

ANNEX I
SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

XGEVA 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 effects

Each 1.7 mL of solution contains 78 mg sorbitol (E420).

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for injection (injection).

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

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Prevention of skeletal related events (pathological fracture, radiation to bone, spinal cord compression or surgery to bone) in adults with advanced malignancies involving bone (see section 5.1).

Treatment of adults and skeletally mature adolescents with giant cell tumour of bone that is unresectable or where surgical resection is likely to result in severe morbidity.

4.2 Posology and method of administration

XGEVA should be administered under the responsibility of a healthcare professional.

Posology

Supplementation of at least 500 mg calcium and 400 IU vitamin D daily is required in all patients, unless hypercalcaemia is present (see section 4.4).

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

Prevention of skeletal related events in adults with advanced malignancies involving bone

The recommended dose is 120 mg administered as a single subcutaneous injection once every 4 weeks into the thigh, abdomen or upper arm.

Giant cell tumour of bone

The recommended dose of XGEVA is 120 mg administered as a single subcutaneous injection once every 4 weeks into the thigh, abdomen or upper arm with additional 120 mg doses on days 8 and 15 of treatment of the first month of therapy.

Patients in the phase II study who underwent complete resection of giant cell tumour of bone did receive an additional 6 months of treatment following the surgery as per study protocol.

Patients with giant cell tumour of bone should be evaluated at regular intervals to determine whether they continue to benefit from treatment. In patients whose disease is controlled by XGEVA, the effect of interruption or cessation of treatment has not been evaluated, however limited data in these patients does not indicate a rebound effect upon cessation of treatment.

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).

Hepatic impairment

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

Elderly patients (age \geq 65)

No dose adjustment is required in elderly patients (see section 5.2).

Paediatric population

The safety and efficacy of XGEVA have not been established in paediatric patients (age < 18) other than skeletally mature adolescents with giant cell tumour of bone.

XGEVA is not recommended in paediatric patients (age < 18) other than skeletally mature adolescents with giant cell tumour of bone (see section 4.4).

Treatment of skeletally mature adolescents with giant cell tumour of bone that is unresectable or where surgical resection is likely to result in severe morbidity: the posology is the same as in adults.

Inhibition of RANK/RANK ligand (RANKL) in animal studies has been coupled to inhibition of bone growth and lack of tooth eruption, and these changes were partially reversible upon cessation of RANKL inhibition (see section 5.3).

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

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 XGEVA.

Hypocalcaemia can occur at any time during therapy with XGEVA. Monitoring of calcium levels should be conducted (i) prior to the initial dose of XGEVA, (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 XGEVA, 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 XGEVA (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 XGEVA 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 XGEVA 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 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 XGEVA 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 giant cell tumour of bone and in patients with growing skeletons

Clinically significant hypercalcaemia requiring hospitalisation and complicated by acute renal injury has been reported in XGEVA-treated patients with giant cell tumour of bone weeks to months following treatment discontinuation.

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).

XGEVA 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.

Others

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

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

Malignancy in giant cell tumour of bone or progression to metastatic disease is an infrequent event and a known risk in patients with giant cell tumour of bone. Patients should be monitored for radiological signs of malignancy, new radiolucency or osteolysis. Available clinical data does not suggest an increased risk of malignancy in giant cell tumour of bone patients treated with XGEVA.

Warnings for excipients

This medicinal product contains sorbitol. Patients with rare hereditary problems of fructose intolerance should not take this medicinal product.

This medicinal product contains less than 1 mmol sodium (23 mg) per 120 mg, i.e. essentially 'sodium-free'.

4.5 Interaction with other medicinal products and other forms of interaction

No interaction studies have been performed.

In clinical trials, XGEVA 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 Fertility, 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).

XGEVA 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 XGEVA. Any effects of XGEVA 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 XGEVA 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

XGEVA 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 XGEVA.

Hypocalcaemia has very commonly been reported following XGEVA 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 XGEVA 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 XGEVA.

