



DENOSUMAB (PROLIA® & XGEVA®)

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[Instructions for Use](#) ⓘ

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Commercial Policy

- Denosumab (Prolia® & Xgeva®)

APPLICATION

This Medical Benefit Drug Policy only applies to the state of Louisiana.

COVERAGE RATIONALE

This policy refers to the following denosumab products:

- Prolia
- Xgeva

Prolia (Denosumab)

- **Prolia is proven and medically necessary for the treatment of postmenopausal patients with osteoporosis, or to increase bone mass in patients with osteoporosis at high risk for fracture, who meet ALL of the following criteria:**
 - Diagnosis of osteoporosis; **and**
 - **One** of the following:
 - BMD T-score \leq -2.5 based on BMD measurements from lumbar spine (at least two vertebral bodies), hip (femoral neck, total hip), or radius (one-third radius site); **or**
 - History of one of the following resulting from minimal trauma:
 - Vertebral compression fracture
 - Fracture of the hip
 - Fracture of the distal radius
 - Fracture of the pelvis
 - Fracture of the proximal humerus;**or**
 - **Both** of the following:
 - BMD T-score between -1 and -2.5 (BMD T-score greater than -2.5 and less than or equal to -1) based on BMD measurements from lumbar spine (at least two vertebral bodies), hip (femoral neck, total hip), or radius (one-third radius site)
 - **One** of the following:
 - FRAX 10-year fracture probabilities: major osteoporotic fracture at 20% or more
 - FRAX 10-year fracture probabilities: hip fracture at 3% or more;
- and**
- History of failure, contraindication, or intolerance to oral or intravenous bisphosphonate therapy; **and**

- Prolia dosing is in accordance with the United States Food and Drug Administration approved labeling: maximum dosing of 60 mg every 6 months; **and**
- Authorization is for no more than 12 months

Reauthorization/Continuation of Care Criteria

For patients currently on Prolia for the treatment of postmenopausal patients with osteoporosis, or to increase bone mass in patients with osteoporosis at high risk for fracture, continued use will be approved based on the following criteria:

- Provider attests to a positive clinical response; **and**
- Prolia dosing is in accordance with the United States Food and Drug Administration approved labeling: maximum dosing of 60 mg every 6 months; **and**
- Authorization is for no more than 12 months

- **Prolia is proven and medically necessary to increase bone mass in patients at high risk for fracture receiving androgen deprivation therapy for non-metastatic prostate cancer in patients who meet ALL of the following criteria:**

- Diagnosis of non-metastatic prostate cancer; **and**
- Patient is receiving androgen deprivation therapy; **and**
- History of failure, contraindication, or intolerance to oral or intravenous bisphosphonate therapy; **and**
- Prolia dosing is in accordance with the United States Food and Drug Administration approved labeling: maximum dosing of 60 mg every 6 months; **and**
- Authorization is for no more than 12 months

Reauthorization/Continuation of Care Criteria

For patients currently on Prolia to increase bone mass in patients at high risk for fracture receiving androgen deprivation therapy for non-metastatic prostate cancer, continued use will be approved based on the following criteria:

- Patient is receiving androgen deprivation therapy; **and**
- Provider attests to a positive clinical response; **and**
- Prolia dosing is in accordance with the United States Food and Drug Administration approved labeling: maximum dosing of 60 mg every 6 months; **and**
- Authorization is for no more than 12 months

- **Prolia is proven and medically necessary to treat patients at high risk for fracture receiving adjuvant aromatase inhibitor therapy for breast cancer in patients who meet ALL of the following criteria:**

- Diagnosis of breast cancer; **and**
- Patient is receiving aromatase inhibitor therapy; **and**
- History of failure, contraindication, or intolerance to oral or intravenous bisphosphonate therapy; **and**
- Prolia dosing is in accordance with the United States Food and Drug Administration approved labeling: maximum dosing of 60 mg every 6 months; **and**
- Authorization is for no more than 12 months

Reauthorization/Continuation of Care Criteria

For patients currently on Prolia to treat patients at high risk for fracture receiving adjuvant aromatase inhibitor therapy for breast cancer, continued use will be approved based on the following criteria:

- Patient is receiving aromatase inhibitor therapy; **and**
- Provider attests to a positive clinical response; **and**
- Prolia dosing is in accordance with the United States Food and Drug Administration approved labeling: maximum dosing of 60 mg every 6 months; **and**
- Authorization is for no more than 12 months

- **Prolia is proven and medically necessary to treat glucocorticoid-induced osteoporosis in patients at high risk for fracture when ALL of the following criteria are met:**

