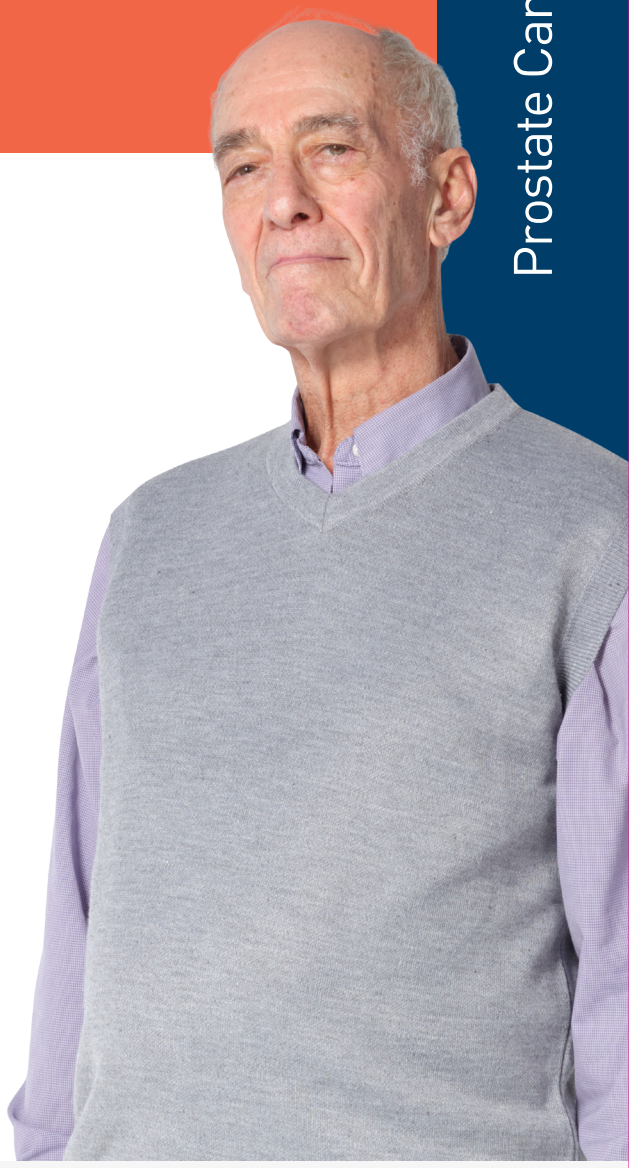
Dimensions: 8.5" x 11"

In men with prostate cancer and bone metastases

Prostate Cancer



# Are you preventing bone complications* with denosumab (XGEVA®), the *only* Category 1† Preferred bone-targeting agent?[1,‡]

**At the first diagnosis of a bone metastasis, reduce the risk of bone complications with the superior efficacy of XGEVA® Q4W (vs ZA)[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.[2]

†NCCN Clinical Practice Guidelines (NCCN Guidelines®) Category 1: based on high-level evidence, there is uniform NCCN consensus that the intervention is appropriate.[1]
‡See study details on page 4.
Q4W, once every 4 weeks; 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"

# Men with prostate cancer and bone metastases may be at risk for suffering from one or more bone complications[3,4]

## At risk for a first bone complication[3]

In the placebo arm of a randomized clinical trial,

**49%**

of men with prostate cancer and bone metastases within 2 years*

## At risk for a subsequent bone complication[4]

In another study, after experiencing a first bone complication,

**63%**

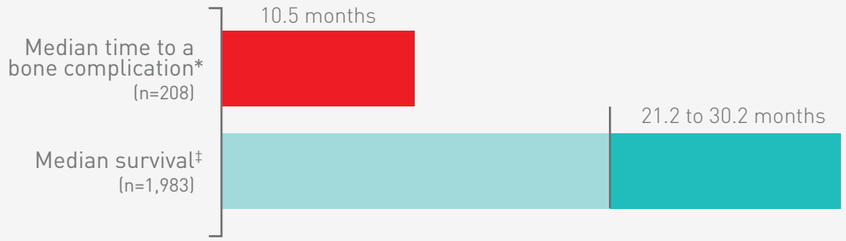
of men suffered a subsequent bone complication†

**An initial bone complication increases the risk for additional bone complications[4,†]**

*Data from the placebo arm (n=208) of a randomized trial evaluating the efficacy of an intravenous bisphosphonate in the reduction of bone complications in men with bone metastases from prostate cancer. In this trial, bone complications or SREs were defined as pathologic fracture, surgery to bone, radiation to bone, spinal cord compression, and change in antineoplastic therapy to treat bone pain.[3]

