

XGEVA™

1. NAME OF THE MEDICINAL PRODUCT

XGEVA™ 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 (CHO) 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 bone metastases from solid tumours.

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

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).

Patient Card:

This product is marketed with patient safety information card (patient card). Please explain to the patient the implications of this treatment including the need for compliance. Please also explain the signs of important adverse events and instruct the patient when to seek medical care.

Bone metastases from solid tumours

The recommended dose of XGEVA for the prevention of skeletal related events 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 for the treatment of giant cell tumour of bone 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

Patients with renal impairment

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

Patients with hepatic impairment

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

Elderly patients (age ≥ 65)

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

Paediatric population

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.

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

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.

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.

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

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

4.3 Contraindications

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

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 XGEVA.

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 XGEVA.

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.

Atypical fractures of the femur

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

XGEVA 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.

Patients with growing skeletons

Xgeva is not recommended in patients with growing skeletons (see section 4.2). Clinically significant hypercalcaemia has been reported in XGEVA-treated patients with growing skeletons 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 GCTB patients treated with XGEVA.

Warnings for excipients

Patients with rare hereditary problems of fructose intolerance should not use XGEVA.

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

Risk Summary

XGEVA can cause fetal harm when administered to a pregnant woman, based on findings in animals. In utero denosumab exposure in cynomolgus monkeys resulted in increased fetal loss, stillbirths, and postnatal mortality, along with evidence of absent lymph nodes, abnormal bone growth, and decreased neonatal growth.

There are no adequate and well-controlled studies with XGEVA in pregnant women. Women should be advised not to become pregnant when taking XGEVA. If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to the fetus.

Clinical Considerations

The effects of XGEVA are likely to be greater during the second and third trimesters of pregnancy. Monoclonal antibodies are transported across the placenta in a linear fashion as pregnancy progresses, with the largest amount transferred during the third trimester.

If the patient becomes pregnant during XGEVA therapy, consider the risks and benefits in continuing or discontinuing treatment with XGEVA.

Contraception

Females

Counsel patients on pregnancy planning and prevention. Advise females of reproductive potential to use highly effective contraception during therapy, and for at least 5 months after the last dose of XGEVA. Advise patients to

contact their healthcare provider if they become pregnant, or a pregnancy is suspected, during treatment or within 5 months after the last dose of XGEVA.

Males

The extent to which denosumab is present in seminal fluid is unknown. There is potential for fetal exposure to denosumab when a male treated with XGEVA has unprotected sexual intercourse with a pregnant partner. Advise males of this potential risk.

Breast-feeding

It is unknown whether denosumab is excreted in human milk. 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 on whether to abstain from breast-feeding or to abstain from therapy with XGEVA should be made, taking into account the benefit of breast-feeding to the newborn/infant and the benefit of XGEVA therapy to the woman.

Fertility

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

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

Summary of the safety profile

The safety of XGEVA was evaluated in:

- 5,931 patients with advanced malignancies involving bone in active-controlled, clinical trials examining the efficacy and safety of XGEVA versus zoledronic acid in preventing the occurrence of skeletal related events.
- 523 patients with giant cell tumour of bone in single-arm, clinical trials examining the efficacy and safety of XGEVA.

The adverse reactions identified in these clinical trials and from post-marketing experience are presented in table 1.

Tabulated list of adverse reactions

The following convention has been used for the classification of the adverse reactions based on incidence rates in three phase III and two phase II clinical studies (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 $< 1/1,000$) and very rare ($< 1/10,000$). 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 or with giant cell tumour of bone

MedDRA system organ class	Frequency category	Adverse reactions
Immune system disorder	Rare	Drug hypersensitivity ¹
	Rare	Anaphylactic reaction ¹
Metabolism and nutrition disorders	Common	Hypocalcaemia ^{1, 2}
	Common	Hypophosphataemia
Respiratory, thoracic and mediastinal disorders	Very common	Dyspnoea
Gastrointestinal disorders	Very common	Diarrhoea
	Common	Tooth extraction
Skin and subcutaneous tissues disorders	Common	Hyperhidrosis
Musculoskeletal and connective tissue disorders	Very common	Musculoskeletal pain ¹
	Common	Osteonecrosis of the jaw ¹
	Rare	Atypical femoral fracture ¹

¹ See section Description of selected adverse reactions

² See section other special populations

Description of selected adverse reactions

Hypocalcaemia

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 paresthesias 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.

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 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 GCTB 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 program, atypical femoral fractures were reported rarely in patients treated with denosumab (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.

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.

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. Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form

(<http://forms.gov.il/globaldata/getsequence/getsequence.aspx?formType=AdversEffectMedic@moh.gov.il>)

Additionally, you should also report to GSK Israel (il.safety@gsk.com).

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 the 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 characterized 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 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 the phase III clinical trials, median reductions of approximately 80% were maintained in uNTx/Cr after 3 months of treatment in 2075 XGEVA-treated advanced cancer patients' naïve to IV-bisphosphonate.

Immunogenicity

In clinical studies, neutralising antibodies have not been observed for XGEVA. 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 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). 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.

