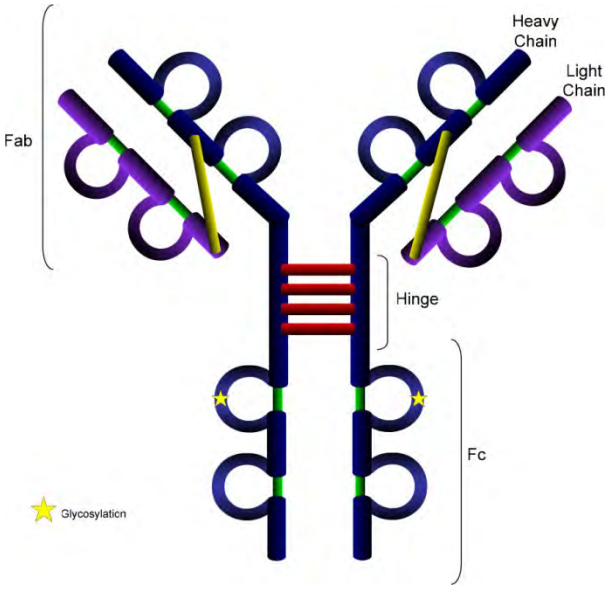
NAME OF THE MEDICINE

XGEVA® is the Amgen Inc. trademark for denosumab (rch).



DESCRIPTION

Denosumab is a fully human IgG2 monoclonal antibody with high affinity and specificity for RANK ligand (RANKL). Denosumab has an approximate molecular weight of 147 kDa and is produced in genetically engineered mammalian (Chinese Hamster Ovary, CHO) cells.

CAS number: 615258-40-7

Xgeva is a sterile, preservative-free, clear, colourless to slightly yellow solution. The solution may contain trace amounts of translucent to white proteinaceous particles. Each single-use vial contains a deliverable dose of 120 mg denosumab, 78 mg sorbitol, 1.8 mg acetate, and sodium hydroxide for adjusting to pH 5.2, in Water for Injection (USP, PhEur, JP).

PHARMACOLOGY

Mechanism of Action

Bone Metastasis from Solid Tumours

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 RANK ligand, is a key mediator of bone destruction in bone disease in metastatic tumours and multiple myeloma. Denosumab binds with high affinity and specificity to RANKL, preventing RANKL from activating its only receptor, RANK, on the surface of osteoclasts and their precursors. Prevention of RANK ligand-RANK interaction results in reduced osteoclast numbers and function, and thereby decreases bone resorption and cancer-induced bone destruction.

RANKL inhibition resulted in reduced bone lesions and delayed formation of *de novo* bone metastases in some nonclinical models. RANKL inhibition reduced skeletal tumour growth and this effect was additive when combined with other anticancer therapies.

Giant cell tumour of bone

Giant cell tumours of bone are characterised by 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 can be replaced with non-proliferative, differentiated, woven new bone which may show an increase in density.

Pharmacodynamics

In a phase 2 study of IV-bisphosphonate naïve patients with breast cancer and bone metastases, subcutaneous (SC) doses of Xgeva 120 mg every 4 weeks (Q4W), caused a rapid reduction in the markers of bone resorption: urinary N-telopeptide corrected for creatinine (uNTx/Cr) and serum C-telopeptide (sCTx) with median reduction of 82% for uNTx/Cr within 1 week. Reductions in bone resorption markers were maintained, with median uNTx/Cr reductions of 74% to 82% from weeks 2 to 25 of continued 120 mg Q4W dosing. Median reduction of approximately 80% in uNTx/Cr from baseline after 3 months of treatment were also observed across 2075 Xgeva-treated advanced cancer patients (breast, prostate, multiple myeloma or other solid tumours) naïve to IV-bisphosphonate in the phase 3 clinical trials.

Similarly, in a phase 2 study of patients with advanced malignancies and bone metastases (including subjects with multiple myeloma and bone disease) who were receiving intravenous bisphosphonate therapy, yet had uNTx/Cr levels > 50 nM/mM, SC dosing of Xgeva administered either every 4 weeks or every 12 weeks caused an approximate 80% reduction in uNTx/Cr from baseline after 3 and 6 months of treatment. Overall, 97% of patients in the Xgeva groups had at least one uNTx/Cr value < 50 nM/mM up to week 25 of the study.

In a phase 2 study of patients with giant cell tumour of bone who received subcutaneous doses of Xgeva 120 mg every 4 weeks (Q4W) with loading doses on days 8 and 15 of the initial 4-week treatment period, median reductions in uNTx/Cr and sCTx of approximately 80% were observed by week 9. Reductions in bone turnover markers were maintained, with median reductions of 56% to 77% for uNTx/Cr and 79% to 83% for sCTx from weeks 5 to 25 of continued 120 mg Q4W dosing.

