The medicine is not currently marketed in New Zealand

1. PRODUCT NAME
XGEVA 120 mg solution for injection

2. QUALITATIVE AND QUANTITATIVE COMPOSITION
Each vial contains a deliverable dose of 120 mg denosumab in 1.7 mL of solution (70 mg/mL).

Denosumab is produced in genetically engineered mammalian (Chinese Hamster Ovary, CHO) cells.

Excipient(s) with known effect
Each 1.7 mL of solution contains 78 mg sorbitol (E420) (see section 4.4).

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM
Solution for injection.

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.

4. CLINICAL PARTICULARS

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

4.2 Dose and method of administration
Administration should be performed by an individual who has been adequately trained in injection techniques.

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

Daily supplementation with at least 500 mg calcium and 400 IU vitamin D is required in all patients, unless hypercalcaemia is present (see section 4.4, Vitamin Supplementation and Hypocalcaemia).
**Elderly**

No dose adjustment is necessary in elderly patients (see section 4.4, Use in the Elderly).

**Renal impairment**

No dose adjustment is necessary in patients with renal impairment (See section 4.4, Renal Impairment).

**Hepatic impairment**

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

**Paediatric population**

The safety and efficacy of Xgeva in paediatric patients have not been established. Xgeva is not recommended for use in paediatric patients (see section 4.4, Paediatric Population).

**Method of administration**

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.
4.3 Contraindications

Hypersensitivity to the active substance, to CHO-derived proteins or to any of the excipients listed in section 6.1.

Severe untreated hypocalcaemia.

4.4 Special warnings and precautions for use

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. Hypocalcaemia can occur during therapy with Xgeva. Monitoring of calcium levels is recommended during treatment, especially in the first weeks of initiating therapy. In the post-marketing setting, severe symptomatic hypocalcaemia has been reported (see section 4.8, Undesirable effects).

If hypocalcaemia occurs while receiving Xgeva, additional short term calcium supplementation may be necessary (see Use in Renal Impairment and section 4.8).

Use in Multiple Myeloma

The currently available clinical trial data do not support the use of Xgeva in patients with multiple myeloma (see section 5.1, Clinical Efficacy and Safety).

Use in Renal Impairment

No dose adjustment is necessary in patients with renal impairment.

In clinical studies of subjects without advanced cancer, but with varying degrees of renal function (including patients with severe renal impairment [creatinine clearance < 30 mL/min] or receiving dialysis) there was a greater risk of developing hypocalcaemia with increasing degree of renal impairment, and in the absence of calcium supplementation. Monitoring calcium levels and adequate intake of calcium and vitamin D is important in patients with severe renal impairment or receiving dialysis (see 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 section 4.8, Undesirable 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, local gum or oral infection, 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 is recommended prior to treatment with Xgeva, especially in patients with risk factors for ONJ. Good oral hygiene practices should be maintained during treatment with Xgeva.

Patients should avoid invasive dental procedures during treatment with Xgeva. For patients in whom invasive dental procedures cannot be avoided, the clinical judgement of the treating physician should guide the management plan of each patient based on individual benefit/risk assessment.

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, a temporary interruption of treatment should be considered based on individual benefit/risk assessment until the condition resolves.

Atypical Femoral Fractures

Atypical femoral fracture has been reported with Xgeva (see section 4.8, Undesirable 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 characterize 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.
Hypercalcaemia Following Treatment Discontinuation in Patients with Giant Cell Tumour of Bone and in Patients with Growing Skeletons

Clinically significant hypercalcaemia requiring hospitalization and complicated by acute renal injury has been reported in Xgeva-treated patients with giant cell tumour of bone (a patient population for which Xgeva is not indicated) and patients with growing skeletons weeks to months following treatment discontinuation. After treatment is discontinued, monitor patients for signs and symptoms of hypercalcaemia, consider periodic assessment of serum calcium as clinically indicated, and reevaluate the patients’ calcium and vitamin D supplementation requirements. Manage hypercalcaemia as clinically appropriate (see section 4.8, Undesirable effects).

Multiple Vertebral Fractures (MVF) following Treatment Discontinuation

Multiple vertebral fractures (MVF), not due to bone metastases, may occur following discontinuation of treatment with Xgeva, particularly in patients with risk factors such as osteonecrosis or prior fractures.

Advise patients not to interrupt Xgeva therapy without their physician’s advice. When Xgeva treatment is discontinued, evaluate the individual patient’s risk for vertebral fractures (see section 4.8, Undesirable effects).

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.

Excipients with Known Effects

Xgeva contains sorbitol. Patients with rare hereditary problems of fructose intolerance should not use Xgeva.

