Dimensions: 8.5"x11"
Saddle stitch binding with weld glue

At first diagnosis of a bone metastasis in breast cancer

Breast Cancer

Help keep what matters intact with the bone-targeting agent **proven superior** for the prevention of bone complications* vs ZA[1,2,†]

*Bone complications, also known as skeletal-related events (SREs), are defined as radiation to bone, pathologic fracture, surgery to bone, and spinal cord compression.[1]

†Please see study details on page 4.
ZA, zoledronic acid.

Indication

XGEVA® is indicated for the prevention of skeletal-related events in patients with multiple myeloma and in patients with bone metastases from solid tumors.

Important Safety Information

Hypocalcemia

- Pre-existing hypocalcemia must be corrected prior to initiating therapy with XGEVA®. XGEVA® can cause severe symptomatic hypocalcemia, and fatal cases have been reported. Monitor calcium levels, especially in the first weeks of initiating therapy, and administer calcium, magnesium, and vitamin D as necessary. Concomitant use of calcimimetics and other drugs that can lower calcium levels may worsen hypocalcemia risk and serum calcium should be closely monitored. Advise patients to contact a healthcare professional for symptoms of hypocalcemia.
- An increased risk of hypocalcemia has been observed in clinical trials of patients with increasing renal dysfunction, most commonly with severe dysfunction (creatinine clearance less than 30 mL/minute and/or on dialysis), and with inadequate/no calcium supplementation. Monitor calcium levels and calcium and vitamin D intake.

Please see additional Important Safety Information throughout.

XGEVA®
(denosumab) injection
120 mg/1.7 mL vial

Spread Dimensions: 17"x 11"

Women are living longer with metastatic breast cancer (mBC), leaving them vulnerable to bone complications[3]

At risk for a first bone complication[4]

In the placebo arm of a randomized clinical trial,

64%

of women with breast cancer and bone metastases experienced a bone complication*

At risk for a subsequent bone complication[5]

In another study, after experiencing a first bone complication,

69%

of women with breast cancer and bone metastases suffered a subsequent bone complication†

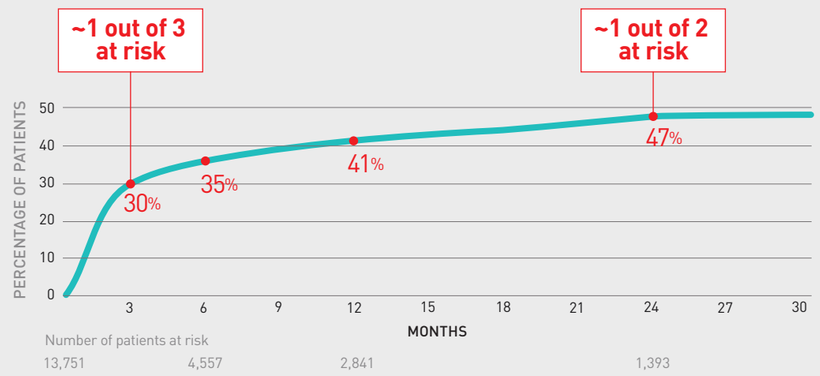
An initial bone complication increases the risk for additional bone complications[5,6]

*Data from the placebo arm (n=384) of a randomized clinical trial evaluating the efficacy of an intravenous (IV) bisphosphonates in the reduction of bone complications in women with bone metastases from breast cancer.[4]

†Based on a linked Surveillance, Epidemiology, and End Results cancer registry and Medicare (SEER-Medicare) claims database analysis of 3,731 elderly metastatic breast cancer patients from 2005-2009, 1,808 of whom experienced at least one SRE, which was defined as spinal cord compression, pathologic fracture, bone surgery, or radiation therapy (although specific anatomical site of radiation was unknown). Of these patients, 69% experienced a subsequent SRE.[5]

The risk of bone complications is immediate and continues to increase over time[6,7,‡]

Proportion of breast cancer patients with at least one bone complication over time[6,7]



‡Results from observational cohort research using MarketScan® commercial and Medicare supplemental databases of patients with bone metastases secondary to solid tumors, including breast cancer, from 2007-2015, who did not receive a bone-targeting agent.[6]

Bone complications can be devastating[8-11]

Radiation therapy can require multiple treatments, commonly 10 to 14 treatments daily over 2 to 3 weeks[8]