Pharmacokinetics

Following subcutaneous administration, bioavailability was 62% and 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.

In subjects with advanced cancer who received multiple doses of 120 mg every 4 weeks (Q4W) an approximate 2-fold accumulation in serum denosumab concentrations was observed and steady-state was achieved by 6 months, consistent with time-independent pharmacokinetics. At steady-state, the mean serum trough concentration was 20.6 µg/mL (range: 0.456 to 56.9 µg/mL). In subjects who discontinued 120 mg every 4 weeks, the mean half-life was 28 days (range: 14 to 55 days). 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%.

A population pharmacokinetic analysis showed no notable difference in pharmacokinetics with age (18 to 87 years), race, body weight (36 to 174 kg), or across patients with solid tumours and giant cell tumour of bone. Denosumab pharmacokinetics and pharmacodynamics were not affected by the formation of binding antibodies to denosumab and were similar in men and women.

The pharmacokinetics and pharmacodynamics of denosumab were similar in patients transitioning from IV bisphosphonate therapy.
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.

Special populations

Elderly
The pharmacokinetics of denosumab were not affected by age (18 to 87 years).

Paediatric
The pharmacokinetic profile has not been assessed in those < 18 years.

Impaired hepatic function
The pharmacokinetic profile has not been assessed in patients with impaired hepatic function.

Impaired renal function

- In a study of 55 patients without advanced malignancies but with varying degrees of renal function, including patients on dialysis, the degree of renal impairment had no effect on the pharmacokinetics and pharmacodynamics of denosumab. Dose adjustment for renal impairment is not necessary.

Immunogenicity

- In clinical studies, no neutralising antibodies for denosumab have been observed. 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.
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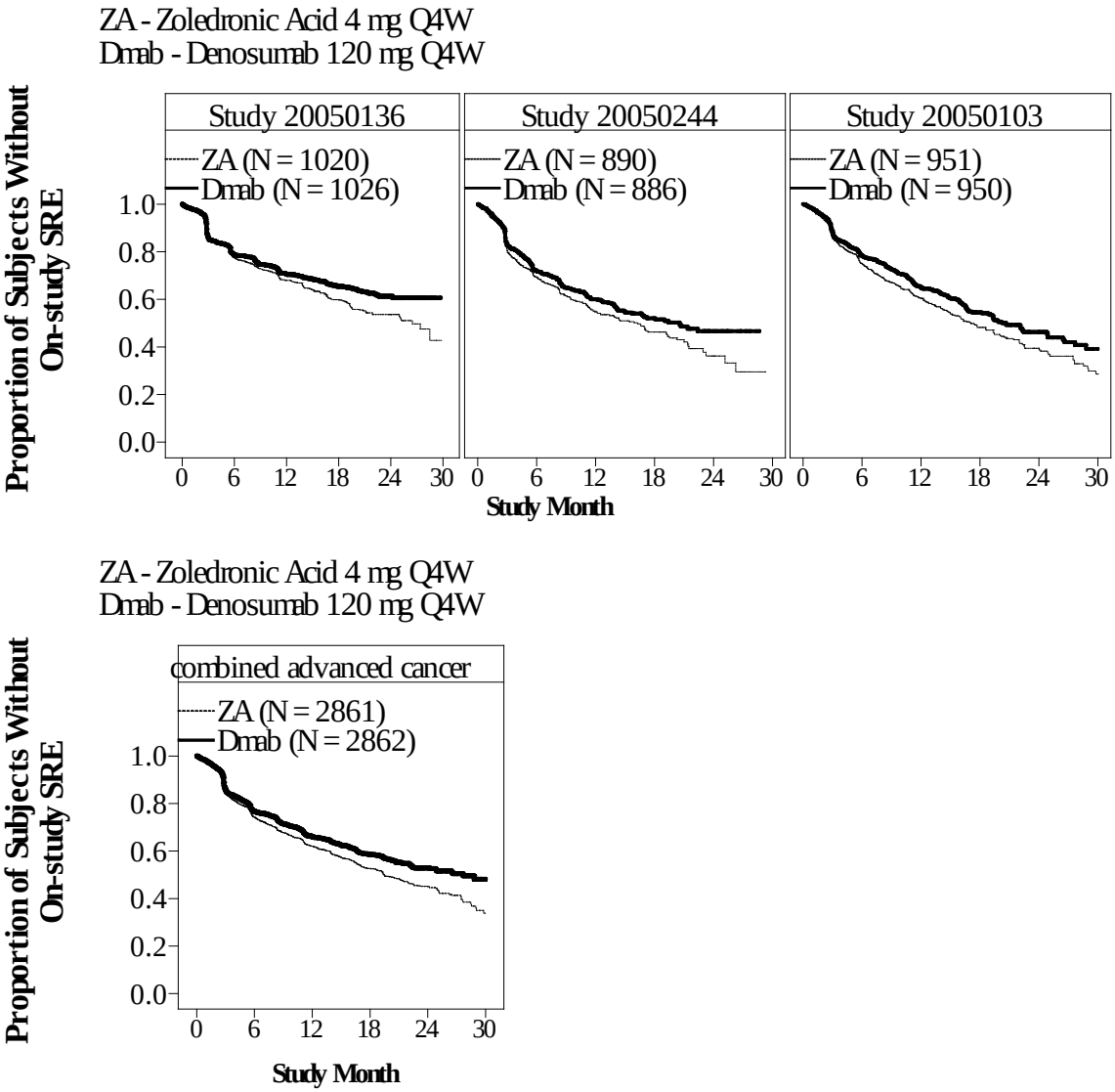
CLINICAL TRIALS