†Based on a SEER-Medicare linked database analysis of 4,176 prostate cancer patients who experienced at least one SRE. Of these patients, 2,619 experienced a subsequent SRE.[4]

## Median survival exceeds the median time to a first bone complication[3,5-7]




‡Data from the control arms of 3 distinct trials in patients with metastatic castration-resistant prostate cancer (mCRPC): Trial A, the docetaxel, prednisone, plus placebo arm of a randomized controlled trial (RCT) (vs docetaxel, prednisone, plus bevacizumab) of 1,050 men with mCRPC; Trial B, the docetaxel and prednisone plus placebo arm of a RCT (vs aflibercept, docetaxel, and prednisone) of 1,224 men with mCRPC; and,Trial C, the placebo arm of a RCT (vs enzalutamide) of 1,717 men with mCRPC.[5-7]

# The threat of bone complications is immediate and continues to increase over time[8]

## Bone complications in patients with prostate cancer and bone metastases not receiving a bone-targeting agent

### Within 3 months of a bone metastasis[8]

**~1 out of 4** patients develop a bone complication[§]

### Within 12 months of a bone metastasis[8]

**~1 out of 3** patients develop a bone complication[§]

[§]Results from observational matched cohort research using MarketScan® commercial and Medicare supplemental databases of patients with bone metastases secondary to solid tumors, including prostate cancer, from 2007 to 2015, who did not receive a bone-targeting agent.[8]

## Bone complications can be devastating[9-12]

**Radiation therapy can require multiple treatments, commonly 10 to 14 treatments daily over 2 to 3 weeks[9]**

- Used commonly to manage pain, it is also used to prevent fracture or in conjunction with surgery to reduce risk of bone complications[9,13]

**Spinal cord compression is considered to be an oncologic emergency[10]**

- Breast, prostate, and lung cancer account for the majority of cases[14]

**Pathologic fractures can be painful for patients and often do not heal, resulting in bone destruction[11]**

- Fractures of weight-bearing bones often require surgical stabilization[15]

**Bone surgery often requires postsurgical rehabilitation[12]**

- May be required to treat pain, pathologic fracture, or other complications[11,15]

**To prevent bone complications in men with metastatic prostate cancer, the NCCN Guidelines® recommend the use of a bone-targeting agent at first diagnosis of a bone metastasis[1]**

In men with prostate cancer and bone metastases

# XGEVA® Q4W—superior to zoledronic acid (ZA) in preventing bone complications[2,16]

XGEVA® delayed the median time to first bone complication vs ZA[2,16]

**20.7**
**months with XGEVA®**
vs 17.1 months with ZA

**18%**
**risk reduction vs ZA**
HR*=0.82 (95% CI: 0.71-0.95); *P*=0.008†

**Study design:** Based on a phase 3, blinded, randomized (1:1) trial comparing XGEVA® with ZA for the prevention of bone complications in 1,901 patients with prostate cancer and bone metastases. Patients received 120 mg XGEVA® subcutaneously every 4 weeks or 4 mg ZA intravenously (IV) every 4 weeks. 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 complication.[2,16]

Zoledronic acid 4 mg was administered as an IV infusion over a minimum of 15 minutes, once every 4 weeks, in accordance with prescribing information. Select exclusion criteria: patients with creatinine clearance <30 mL/min, patients receiving current or prior IV or oral bisphosphonate therapy for bone metastases were excluded. Patients who received prior oral bisphosphonates for the treatment of osteoporosis were not excluded, as long as treatment was stopped before the first dose of the investigational drug.[16]

*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.
CI, confidence interval.

## 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).

**Please see additional Important Safety Information throughout.**

# Importance of Q4W dosing with XGEVA®

## Deviation from standard XGEVA® Q4W demonstrated an increased rate of bone complications[17]

- 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.[17]
§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.[17]

Denosumab (XGEVA®), the only NCCN Guidelines Category 1 Preferred bone-targeting agent for men with prostate cancer and bone metastases[1]

**For the best chance of achieving results like those seen in the phase 3 clinical trials, dose your patients every 4 weeks[2,16,17]**

## Important Safety Information (cont'd)

### 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

Pocket for PI

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

AMGEN ASSIST 360™
Support, Simplified

## For eligible* commercially insured patients

**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.**

- $0 out-of-pocket for first dose or cycle
- $5 out-of-pocket for subsequent doses or cycles, up to the brand program benefit maximum
- No income eligibility requirement

## For patients on government insurance (like Medicare)

**Our Amgen Nurse Ambassadors† can refer patients to independent nonprofit patient assistance programs that may be able to help them afford the co-pay costs of their prescribed medicine.‡**