Xgeva contains less than 1 mmol sodium (23 mg) per 120 mg, i.e. essentially ‘sodium free’.

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 population

The safety and efficacy of Xgeva in paediatric patients have not been established. Xgeva is not recommended for use in paediatric patients. 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 cynomolgus monkeys exposed in utero to denosumab at 50 mg/kg, there was increased postnatal mortality; abnormal bone growth resulting in reduced bone strength, reduced haematopoiesis, and tooth enamel malalignment; absence of peripheral lymph nodes; and decreased neonatal growth. Following a recovery period from birth out to 6 months of age, the effects on bone returned to normal; there was no adverse effects on tooth eruption; and minimal to moderate mineralization in multiple tissues was seen in one recovery animal. 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.

Clinically significant hypercalcaemia after treatment discontinuation has been reported in the post-marketing setting in paediatric patients with growing skeletons who received denosumab for giant cell tumour of bone or for other unapproved indications (see section 4.4, Hypercalcaemia Following Treatment Discontinuation in Patients with Giant Cell Tumour of Bone and in Patients with Growing Skeletons).

4.5 Interaction with other medicines and other forms of interaction

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.

No interactions with laboratory and diagnostic tests have been identified.
4.6 Fertility, pregnancy and lactation

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.

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 impaired fertility was observed.

In a study of cynomolgus monkeys dosed with denosumab during the period equivalent to the first trimester at AUC exposures up to 10-fold higher than the human dose (120 mg every 4 weeks), there was no evidence of maternal or foetal harm. In this study, foetal lymph nodes were not examined.

In another study of cynomolgus monkeys dosed with denosumab throughout pregnancy at AUC exposures 12-fold higher than the human dose (120 mg every 4 weeks), 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. There was no evidence of maternal harm prior to labour; adverse maternal effects occurred infrequently during labour. Maternal mammary gland development was normal.

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.
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. 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. 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 120 mg subcutaneous administered once every month.

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

Summary of safety profile

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 1 describes adverse events that were reported by ≥ 10% of patients in these studies regardless of presumed causality to study drug.
### Table 1: Percentage of Patients with Adverse Events in Patients with Advanced Malignancies Involving Bone by Body System (≥ 10% Incidence in Either Treatment Group)

<table>
<thead>
<tr>
<th>System Organ Class</th>
<th>Preferred Term</th>
<th>Xgeva (N = 2841) n (%)</th>
<th>Zoledronic Acid (N = 2836) n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood and lymphatic system disorders</td>
<td>Anaemia</td>
<td>771 (27.1)</td>
<td>859 (30.3)</td>
</tr>
<tr>
<td>Gastrointestinal disorders</td>
<td>Nausea</td>
<td>876 (30.8)</td>
<td>895 (31.6)</td>
</tr>
<tr>
<td></td>
<td>Constipation</td>
<td>603 (21.2)</td>
<td>670 (23.6)</td>
</tr>
<tr>
<td></td>
<td>Diarrhoea</td>
<td>577 (20.3)</td>
<td>530 (18.7)</td>
</tr>
<tr>
<td></td>
<td>Vomiting</td>
<td>566 (19.9)</td>
<td>570 (20.1)</td>
</tr>
<tr>
<td></td>
<td>Abdominal pain</td>
<td>292 (10.3)</td>
<td>280 (9.9)</td>
</tr>
<tr>
<td>General disorders and administration site conditions</td>
<td>Fatigue</td>
<td>769 (27.1)</td>
<td>766 (27.0)</td>
</tr>
<tr>
<td></td>
<td>Asthenia</td>
<td>607 (21.4)</td>
<td>621 (21.9)</td>
</tr>
<tr>
<td></td>
<td>Oedema peripheral</td>
<td>472 (16.6)</td>
<td>462 (16.3)</td>
</tr>
<tr>
<td></td>
<td>Pyrexia</td>
<td>409 (14.4)</td>
<td>562 (19.8)</td>
</tr>
<tr>
<td>Investigations</td>
<td>Weight decreased</td>
<td>330 (11.6)</td>
<td>332 (11.7)</td>
</tr>
<tr>
<td>Metabolism and nutrition disorders</td>
<td>Decreased appetite</td>
<td>656 (23.1)</td>
<td>694 (24.5)</td>
</tr>
<tr>
<td>Musculoskeletal and connective tissue disorders</td>
<td>Back pain</td>
<td>718 (25.3)</td>
<td>747 (26.3)</td>
</tr>
<tr>
<td></td>
<td>Arthralgia</td>
<td>570 (20.1)</td>
<td>632 (22.3)</td>
</tr>
<tr>
<td></td>
<td>Bone pain</td>
<td>564 (19.9)</td>
<td>639 (22.5)</td>
</tr>
<tr>
<td></td>
<td>Pain in extremity</td>
<td>524 (18.4)</td>
<td>550 (19.4)</td>
</tr>
<tr>
<td></td>
<td>Musculoskeletal pain</td>
<td>357 (12.6)</td>
<td>385 (13.6)</td>
</tr>
<tr>
<td>Nervous system disorders</td>
<td>Headache</td>
<td>360 (12.7)</td>
<td>382 (13.5)</td>
</tr>
<tr>
<td>Psychiatric disorders</td>
<td>Insomnia</td>
<td>302 (10.6)</td>
<td>324 (11.4)</td>
</tr>
<tr>
<td>Respiratory, thoracic, and mediastinal disorders</td>
<td>Dyspnea</td>
<td>585 (20.6)</td>
<td>507 (17.9)</td>
</tr>
<tr>
<td></td>
<td>Cough</td>
<td>437 (15.4)</td>
<td>419 (14.8)</td>
</tr>
</tbody>
</table>