Clinical efficacy in patients with advanced malignancies involving bone
Efficacy and safety of 120 mg Xgeva subcutaneously 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-bisphosphonates naïve patients with advanced malignancies involving bone. A total of 2,046 adults with breast cancer with at least one bone metastasis (Study 20050136), 1,776 adults with other solid tumours (including non-small cell lung cancer, renal cell cancer, colorectal cancer, small cell lung cancer, bladder cancer, head and neck cancer, gastrointestinal/genitourinary cancer and others, excluding breast and prostate cancer) with at least one bone metastasis or multiple myeloma (Study 20050244), and 1,901 men with castrate-resistant prostate cancer with at least one bone metastasis (Study 20050103) were included. The primary and secondary endpoints evaluated the occurrence of one or more skeletal related events (SREs) defined

as any of the following: pathologic fracture, radiation therapy to bone, surgery to bone or spinal cord compression.

Xgeva reduced the risk of developing a SRE, or developing multiple SREs (first and subsequent) in patients with advanced malignancies involving bone (see Figure 1 and Table 1).

· **Figure 1. Kaplan-Meier plot of time to first on-study SRE**



N = number of subjects randomised

Table 1: Efficacy results in patients with advanced malignancies involving bone

	Study 20050136 breast cancer		**Study 20050244 other solid tumours or multiple myeloma**		**Study 20050103 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
Diff in median time (months)	NA		4.2		3.5		8.2	
Hazard ratio (95% CI)	0.82 (0.71, 0.95)		0.84 (0.71, 0.98)		0.82 (0.71, 0.95)		0.83 (0.76, 0.90)	
Risk reduction (%)	18		16		18		17	
Non-inferiority p-value	< 0.0001†		0.0007†		0.0002†		< 0.0001	
Superiority p-value	0.0101†		0.0619†		0.0085†		< 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)	0.77 (0.66, 0.89)		0.90 (0.77, 1.04)		0.82 (0.71, 0.94)		0.82 (0.75, 0.89)	
Risk reduction (%)	23		10		18		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 Radiation to Bone								

	Study 20050136 breast cancer		**Study 20050244 other solid tumours or multiple myeloma**		**Study 20050103 prostate cancer**		**Combined advanced cancer**	
	Xgeva	zoledronic acid	Xgeva	zoledronic acid	Xgeva	zoledronic acid	Xgeva	zoledronic acid
Median time (months)	NR	NR	NR	NR	NR	28.6	NR	33.2
Hazard ratio (95% CI)	0.74 (0.59, 0.94)		0.78 (0.63, 0.97)		0.78 (0.66, 0.94)		0.77 [0.69, 0.87]	
Risk reduction (%)	26		22		22		23	
Superiority p-value	0.0121		0.0256		0.0071		< 0.0001	

NR = not reached; NA = not available; SRE = skeletal related event; SMR = skeletal morbidity rate: defined as the ratio of the number of occurrence of any SRE for a subject, allowing 1 event per assessing period (eg, 3 weeks), divided by the subject's time at risk; †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.

In a post-hoc analysis of Study 20050244 (including solid tumours, excluding multiple myeloma), Xgeva reduced the risk of developing a SRE by 19% (p = 0.0168) and developing multiple SREs by 15% (p = 0.0479) compared with zoledronic acid with the median time to first SRE delayed by 6 months.