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 ($\geq 1/10$), common ($\geq 1/100$ to $< 1/10$), uncommon ($\geq 1/1,000$ to $< 1/100$), rare ($\geq 1/10,000$ 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 advanced malignancies involving bone, multiple myeloma, or with giant cell tumour of 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	Drug hypersensitivity ¹
	Rare	Anaphylactic reaction ¹
Metabolism and nutrition disorders	Very common	Hypocalcaemia ^{1,2}
	Common	Hypophosphataemia
	Uncommon	Hypercalcaemia following treatment discontinuation in patients with giant cell tumour of bone ³
Respiratory, thoracic and mediastinal disorders	Very common	Dyspnoea
Gastrointestinal disorders	Very common	Diarrhoea
	Common	Tooth extraction
Skin and subcutaneous tissue disorders	Common	Hyperhidrosis
	Uncommon	Lichenoid drug eruptions ¹
Musculoskeletal and connective tissue disorders	Very common	Musculoskeletal pain ¹
	Common	Osteonecrosis of the jaw ¹
	Uncommon	Atypical femoral fracture ¹
	Not known	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 XGEVA 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 XGEVA 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 XGEVA 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 XGEVA 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 XGEVA 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 XGEVA and 0.2% of patients treated with zoledronic acid (see section 4.4).

In two phase II single-arm clinical trials in patients with giant cell tumour of bone, hypocalcaemia was reported in 5.7% of patients. None of the adverse events was considered serious.

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 XGEVA 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 XGEVA (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 (number of events per 100 patient years) of confirmed ONJ in the XGEVA group (median exposure of 19.4 months; range 1 - 52), was 2.0% during the first year of treatment, 5.0% in the second year, and 4.5% per year 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 XGEVA (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 XGEVA 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 (number of events per 100 patient years) of confirmed ONJ was 1.1% during the first year of treatment, 3.7% in the second year and 4.6% per year thereafter. The median time to ONJ was 20.6 months (range: 4 - 53).

In two phase II single-arm clinical trials in patients with giant cell tumour of bone, ONJ occurred in 2.3% (12 of 523) of patients treated with XGEVA (median overall exposure of 20.3 months; range: 0 - 83.4). The patient-year adjusted incidence of ONJ was 0.2% during the first year of treatment and 1.7% in the second year. The median time to ONJ was 19.4 months (range: 11 - 40). Based on duration of exposure, there are insufficient data in giant cell tumour of bone patients to assess risk of ONJ beyond 2 years.

In a phase III trial in patients with non-metastatic prostate cancer (a patient population for which XGEVA is not indicated), with longer treatment exposure of up to 7 years, the patient-year adjusted incidence of confirmed ONJ was 1.1% during the first year of treatment, 3.0% in the second year, and 7.1% per year thereafter.

Drug related hypersensitivity reactions

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

Atypical fractures of the femur

In the clinical trial programme, atypical femoral fractures have been reported uncommonly in patients treated with XGEVA 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 XGEVA. 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 XGEVA (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

XGEVA was studied in an open-label trial that enrolled 18 skeletally mature adolescents with giant cell tumour of bone. Based on these limited data, the adverse event profile appeared to be similar to adults.

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 XGEVA 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 XGEVA 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 the national reporting system listed in [Appendix V](#).

4.9 Overdose

There is no experience with overdose in clinical studies. XGEVA has been administered in clinical studies using doses up to 180 mg every 4 weeks and 120 mg weekly for 3 weeks.

5. PHARMACOLOGICAL 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 cancer-induced bone destruction.

Giant cell tumours of bone are characterised by neoplastic stromal cells expressing RANK ligand and osteoclast-like giant cells expressing RANK. In patients with giant cell tumour of bone, denosumab binds to RANK ligand, significantly reducing or eliminating osteoclast-like giant cells. Consequently, osteolysis is reduced and proliferative tumour stroma is replaced with non-proliferative, differentiated, densely woven new bone.

Pharmacodynamic effects

In phase II clinical studies of patients with advanced malignancies involving bone, subcutaneous (SC) dosing of XGEVA 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 XGEVA treatment (120 mg every Q4W).

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 3 years tested positive for non neutralising binding antibodies with no evidence of altered pharmacokinetics, toxicity, or clinical response.

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

Efficacy and safety of 120 mg XGEVA 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 XGEVA to zoledronic acid, patients were offered open-label XGEVA 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.

XGEVA 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).

