah semua selebaran ini dengan seksama sebelum Anda mulai menggunakan obat ini karena berisi informasi penting untuk Anda.
- Simpan selebaran ini. Anda mungkin perlu membacanya lagi.
- Jika Anda memiliki pertanyaan lebih lanjut, tanyakan kepada dokter, apoteker, atau perawat Anda.
- Obat ini hanya diresepkan untuk Anda. Jangan memberikannya kepada orang lain. Obat ini dapat membahayakan mereka, meskipun tanda-tanda penyakit mereka sama dengan Anda.
- Jika Anda mengalami efek samping, konsultasikan dengan dokter, apoteker, atau perawat Anda. Termasuk efek samping yang mungkin tidak tercantum dalam selebaran ini. Lihat bagian 4.
- Dokter Anda akan memberikan kartu pengingat pasien, yang berisi informasi keselamatan penting yang perlu Anda ketahui sebelum dan selama pengobatan dengan Dnoclast® .

Isi selebaran ini

1. Apakah Dnoclast® dan apa kegunaannya

Dnoclast® mengandung denosumab, suatu protein (antibodi monoklonal) yang bekerja untuk memperlambat kerusakan tulang yang disebabkan oleh kanker yang menyebar ke tulang (metastasis tulang)

Dnoclast® digunakan pada orang dewasa dengan kanker stadium lanjut untuk mencegah komplikasi serius yang disebabkan oleh metastasis tulang (misalnya patah tulang, tekanan pada sumsum tulang belakang atau kebutuhan untuk menerima terapi radiasi atau pembedahan).

2. Apa yang perlu Anda ketahui sebelum Anda menggunakan Dnoclast®

Jangan menggunakan Dnoclast®
- jika Anda alergi terhadap denosumab atau kandungan lain dari obat ini (tercantum dalam bagian 6).

Petugas kesehatan Anda tidak akan memberikan Dnoclast® kepada Anda jika Anda memiliki kadar kalsium darah yang sangat rendah yang belum diobati.

Petugas kesehatan Anda tidak akan memberikan Dnoclast® kepada Anda jika Anda memiliki luka yang belum sembuh dari operasi gigi atau mulut.

Peringatan dan pencegahan
Konsultasikan dengan dokter Anda sebelum menggunakan Dnoclast® .

Asupan kalsium dan vitamin D
Anda harus mengonsumsi suplemen kalsium dan vitamin D selama menjalani pengobatan dengan denosumab kecuali jika kalsium darah Anda tinggi. Dokter Anda akan mendiskusikan hal ini dengan Anda. Jika kadar kalsium darah Anda rendah, dokter Anda mungkin memutuskan untuk memberikan suplemen kalsium sebelum memulai pengobatan dengan Dnoclast® .

Rendahnya kadar kalsium dalam darah
Segera beritahukan kepada dokter Anda jika Anda mengalami kejang, kedutan, atau kram pada otot, dan/atau mati rasa atau kesemutan pada jari tangan, jari kaki, atau di sekitar mulut, dan/atau kejang, kebingungan, atau kehilangan kesadaran selama pengobatan dengan denosumab. Anda mungkin memiliki kadar kalsium darah yang rendah.

Gangguan ginjal
Beritahukan kepada dokter Anda jika Anda memiliki atau pernah memiliki masalah ginjal yang parah, gagal ginjal atau memerlukan dialisis, yang dapat meningkatkan risiko terkena kalsium darah rendah, terutama jika Anda tidak mengonsumsi suplemen kalsium.

Masalah pada mulut, gigi, atau rahang Anda
Efek samping yang disebut osteonekrosis rahang (kerusakan tulang pada rahang) telah dilaporkan secara umum (dapat mempengaruhi hingga 1 dari 10 orang) pada pasien yang menerima suntikan denosumab untuk kondisi terkait kanker. Osteonekrosis rahang juga dapat terjadi setelah menghentikan pengobatan.

Penting untuk mencoba mencegah berkembangnya osteonekrosis rahang karena ini merupakan kondisi yang menyakitkan dan sulit diobati. Untuk mengurangi risiko terjadinya osteonekrosis pada rahang, ada beberapa tindakan pencegahan yang harus Anda lakukan:

- Sebelum menerima pengobatan, beritahukan kepada dokter/perawat (petugas kesehatan) jika Anda memiliki masalah dengan mulut atau gigi Anda. Dokter Anda harus menunda dimulainya pengobatan jika Anda memiliki luka yang belum sembuh di mulut Anda dari perawatan gigi atau bedah mulut. Dokter Anda mungkin akan merekomendasikan pemeriksaan gigi sebelum memulai pengobatan dengan denosumab.
- Selama pengobatan, Anda harus menjaga kebersihan mulut dengan baik dan melakukan pemeriksaan gigi secara rutin. Jika Anda memakai gigi palsu, Anda harus memastikan bahwa gigi palsu tersebut terpasang dengan benar.
- Jika Anda sedang menjalani perawatan gigi atau akan menjalani operasi gigi (misalnya pencabutan gigi), beritahukan kepada dokter Anda mengenai perawatan gigi Anda dan beritahukan kepada dokter gigi Anda bahwa Anda sedang diobati dengan denosumab.
- Segera hubungi dokter dan dokter gigi Anda jika Anda mengalami masalah pada mulut atau gigi seperti gigi goyang, nyeri atau bengkak, luka yang tidak kunjung sembuh atau keluarnya cairan, karena hal ini dapat merupakan tanda-tanda osteonekrosis rahang.