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 [95% CI] was 0.95 [0.81, 1.11]), patients with prostate cancer (hazard ratio [95% CI] was 1.03 [0.91, 1.17]), and patients with other solid tumours or multiple myeloma (hazard ratio [95% CI] was 0.95 [0.83, 1.08]. A post-hoc analysis in Study 20050244 (patients with other solid tumours or multiple myeloma) examined overall survival for the three 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 the Xgeva and zoledronic acid groups 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 all three studies, overall survival was similar between Xgeva and zoledronic acid (hazard ratio [95% CI] of 0.99 [0.91, 1.07]).

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 20040215 and 20062004) that enrolled 305 patients with giant cell tumour of bone that was either unresectable or for which surgery would be associated with severe morbidity. Patients received 120 mg Xgeva subcutaneously every 4 weeks with a loading dose of 120 mg on days 8 and 15 of the initial 4-week treatment period.

Study 20040215 enrolled 37 adult patients with histologically confirmed unresectable or recurrent giant cell tumour of bone. The main outcome measure of the trial was response rate, defined as either at least 90% elimination of giant cells relative to baseline (or complete elimination of giant cells in cases where giant cells represent < 5% of tumour cells), or a lack of progression of the target lesion by radiographic measurements in cases where histopathology was not available.

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 met response criteria. Of the remaining 15 patients, 10 (67%) met response criteria based on radiology data.

Study 20062004 enrolled 282 adult or skeletally mature adolescents with giant cell tumour of bone. Patients were assigned to one of three cohorts: Cohort 1 included patients with surgically unsalvageable disease (e.g., sacral, spinal, or multiple lesions, including pulmonary metastases); Cohort 2 included patients with surgically salvageable disease whose planned surgery was associated with severe morbidity (e.g., joint resection, limb amputation, or hemipelvectomy); Cohort 3 included patients previously participating in 20040215 and rolled over into this study. The secondary outcome measures of the study were time to disease progression (based on investigator assessment) for Cohort 1 and proportion of patients without any surgery at month 6 for Cohort 2. Pain outcomes and investigator determined clinical benefit were also assessed.

In Cohort 1, median time to disease progression was not reached, as only 6 of the 169 treated patients (3.6%) had disease progression. In Cohort 2, Xgeva prolonged the time to surgery, reduced the morbidity of planned surgery, and reduced the proportion of patients undergoing surgery (Table

2). Sixty-four of the 71 (90.1%; 95% CI:80.7%, 95.9%) evaluable patients treated with Xgeva had not undergone surgery by month 6. Overall, of 100 patients for whom surgery was planned, 74 patients (74%) had no surgery performed, and 16 patients (16%) underwent a less morbid surgical procedure from that planned at baseline (Table 2).

A retrospective independent review of radiographic imaging data was performed for patients enrolled in 20040215 and 20062004. Of the 305 patients enrolled in these studies, 190 had at least 1 evaluable timepoint response and were included in the analysis (Table 3).

Patients were evaluated by the following response criteria to determine objective tumour response:

- Modified Response Evaluation Criteria in Solid Tumours (RECIST 1.1) to evaluate tumour burden based on computed tomography (CT)/magnetic resonance imaging (MRI)
- Modified European Organisation for Research and Treatment of Cancer (EORTC) criteria to evaluate metabolic response using fluorodeoxyglucose positron emission tomography (FDG-PET),
- Modified Inverse Choi criteria to evaluate tumour size and density using Hounsfield units based on CT/MRI (Density/Size)

Xgeva achieved objective tumour responses in 136 of these 190 patients (71.6%; 95% CI 64.6, 77.9) (Table 3). The median time to response was 3.1 months (95% CI 2.89, 3.65). The median duration of response was not estimable, as few patients experienced disease progression, with a median follow-up of 13.4 months. Efficacy results in skeletally mature adolescents appeared to be similar to those observed in adults.

Table 2: Distribution of Planned Versus Actual Surgery in Patients with Giant Cell Tumour of Bone (Cohort 2)

Surgical Procedure, n	**Baseline Planned (N = 100)**	**Actual Total (N = 26)**
Total number of surgeries	100	26
Major surgeries	44	3
Hemipelvectomy	4	0
Amputation	17	0
Joint/prosthesis replacement	9	1
Joint resection	14	2
Marginal excision, en bloc excision, or en bloc resection	42	6
Curettage	13	16
Other	1	1
No surgery	0	74

Table 3: Objective Treatment Response in 305 Patients with Giant Cell Tumour of Bone