- Diagnosis of glucocorticoid-induced osteoporosis; **and**
- History of prednisone or its equivalent at a dose ≥ 5 mg/day for ≥ 3 months; **and**
- **One** of the following:
 - BMD T-score ≤ -2.5 based on BMD measurements from lumbar spine (at least two vertebral bodies), hip (femoral neck, total hip), or radius (one-third radius site); **or**
 - History of **one** of the following resulting from minimal trauma:
 - Vertebral compression fracture
 - Fracture of the hip

- Fracture of the distal radius
- Fracture of the pelvis
- Fracture of the proximal humerus;

or

- **One** of the following:
 - FRAX 10-year fracture probabilities: major osteoporotic fracture at 20% or more
 - FRAX 10-year fracture probabilities: hip fracture at 3% or more;

and

- History of failure, contraindication, or intolerance to oral or intravenous bisphosphonate therapy; **and**
- Prolia dosing is in accordance with the United States Food and Drug Administration approved labeling: maximum dosing of 60 mg every 6 months; **and**
- Authorization is for no more than 12 months

Reauthorization/Continuation of Care Criteria

For patients currently on Prolia to treat glucocorticoid-induced osteoporosis in patients at high risk for fracture, continued use will be approved based on the following criteria:

- Provider attests to a positive clinical response; **and**
- Prolia dosing is in accordance with the United States Food and Drug Administration approved labeling: maximum dosing of 60 mg every 6 months; **and**
- Authorization is for no more than 12 months

Xgeva (Denosumab)

- **Xgeva is proven and medically necessary for the prevention of skeletal-related events in patients with multiple myeloma and with bone metastases from solid tumors when ALL of the following criteria are met:**

- Patient is **one** of the following:
 - Patient is ≥ 18 years of age
 - Patient is a skeletally mature adolescent as defined by having at least 1 mature long bone (e.g., closed epiphyseal growth plate of the humerus);

and

- **One** of the following:
 - Diagnosis of multiple myeloma
 - Presence of metastatic disease secondary to a solid tumor (e.g., bladder, kidney, lung, ovarian, thyroid, etc.);

and

- Individual has an expected survival of 3 months or greater; **and**
- Refractory (within the past 30 days), contraindication (including renal insufficiency), or intolerance to treatment with intravenous bisphosphonate therapy (e.g., pamidronate, zoledronic acid); **and**
- Xgeva dosing is in accordance with the United States Food and Drug Administration approved labeling: maximum dosing of 120 mg every 4 weeks; **and**
- Authorization is for no more than 12 months

Reauthorization/Continuation of Care Criteria

For patients currently on Xgeva for the prevention of skeletal-related events in patients with multiple myeloma and with bone metastases from solid tumors, continued use will be approved based on the following criteria:

- Individual has an expected survival of 3 months or greater; **and**
- Provider attests to a positive clinical response; **and**
- Xgeva dosing is in accordance with the United States Food and Drug Administration approved labeling: maximum dosing of 120 mg every 4 weeks; **and**
- Authorization is for no more than 12 months

- **Xgeva is proven and medically necessary for the treatment of giant cell tumor of the bone when ALL of the following criteria are met:**

- Patient is **one** of the following:
 - Patient is ≥ 18 years of age
 - Patient is a skeletally mature adolescent as defined by having at least 1 mature long bone (e.g., closed epiphyseal growth plate of the humerus);

and

- Diagnosis of localized or metastatic giant cell tumor of the bone; **and**
- Disease is **one** of the following:

- Unresectable
- Surgical resection is likely to result in severe morbidity;

and

- Xgeva dosing is in accordance with the United States Food and Drug Administration approved labeling: maximum dosing of 120 mg every 4 weeks (additional 120 mg doses allowed on Day 8 and 15 in the first month of therapy); **and**
- Authorization is for no more than 12 months

Reauthorization/Continuation of Care Criteria

For patients currently on Xgeva for the treatment of giant cell tumor of the bone, continued use will be approved based on the following criteria:

- Provider attests to a positive clinical response; **and**
- Xgeva dosing is in accordance with the United States Food and Drug Administration approved labeling: maximum dosing of 120 mg every 4 weeks; **and**
- Authorization is for no more than 12 months

• **Xgeva is proven and medically necessary for the treatment of hypercalcemia of malignancy when ALL of the following criteria are met:**