- Used commonly to manage pain, it is also used to prevent fracture or in conjunction with surgery to reduce risk of bone complications[8,12]

Spinal cord compression is considered to be an oncologic emergency[9]

- Breast, prostate, and lung cancer account for the majority of cases[13]

Pathologic fractures can be painful for patients and often do not heal, resulting in bone destruction[10]

- Fractures of weight-bearing bones often require surgical stabilization[14]

Bone surgery often requires postsurgical rehabilitation[11]

- May be required to treat pain, pathologic fracture, or other complications[10,14]

Patients with bone complications frequently suffer from pain[15]

86% of patients with a bone complication experienced bone pain§

§Results collected from a retrospective study, which included 176 patients with breast cancer and bone metastases from 2008-2012. Bone complications were defined as: pathologic fracture, surgery to bone, radiation to bone, spinal cord compression, and hypercalcemia of malignancy.[15]

How are you preventing bone complications for your patients with breast cancer and bone metastases?

XGEVA® prevented bone complications for > 2 years[1,2]

XGEVA® Q4W: superior prevention of bone complications[1,2]

~60%

of mBC patients were **free from bone complications** at 27 months (study end)

Median time for first on-study bone complication: 26.4 months for ZA, was not reached for denosumab

18%

risk reduction vs ZA

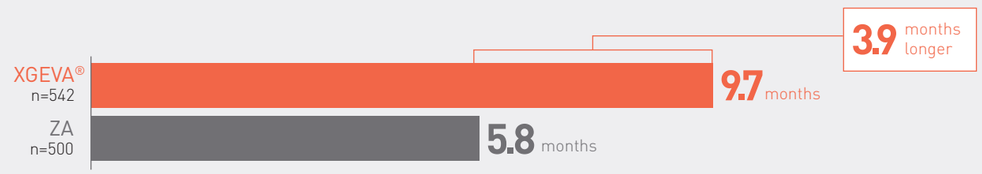
HR*=0.82
(95% CI: 0.71-0.95);
P=0.010†

Study design: Based on a phase 3, double-blind, double-dummy, active-controlled trial comparing XGEVA® with ZA for the prevention of bone complications in patients with breast cancer and bone metastases (XGEVA®: n=1,026; ZA: n=1,020). Patients were randomized 1:1 to receive 120 mg XGEVA® subcutaneously (SC) every 4 weeks or 4 mg ZA intravenously (IV) every 4 weeks. Per label, the IV product was dose-adjusted for baseline creatinine clearance ≤ 60 mL/min. No dose adjustments were made and no doses were withheld, for increased serum creatinine for the SC product. The primary endpoint was noninferiority of time to first bone complication as compared with ZA. If the primary endpoint of noninferiority was met, the superiority test for secondary endpoints was conducted, including time to first bone complication and time to first and subsequent bone complications.[1,2]

*Hazard ratio (HR) is defined as the increase or decrease in likelihood of an event of interest (in this case, a bone complication for one group relative to a comparator group.
†*P* value for superiority.

Post hoc analysis: Time to progression of pain‡

Median time to moderate/severe pain in advanced breast cancer patients[16,§,**,††]



- Results for castration-resistant prostate cancer patients§: XGEVA® (5.8 months) vs ZA (4.9 months)[17]
- Results for advanced solid tumor-only cancer patients (excluding multiple myeloma)§: XGEVA® (4.7 months) vs ZA (3.7 months)[18]
- Not adjusted for multiplicity or powered to assess efficacy in either arm

‡Not included in US label.
§Time to moderate/severe worst pain was defined as the time to first post-baseline score of > 4 on the BPI-SF worst pain score in patients who had no/mild pain at baseline (BPI-SF worst pain score ≤ 4). Pain measures did not account for analgesic use.[16-19]
**On a scale of 0 to 10. A score of ≤ 4 was considered no or mild pain and a score of > 4 was considered moderate or severe pain.[16-18]
††Pain was measured every 4 weeks. Pain progression patient reported outcomes did not account for analgesic use.[16-18]
BPI-SF, Brief Pain Inventory (short form); CI, confidence interval; Q4W, every 4 weeks.

Please see additional Important Safety Information throughout.