	Number of patients evaluable for the endpoint [a]	Number of patients with the endpoint	Proportion (%) (95% CI) [a]	KM estimate of median (95% CI) (Months)
Proportion of patients with an objective tumour response (CR, PR)				
Based on best response	190	136	71.6(64.6, 77.9)	-
RECIST 1.1[1]	187	47	25.1(19.1, 32.0)	-
EORTC[2]	26	25	96.2(80.4, 99.9)	-
Density/Size[3]	176	134	76.1(69.1, 82.2)	-
Duration of objective tumour response (time to PD from the first objective tumor response)				
Based on best response	136	1	0.7	NE (NE, NE)[b]
RECIST 1.1	47	3	6.4	NE (19.94, NE)
EORTC	25	0	0.0	NE (NE, NE)
Density/Size	134	1	0.7	NE (NE, NE)
Time to first objective tumour response				
Based on best response	190	136	71.6	3.1 (2.89, 3.65)
RECIST 1.1	187	47	25.1	NE (20.93, NE)
EORTC	26	25	96.2	2.7 (1.64, 2.79)
Density/Size	176	134	76.1	3.0 (2.79, 3.48)

[a] Exact Confidence Interval
[b] NE = Not Estimable

Effect on pain
In Study 20062004, cohorts 1 and 2 combined, a clinically meaningful reduction in worst pain (ie, ≥ 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 ≥ 50% at week 5. These pain improvements were maintained at all subsequent evaluations. In a post-hoc analysis, at least half of evaluable patients had a ≥ 30% reduction in worst pain score from baseline at all post-baseline time points beginning at week 9. Overall, pain improvement and clinical benefit did not correlate with objective tumour response.

INDICATIONS

Prevention of skeletal related events in patients with bone metastases from solid tumours.

Treatment of giant cell tumour of bone in adults or skeletally mature adolescents that is recurrent, or unresectable, or resectable but associated with severe morbidity.

CONTRAINDICATIONS

Hypersensitivity to the active substance, to CHO-derived proteins or to any of the excipients (see DESCRIPTION).

Severe untreated hypocalcaemia.

PRECAUTIONS

Vitamin Supplementation and Hypocalcaemia

Pre-existing hypocalcaemia must be corrected prior to initiating therapy with Xgeva.

Supplementation with calcium and vitamin D is required in all patients unless hypercalcaemia is present.

If hypocalcaemia occurs while receiving Xgeva, additional short term calcium supplementation may be necessary.

Use in Multiple Myeloma

The currently available clinical trial data do not support the use of Xgeva in patients with multiple myeloma (see CLINICAL TRIALS).

Use in Renal Impairment

No dose adjustment is necessary in patients with renal impairment.

In a study of 55 patients without advanced cancer, but with varying degrees of renal function, patients with severe renal impairment (creatinine clearance < 30 mL/min) or receiving dialysis were at greater risk of developing hypocalcaemia. Adequate intake of calcium and vitamin D is important in patients with severe renal impairment or receiving dialysis (see PRECAUTIONS, Vitamin Supplementation and Hypocalcaemia).

Osteonecrosis of the Jaw

Osteonecrosis of the jaw (ONJ) has occurred in patients treated with denosumab. In clinical trials, the incidence of ONJ was higher with longer duration of exposure (see ADVERSE EFFECTS)[#].

Patients who developed ONJ in clinical studies generally had known risk factors for ONJ, including invasive dental procedures (e.g., tooth extraction, dental implants, oral surgery), poor oral hygiene or other pre-existing dental disease, advanced malignancies, or concomitant therapies (e.g., chemotherapy, corticosteroids, angiogenesis inhibitors). An oral examination should be performed by the prescriber prior to initiation of Xgeva treatment and a dental examination with appropriate preventive dentistry should be considered prior to treatment with Xgeva. While on treatment, these patients should avoid invasive dental procedures if possible.

Good oral hygiene practices should be maintained during treatment with Xgeva. Patients who are suspected of having or who develop ONJ while on Xgeva should receive care by a dentist or an oral surgeon. If ONJ occurs during treatment with Xgeva, use clinical judgment and guide the management plan of each patient based on individual benefit-risk evaluation.

Atypical Femoral Fractures[#]

Atypical femoral fracture has been reported with Xgeva (see ADVERSE EFFECTS). Atypical femoral

fractures may occur with little or no trauma in the subtrochanteric and diaphyseal regions of the femur and may be bilateral. 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. 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, and the contralateral femur should also be examined.

Drugs with Same Active Ingredient

Xgeva contains the same active ingredient found in Prolia® (denosumab), used for the treatment of postmenopausal osteoporosis. Patients being treated with Xgeva should not be treated with Prolia® concomitantly.

Warnings for Excipients

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

Use in the Elderly

Of the total number of patients in clinical studies in patients with advanced cancer, 1260 patients (44.4%) treated with Xgeva were ≥ 65 years old. No overall differences in safety or efficacy were observed between these patients and younger patients.