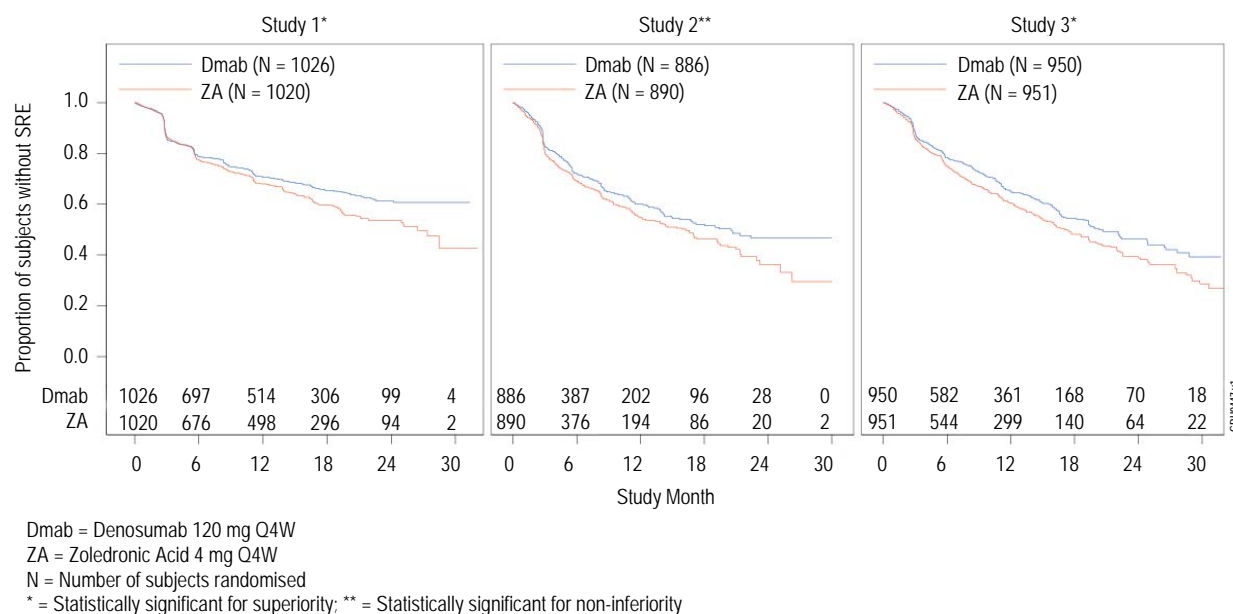
Table 2. Efficacy results in patients with advanced malignancies involving bone

	Study 1 breast cancer		Study 2 other solid tumours** or multiple myeloma		Study 3 prostate cancer		Combined advanced cancer	
	XGEVA	zoledronic acid	XGEVA	zoledronic acid	XGEVA	zoledronic acid	XGEVA	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



Disease progression and overall survival with bone metastases from solid tumours

Disease progression was similar between XGEVA 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 XGEVA 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 XGEVA in non-small cell lung cancer (hazard ratio [95% 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 XGEVA 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 XGEVA 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 XGEVA compared to zoledronic acid (198 versus 143 days) (p = 0.0002).

Clinical efficacy in patients with multiple myeloma

XGEVA was evaluated in an international, randomised (1:1), double-blind, active-controlled study comparing XGEVA 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 XGEVA 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 XGEVA 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

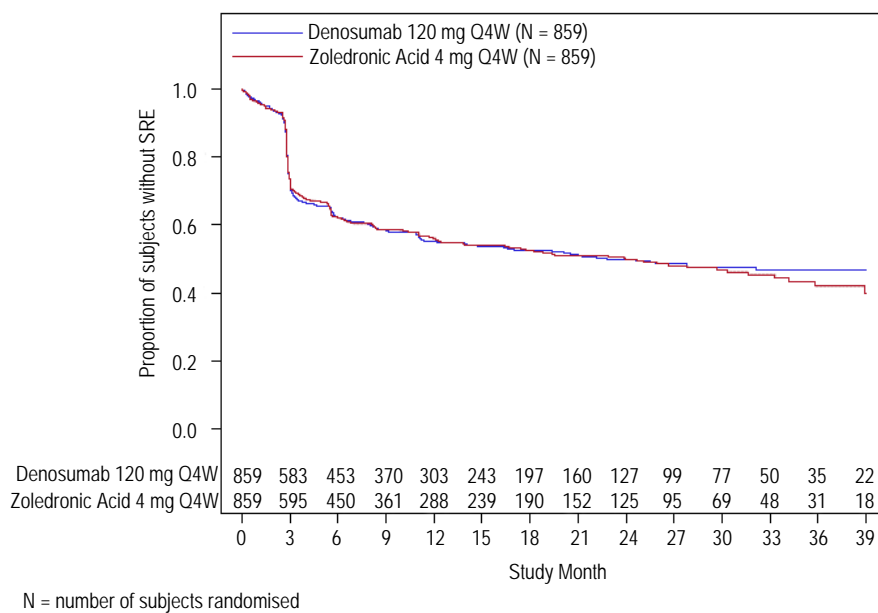


Table 3. Efficacy results for XGEVA compared to zoledronic acid in patients with newly diagnosed multiple myeloma

