XGEVA™
Denosumab Solution for Injection

1. NAME OF THE MEDICINAL PRODUCT
Denosumab 120mg/1.7ml 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 List of Excipients.

3. PHARMACEUTICAL FORM
Solution for subcutaneous 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
XGEVA is indicated for the prevention of skeletal related events in patients with advanced malignancies involving bone.

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 Special Warnings and Precautions for use).

Advanced malignancies involving bone
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.
Patients with renal impairment

No dose adjustment is required in patients with renal impairment (see section 4.4 Special Warnings and Precautions for Use for recommendations relating to monitoring of calcium, 4.8 Undesirable effects and 5.2 Pharmacokinetic properties).

Patients with hepatic impairment

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

Elderly patients (age ≥ 65)

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

Paediatric population

XGEVA is not recommended in paediatric patients (age < 18). The safety and efficacy of XGEVA have not been established in paediatric patients (age < 18) (see section 4.4 Special Warnings and Precautions for Use).

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 Preclinical Safety Data).

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 Special Precautions for Disposal and Other Handling.

4.3 Contraindications

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

Severe, untreated hypocalcaemia (see section 4.4 Special Warnings and Precautions for Use).

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 Posology and Method of Administration).

**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 Undesirable effects 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 Undesirable Effects), 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 Undesirable Effects).

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 Undesirable Effects). 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 Posology and Method of Administration). 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.

**Warnings for excipients**

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

**Overall Survival in Patients with Multiple Myeloma**
In a study of patients with advanced malignancies involving bone (excluding breast and prostate cancer), overall survival was similar between the zoledronic acid and XGEVA treatment groups (hazard ratio and 95% CI of 0.95 [0.83, 1.08]; n=1776). In an ad-hoc subgroup analysis of multiple myeloma patients, mortality was higher in the XGEVA treatment group (hazard ratio [95% CI] of 2.26 [1.13, 4.50]; n=180). This study did not control for prognostic factors and anti-neoplastic treatments for multiple myeloma.

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 Pregnancy and Lactation

Pregnancy

There are no adequate data from the use of XGEVA in pregnant women. Reproductive toxicity was shown in a study of cynomolgus monkeys, dosed throughout pregnancy with denosumab at AUC exposures 12-fold higher than the human dose (see section 5.3 Preclinical Safety Data).

XGEVA is not recommended for use in pregnant women and women of childbearing potential not using highly effective contraception. Women should be advised not to become pregnant during and for at least 5 months after treatment with XGEVA. Any effects of XGEVA are likely to be greater during the second and third trimesters of pregnancy since monoclonal antibodies are transported across the placenta in a linear fashion as pregnancy progresses, with the largest amount transferred during the third trimester.

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 (see section 5.3 Preclinical Safety Data). 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 Preclinical Safety Data).
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.

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 (≥ 1/10), common (≥ 1/100 to < 1/10), uncommon (≥ 1/1,000 to < 1/100), rare (≥ 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**

<table>
<thead>
<tr>
<th>MedDRA system organ class</th>
<th>Frequency category</th>
<th>Adverse reactions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Immune system disorder</td>
<td>Rare</td>
<td>Drug hypersensitivity¹</td>
</tr>
<tr>
<td></td>
<td>Rare</td>
<td>Anaphylactic reaction¹</td>
</tr>
<tr>
<td>Metabolism and nutrition disorders</td>
<td>Common</td>
<td>Hypocalcaemia¹,²</td>
</tr>
<tr>
<td></td>
<td>Common</td>
<td>Hypophosphataemia</td>
</tr>
<tr>
<td>Respiratory, thoracic and mediastinal disorders</td>
<td>Very common</td>
<td>Dyspnoea</td>
</tr>
<tr>
<td>Gastrointestinal disorders</td>
<td>Very common</td>
<td>Diarrhoea</td>
</tr>
<tr>
<td></td>
<td>Common</td>
<td>Tooth extraction</td>
</tr>
<tr>
<td>Skin and subcutaneous tissues disorders</td>
<td>Common</td>
<td>Hyperhidrosis</td>
</tr>
<tr>
<td>Musculoskeletal and connective tissue disorders</td>
<td>Very common</td>
<td>Musculoskeletal pain¹</td>
</tr>
<tr>
<td></td>
<td>Common</td>
<td>Osteonecrosis of the jaw¹</td>
</tr>
<tr>
<td></td>
<td>Rare</td>
<td>Atypical femoral fracture¹</td>
</tr>
</tbody>
</table>

¹See section Description of selected adverse reactions
²See 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 Special Warnings and Precautions for Use).