- Patient is **one** of the following:
 - Patient is ≥ 18 years of age
 - Patient is a skeletally mature adolescent as defined by having at least 1 mature long bone (e.g., closed epiphyseal growth plate of the humerus);
- and**
- Diagnosis of hypercalcemia of malignancy as defined as: albumin-corrected serum calcium level greater than 12.5 mg/dL (3.1 mmol/L); **and**
 - No pre-existing hypocalcemia (i.e., serum calcium or corrected calcium within normal limits per laboratory reference); **and**
 - Refractory (within the past 30 days), contraindication (including renal insufficiency), or intolerance to treatment with intravenous bisphosphonate therapy (e.g., pamidronate, zoledronic acid); **and**
 - Xgeva dosing is in accordance with the United States Food and Drug Administration approved labeling: maximum dosing of 120 mg every 4 weeks (additional 120 mg doses allowed on Day 8 and 15 in the first month of therapy); **and**
 - Authorization is for no more than 12 months

Reauthorization/Continuation of Care Criteria

For patients currently on Xgeva for the treatment of hypercalcemia of malignancy, continued use will be approved based on the following criteria:

- Provider attests to a positive clinical response; **and**
- Xgeva dosing is in accordance with the United States Food and Drug Administration approved labeling: maximum dosing of 120 mg every 4 weeks; **and**
- Authorization is for no more than 12 months

• **Xgeva is proven and medically necessary for the prevention of skeletal-related events in men with castration-resistant prostate cancer who have bone metastases when ALL of the following criteria are met:**

- Diagnosis of castration-resistant prostate cancer; **and**
- Presence of metastatic disease; **and**
- Refractory (within the past 30 days), contraindication (including renal insufficiency), or intolerance to treatment with intravenous bisphosphonate therapy (e.g., pamidronate, zoledronic acid); **and**
- Xgeva dosing is in accordance with the United States Food and Drug Administration approved labeling: maximum dosing of 120 mg every 4 weeks; **and**
- Authorization is for no more than 12 months

Reauthorization/Continuation of Care Criteria

For patients currently on Xgeva for the prevention of skeletal-related events in men with castration-resistant prostate cancer who have bone metastases, continued use will be approved based on the following criteria:

- Provider attests to a positive clinical response; **and**
- Xgeva dosing is in accordance with the United States Food and Drug Administration approved labeling: maximum dosing of 120 mg every 4 weeks; **and**
- Authorization is for no more than 12 months

- **Xgeva is proven and medically necessary for the treatment of osteopenia/osteoporosis in patients with systemic mastocytosis with bone pain not responding to bisphosphonates when ALL of the following criteria are met:**
 - Diagnosis of systemic mastocytosis; **and**
 - Patient has bone pain; **and**
 - Diagnosis of osteoporosis or osteopenia based on **one** of the following:
 - BMD T-score ≤ -1 based on BMD measurements from lumbar spine (at least two vertebral bodies), hip (femoral neck, total hip), or radius (one-third radius site); **or**
 - History of one of the following resulting from minimal trauma:
 - Vertebral compression fracture
 - Fracture of the hip
 - Fracture of the distal radius
 - Fracture of the pelvis
 - Fracture of the proximal humerus;
- and**
- Refractory (within the past 30 days), contraindication (including renal insufficiency), or intolerance to treatment with intravenous bisphosphonate therapy (e.g., pamidronate, zoledronic acid); **and**
 - Xgeva dosing is in accordance with the United States Food and Drug Administration approved labeling: maximum dosing of 120 mg every 4 weeks; **and**
 - Authorization for no more than 12 months

Reauthorization/Continuation of Care Criteria

For patients currently on Xgeva for the treatment of osteopenia/osteoporosis in patients with systemic mastocytosis with bone pain not responding to bisphosphonates, continued use will be approved based on the following criteria:

- Provider attests to a positive clinical response; **and**
- Xgeva dosing is in accordance with the United States Food and Drug Administration approved labeling: maximum dosing of 120 mg every 4 weeks; **and**
- Authorization is for no more than 12 months

Unproven

Xgeva/Denosumab is unproven and not medically necessary for the following indications:

- Combination therapy of denosumab and intravenous bisphosphonates
- Bone loss associated with hormone-ablation therapy (other than aromatase inhibitors) in breast cancer
- Cancer pain
- Central giant cell granuloma
- Hyper-parathyroidism
- Immobilization hypercalcemia
- Osteogenesis imperfecta
- Osteopenia

APPLICABLE CODES

The following list(s) of procedure and/or diagnosis codes is provided for reference purposes only and may not be all inclusive. Listing of a code in this policy does not imply that the service described by the code is a covered or non-covered health service. Benefit coverage for health services is determined by federal, state or contractual requirements and applicable laws that may require coverage for a specific service. The inclusion of a code does not imply any right to reimbursement or guarantee claim payment. Other Policies and Coverage Determination Guidelines may apply.