	XGEVA (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

Clinical efficacy and safety in adults and skeletally mature adolescents with giant cell tumour of bone

The safety and efficacy of XGEVA was studied in two phase II open-label, single-arm trials (studies 5 and 6) that enrolled 529 patients with giant cell tumour of bone that was either unresectable or for which surgery would be associated with severe morbidity.

Study 5 enrolled 37 adult patients with histologically confirmed unresectable or recurrent giant cell tumour of bone. Response criteria included elimination of giant cells based on histopathology or lack of progression by radiography.

Of the 35 patients included in the efficacy analysis, 85.7% (95% CI: 69.7, 95.2) had a treatment response to XGEVA. All 20 patients (100%) with histology assessments responded. Of the remaining 15 patients, 10 (67%) radiographic measurements showed no progression of the target lesion.

Study 6 enrolled 507 adult or skeletally mature adolescents with giant cell tumour of bone and evidence of measurable active disease.

In Cohort 1 (patients with surgically unsalvageable disease), median time to disease progression was not reached, 21 of the 258 treated patients had disease progression. In Cohort 2 (patients with surgically salvageable disease whose planned surgery was associated with severe morbidity), 209 of the 228 evaluable patients treated with XGEVA had not undergone surgery by month 6. Overall of 225 patients for whom giant cell tumours of bone surgery (excluding lung metastases only) was planned, 109 had no surgery performed and 84 underwent a less morbid procedure than planned at baseline. The median time to surgery was 261 days.

Upon enrolment of 305 patients in studies 5 and 6 a retrospective independent review of radiographic imaging data was performed. One hundred and ninety had at least 1 evaluable time point response and were included in the analysis (table 4). Overall, XGEVA achieved objective tumour responses in

71.6% (95% CI: 64.6, 77.9) of patients (table 4) assessed by any of the modalities, with the majority of responses defined by a reduction in fluorodeoxyglucose PET activity or increase in density measured in CT/HU, only 25.1% of the patients had a response per RECIST. The median time to response was 3.1 months (95% CI: 2.89, 3.65). The median duration of response was not estimable (four patients experienced disease progressions following an objective response). In 190 subjects evaluable for objective tumour response, 55 subjects had giant cell tumour of bone surgery, out of which 40 subjects had complete resections.

Table 4. Objective treatment response in patients with giant cell tumour of bone

	Number of patients evaluable for response	Number of patients with an objective response	Proportion (%) (95% CI)¹
Based on best response	190	136	71.6 (64.6, 77.9)
RECIST 1.1 ²	187	47	25.1 (19.1, 32.0)
EORTC ³	26	25	96.2 (80.4, 99.9)
Density/Size ⁴	176	134	76.1 (69.1, 82.2)

¹ CI = Exact Confidence Interval

² RECIST 1.1: Modified Response Evaluation Criteria in Solid Tumours to evaluate tumour burden based on computed tomography (CT)/magnetic resonance imaging (MRI)

³ EORTC: Modified European Organisation for Research and Treatment of Cancer criteria to evaluate metabolic response using fluorodeoxyglucose positron emission tomography (FDG-PET)

⁴ Density/Size: Modified Inverse Choi criteria to evaluate tumour size and density using Hounsfield units based on CT/MRI

Effect on pain

Upon enrolment of 282 patients, in Study 6 cohorts 1 and 2 combined, a clinically meaningful reduction in worst pain (i.e. ≥ 2 -point decrease from baseline) was reported for 31.4% of patients at risk (i.e. those who had a worst pain score of ≥ 2 at baseline) within 1 week of treatment, and $\geq 50\%$ at week 5. These pain improvements were maintained at all subsequent evaluations. Baseline pre-treatment analgesic use in cohort 1 and cohort 2 was graded on a seven point scale, where 74.8% of patients reported no or mild analgesic use (i.e. analgesic score ≤ 2) and 25.2% of patients used strong opioids (i.e. analgesic score 3 to 7).