In the postmarketing 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 Special Warnings and Precautions for Use). 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 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 Special Warnings and Precautions for Use).

**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.

**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 Special warnings and precautions for use).

**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.

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, neutralizing 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 neutralizing 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

<table>
<thead>
<tr>
<th>Study 1 breast cancer</th>
<th>Study 2 other solid tumours** or multiple myeloma</th>
<th>Study 3 prostate cancer</th>
<th>Combined advanced cancer</th>
</tr>
</thead>
<tbody>
<tr>
<td>XGEVA</td>
<td>zoledronic acid</td>
<td>XGEVA</td>
<td>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>Median time (months)</th>
<th>NR</th>
<th>26.4</th>
<th>20.6</th>
<th>16.3</th>
<th>20.7</th>
<th>17.1</th>
<th>27.6</th>
<th>19.4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Difference in median time (months)</td>
<td>NA</td>
<td>4.2</td>
<td>3.5</td>
<td>8.2</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HR (95% CI) / RRR(%)</td>
<td>0.82 (0.71, 0.95)/18</td>
<td>0.84 (0.71, 0.98)/16</td>
<td>0.82 (0.71, 0.95)/18</td>
<td>0.83 (0.76, 0.90)/17</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-inferiority / Superiority p-values</td>
<td>&lt; 0.0001† / 0.0101†</td>
<td>0.0007† / 0.0619†</td>
<td>0.0002† / 0.0085†</td>
<td>&lt; 0.0001 / &lt; 0.0001</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Proportion of subjects (%)</td>
<td>30.7</td>
<td>36.5</td>
<td>31.4</td>
<td>36.3</td>
<td>35.9</td>
<td>40.6</td>
<td>32.6</td>
<td>37.8</td>
</tr>
</tbody>
</table>

**First and subsequent SRE***

<table>
<thead>
<tr>
<th>Mean number/patient</th>
<th>0.46</th>
<th>0.60</th>
<th>0.44</th>
<th>0.49</th>
<th>0.52</th>
<th>0.61</th>
<th>0.48</th>
<th>0.57</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rate ratio (95% CI) / RRR (%)</td>
<td>0.77 (0.66, 0.89) / 23</td>
<td>0.90 (0.77, 1.04) / 10</td>
<td>0.82 (0.71, 0.94) / 18</td>
<td>0.82 (0.75, 0.89) / 18</td>
<td></td>
<td></td>
<td></td>
<td></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>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SMR per year</td>
<td>0.45</td>
<td>0.58</td>
<td>0.86</td>
<td>1.04</td>
<td>0.79</td>
<td>0.83</td>
<td>0.69</td>
<td>0.81</td>
</tr>
</tbody>
</table>

**First SRE or HCM**

<p>| Median time (months) | NR | 25.2 | 19.0 | 14.4 | 20.3 | 17.1 | 26.6 | 19.4 |</p>
<table>
<thead>
<tr>
<th>Study</th>
<th>Disease Category</th>
<th>XGEVA</th>
<th>Zoledronic Acid</th>
<th>XGEVA</th>
<th>Zoledronic Acid</th>
<th>XGEVA</th>
<th>Zoledronic Acid</th>
<th>XGEVA</th>
<th>Zoledronic Acid</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>breast cancer</td>
<td>0.82</td>
<td>(0.70, 0.95) / 18</td>
<td>0.83</td>
<td>(0.71, 0.97) / 17</td>
<td>0.83</td>
<td>(0.72, 0.96) / 17</td>
<td>0.83</td>
<td>(0.76, 0.90) / 17</td>
</tr>
<tr>
<td></td>
<td>Superiority p-value</td>
<td>0.0074</td>
<td>0.0215</td>
<td>0.0134</td>
<td>&lt; 0.0001</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>other solid tumours** or multiple myeloma</td>
<td>0.74</td>
<td>(0.59, 0.94) / 26</td>
<td>0.78</td>
<td>(0.63, 0.97) / 22</td>
<td>0.78</td>
<td>(0.66, 0.94) / 22</td>
<td>0.77</td>
<td>(0.69, 0.87) / 23</td>
</tr>
<tr>
<td></td>
<td>Superiority p-value</td>
<td>0.0121</td>
<td>0.0256</td>
<td>0.0071</td>
<td>&lt; 0.0001</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

** First Radiation to Bone

<table>
<thead>
<tr>
<th>Median time (months)</th>
<th>ZA (N = 1020)</th>
<th>Dmab (N = 1026)</th>
<th>ZA (N = 890)</th>
<th>Dmab (N = 886)</th>
<th>ZA (N = 951)</th>
<th>Dmab (N = 950)</th>
</tr>
</thead>
<tbody>
<tr>
<td>HR (95% CI) / RRR (%)</td>
<td>0.74 (0.59, 0.94) / 26</td>
<td>0.78 (0.63, 0.97) / 22</td>
<td>0.78 (0.66, 0.94) / 22</td>
<td>0.77 (0.69, 0.87) / 23</td>
<td></td>
<td></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>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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
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).