HCPCS Code	Description
J0897	Injection, denosumab, 1 mg

ICD-10 Diagnosis Code	Description
Prolia	
M81.0	Age-related osteoporosis without current pathological fracture
M81.8	Other osteoporosis without current pathological fracture
Z78.310	Personal history of (healed) osteoporosis fracture

ICD-10 Diagnosis Code	Description
M80.00XA	Age-related osteoporosis with current pathological fracture, unspecified site, initial encounter for fracture
M80.00XD	Age-related osteoporosis with current pathological fracture, unspecified site, subsequent encounter for fracture with routine healing
M80.00XG	Age-related osteoporosis with current pathological fracture, unspecified site, subsequent encounter for fracture with delayed healing
M80.00XK	Age-related osteoporosis with current pathological fracture, unspecified site, subsequent encounter for fracture with nonunion
M80.00XP	Age-related osteoporosis with current pathological fracture, unspecified site, subsequent encounter for fracture with malunion
M80.00XS	Age-related osteoporosis with current pathological fracture, unspecified site, sequela
M80.011A	Age-related osteoporosis with current pathological fracture, right shoulder, initial encounter for fracture
M80.011D	Age-related osteoporosis with current pathological fracture, right shoulder, subsequent encounter for fracture with routine healing
Prolia	
M80.011G	Age-related osteoporosis with current pathological fracture, right shoulder, subsequent encounter for fracture with delayed healing
M80.011K	Age-related osteoporosis with current pathological fracture, right shoulder, subsequent encounter for fracture with nonunion
M80.011P	Age-related osteoporosis with current pathological fracture, right shoulder, subsequent encounter for fracture with malunion
M80.011S	Age-related osteoporosis with current pathological fracture, right shoulder, sequela
M80.012A	Age-related osteoporosis with current pathological fracture, left shoulder, initial encounter for fracture
M80.012D	Age-related osteoporosis with current pathological fracture, left shoulder, subsequent encounter for fracture with routine healing
M80.012G	Age-related osteoporosis with current pathological fracture, left shoulder, subsequent encounter for fracture with delayed healing
M80.012K	Age-related osteoporosis with current pathological fracture, left shoulder, subsequent encounter for fracture with nonunion
M80.012P	Age-related osteoporosis with current pathological fracture, left shoulder, subsequent encounter for fracture with malunion
M80.012S	Age-related osteoporosis with current pathological fracture, left shoulder, sequela
M80.019A	Age-related osteoporosis with current pathological fracture, unspecified shoulder, initial encounter for fracture
M80.019D	Age-related osteoporosis with current pathological fracture, unspecified shoulder, subsequent encounter for fracture with routine healing
M80.019G	Age-related osteoporosis with current pathological fracture, unspecified shoulder, subsequent encounter for fracture with delayed healing
M80.019K	Age-related osteoporosis with current pathological fracture, unspecified shoulder, subsequent encounter for fracture with nonunion
M80.019P	Age-related osteoporosis with current pathological fracture, unspecified shoulder, subsequent encounter for fracture with malunion
M80.019S	Age-related osteoporosis with current pathological fracture, unspecified shoulder, sequela
M80.021A	Age-related osteoporosis with current pathological fracture, right humerus, initial encounter for fracture