Paediatric population

The European Medicines Agency has waived the obligation to submit the results of studies with XGEVA in all subsets of the paediatric population in the prevention of skeletal related events in patients with bone metastases and subsets of the paediatric population below the age of 12 in the treatment of giant cell tumour of bone (see section 4.2 for information on paediatric use).

In Study 6, XGEVA has been evaluated in a subset of 18 adolescent patients (aged 13-17 years) with giant cell tumour of bone who had reached skeletal maturity defined by at least 1 mature long bone (e.g. closed epiphyseal growth plate of the humerus) and body weight ≥ 45 kg. An objective response was observed for four of six evaluable adolescents in an interim analysis of Study 6. An investigator assessment reported that all 18 adolescent patients had a best response of stable disease or better (complete response in 2 patients, partial response in 8 patients, and stable disease in 8 patients). The European Medicines Agency has deferred the obligation to submit the final results of this study.

5.2 Pharmacokinetic properties

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 with multiple myeloma who received 120 mg every 4 weeks, median trough levels varied by less than 8% between months 6 and 12. In subjects with giant cell tumour of bone who received 120 mg every 4 weeks with a loading dose on days 8 and 15, steady-state levels were achieved within the first month of treatment. Between weeks 9 and 49, median trough levels varied by less than 9%. 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 or patients with multiple myeloma. 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.

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 XGEVA 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 XGEVA 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.

Paediatric population

The pharmacokinetic profile in paediatric populations has not been assessed.

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 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

3 years.

Once removed from the refrigerator, XGEVA 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 vial (type I glass) with stopper (fluoropolymer coated elastomeric) and seal (aluminium) with flip-off cap.

Pack sizes of one, three or four.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

- Before administration, the XGEVA 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.

7. MARKETING AUTHORISATION HOLDER

Amgen Europe B.V.
Minervum 7061,
4817 ZK Breda,
The Netherlands

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/11/703/001
EU/1/11/703/002
EU/1/11/703/003

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 13 July 2011
Date of latest renewal: 4 April 2016

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency <http://www.ema.europa.eu/>.

ANNEX II

- A. MANUFACTURER OF THE BIOLOGICAL ACTIVE SUBSTANCE AND MANUFACTURERS RESPONSIBLE FOR BATCH RELEASE**
- B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE**
- C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION**
- D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT**

A. MANUFACTURER OF THE BIOLOGICAL ACTIVE SUBSTANCE AND MANUFACTURERS RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer of the biological active substance

Amgen Singapore Manufacturing
1 Tuas View Drive
Singapore 637026

Name and address of the manufacturers responsible for batch release

Amgen Europe B.V.
Minervum 7061,
4817 ZK Breda,
The Netherlands

Amgen Technology (Ireland) Unlimited Company
Pottery Road
Dun Laoghaire
Co Dublin
Ireland

Amgen NV
Telecomlaan 5-7
1831 Diegem
Belgium

The printed package leaflet of the medicinal product must state the name and address of the manufacturer responsible for the release of the concerned batch.

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

• **Periodic Safety Update Reports**

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

• **Risk Management Plan (RMP)**

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing Authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.
- **Additional risk minimisation measures**

The MAH shall ensure that a patient reminder card regarding osteonecrosis of the jaw is implemented.

ANNEX III
LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON

1. NAME OF THE MEDICINAL PRODUCT

XGEVA 120 mg solution for injection
denosumab

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each vial contains 120 mg of denosumab in 1.7 mL of solution (70 mg/mL).

3. LIST OF EXCIPIENTS

Acetic acid, glacial, sodium hydroxide, sorbitol (E420), polysorbate 20, water for injections.

4. PHARMACEUTICAL FORM AND CONTENTS

Solution for injection.

1 single use vial

3 single use vials

4 single use vials

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.

Subcutaneous use.

Do not shake.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator.
Do not freeze.
Keep the vial in the outer carton in order to protect from light.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Amgen Europe B.V.
Minervum 7061,
4817 ZK Breda,
The Netherlands

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/11/703/001 1 single use vial
EU/1/11/703/002 4 single use vials
EU/1/11/703/003 3 single use vials

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

xgeva

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER – HUMAN READABLE DATA

PC
SN
NN

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS
VIAL LABEL

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

XGEVA 120 mg injection
denosumab
SC

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

1.7 mL

6. OTHER

B. PACKAGE LEAFLET

Package leaflet: Information for the patient

XGEVA 120 mg solution for injection denosumab

Read all of this leaflet carefully before you start using this medicine because it contains important information for you.