Importance of Q4W dosing

Deviation from standard XGEVA® Q4W demonstrated an increased rate of bone complications[20]

- Results from a retrospective study (N=60) showed patients in the deviated interval arm (dosing once every 31 to 56 days) experienced more bone complications compared with the standard interval arm (Q4W)‡‡,§§
  - Study demographics: standard interval (31% breast cancer, 34.5% prostate cancer, 6.9% lung cancer); deviated interval (41.9% breast cancer, 16.1% prostate cancer, 19.4% lung cancer)

Standard interval		Deviated interval
31%	vs	**61%**
Incidence of bone complications (N=29)		Incidence of bone complications (N=31)

‡‡Dosing was considered once every 27-30 days in this study.[20]
§§ A retrospective case cohort study of sixty patients treated from 2012 to 2015 at a single cancer center. Subjects must have received two or more doses.[20]

NCCN Clinical Practice Guidelines (NCCN Guidelines®)

Denosumab (XGEVA® Q4W)—Category 1* recommended option for the prevention of bone complications in women with breast cancer and bone metastases[1,21]**

***Category 1: Based on high-level evidence, there is uniform NCCN consensus that the intervention is appropriate.[21]

For the best chance of achieving results like those seen in the phase 3 clinical trials, dose your patients every 4 weeks[1,2,20]

Important Safety Information (cont'd)

Hypersensitivity

- XGEVA® is contraindicated in patients with known clinically significant hypersensitivity to XGEVA®, including anaphylaxis that has been reported with use of XGEVA®. Reactions may include hypotension, dyspnea, upper airway edema, lip swelling, rash, pruritus, and urticaria. If an anaphylactic or other clinically significant allergic reaction occurs, initiate appropriate therapy and discontinue XGEVA® therapy permanently.

Drug Products with Same Active Ingredient

- Patients receiving XGEVA® should not take Prolia® (denosumab).

Osteonecrosis of the Jaw

- Osteonecrosis of the jaw (ONJ) has been reported in patients receiving XGEVA®, manifesting as jaw pain, osteomyelitis, osteitis, bone erosion, tooth or periodontal infection, toothache, gingival ulceration, or gingival erosion. Persistent pain or slow healing of the mouth or jaw after dental surgery may also be manifestations of ONJ. In clinical trials in patients with cancer, the incidence of ONJ was higher with longer duration of exposure.

Please see additional Important Safety Information throughout.

XGEVA®
(denosumab) injection
120 mg/1.7 mL vial

We're committed to helping patients access Amgen® medicines whenever possible

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The Amgen FIRST STEP™ program can help your eligible commercially insured patients cover their out-of-pocket prescription costs, including deductible, co-insurance, and co-payment.

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- $5 out-of-pocket for subsequent doses or cycles, up to the brand program benefit maximum
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For uninsured patients

The Amgen Safety Net Foundation is a nonprofit patient assistance program sponsored by Amgen that helps qualifying patients access Amgen medicines at no cost.

*Terms, conditions, and program maximums apply. This program is not open to patients receiving prescription reimbursement under any federal, state, or government-funded healthcare program. Not valid where prohibited by law.
† Amgen Nurse Ambassadors are there to support, not replace, your treatment plan and do not provide medical advice or case management services. Patients should always consult their healthcare provider regarding medical decisions or treatment concerns.
‡ Resources include referrals to independent nonprofit patient assistance programs. Eligibility for resources provided by independent nonprofit patient assistance programs is based on the nonprofits' criteria. Amgen has no control over these programs and provides referrals as a courtesy only.

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Pocket for PI

Important Safety Information (cont'd)

Osteonecrosis of the Jaw (cont'd)

- Patients with a history of tooth extraction, poor oral hygiene, or use of a dental appliance are at a greater risk to develop ONJ. Other risk factors for the development of ONJ include immunosuppressive therapy, treatment with angiogenesis inhibitors, systemic corticosteroids, diabetes, and gingival infections.
- Perform an oral examination and appropriate preventive dentistry prior to the initiation of XGEVA® and periodically during XGEVA® therapy. Advise patients regarding oral hygiene practices. Avoid invasive dental procedures during treatment with XGEVA®. Consider temporarily interrupting XGEVA® therapy if an invasive dental procedure must be performed.
- Patients who are suspected of having or who develop ONJ while on XGEVA® should receive care by a dentist or an oral surgeon. In these patients, extensive dental surgery to treat ONJ may exacerbate the condition.