Paediatric Use

The safety and efficacy of Xgeva in paediatric patients have not been established other than skeletally mature adolescents with giant cell tumour of bone. Xgeva is not recommended for use in paediatric patients other than skeletally mature adolescents with giant cell tumour of bone.

In Study 20062004, Xgeva has been evaluated in a subset of 10 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 (eg, closed epiphyseal growth plate of the humerus) and body weight ≥ 45 kg. Efficacy results in skeletally mature adolescents appeared to be similar to those observed in adults (see CLINICAL TRIALS).

Adolescent primates had abnormal growth plates when administered denosumab at doses of 10 mg/kg and higher, which resulted in exposures up to 2.8 times those observed in adult humans dosed at 120 mg subcutaneously every 4 weeks based on AUC. In neonatal rats, inhibition of RANKL (target of denosumab therapy) with a construct of osteoprotegerin bound to Fc (OPG-Fc) was associated with inhibition of bone growth and tooth eruption and lower body weight gain. These changes were partially reversible when dosing of RANKL inhibitor was discontinued. Therefore, treatment with denosumab may impair bone growth in children with open growth plates and may inhibit eruption of dentition.

Effects on Fertility

No data are available on the effect of denosumab on human fertility. Denosumab had no effect on female fertility or male reproductive organs or sperm motility in cynomolgus monkeys at subcutaneous doses up to 12.5 mg/kg/week (females) or 50 mg/kg/month (males), yielding exposures that were approximately 15-fold higher than the human exposure at 120mg subcutaneous administered once every month.

Use in Pregnancy

Pregnancy Category: D

There are no adequate and well-controlled studies of Xgeva in pregnant women. Xgeva is not recommended for use during pregnancy. Advise females of reproductive potential to use highly effective contraception during therapy, and for at least 5 months after the last dose of Xgeva. Encourage women who become pregnant during Xgeva treatment to enrol in Amgen's Pregnancy Surveillance Program. Enrolment may be arranged by telephoning Amgen's Medical Information line on 1800 803 638 (freecall within Australia).

Developmental toxicity studies have been performed with denosumab in cynomolgus monkeys at subcutaneous doses up to 12.5 mg/kg/week, yielding exposures up to 9.5 fold higher than the human exposure. No evidence of harm to the foetus was observed. Preclinical studies in RANK/RANKL-knockout mice suggest absence of RANKL could interfere with the development of lymph nodes in the foetus; the potential for adverse effects on lymph node development was not examined in studies with denosumab in monkeys. Knockout mice lacking RANK or RANKL also exhibited decreased body weight, reduced bone growth and a lack of tooth eruption. Similar phenotypic changes (inhibition of bone growth and tooth eruption) were observed in a study in neonatal rats using a surrogate for denosumab, the RANKL inhibitor osteoprotegerin bound to Fc (OPG-Fc). These changes were partially reversible when dosing of RANKL inhibitor was discontinued. Therefore, treatment with denosumab may impair bone growth in children with open growth plates and may inhibit eruption of dentition.

Preclinical studies in RANK/RANKL-knockout mice suggest absence of RANKL during pregnancy may interfere with maturation of the mammary gland leading to impaired lactation post-partum.

Use in Lactation

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. 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. Encourage women who are breast-feeding during Xgeva treatment to enrol in Amgen's Lactation Surveillance Program. Enrolment may be arranged by telephoning Amgen's Medical Information line on 1800 803 638 (freecall within Australia).

Use in Hepatic Impairment

The safety and efficacy of Xgeva has not been studied in patients with hepatic impairment.

Carcinogenicity

The carcinogenic potential of denosumab has not been evaluated in long-term animal studies. In view of the mechanism of action of denosumab, it is unlikely that the molecule would be capable of inducing tumour development or proliferation.

Genotoxicity

The genotoxic potential of denosumab has not been evaluated. Denosumab is a recombinant protein comprised entirely of naturally occurring amino acids and contains no inorganic or synthetic organic linkers or other non-protein portions. Therefore, it is unlikely that denosumab or any of its derived fragments would react with DNA or other chromosomal material.

Interactions with Other Medicines

No drug-drug interaction studies have been conducted.

In clinical studies, Xgeva has been administered in combination with standard anticancer treatment and in patients previously receiving bisphosphonates. The pharmacokinetics and pharmacodynamics

of denosumab were not altered by concomitant chemotherapy and/or hormone therapy nor by previous IV bisphosphonate exposure**.**

Denosumab should not be administered concomitantly with bisphosphonates.

Effects on Laboratory Tests

No interactions with laboratory and diagnostic tests have been identified.

Effects on Ability to Drive and Use Machines

No studies on the effects on the ability to drive or use machinery have been performed.