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

The adverse reactions identified in the clinical trials and from post-marketing experience with Xgeva are presented in the table below.

Frequency is provided by CIOMS category (e.g. very common (≥ 10%), common (≥ 1% and < 10%), uncommon (≥ 0.1% and < 1%), rare (≥ 0.01% and < 0.1%) and very rare (< 0.01%).

<table>
<thead>
<tr>
<th>System Organ Class</th>
<th>Adverse reaction</th>
<th>Frequency category</th>
</tr>
</thead>
<tbody>
<tr>
<td>Immune system disorder</td>
<td>Drug hypersensitivity(^a)</td>
<td>Rare</td>
</tr>
<tr>
<td>Metabolism and nutrition disorders</td>
<td>Hypocalcaemia(^a,b)</td>
<td>Very common</td>
</tr>
<tr>
<td></td>
<td>Hypophosphataemia</td>
<td>Common</td>
</tr>
<tr>
<td></td>
<td>Hypercalcemia following treatment discontinuation in patients with giant cell tumor of bone(^b)</td>
<td>Uncommon</td>
</tr>
<tr>
<td></td>
<td>Hypercalcemia following treatment discontinuation in patients with growing skeletons(^b)</td>
<td>Rare</td>
</tr>
<tr>
<td>Musculoskeletal and connective tissue disorders</td>
<td>Musculoskeletal pain</td>
<td>Very common</td>
</tr>
<tr>
<td></td>
<td>Osteonecrosis of the jaw (ONJ)(^a,b)</td>
<td>Common</td>
</tr>
<tr>
<td></td>
<td>Atypical femoral fracture (AFF)(^b)</td>
<td>Uncommon</td>
</tr>
<tr>
<td></td>
<td>Multiple vertebral fractures following treatment discontinuation(^b)</td>
<td>Rare</td>
</tr>
<tr>
<td>Respiratory, thoracic and mediastinal disorders</td>
<td>Dyspnea</td>
<td>Very common</td>
</tr>
<tr>
<td>Skin and subcutaneous tissue disorders</td>
<td>Alopecia</td>
<td>Common</td>
</tr>
<tr>
<td></td>
<td>Lichenoid drug eruption(^a)</td>
<td>Uncommon</td>
</tr>
</tbody>
</table>

\(^a\) See Section Description of selected adverse reactions

\(^b\) See Section 4.4 Special warnings and precautions for use
Description of selected adverse reactions

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.

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, 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 a phase III placebo-controlled clinical trial with an extension treatment phase evaluating Xgeva for the prevention of bone metastases 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.

Atypical Femoral Fractures

In the clinical trial program, atypical femoral fracture has 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.
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.

Hypercalcaemia

Hypercalcaemia has been observed following treatment discontinuation in patients with growing skeletons (a patient population for which Xgeva is not indicated).

Hypercalcaemia following treatment discontinuation in patients with giant cell tumour of bone has been observed uncommonly (see section 4.4, Hypercalcaemia Following Treatment Discontinuation in Patients with Giant Cell Tumour of Bone and in Patients with Growing Skeletons).

Multiple Vertebral Fractures

Multiple vertebral fractures, not due to bone metastases, have occurred in patients with risk factors such as osteoporosis or prior fractures following treatment discontinuation.

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.

Lichenoid drug eruptions (e.g., lichen planus-like reactions).

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorization of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions to

https://nzphvc.otago.ac.nz/reporting/
4.9 Overdose

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.