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor, pharmacist, or nurse.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. See section 4.
- Your doctor will give you a patient reminder card, which contains important safety information you need to be aware of before and during your treatment with XGEVA.

What is in this leaflet

1. What XGEVA is and what it is used for
2. What you need to know before you use XGEVA
3. How to use XGEVA
4. Possible side effects
5. How to store XGEVA
6. Contents of the pack and other information

1. What XGEVA is and what it is used for

XGEVA contains denosumab, a protein (monoclonal antibody) that works to slow down bone destruction caused by cancer spreading to the bone (bone metastasis) or by giant cell tumour of bone.

XGEVA is used in adults with advanced cancer to prevent serious complications caused by bone metastasis (e.g. fracture, pressure on the spinal cord or the need to receive radiation therapy or surgery).

XGEVA is also used to treat giant cell tumour of bone, which cannot be treated by surgery or where surgery is not the best option, in adults and adolescents whose bones have stopped growing.

2. What you need to know before you use XGEVA

Do not use XGEVA:

- if you are allergic to denosumab or any of the other ingredients of this medicine (listed in section 6).

Your healthcare professional will not administer XGEVA to you if you have a very low level of calcium in your blood which has not been treated.

Your healthcare professional will not administer XGEVA to you if you have unhealed wounds from dental or oral surgery.

Warnings and precautions

Talk to your doctor before using XGEVA.

Calcium and vitamin D supplementation

You should take calcium and vitamin D supplements while being treated with XGEVA unless your blood calcium is high. Your doctor will discuss this with you. If the level of calcium in your blood is low, your doctor may decide to give you calcium supplements before you start treatment with XGEVA.

Low calcium levels in the blood

Please tell your doctor immediately if you have spasms, twitches, or cramps in your muscles, and/or numbness or tingling in your fingers, toes or around your mouth and/or seizures, confusion or loss of consciousness while being treated with XGEVA. You may have low levels of calcium in your blood.

Renal impairment

Tell your doctor if you have or have had severe kidney problems, kidney failure or have needed dialysis, which may increase your risk of getting low blood calcium, especially if you do not take calcium supplements.

Problems with your mouth, teeth or jaw

A side effect called osteonecrosis of the jaw (bone damage in the jaw) has been reported commonly (may affect up to 1 in 10 people) in patients receiving XGEVA injections for cancer-related conditions. Osteonecrosis of the jaw can also occur after stopping treatment.

It is important to try to prevent osteonecrosis of the jaw developing as it may be a painful condition that can be difficult to treat. In order to reduce the risk of developing osteonecrosis of the jaw, there are some precautions you should take:

- Before receiving treatment, tell your doctor/nurse (healthcare professional) if you have any problems with your mouth or teeth. Your doctor should delay the start of your treatment if you have unhealed wounds in your mouth from dental procedures or oral surgery. Your doctor may recommend a dental examination before you start treatment with XGEVA.
- While being treated, you should maintain good oral hygiene and receive routine dental check-ups. If you wear dentures you should make sure these fit properly.
- If you are under dental treatment or will undergo dental surgery (e.g. tooth extractions), inform your doctor about your dental treatment and tell your dentist that you are being treated with XGEVA.
- Contact your doctor and dentist immediately if you experience any problems with your mouth or teeth such as loose teeth, pain or swelling, non-healing of sores or discharge, as these could be signs of osteonecrosis of the jaw.

Patients undergoing chemotherapy and/or radiotherapy, taking steroids or anti-angiogenic medicines (used to treat cancer), undergoing dental surgery, who do not receive routine dental care, have gum disease or who are smokers, may have a higher risk of developing osteonecrosis of the jaw.

Unusual thigh bone fractures

Some people have developed unusual fractures in their thigh bone while being treated with XGEVA. Contact your doctor if you experience new or unusual pain in your hip, groin, or thigh.

High calcium levels in the blood after stopping treatment with XGEVA

Some patients with giant cell tumour of the bone have developed high calcium levels in the blood weeks to months after stopping treatment. Your doctor will monitor you for signs and symptoms of high levels of calcium, after you stop receiving XGEVA.