ADVERSE EFFECTS

Bone metastasis from solid tumours

Data from three active-controlled multicentre trials were used for the safety analysis in 5677 patients with bone metastases from either prostate cancer, breast cancer, other solid tumours or patients with multiple myeloma (all patients with advanced cancer). A total of 2841 patients were exposed to 120 mg of Xgeva administered once every 4 weeks as a single subcutaneous injection, and 2836 patients were exposed to 4 mg (dose-adjusted for reduced renal function) of zoledronic acid administered once every 4 weeks as an IV infusion. The median (Q1, Q3) duration of exposure to Xgeva for the safety analysis was 12 months (6, 18) for prostate cancer, 17 months (10, 21) for breast cancer, and 7 months (4, 14) for other solid tumours and multiple myeloma.

Table 4 describes adverse events that were reported by ≥ 10% of patients in these studies regardless of presumed causality to study drug.

Table 4: Percentage of Patients with Adverse Events in Patients with Advanced Malignancies Involving Bone by Body System (≥ 10% Incidence in Either Treatment Group)

SYSTEM ORGAN CLASS Preferred Term	Xgeva (N = 2841) n (%)	Zoledronic Acid (N = 2836) n (%)
BLOOD AND LYMPHATIC SYSTEM DISORDERS		
Anaemia	771 (27.1)	859 (30.3)
GASTROINTESTINAL DISORDERS		
Nausea	876 (30.8)	895 (31.6)
Constipation	603 (21.2)	670 (23.6)
Diarrhoea	577 (20.3)	530 (18.7)
Vomiting	566 (19.9)	570 (20.1)
Abdominal pain	292 (10.3)	280 (9.9)
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS		
Fatigue	769 (27.1)	766 (27.0)
Asthenia	607 (21.4)	621 (21.9)
Oedema peripheral	472 (16.6)	462 (16.3)
Pyrexia	409 (14.4)	562 (19.8)

SYSTEM ORGAN CLASS Preferred Term	Xgeva (N = 2841) n (%)	Zoledronic Acid (N = 2836) n (%)
INVESTIGATIONS		
Weight decreased	330 (11.6)	332 (11.7)
METABOLISM AND NUTRITION DISORDERS		
Decreased appetite	656 (23.1)	694 (24.5)
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS		
Back pain	718 (25.3)	747 (26.3)
Arthralgia	570 (20.1)	632 (22.3)
Bone pain	564 (19.9)	639 (22.5)
Pain in extremity	524 (18.4)	550 (19.4)
Musculoskeletal pain	357 (12.6)	385 (13.6)
NERVOUS SYSTEM DISORDERS		
Headache	360 (12.7)	382 (13.5)
PSYCHIATRIC DISORDERS		
Insomnia	302 (10.6)	324 (11.4)
RESPIRATORY, THORACIC, AND MEDIASTINAL DISORDERS		
Dyspnoea	585 (20.6)	507 (17.9)
Cough	437 (15.4)	419 (14.8)

N = number of patients who received ≥ 1 active dose of investigational product
n = number of patients reporting ≥ 1 event

Giant cell tumour of bone

The safety of Xgeva was evaluated in two Phase 2 open-label, single arm studies in which a total of 304 patients with giant cell tumour of bone received at least 1 dose of Xgeva. Patients received 120 mg Xgeva subcutaneously every 4 weeks with a loading dose of 120 mg on days 8 and 15 of the initial 4-week period. Of the 304 patients who received Xgeva, 147 patients were treated with Xgeva for ≥ 1 year, 46 patients for ≥ 2 years, and 15 patients for ≥ 3 years. The median (Q1, Q3) number of doses received was 14 (8.0, 22); the minimum number of doses received was 1 and the maximum was 60. The median (Q1, Q3) number of months on study was 11.2 (5.4, 18.2).The median (range) age was 33 (13 to 83) years; 10 subjects were skeletally mature adolescents (aged 13 to 17 years).

The overall safety and tolerability profile of Xgeva in patients with giant cell tumour of bone was similar to that reported in trials of patients with bone metastases from solid tumours. For skeletally mature adolescent subjects with GCTB, the safety profile appears to be similar to that in adult subjects with GCTB.

The most common adverse reactions in patients with giant cell tumour of bone receiving Xgeva (per-patient incidence greater than or equal to 10%) were arthralgia, headache, nausea, fatigue, back pain, and pain in extremity.

Hypocalcaemia

In three phase 3 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 decrease in serum calcium levels to the range between 1.5 to 1.75 mmol/L was experienced in 2.5% of patients treated with Xgeva and 1.2% of patients treated with zoledronic acid. A decrease in serum calcium levels to < 1.5 mmol/L was experienced in 0.6% of patients treated with Xgeva and 0.2% of patients treated with zoledronic acid.