ICD-10 Diagnosis Code	Description
M80.021D	Age-related osteoporosis with current pathological fracture, right humerus, subsequent encounter for fracture with routine healing
M80.021G	Age-related osteoporosis with current pathological fracture, right humerus, subsequent encounter for fracture with delayed healing
M80.021K	Age-related osteoporosis with current pathological fracture, right humerus, subsequent encounter for fracture with nonunion
M80.021P	Age-related osteoporosis with current pathological fracture, right humerus, subsequent encounter for fracture with malunion
M80.021S	Age-related osteoporosis with current pathological fracture, right humerus, sequela
M80.022A	Age-related osteoporosis with current pathological fracture, left humerus, initial encounter for fracture
M80.022D	Age-related osteoporosis with current pathological fracture, left humerus, subsequent encounter for fracture with routine healing
M80.022G	Age-related osteoporosis with current pathological fracture, left humerus, subsequent encounter for fracture with delayed healing
M80.022K	Age-related osteoporosis with current pathological fracture, left humerus, subsequent encounter for fracture with nonunion
M80.022P	Age-related osteoporosis with current pathological fracture, left humerus, subsequent encounter for fracture with malunion
M80.022S	Age-related osteoporosis with current pathological fracture, left humerus, sequela
Prolia	
M80.029A	Age-related osteoporosis with current pathological fracture, unspecified humerus, initial encounter for fracture
M80.029D	Age-related osteoporosis with current pathological fracture, unspecified humerus, subsequent encounter for fracture with routine healing
M80.029G	Age-related osteoporosis with current pathological fracture, unspecified humerus, subsequent encounter for fracture with delayed healing
M80.029K	Age-related osteoporosis with current pathological fracture, unspecified humerus, subsequent encounter for fracture with nonunion
M80.029P	Age-related osteoporosis with current pathological fracture, unspecified humerus, subsequent encounter for fracture with malunion
M80.029S	Age-related osteoporosis with current pathological fracture, unspecified humerus, sequela
M80.031A	Age-related osteoporosis with current pathological fracture, right forearm, initial encounter for fracture
M80.031D	Age-related osteoporosis with current pathological fracture, right forearm, subsequent encounter for fracture with routine healing
M80.031G	Age-related osteoporosis with current pathological fracture, right forearm, subsequent encounter for fracture with delayed healing
M80.031K	Age-related osteoporosis with current pathological fracture, right forearm, subsequent encounter for fracture with nonunion
M80.031P	Age-related osteoporosis with current pathological fracture, right forearm, subsequent encounter for fracture with malunion
M80.031S	Age-related osteoporosis with current pathological fracture, right forearm, sequela
M80.032A	Age-related osteoporosis with current pathological fracture, left forearm, initial encounter for fracture
M80.032D	Age-related osteoporosis with current pathological fracture, left forearm, subsequent encounter for fracture with routine healing

ICD-10 Diagnosis Code	Description
M80.032G	Age-related osteoporosis with current pathological fracture, left forearm, subsequent encounter for fracture with delayed healing
M80.032K	Age-related osteoporosis with current pathological fracture, left forearm, subsequent encounter for fracture with nonunion
M80.032P	Age-related osteoporosis with current pathological fracture, left forearm, subsequent encounter for fracture with malunion
M80.032S	Age-related osteoporosis with current pathological fracture, left forearm, sequela
M80.039A	Age-related osteoporosis with current pathological fracture, unspecified forearm, initial encounter for fracture
M80.039D	Age-related osteoporosis with current pathological fracture, unspecified forearm, subsequent encounter for fracture with routine healing
M80.039G	Age-related osteoporosis with current pathological fracture, unspecified forearm, subsequent encounter for fracture with delayed healing
M80.039K	Age-related osteoporosis with current pathological fracture, unspecified forearm, subsequent encounter for fracture with nonunion
M80.039P	Age-related osteoporosis with current pathological fracture, unspecified forearm, subsequent encounter for fracture with malunion
M80.039S	Age-related osteoporosis with current pathological fracture, unspecified forearm, sequela
M80.041A	Age-related osteoporosis with current pathological fracture, right hand, initial encounter for fracture
M80.041D	Age-related osteoporosis with current pathological fracture, right hand, subsequent encounter for fracture with routine healing
M80.041G	Age-related osteoporosis with current pathological fracture, right hand, subsequent encounter for fracture with delayed healing
Prolia	
M80.041K	Age-related osteoporosis with current pathological fracture, right hand, subsequent encounter for fracture with nonunion
M80.041P	Age-related osteoporosis with current pathological fracture, right hand, subsequent encounter for fracture with malunion
M80.041S	Age-related osteoporosis with current pathological fracture, right hand, sequela
M80.042A	Age-related osteoporosis with current pathological fracture, left hand, initial encounter for fracture
M80.042D	Age-related osteoporosis with current pathological fracture, left hand, subsequent encounter for fracture with routine healing
M80.042G	Age-related osteoporosis with current pathological fracture, left hand, subsequent encounter for fracture with delayed healing
M80.042K	Age-related osteoporosis with current pathological fracture, left hand, subsequent encounter for fracture with nonunion
M80.042P	Age-related osteoporosis with current pathological fracture, left hand, subsequent encounter for fracture with malunion
M80.042S	Age-related osteoporosis with current pathological fracture, left hand, sequela
M80.049A	Age-related osteoporosis with current pathological fracture, unspecified hand, initial encounter for fracture
M80.049D	Age-related osteoporosis with current pathological fracture, unspecified hand, subsequent encounter for fracture with routine healing
M80.049G	Age-related osteoporosis with current pathological fracture, unspecified hand, subsequent encounter for fracture with delayed healing