Children and adolescents

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

Other medicines and XGEVA

Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines. This includes medicines obtained without a prescription. It is especially important that you tell your doctor if you are being treated with

- another medicine containing denosumab
- a bisphosphonate

You should not take XGEVA together with other medicines containing denosumab or bisphosphonates.

Pregnancy and breast-feeding

XGEVA has not been tested in pregnant women. It is important to tell your doctor if you are pregnant, think you may be pregnant, or plan to get pregnant. XGEVA is not recommended for use if you are pregnant. Women of child-bearing potential should use effective methods of contraception while being treated with XGEVA and for at least 5 months after stopping treatment with XGEVA.

If you become pregnant during treatment with XGEVA or less than 5 months after stopping treatment with XGEVA, please inform your doctor.

It is not known whether XGEVA is excreted in breast milk. It is important to tell your doctor if you are breast-feeding or plan to do so. Your doctor will then help you decide whether to stop breast-feeding or whether to stop taking XGEVA, considering the benefit of breast-feeding to the baby and the benefit of XGEVA to the mother.

If you are nursing during treatment with XGEVA, please inform your doctor.

Ask your doctor or pharmacist for advice before taking any medicine.

Driving and using machines

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

XGEVA contains sorbitol

If you have been told by your doctor that you have an intolerance to some sugars, contact your doctor before taking this medicine, since it contains sorbitol (E420).

XGEVA contains sodium

This medicine contains less than 1 mmol sodium (23 mg) per 120 mg, i.e. essentially 'sodium-free'.

3. How to use XGEVA

XGEVA should be administered under the responsibility of a healthcare professional.

The recommended dose of XGEVA is 120 mg administered once every 4 weeks, as a single injection under the skin (subcutaneous). XGEVA will be injected into your thigh, abdomen or upper arm. If you are being treated for giant cell tumour of bone, you will receive an additional dose 1 week and 2 weeks after the first dose.

Do not shake.

You should also take calcium and vitamin D supplements while being treated with XGEVA unless you have an excess of calcium in the blood. Your doctor will discuss this with you.

If you have any further questions on the use of this medicine, ask your doctor, pharmacist or nurse.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

Please tell your doctor immediately if you develop any of these symptoms while being treated with XGEVA (may affect more than 1 in 10 people):

- spasms, twitches, cramps in your muscles, numbness or tingling in your fingers, toes or around your mouth and/or seizures, confusion or loss of consciousness. These could be signs that you have low calcium levels in the blood. Low calcium in the blood may also lead to a change in heart rhythm called QT prolongation, which is seen by electrocardiogram (ECG).

Please tell your doctor and dentist immediately if you experience any of these symptoms while being treated with XGEVA or after stopping treatment (may affect up to 1 in 10 people):

- persistent pain in the mouth and/or jaw, and/or swelling or non-healing of sores in the mouth or jaw, discharge, numbness or feeling of heaviness in the jaw, or loosening of a tooth could be signs of bone damage in the jaw (osteonecrosis).

Very common side effects (may affect more than 1 in 10 people):

- bone, joint, and/or muscle pain which is sometimes severe,
- shortness of breath,
- diarrhoea.

Common side effects (may affect up to 1 in 10 people):

- low phosphate levels in the blood (hypophosphataemia),
- removal of a tooth,
- excessive sweating,
- in patients with advanced cancer: development of another form of cancer.

Uncommon side effects (may affect up to 1 in 100 people):

- high calcium levels in the blood (hypercalcaemia) after stopping treatment in patients with giant cell tumour of the bone,
- new or unusual pain in your hip, groin or thigh (this may be an early indication of a possible fracture of the thigh bone),
- rash that may occur on the skin or sores in the mouth (lichenoid drug eruptions).

Rare side effects (may affect up to 1 in 1,000 people):

- allergic reactions (e.g. wheezing or difficulty breathing; swelling of the face, lips, tongue, throat or other parts of the body; rash, itching or hives on the skin). In rare cases allergic reactions may be severe.

Not known (frequency cannot be estimated from the available data):

- Talk to your doctor if you have ear pain, discharge from the ear, and/or an ear infection. These could be signs of bone damage in the ear.

Reporting of side effects

If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via [the national reporting system](#) listed in [Appendix V](#). By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store XGEVA

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the label and carton after EXP. The expiry date refers to the last day of that month.

Store in a refrigerator (2°C – 8°C).