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

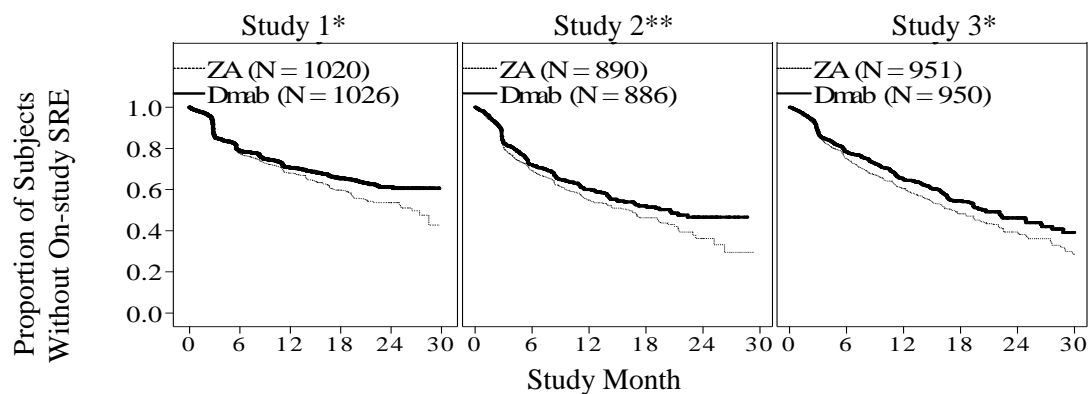
	Study 1 breast cancer		Study 2 other solid tumours** or multiple myeloma		Study 3 prostate cancer		Combined advanced cancer	
	XGEVA	zoledronic acid	XGEVA	zoledronic acid	XGEVA	zoledronic acid	XGEVA	zoledronic acid
N	1026	1020	886	890	950	951	2862	2861
First SRE								
Median time (months)	NR	26.4	20.6	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

ZA – Zoledronic Acid 4 mg Q4W

Dmab – Denosumab 120 mg Q4W



N = Number of subjects randomised

*= Statistically significant for superiority; **= Statistically significant for non-inferiority

Disease progression and overall survival

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 all three studies 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 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 4 and 5) 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 4 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 5 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 4 and 5 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 3). Overall, XGEVA achieved objective tumour responses in 71.6% (95% CI 64.6, 77.9) of patients (table 3) 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 GCTB surgery, out of which 40 subjects had complete resections.

Table 3: 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 5 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 5, 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 adolescent in an interim analysis of Study 5. 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 SC 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 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. 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 a 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.

Animal Data

The effects of denosumab on prenatal development have been studied in both cynomolgus monkeys and genetically engineered mice in which RANK ligand (RANKL) expression was turned off by gene removal (a “knockout mouse”). In cynomolgus monkeys dosed subcutaneously with denosumab throughout pregnancy at a pharmacologically active dose, there was increased fetal loss during gestation, stillbirths, and postnatal mortality. Other findings in offspring included absence of axillary, inguinal, mandibular, and mesenteric lymph nodes; abnormal bone growth, reduced bone strength, reduced hematopoiesis, dental dysplasia and tooth malalignment; and decreased neonatal growth. At birth out to one month of age, infants had measurable blood levels of denosumab (22-621% of maternal levels).

Following a recovery period from birth out to 6 months of age, the effects on bone quality and strength returned to normal; there were no adverse effects on tooth eruption, though dental dysplasia was still apparent; axillary and inguinal lymph nodes remained absent, while mandibular and mesenteric lymph nodes were present, though small; and minimal to moderate mineralization in multiple tissues was seen in one recovery animal. There was no evidence of maternal harm prior to labor; adverse maternal effects occurred infrequently during labor. Maternal mammary gland development was normal. There was no fetal NOAEL (no observable adverse effect level) established for this study because only one dose of 50 mg/kg was evaluated.

In RANKL knockout mice, absence of RANKL (the target of denosumab) also caused fetal lymph node agenesis and led to postnatal impairment of dentition and bone growth. Pregnant RANKL knockout mice showed altered maturation of the maternal mammary gland, leading to impaired lactation.

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

Sorbitol

Glacial acetic acid*

Sodium hydroxide (for pH adjustment)*

Water for injection

* 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 of the product is indicated on the label and packaging.

XGEVA may be stored at room temperature (up to 25°C) for up to 30 days in the original container. Once removed from the refrigerator, XGEVA must be used within this 30 day 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 and seal (aluminium) with flip-off cap.

Pack size of one 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 excessively. To avoid discomfort at the site of injection, allow the vial to reach room temperature (up to 25°C) before injecting and inject slowly. Inject the entire contents of the vial. A 27 gauge needle is recommended for the administration of denosumab. Do not re-enter the vial.

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

7. MANUFACTURER

Amgen Europe B.V., Breda, The Netherlands.

8. LICENSE HOLDER AND IMPORTER

GlaxoSmithKline (Israel) Ltd., 25 Basel St., Petach Tikva.

9. LICENSE NUMBER

147-01-33411

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