Pasien yang menjalani kemoterapi dan/atau radioterapi, mengonsumsi steroid atau obat anti- angiogenik (digunakan untuk mengobati kanker), menjalani pembedahan gigi, yang tidak menerima perawatan gigi rutin, memiliki penyakit gusi, atau perokok, mungkin memiliki risiko lebih tinggi terkena osteonekrosis rahang.

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

Kadar kalsium tinggi dalam darah setelah menghentikan pengobatan dengan Dnoclast® . Dokter Anda akan memantau tanda dan gejala kadar kalsium yang tinggi, setelah Anda berhenti menerima denosumab.

Anak-anak dan remaja

Pengunaan denosumab belum diteliti pada anak-anak dan remaja dengan kanker lain yang telah menyebar ke tulang.

Obat-obatan lain dan Dnoclast®
Beritahu dokter atau apoteker Anda jika sedang, baru saja, atau mungkin akan menggunakan obat lain. Ini termasuk obat-obatan yang diperoleh tanpa resep dokter. Sangatlah penting bagi Anda untuk memberi tahu dokter Anda jika Anda sedang diobati dengan

- obat lain yang mengandung denosumab
- bifosfonat

Anda tidak boleh mengonsumsi Dnoclast® bersama dengan obat lain yang mengandung denosumab atau bifosfonat.

Kehamilan dan menyusui
Dnoclast® belum diuji pada wanita hamil. Jika Anda hamil, merasa hamil atau berencana untuk memiliki bayi, mintalah saran dari dokter Anda sebelum menggunakan obat ini. Denosumab tidak dianjurkan untuk digunakan jika Anda sedang hamil. Wanita yang berpotensi melahirkan anak harus menggunakan metode kontrasepsi yang efektif selama pengobatan dengan denosumab dan setidaknya selama 5 bulan setelah menghentikan pengobatan dengan denosumab.

Jika Anda hamil selama pengobatan dengan denosumab atau kurang dari 5 bulan setelah menghentikan pengobatan dengan denosumab, beritahukanlah kepada dokter Anda.

Tidak diketahui apakah denosumab terserap ke dalam ASI. Penting untuk memberi tahu dokter Anda jika Anda sedang menyusui atau berencana untuk melakukannya. Dokter Anda kemudian akan membantu Anda memutuskan apakah akan berhenti menyusui, atau berhenti mengonsumsi denosumab, dengan mempertimbangkan manfaat menyusui bagi bayi dan manfaat denosumab bagi ibu.

Jika Anda sedang menyusui selama pengobatan dengan Dnoclast® , beritahukanlah kepada dokter Anda.

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

Mengemudi dan menjalankan mesin

Dnoclast® berpengaruh kecil atau tidak memiliki pengaruh terhadap kemampuan mengemudi dan menggunakan mesin.

Dnoclast® mengandung sorbitol
Obat ini mengandung 78 mg sorbitol dalam setiap vial.

Dnoclast® mengandung natrium

Obat ini mengandung kurang dari 1 mmol natrium (23 mg) per 120 mg, yang pada dasarnya berarti 'bebas natrium'.

Dnoclast® mengandung polysorbate 20 (E432)

Obat ini mengandung 0,17 mg Polysorbate 20 (E432) pada tiap vial yang setara dengan 0.1 mg/mL. Polysorbate dapat menyebabkan reaksi alergi. Beritahu dokter Anda jika Anda memiliki alergi.

3. Bagaimana cara menggunakan Dnoclast®

Dnoclast® harus diberikan di bawah tanggung jawab petugas kesehatan.

Dosis Dnoclast® yang direkomendasikan adalah 120 mg yang diberikan setiap 4 minggu sekali, berupa suntikan tunggal di bawah kulit (subkutan). Dnoclast® akan disuntikkan ke paha, perut, atau lengan atas.

Jangan dikocok.

Anda juga harus mengonsumsi suplemen kalsium dan vitamin D selama menjalani pengobatan dengan denosumab, kecuali jika Anda memiliki kelebihan kalsium dalam darah. Dokter Anda akan mendiskusikan hal ini dengan Anda. Jika Anda memiliki pertanyaan lebih lanjut mengenai penggunaan obat ini, tanyakan kepada dokter, apoteker, atau perawat Anda.

4. Kemungkinan Efek Samping

Seperti semua obat, obat ini dapat menyebabkan efek samping, meskipun tidak semua orang mengalaminya.