Do not freeze.

Keep the vial in the outer carton in order to protect from light.

The vial may be left outside the refrigerator to reach room temperature (up to 25°C) before injection. This will make the injection more comfortable. Once your vial has been left to reach room temperature (up to 25°C), it must be used within 30 days.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help to protect the environment.

6. Contents of the pack and other information

What XGEVA contains

- The active substance is denosumab. Each vial contains 120 mg of denosumab in 1.7 mL of solution (corresponding to 70 mg/mL).
- The other ingredients are acetic acid, glacial, sodium hydroxide, sorbitol (E420), polysorbate 20 and water for injections.

What XGEVA looks like and contents of the pack

XGEVA is a solution for injection (injection).

XGEVA is a clear, colourless to slightly yellow solution. It may contain trace amounts of clear to white particles.

Each pack contains one, three or four single use vials.

Not all pack sizes may be marketed.

Marketing Authorisation Holder and Manufacturer

Amgen Europe B.V.
Minervum 7061,
4817 ZK Breda,
The Netherlands

Marketing Authorisation Holder

Amgen Europe B.V.
Minervum 7061,
4817 ZK Breda,
The Netherlands

Manufacturer

Amgen Technology (Ireland) Unlimited Company
Pottery Road
Dun Laoghaire
Co Dublin
Ireland

Manufacturer

Amgen NV
Telecomlaan 5-7
1831 Diegem
Belgium

For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder:

België/Belgique/Belgien

s.a. Amgen n.v.
Tel/Tél: +32 (0)2 7752711

Lietuva

Amgen Switzerland AG Vilniaus filialas
Tel: +370 5 219 7474

България

Амджен България ЕООД
Тел.: +359 (0)2 424 7440

Luxembourg/Luxemburg

s.a. Amgen
Belgique/Belgien
Tel/Tél: +32 (0)2 7752711

Česká republika

Amgen s.r.o.
Tel: +420 221 773 500

Magyarország

Amgen Kft.
Tel.: +36 1 35 44 700

Danmark

Amgen, filial af Amgen AB, Sverige
Tlf: +45 39617500

Malta

Amgen B.V.
The Netherlands
Tel: +31 (0)76 5732500

Deutschland

AMGEN GmbH
Tel.: +49 89 1490960

Nederland

Amgen B.V.
Tel: +31 (0)76 5732500

Eesti

Amgen Switzerland AG Vilniaus filialas
Tel: +372 586 09553

Norge

Amgen AB
Tlf: +47 23308000

Ελλάδα

Amgen Ελλάς Φαρμακευτικά Ε.Π.Ε.
Τηλ.: +30 210 3447000

Österreich

Amgen GmbH
Tel: +43 (0)1 50 217

España

Amgen S.A.
Tel: +34 93 600 18 60

Polska

Amgen Biotechnologia Sp. z o.o.
Tel.: +48 22 581 3000

France

Amgen S.A.S.
Tél: +33 (0)9 69 363 363

Portugal

Amgen Biofarmacêutica, Lda.
Tel: +351 21 4220606

Hrvatska

Amgen d.o.o.
Tel: +385 (0)1 562 57 20

Ireland

Amgen Ireland Limited
Tel: +353 1 8527400

Ísland

Vistor hf.
Sími: +354 535 7000

Italia

Amgen S.r.l.
Tel: +39 02 6241121

Κύπρος

C.A. Papaellinas Ltd
Τηλ.: +357 22741 741

Latvija

Amgen Switzerland AG Rīgas filiāle
Tel: +371 257 25888

România

Amgen România SRL
Tel: +4021 527 3000

Slovenija

AMGEN zdravila d.o.o.
Tel: +386 (0)1 585 1767

Slovenská republika

Amgen Slovakia s.r.o.
Tel: +421 2 321 114 49

Suomi/Finland

Amgen AB, sivuliike Suomessa/Amgen AB, filial
i Finland
Puh/Tel: +358 (0)9 54900500

Sverige

Amgen AB
Tel: +46 (0)8 6951100

United Kingdom

Amgen Limited
Tel: +44 (0)1223 420305

This leaflet was last revised in

Detailed information on this medicine is available on the European Medicines Agency web site:
<http://www.ema.europa.eu/>.

The following information is intended for healthcare professionals only:

- Before administration, the XGEVA 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 product or waste material should be disposed of in accordance with local requirements.