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

**Hepatic impairment**

No specific study in patients with hepatic impairment was performed. In general, monoclonal antibodies are not eliminated via hepatic metabolic mechanisms. The pharmacokinetics of denosumab is not expected to be affected by hepatic impairment.

**Elderly**

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

**Paediatric population**

The pharmacokinetic profile in paediatric populations has not been assessed.
5.3 Preclinical Safety Data

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

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

Standard tests to investigate the genotoxicity potential of denosumab have not been evaluated, since such tests are not relevant for this molecule. However, due to its character it is unlikely that denosumab has any potential for genotoxicity.

The carcinogenic potential of denosumab has not been evaluated in long-term animal studies.

In single and repeated dose toxicity studies in cynomolgus monkeys, denosumab doses resulting in 2.7 to 15 times greater systemic exposure than the recommended human dose had no impact on cardiovascular physiology, male or female fertility, or produced specific target organ toxicity.

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

In another study of cynomolgus monkeys dosed with denosumab throughout pregnancy at systemic exposures 12-fold higher than the human dose, there were increased stillbirths and postnatal mortality; abnormal bone growth resulting in reduced bone strength, reduced haematopoiesis, and tooth malalignment; absence of peripheral lymph nodes; and decreased neonatal growth. A no observed adverse effect level for reproductive effects was not established. Following a 6 month period after birth, bone related changes showed recovery and there was no effect on tooth eruption. However, the effects on lymph nodes and tooth malalignment persisted, and minimal to moderate mineralisation in multiple tissues was seen in one animal (relation to treatment uncertain). There was no evidence of maternal harm prior to labour; adverse maternal effects occurred infrequently during labour. Maternal mammary gland development was normal.
In preclinical bone quality studies in monkeys on long-term denosumab treatment, decreases in bone turnover were associated with improvement in bone strength and normal bone histology.

In male mice genetically engineered to express huRANKL (knock-in mice), which were subjected to a transcortical fracture, denosumab delayed the removal of cartilage and remodelling of the fracture callus compared to control, but biomechanical strength was not adversely affected.

In preclinical studies knockout mice lacking RANK or RANKL had an absence of lactation due to inhibition of mammary gland maturation (lobulo-alveolar gland development during pregnancy) and exhibited impairment of lymph node formation. Neonatal RANK/RANKL knockout mice exhibited decreased body weight, reduced bone growth, altered growth plates and lack of tooth eruption. Reduced bone growth, altered growth plates and impaired tooth eruption were also seen in studies of neonatal rats administered RANKL inhibitors, and these changes were partially reversible when dosing of RANKL inhibitor was discontinued. Adolescent primates dosed with denosumab at 2.7 and 15 times (10 and 50 mg/kg dose) the clinical exposure had abnormal growth plates. Therefore, treatment with denosumab may impair bone growth in children with open growth plates and may inhibit eruption of dentition.

6. PHARMACEUTICAL PARTICULARS

6.1 List of Excipients

Acetic acid, glacial*
Sodium hydroxide (for pH adjustment)*
Sorbitol (E420)
Water for injections
* Acetate buffer is formed by mixing acetic acid with sodium hydroxide

6.2 Incompatibilities

In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products.

6.3 Shelf Life

36 months

The expiry date 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.

Keep out of reach of children.

6.5 Nature and Contents of Container

1.7 ml solution in a single use vial (type I glass) with stopper (fluoropolymer coated elastomeric) and seal (aluminium) with flip-off cap.

Pack size of one.

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. MARKETING AUTHORISATION HOLDER

GlaxoSmithKline Pharmaceuticals Limited
Registered Office:
Dr Annie Besant Road,
Worli,
Mumbai 400030, India.

8. MARKETING AUTHORISATION NUMBER(S)

Import Permission No.: IMP-193/2012

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorization (Form 45): 03 October 2012.

Manufactured by:
Amgen Manufacturing Limited,
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Kilometer 24.6,
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USA.

**Imported and Marketed by:**
GlaxoSmithKline Pharmaceuticals Limited,
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Dist Thane, Bhiwandi.

**Registered Office:**
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Worli,
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