Segera beritahu dokter Anda jika Anda mengalami gejala-gejala ini ketika diobati dengan Dnoclast® (dapat mempengaruhi lebih dari 1 dari 10 orang):
- kejang, kedutan, kram pada otot, mati rasa atau kesemutan pada jari tangan, jari kaki atau di sekitar mulut dan/atau kejang, kebingungan atau kehilangan kesadaran. Ini bisa merupakan tanda bahwa Anda memiliki kadar kalsium darah yang rendah. Kalsium darah yang rendah juga dapat menyebabkan perubahan irama jantung yang disebut *QT prolongation*, yang dapat dilihat dengan elektrokardiogram (EKG).

Segera beritahukan kepada dokter dan dokter gigi Anda jika Anda mengalami gejala-gejala ini selama pengobatan dengan denosumab atau setelah menghentikan pengobatan (dapat terjadi pada 1 dari 10 orang):
- rasa sakit yang terus-menerus pada mulut dan/atau rahang, dan/atau pembengkakan atau luka yang tidak kunjung sembuh pada mulut atau rahang, keluarnya cairan, mati rasa atau rasa berat pada rahang, atau gigi yang goyah dapat menjadi tanda kerusakan tulang pada rahang (osteonekrosis).

Efek samping sangat umum (dapat dialami lebih dari 1 dari 10 orang):
- nyeri tulang, sendi, dan/atau otot yang terkadang parah,
- sesak napas,
- diare.

Efek samping umum (dapat dialami hingga 1 dari 10 orang):
- kadar fosfat darah yang rendah (hipofosfatemia),
- pencabutan gigi,
- keringat berlebih,
- pada pasien dengan kanker stadium lanjut: berkembangnya jenis kanker lain.

Efek samping yang tidak umum (dapat dialami hingga 1 dari 100 orang):
- kadar kalsium yang tinggi dalam darah (hiperkalsemia) dapat terjadi setelah menghentikan pengobatan pada pasien dengan tumor sel raksasa pada tulang.
- nyeri baru atau yang tidak biasa pada pinggul, selangkangan, atau paha Anda (ini mungkin indikasi awal kemungkinan patah tulang paha),
- ruam yang mungkin terjadi pada kulit atau luka di mulut (erupsi obat lichenoid).

Efek samping yang sangat jarang (dapat dialami hingga 1 dari 1.000 orang):
- reaksi alergi (misalnya mengi atau kesulitan bernapas; pembengkakan pada wajah, bibir, lidah,

tenggorokan, atau bagian tubuh lainnya; ruam, gatal, atau gatal-gatal pada kulit). Dalam kasus langka, reaksi alergi bisa sangat parah.

Tidak diketahui (frekuensi tidak dapat diperkirakan dari data yang tersedia):
- konsultasikan dengan dokter Anda jika Anda mengalami sakit telinga, keluar cairan dari telinga dan/atau infeksi telinga. Ini bisa merupakan tanda-tanda kerusakan tulang di telinga.

Pelaporan efek samping
Jika Anda mengalami efek samping manapun, konsultasikan dengan dokter atau apoteker Anda. Termasuk efek samping yang mungkin tidak tercantum dalam selebaran ini. Anda juga dapat melaporkan efek samping secara langsung melalui email pv.indonesia@abbott.com.

Dengan melaporkan efek samping, Anda dapat membantu memberikan lebih banyak informasi tentang keamanan obat ini.

5. Cara penyimpanan Dnoclast®

Jauhkan obat ini dari pandangan dan jangkauan anak-anak. Jangan gunakan obat ini setelah tanggal kadaluwarsa yang tertera pada label dan karton setelah EXP. Tanggal kadaluwarsa mengacu pada hari terakhir pada bulan tersebut.

Simpan dalam lemari es (2°C-8°C).
Jangan dibekukan.
Simpan vial di dalam karton luar untuk melindungi dari cahaya.

Vial dapat dibiarkan di luar lemari es untuk mencapai suhu ruangan (hingga 25°C) sebelum disuntikkan. Hal ini akan membuat penyuntikan lebih nyaman. Setelah vial Anda dibiarkan mencapai suhu ruangan (hingga 25°C), vial harus digunakan dalam waktu 30 hari.

Jangan membuang obat apa pun melalui air limbah atau limbah rumah tangga. Tanyakan kepada apoteker Anda bagaimana cara membuang obat yang sudah tidak digunakan lagi. Langkah-langkah ini akan membantu melindungi lingkungan.

6. Isi kemasan dan informasi lainnya

Kandungan dalam Dnoclast®
- Zat aktifnya adalah denosumab. Setiap vial mengandung 120 mg denosumab dalam 1,7 mL larutan (setara dengan 70 mg/mL).
- Kandungan lainnya adalah asam asetat, glasial, natrium hidroksida, sorbitol (E420), polisorbat 20 dan air untuk suntikan

Tampilan Dnoclast® dan isi kemasannya

Dnoclast® adalah larutan untuk injeksi (penyuntikan).

Dnoclast® adalah larutan bening, tidak berwarna hingga kekuningan. Dnoclast® mungkin mengandung sejumlah kecil partikel bening hingga putih.

Besar Kemasan dan Nomor Registrasi

Dnoclast® tersedia dalam kemasan 1 vial sekali pakai berisi Denosumab larutan injeksi 120 mg/1.7 mL
Reg.No DKIxxxxxxxxxxx

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