## 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.

**Help your eligible patient enroll today**
Visit amgenassist360.com/enroll or call 888-4assist (888-427-7478)

**References: 1.** Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Prostate Cancer V.4.2019. © National Comprehensive Cancer Network, Inc. 2019. All rights reserved. Accessed December 18, 2019. To view the most recent and complete version of the guideline, go online to NCCN.org. NCCN makes no warranties of any kind whatsoever regarding their content, use or application and disclaims any responsibility for their application or use in any way. **2.** XGEVA® (denosumab) prescribing information, Amgen. **3.** Saad F, Gleason DM, Murray R, et al. Long-term efficacy of zoledronic acid for the prevention of skeletal complications in patients with metastatic hormone-refractory prostate cancer. *J Natl Cancer Inst*. 2004;96:879-882. **4.** Hussain A, Abdulhalim AM, Mullins CD, Qian Y, Arellano J, Balakumaran A. Prevalence of first and subsequent skeletal-related events (SREs) in U.S. elderly patients with metastatic prostate cancer (mPC). *J Clin Oncol*. 2017;32:abstract e16006. **5.** Kelly WK, Halabi S, Carducci M, et al. Randomized, double-blind, placebo-controlled phase III trial comparing docetaxel and prednisone with or without bevacizumab in men with metastatic castration-resistant prostate cancer: CALGB 90401. *J Clin Oncol*. 2012;30:1534-1540. **6.** Tannock IF, Fizazi K, Ivanov S, et al. Aflibercept versus placebo in combination with docetaxel and prednisone for treatment of men with metastatic castration-resistant prostate cancer (VENICE): a phase 3, double-blind randomised trial. *Lancet Oncol*. 2013;14:760-768. **7.** Beer TM, Armstrong AJ, Rathkopf DE, et al. Enzalutamidein metastatic prostate cancer before chemotherapy. *N Engl J Med*. 2014;371:424-433. **8.** Bhowmik D, Song X, Intorcia M, Gray S, Shi N. Examination of burden of skeletal-related events in patients naive to denosumab and intravenous bisphosphonate therapy in bone metastases from solid tumors population. *Curr Med Res Opin*. 2019;35(3):513-523. **9.** Lutz ST, Chow EL, Hartsell WF, Konski AA. A review of hypofractionated palliative radiotherapy. *Cancer*. 2007;109(8):1462-1470. **10.** Osborn JL, Getzenberg RH, Trump DL. Spinal cord compression in prostate cancer. *J Neuro-Oncol*. 1995;23:135-147. **11.** Wedin R. Surgical treatment for pathologic fracture. *Acta Orthop Scand Suppl*. 2001;72:1-29. **12.** Torbert JT, et al. Pathologic fractures. In: Pignolo RJ, et al, eds. *Fractures in the Elderly*: A Guide to Practical Management. 1st ed. New York, NY: Springer Science and Business Media. 2011:43-63. **13.** Mercadante S. Malignant bone pain: pathophysiology and treatment. *Pain*. 1997;69:1-18. **14.** Robson P. Metastatic spinal cord compression: a rare but important complication of cancer. *Clin Med*. 2014;14(5)542-545. **15.** Moore RE, Lackman RD. Metastatic bone disease. *UPOJ*. 2010;20:117-120. **16.** Fizazi K, Carducci M, Smith M, et al. Denosumab versus zoledronic acid for treatment of bone metastases in men with castration-resistant prostate cancer: a randomized, double-blind study. *Lancet*. 2011;377:813-822. **17.** Kettle JK, Patel PB. Feasibility of extended dosing intervals of denosumab. *J Oncol Pharm Pract*. 2018;24(5):343-347. **18.** Data on file, Amgen; 2020.

## 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

At the first diagnosis of a bone metastasis

# Choose XGEVA® to prevent bone complications in your patients with prostate cancer[2]

Denosumab (XGEVA® Q4W) is the only NCCN Guidelines Category 1 Preferred agent to prevent bone complications in men with bone metastases[1,2]

**XGEVA® demonstrated superiority vs ZA in delaying bone complications[2]**

**Since 2010, nearly 1.5 million people with cancer worldwide have been treated with XGEVA®[2,18,*]**

**XGEVA® is a 120-mg subcutaneous injection administered once every 4 weeks[2]**

**The only bone-targeting agent that blocks the function of RANK Ligand (RANKL)[2]**
- XGEVA® inhibits RANKL to prevent bone complications

**No need to adjust XGEVA® dosing for patients with impaired renal function[2]**
- 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.[18]

**Take action with XGEVA® to reduce the risk of bone complications[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.**

AMGEN®



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