Atypical Subtrochanteric and Diaphyseal Femoral Fracture

- Atypical femoral fracture has been reported with XGEVA®. These fractures can occur anywhere in the femoral shaft from just below the lesser trochanter to above the supracondylar flare and are transverse or short oblique in orientation without evidence of comminution.
- Atypical femoral fractures most commonly occur with minimal or no trauma to the affected area. They may be bilateral and many patients report prodromal pain in the affected area, usually presenting as dull, aching thigh pain, weeks to months before a complete fracture occurs. A number of reports note that patients were also receiving treatment with glucocorticoids (e.g. prednisone) at the time of fracture. During XGEVA® treatment, patients should be advised to report new or unusual thigh, hip, or groin pain. Any patient who presents with thigh or groin pain should be suspected of having an atypical fracture and should be evaluated to rule out an incomplete femur fracture. Patients presenting with an atypical femur fracture should also be assessed for symptoms and signs of fracture in the contralateral limb. Interruption of XGEVA® therapy should be considered, pending a risk/benefit assessment, on an individual basis.

Hypercalcemia Following Treatment Discontinuation in Patients with Giant Cell Tumor of Bone (GCTB) and in Patients with Growing Skeletons

- Clinically significant hypercalcemia requiring hospitalization and complicated by acute renal injury has been reported in XGEVA®-treated patients with GCTB and in patients with growing skeletons within one year of treatment discontinuation. Monitor patients for signs and symptoms of hypercalcemia after treatment discontinuation and treat appropriately.

Multiple Vertebral Fractures (MVF) Following Treatment Discontinuation

- Multiple vertebral fractures (MVF) have been reported following discontinuation of treatment with denosumab. Patients at higher risk for MVF include those with risk factors for or a history of osteoporosis or prior fractures. When XGEVA® treatment is discontinued, evaluate the individual patient's risk for vertebral fractures.

Embryo-Fetal Toxicity

- XGEVA® can cause fetal harm when administered to a pregnant woman. Based on findings in animals, XGEVA® is expected to result in adverse reproductive effects.
- Advise females of reproductive potential to use effective contraception during therapy, and for at least 5 months after the last dose of XGEVA®. Apprise the patient of the potential hazard to a fetus if XGEVA® is used during pregnancy or if the patient becomes pregnant while patients are exposed to XGEVA®.

Please see additional Important Safety Information throughout.

XGEVA®
(denosumab) injection
120 mg/1.7 mL vial

Pocket for PI

At the first diagnosis of a bone metastasis

Give her the superiority of XGEVA®[1,2]

Denosumab (XGEVA® Q4W) is an NCCN Guidelines® Category 1 option to prevent bone complications in women with breast cancer and bone metastases[1,21]

XGEVA® demonstrated superiority vs ZA in delaying bone complications[1]

Since 2010, nearly 1.5 million people with cancer worldwide have been treated with XGEVA®[1,22,*]

XGEVA® is a 120-mg subcutaneous injection administered once every 4 weeks[1]

The only bone-targeting agent that blocks the function of RANK Ligand (RANKL)[1]
- XGEVA® inhibits RANKL to prevent bone complications

No need to adjust XGEVA® dosing for patients with impaired renal function[1]
- XGEVA® is a monoclonal antibody and is not cleared by the kidneys
- The risk of hypocalcemia increases with decreasing renal function
- In patients with renal impairment, monitor calcium levels and calcium and vitamin D intake closely

*Cumulative number of patients with cancer treated worldwide is calculated based on total global unit sales since 2010 and assumes patients received an average of 10 treatments.[22]

Make prevention of bone complications with XGEVA® a treatment goal[1,2]

Important Safety Information (cont'd)

Adverse Reactions

- The most common adverse reactions in patients receiving XGEVA® with bone metastasis from solid tumors were fatigue/asthenia, hypophosphatemia, and nausea. The most common serious adverse reaction was dyspnea. The most common adverse reactions resulting in discontinuation were osteonecrosis and hypocalcemia.
- For multiple myeloma patients receiving XGEVA®, the most common adverse reactions were diarrhea, nausea, anemia, back pain, thrombocytopenia, peripheral edema, hypocalcemia, upper respiratory tract infection, rash, and headache. The most common serious adverse reaction was pneumonia. The most common adverse reaction resulting in discontinuation of XGEVA® was osteonecrosis of the jaw.

Please see additional Important Safety Information throughout and full Prescribing Information in pocket.

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XGEVA® (denosumab) injection
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