ICD-10 Diagnosis Code	Description
M80.049K	Age-related osteoporosis with current pathological fracture, unspecified hand, subsequent encounter for fracture with nonunion
M80.049P	Age-related osteoporosis with current pathological fracture, unspecified hand, subsequent encounter for fracture with malunion
M80.049S	Age-related osteoporosis with current pathological fracture, unspecified hand, sequela
M80.051A	Age-related osteoporosis with current pathological fracture, right femur, initial encounter for fracture
M80.051D	Age-related osteoporosis with current pathological fracture, right femur, subsequent encounter for fracture with routine healing
M80.051G	Age-related osteoporosis with current pathological fracture, right femur, subsequent encounter for fracture with delayed healing
M80.051K	Age-related osteoporosis with current pathological fracture, right femur, subsequent encounter for fracture with nonunion
M80.051P	Age-related osteoporosis with current pathological fracture, right femur, subsequent encounter for fracture with malunion
M80.051S	Age-related osteoporosis with current pathological fracture, right femur, sequela
M80.052A	Age-related osteoporosis with current pathological fracture, left femur, initial encounter for fracture
M80.052D	Age-related osteoporosis with current pathological fracture, left femur, subsequent encounter for fracture with routine healing
M80.052G	Age-related osteoporosis with current pathological fracture, left femur, subsequent encounter for fracture with delayed healing
M80.052K	Age-related osteoporosis with current pathological fracture, left femur, subsequent encounter for fracture with nonunion
M80.052P	Age-related osteoporosis with current pathological fracture, left femur, subsequent encounter for fracture with malunion
M80.052S	Age-related osteoporosis with current pathological fracture, left femur, sequela
M80.059A	Age-related osteoporosis with current pathological fracture, unspecified femur, initial encounter for fracture
Prolia	
M80.059D	Age-related osteoporosis with current pathological fracture, unspecified femur, subsequent encounter for fracture with routine healing
M80.059G	Age-related osteoporosis with current pathological fracture, unspecified femur, subsequent encounter for fracture with delayed healing
M80.059K	Age-related osteoporosis with current pathological fracture, unspecified femur, subsequent encounter for fracture with nonunion
M80.059P	Age-related osteoporosis with current pathological fracture, unspecified femur, subsequent encounter for fracture with malunion
M80.059S	Age-related osteoporosis with current pathological fracture, unspecified femur, sequela
M80.061A	Age-related osteoporosis with current pathological fracture, right lower leg, initial encounter for fracture
M80.061D	Age-related osteoporosis with current pathological fracture, right lower leg, subsequent encounter for fracture with routine healing
M80.061G	Age-related osteoporosis with current pathological fracture, right lower leg, subsequent encounter for fracture with delayed healing
M80.061K	Age-related osteoporosis with current pathological fracture, right lower leg, subsequent encounter for fracture with nonunion

ICD-10 Diagnosis Code	Description
M80.061P	Age-related osteoporosis with current pathological fracture, right lower leg, subsequent encounter for fracture with malunion
M80.061S	Age-related osteoporosis with current pathological fracture, right lower leg, sequela
M80.062A	Age-related osteoporosis with current pathological fracture, left lower leg, initial encounter for fracture
M80.062D	Age-related osteoporosis with current pathological fracture, left lower leg, subsequent encounter for fracture with routine healing
M80.062G	Age-related osteoporosis with current pathological fracture, left lower leg, subsequent encounter for fracture with delayed healing
M80.062K	Age-related osteoporosis with current pathological fracture, left lower leg, subsequent encounter for fracture with nonunion
M80.062P	Age-related osteoporosis with current pathological fracture, left lower leg, subsequent encounter for fracture with malunion
M80.062S	Age-related osteoporosis with current pathological fracture, left lower leg, sequela
M80.069A	Age-related osteoporosis with current pathological fracture, unspecified lower leg, initial encounter for fracture
M80.069D	Age-related osteoporosis with current pathological fracture, unspecified lower leg, subsequent encounter for fracture with routine healing
M80.069G	Age-related osteoporosis with current pathological fracture, unspecified lower leg, subsequent encounter for fracture with delayed healing
M80.069K	Age-related osteoporosis with current pathological fracture, unspecified lower leg, subsequent encounter for fracture with nonunion
M80.069P	Age-related osteoporosis with current pathological fracture, unspecified lower leg, subsequent encounter for fracture with malunion
M80.069S	Age-related osteoporosis with current pathological fracture, unspecified lower leg, sequela
M80.071A	Age-related osteoporosis with current pathological fracture, right ankle and foot, initial encounter for fracture
M80.071D	Age-related osteoporosis with current pathological fracture, right ankle and foot, subsequent encounter for fracture with routine healing
M80.071G	Age-related osteoporosis with current pathological fracture, right ankle and foot, subsequent encounter for fracture with delayed healing
M80.071K	Age-related osteoporosis with current pathological fracture, right ankle and foot, subsequent encounter for fracture with nonunion
Prolia	
M80.071P	Age-related osteoporosis with current pathological fracture, right ankle and foot, subsequent encounter for fracture with malunion
M80.071S	Age-related osteoporosis with current pathological fracture, right ankle and foot, sequela
M80.072A	Age-related osteoporosis with current pathological fracture, left ankle and foot, initial encounter for fracture
M80.072D	Age-related osteoporosis with current pathological fracture, left ankle and foot, subsequent encounter for fracture with routine healing
M80.072G	Age-related osteoporosis with current pathological fracture, left ankle and foot, subsequent encounter for fracture with delayed healing
M80.072K	Age-related osteoporosis with current pathological fracture, left ankle and foot, subsequent encounter for fracture with nonunion
M80.072P	Age-related osteoporosis with current pathological fracture, left ankle and foot, subsequent encounter for fracture with malunion