For advice on the management of overdose please contact the National Poisons Centre on 0800 POISON (0800 764766).

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

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.

CAS number: 615258-40-7

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

Pharmacodynamic effects

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
Increased osteoclast activity, stimulated by RANKL, 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 RANKL-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.

**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.

**Clinical efficacy and safety**

**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 2).
Figure 1. Kaplan-Meier plot of time to first on-study SRE

<table>
<thead>
<tr>
<th>Study</th>
<th>ZA (N)</th>
<th>Dmab (N)</th>
</tr>
</thead>
<tbody>
<tr>
<td>20050136</td>
<td>1020</td>
<td>1026</td>
</tr>
<tr>
<td>20050244</td>
<td>890</td>
<td>886</td>
</tr>
<tr>
<td>20050103</td>
<td>951</td>
<td>950</td>
</tr>
</tbody>
</table>

N = number of subjects randomised
Table 2: Efficacy results in patients with advanced malignancies involving bone

<table>
<thead>
<tr>
<th>Study 2005136 breast cancer</th>
<th>Study 20050244 other solid tumours or multiple myeloma</th>
<th>Study 20050103 prostate cancer</th>
<th>Combined advanced cancer</th>
</tr>
</thead>
<tbody>
<tr>
<td>Xgeva Zoledronic acid</td>
<td>Xgeva Zoledronic acid</td>
<td>Xgeva Zoledronic acid</td>
<td>Xgeva Zoledronic acid</td>
</tr>
<tr>
<td>N</td>
<td>1026</td>
<td>1020</td>
<td>886</td>
</tr>
</tbody>
</table>

**First SRE**

<table>
<thead>
<tr>
<th></th>
<th>Study 2005136 breast cancer</th>
<th>Study 20050244 other solid tumours or multiple myeloma</th>
<th>Study 20050103 prostate cancer</th>
<th>Combined advanced cancer</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median time (months)</td>
<td>NR</td>
<td>26.4</td>
<td>20.6</td>
<td>16.3</td>
</tr>
<tr>
<td>Diff in median time (months)</td>
<td>NA</td>
<td>4.2</td>
<td>3.5</td>
<td>8.2</td>
</tr>
<tr>
<td>Hazard ratio (95% CI)</td>
<td>0.82 (0.71, 0.95)</td>
<td>0.84 (0.71, 0.98)</td>
<td>0.82 (0.71, 0.95)</td>
<td>0.83 (0.76, 0.90)</td>
</tr>
<tr>
<td>Risk reduction (%)</td>
<td>18</td>
<td>16</td>
<td>18</td>
<td>17</td>
</tr>
<tr>
<td>Non-inferiority p-value</td>
<td>&lt;0.0001†</td>
<td>0.0007†</td>
<td>0.0002†</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Superiority p-value</td>
<td>0.0101†</td>
<td>0.0619†</td>
<td>0.0085†</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Proportion of subjects (%)</td>
<td>30.7</td>
<td>36.5</td>
<td>31.4</td>
<td>36.3</td>
</tr>
</tbody>
</table>

**First and subsequent SRE**

<table>
<thead>
<tr>
<th></th>
<th>Study 2005136 breast cancer</th>
<th>Study 20050244 other solid tumours or multiple myeloma</th>
<th>Study 20050103 prostate cancer</th>
<th>Combined advanced cancer</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean number/patient</td>
<td>0.46</td>
<td>0.60</td>
<td>0.44</td>
<td>0.49</td>
</tr>
<tr>
<td>Rate ratio (95% CI)</td>
<td>0.77 (0.66, 0.89)</td>
<td>0.90 (0.77, 1.04)</td>
<td>0.82 (0.71, 0.94)</td>
<td>0.82 (0.75, 0.89)</td>
</tr>
<tr>
<td>Risk reduction (%)</td>
<td>23</td>
<td>10</td>
<td>18</td>
<td>18</td>
</tr>
<tr>
<td>Superiority p-value</td>
<td>0.0012†</td>
<td>0.1447†</td>
<td>0.0085†</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>SMR per year</td>
<td>0.45</td>
<td>0.58</td>
<td>0.86</td>
<td>1.04</td>
</tr>
</tbody>
</table>

**First Radiation to Bone**

<table>
<thead>
<tr>
<th></th>
<th>Study 2005136 breast cancer</th>
<th>Study 20050244 other solid tumours or multiple myeloma</th>
<th>Study 20050103 prostate cancer</th>
<th>Combined advanced cancer</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median time (months)</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Hazard ratio (95% CI)</td>
<td>0.74 (0.59, 0.94)</td>
<td>0.78 (0.63, 0.97)</td>
<td>0.78 (0.66, 0.94)</td>
<td>0.77 (0.69, 0.87)</td>
</tr>
<tr>
<td>Risk reduction (%)</td>
<td>26</td>
<td>22</td>
<td>22</td>
<td>23</td>
</tr>
<tr>
<td>Superiority p-value</td>
<td>0.0121</td>
<td>0.0256</td>
<td>0.0071</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

NR = not reached; NA = not available; SRE = skeletal related event; SMR = skeletal morbidity rate: defined as the ration of the number of occurrence of any SRE for a subject, allowing 1 event per assessing period (e.g. 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]).