In two phase II open-label studies with in patients with giant cell tumour of bone, hypocalcaemia was reported in 4.9% of patients. None of the adverse events was considered serious.

Osteonecrosis of the Jaw (ONJ)

In the primary treatment phase of three phase 3 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 months; range 0.1 to 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 had a history of tooth extraction, poor oral hygiene, and/or use of a dental appliance. In addition, most subjects were receiving or had received chemotherapy. The trials in patients with breast or prostate cancer included a pre-specified Xgeva extension treatment phase (median overall exposure of 14.9 months; range 0.1 – 67.2) where patients were offered open label Xgeva. The patient-year adjusted incidence of confirmed ONJ was 1.1% during the first year of treatment and 4.1% thereafter. The median time to ONJ was 20.6 months (range: 4 - 53)[#].

In two Phase II open-label studies in patients with giant cell tumour of bone, ONJ occurred in 4 of 304 (1.3%) of patients. The median time to ONJ was 16 months (range 13-20).

Atypical Femoral Fractures

Atypical femoral fracture has been reported with Xgeva.

Paediatric patients

The safety profile of Xgeva in 10 skeletally mature adolescent patients with giant cell tumour of bone was consistent with that in adult patients.

Drug Hypersensitivity Events

In clinical trials in patients with advanced cancer, drug hypersensitivity events were reported in 0.9% and 0.4% of patients treated with Xgeva and zoledronic acid, respectively.

Pancreatitis

In a randomised controlled trial in postmenopausal women with osteoporosis receiving 60 mg denosumab or placebo once every 6 months, pancreatitis was reported in 8 patients (0.2%) in the denosumab and 4 patients (0.1%) in the placebo groups. An increased incidence has not been observed in randomised controlled trials in the oncology setting.

Postmarketing experience

The following adverse reactions have been identified during post approval use of Xgeva:
Severe symptomatic hypocalcaemia, including fatal cases.
Hypersensitivity, including anaphylactic reactions.#
Musculoskeletal pain, including severe cases.#

DOSAGE AND ADMINISTRATION

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

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. Inject the entire contents of the vial. Do not re-enter the vial.

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 a loading dose of 120 mg on days 8 and 15 of the initial 4-week treatment period.

Daily supplementation with at least 500 mg calcium and 400 IU vitamin D is required in all patients, unless hypercalcaemia is present (see PRECAUTIONS, Vitamin Supplementation and Hypocalcaemia).

Use in elderly
No dose adjustment is necessary in elderly patients (see PRECAUTIONS, Use in the Elderly) or in patients with renal impairment (See PRECAUTIONS, Renal Impairment).

Use in paediatrics
For treatment of giant cell tumour of bone in skeletally mature adolescents, the posology is the same as in adults.

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

Xgeva is a sterile and preservative-free product. Before administration, the Xgeva solution should be inspected for particulate matter and discolouration. Do not use if the solution 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. A 27 gauge needle or larger needle (e.g. 25 gauge) is recommended for the administration of Xgeva.

Product is for single-use in one patient only. Dispose of any medicinal product remaining in the vial.

OVERDOSAGE

There is no experience with overdosage with Xgeva. Xgeva has been administered in clinical studies using doses up to 180 mg every 4 weeks (cumulative doses up to 1080 mg over 6 months), and 120 mg weekly for 3 weeks.

PRESENTATION AND STORAGE CONDITIONS

Xgeva is supplied as a sterile, preservative-free, clear, colourless to slightly yellow solution for injection at pH 5.2. The solution should not be used if cloudy or discoloured. The solution may contain trace amounts of translucent to white proteinaceous particles.
Each vial contains a deliverable dose of 120 mg denosumab in 1.7 mL of solution (70 mg/mL).
Product is for single use in one patient only. Dispose of any medicinal product remaining in the vial.

It is recommended to store vials in a refrigerator at 2°C to 8°C in the original carton. Do not freeze. Protect from direct light. Do not excessively shake the vial. Do not expose to temperatures above 25°C.

If removed from the refrigerator, Xgeva should be kept at room temperature (up to 25°C) in the original container and must be used within 30 days.

Pack size of one or *four.

* Not marketed in Australia.

NAME AND ADDRESS OF THE SPONSOR

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POISON SCHEDULE OF THE MEDICINE

S4 Prescription Medicine

DATE OF APPROVAL

23 December 2013

DATE OF MOST RECENT AMENDMENT

3 December 2013

XGEVA® is a trademark of Amgen.

Please note changes in Product Information