ICD-10 Diagnosis Code	Description
M80.072S	Age-related osteoporosis with current pathological fracture, left ankle and foot, sequela
M80.079A	Age-related osteoporosis with current pathological fracture, unspecified ankle and foot, initial encounter for fracture
M80.079D	Age-related osteoporosis with current pathological fracture, unspecified ankle and foot, subsequent encounter for fracture with routine healing
M80.079G	Age-related osteoporosis with current pathological fracture, unspecified ankle and foot, subsequent encounter for fracture with delayed healing
M80.079K	Age-related osteoporosis with current pathological fracture, unspecified ankle and foot, subsequent encounter for fracture with nonunion
M80.079P	Age-related osteoporosis with current pathological fracture, unspecified ankle and foot, subsequent encounter for fracture with malunion
M80.079S	Age-related osteoporosis with current pathological fracture, unspecified ankle and foot, sequela
M80.08XA	Age-related osteoporosis with current pathological fracture, vertebra(e), initial encounter for fracture
M80.08XD	Age-related osteoporosis with current pathological fracture, vertebra(e), subsequent encounter for fracture with routine healing
M80.08XG	Age-related osteoporosis with current pathological fracture, vertebra(e), subsequent encounter for fracture with delayed healing
M80.08XK	Age-related osteoporosis with current pathological fracture, vertebra(e), subsequent encounter for fracture with nonunion
M80.08XP	Age-related osteoporosis with current pathological fracture, vertebra(e), subsequent encounter for fracture with malunion
M80.08XS	Age-related osteoporosis with current pathological fracture, vertebra(e), sequela
M80.811A	Other osteoporosis with current pathological fracture, right shoulder, initial encounter for fracture
M80.811D	Other osteoporosis with current pathological fracture, right shoulder, subsequent encounter for fracture with routine healing
M80.811G	Other osteoporosis with current pathological fracture, right shoulder, subsequent encounter for fracture with delayed healing
M80.811K	Other osteoporosis with current pathological fracture, right shoulder, subsequent encounter for fracture with nonunion
M80.811P	Other osteoporosis with current pathological fracture, right shoulder, subsequent encounter for fracture with malunion
M80.811S	Other osteoporosis with current pathological fracture, right shoulder, sequela
M80.812A	Other osteoporosis with current pathological fracture, left shoulder, initial encounter for fracture
Prolia	
M80.812D	Other osteoporosis with current pathological fracture, left shoulder, subsequent encounter for fracture with routine healing
M80.812G	Other osteoporosis with current pathological fracture, left shoulder, subsequent encounter for fracture with delayed healing
M80.812K	Other osteoporosis with current pathological fracture, left shoulder, subsequent encounter for fracture with nonunion
M80.812P	Other osteoporosis with current pathological fracture, left shoulder, subsequent encounter for fracture with malunion
M80.812S	Other osteoporosis with current pathological fracture, left shoulder, sequela