### 5.2 Pharmacokinetic properties

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).

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. 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.

**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.

**Paediatric population**

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

**Elderly**

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

**Impaired hepatic function**

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

**Impaired renal function**

In studies of denosumab (60 mg, N=55 and 120 mg, N = 32) in 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.
5.3 Preclinical safety data

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.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sorbitol

Acetate

Sodium hydroxide for adjusting pH

Water for Injection (USP)

Xgeva is a sterile, preservative-free, clear, colourless to slightly yellow solution. The solution may contain trace amounts of translucent to white proteinaceous particles.

6.2 Incompatibilities

In the absence of compatibility studies, this medicine must not be mixed with other medicines.

6.3 Shelf life

3 years

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.

6.4 Special precautions for storage

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.
6.5  Nature and contents of container
Glass Type I vial. Pack size of one or four*.

* Not marketed in Australia or New Zealand.

6.6  Special precautions for disposal and other handling
Any unused medicine or waste material should be disposed of in accordance with local requirements.

7.  MEDICINE SCHEDULE
Prescription Medicine

8.  SPONSOR
Amgen (New Zealand) Limited
Level 20, Lumley Centre
88 Shortland Street
Auckland
New Zealand
Telephone: 0800 443 885
Email: medinfo.JAPAC@amgen.com

9.  DATE OF FIRST APPROVAL
Date of publication in the New Zealand Gazette of consent to distribute the medicine:
3 May 2012

10. DATE OF REVISION OF THE TEXT
08 February 2019
### SUMMARY TABLE OF CHANGES

<table>
<thead>
<tr>
<th>Section changed</th>
<th>Summary of new information</th>
</tr>
</thead>
<tbody>
<tr>
<td>4.8</td>
<td>Inclusion of alopecia and lichenoid drug eruptions as adverse drug reactions.</td>
</tr>
<tr>
<td>4.8</td>
<td>Update to safety information relating to atypical femoral fractures.</td>
</tr>
<tr>
<td>Multiple sections</td>
<td>Reformatted and updated to align with new data sheet template requirements.</td>
</tr>
<tr>
<td>4.4</td>
<td>Addition of precaution for risk of hypocalcaemia during treatment, and recommendation to monitor calcium levels during treatment.</td>
</tr>
<tr>
<td>4.4</td>
<td>Update to the precaution for use in patients with renal impairment, and advice to monitor calcium levels.</td>
</tr>
<tr>
<td>4.4</td>
<td>Revision of the precaution relating to risk of osteonecrosis of the jaw, to include updated information on dental hygiene and procedures.</td>
</tr>
<tr>
<td>4.4</td>
<td>Addition of a precaution for risk of Hypercalcaemia following treatment discontinuation in patients with giant cell tumour of bone and in patients with growing skeletons.</td>
</tr>
<tr>
<td>4.4</td>
<td>Inclusion of a precaution relating to the risk of multiple vertebral fractures after treatment discontinuation.</td>
</tr>
<tr>
<td>4.4</td>
<td>Removal of the precaution relating to skin infections.</td>
</tr>
<tr>
<td>4.4</td>
<td>Revision of the precaution for paediatric use and inclusion of risk of clinically significant hypercalcaemia post treatment.</td>
</tr>
<tr>
<td>4.6</td>
<td>Revision of section to remove references to pregnancy and lactation surveillance programs.</td>
</tr>
<tr>
<td>4.8</td>
<td>Revision of description of osteonecrosis of the jaw as an adverse drug reaction based upon data.</td>
</tr>
<tr>
<td>4.8</td>
<td>Inclusion of relevant information relating to hypercalcaemia and multiple vertebral fractures as adverse drug reactions.</td>
</tr>
<tr>
<td>4.8</td>
<td>Removal of skin infections as an adverse drug reaction.</td>
</tr>
<tr>
<td>8.0</td>
<td>Inclusion of additional sponsor contact information.</td>
</tr>
</tbody>
</table>