ICD-10 Diagnosis Code	Description
M80.819A	Other osteoporosis with current pathological fracture, unspecified shoulder, initial encounter for fracture
M80.819D	Other osteoporosis with current pathological fracture, unspecified shoulder, subsequent encounter for fracture with routine healing
M80.819G	Other osteoporosis with current pathological fracture, unspecified shoulder, subsequent encounter for fracture with delayed healing
M80.819K	Other osteoporosis with current pathological fracture, unspecified shoulder, subsequent encounter for fracture with nonunion
M80.819P	Other osteoporosis with current pathological fracture, unspecified shoulder, subsequent encounter for fracture with malunion
M80.819S	Other osteoporosis with current pathological fracture, unspecified shoulder, sequela
M80.821A	Other osteoporosis with current pathological fracture, right humerus, initial encounter for fracture
M80.821D	Other osteoporosis with current pathological fracture, right humerus, subsequent encounter for fracture with routine healing
M80.821G	Other osteoporosis with current pathological fracture, right humerus, subsequent encounter for fracture with delayed healing
M80.821K	Other osteoporosis with current pathological fracture, right humerus, subsequent encounter for fracture with nonunion
M80.821P	Other osteoporosis with current pathological fracture, right humerus, subsequent encounter for fracture with malunion
M80.821S	Other osteoporosis with current pathological fracture, right humerus, sequela
M80.822A	Other osteoporosis with current pathological fracture, left humerus, initial encounter for fracture
M80.822D	Other osteoporosis with current pathological fracture, left humerus, subsequent encounter for fracture with routine healing
M80.822G	Other osteoporosis with current pathological fracture, left humerus, subsequent encounter for fracture with delayed healing
M80.822K	Other osteoporosis with current pathological fracture, left humerus, subsequent encounter for fracture with nonunion
M80.822P	Other osteoporosis with current pathological fracture, left humerus, subsequent encounter for fracture with malunion
M80.822S	Other osteoporosis with current pathological fracture, left humerus, sequela
M80.829A	Other osteoporosis with current pathological fracture, unspecified humerus, initial encounter for fracture
M80.829D	Other osteoporosis with current pathological fracture, unspecified humerus, subsequent encounter for fracture with routine healing
M80.829G	Other osteoporosis with current pathological fracture, unspecified humerus, subsequent encounter for fracture with delayed healing
M80.829K	Other osteoporosis with current pathological fracture, unspecified humerus, subsequent encounter for fracture with nonunion
M80.829P	Other osteoporosis with current pathological fracture, unspecified humerus, subsequent encounter for fracture with malunion
Prolia	
M80.829S	Other osteoporosis with current pathological fracture, unspecified humerus, sequela
M80.831A	Other osteoporosis with current pathological fracture, right forearm, initial encounter for fracture
M80.831D	Other osteoporosis with current pathological fracture, right forearm, subsequent encounter for fracture with routine healing

ICD-10 Diagnosis Code	Description
M80.831G	Other osteoporosis with current pathological fracture, right forearm, subsequent encounter for fracture with delayed healing
M80.831K	Other osteoporosis with current pathological fracture, right forearm, subsequent encounter for fracture with nonunion
M80.831P	Other osteoporosis with current pathological fracture, right forearm, subsequent encounter for fracture with malunion
M80.831S	Other osteoporosis with current pathological fracture, right forearm, sequela
M80.832A	Other osteoporosis with current pathological fracture, left forearm, initial encounter for fracture
M80.832D	Other osteoporosis with current pathological fracture, left forearm, subsequent encounter for fracture with routine healing
M80.832G	Other osteoporosis with current pathological fracture, left forearm, subsequent encounter for fracture with routine healing
M80.832K	Other osteoporosis with current pathological fracture, left forearm, subsequent encounter for fracture with nonunion
M80.832P	Other osteoporosis with current pathological fracture, left forearm, subsequent encounter for fracture with malunion
M80.832S	Other osteoporosis with current pathological fracture, left forearm, sequela
M80.839A	Other osteoporosis with current pathological fracture, unspecified forearm, initial encounter for fracture
M80.839D	Other osteoporosis with current pathological fracture, unspecified forearm, subsequent encounter for fracture with routine healing
M80.839G	Other osteoporosis with current pathological fracture, unspecified forearm, subsequent encounter for fracture with delayed healing
M80.839K	Other osteoporosis with current pathological fracture, unspecified forearm, subsequent encounter for fracture with nonunion
M80.839P	Other osteoporosis with current pathological fracture, unspecified forearm, subsequent encounter for fracture with malunion
M80.839S	Other osteoporosis with current pathological fracture, unspecified forearm, sequela
M80.841A	Other osteoporosis with current pathological fracture, right hand, initial encounter for fracture
M80.841D	Other osteoporosis with current pathological fracture, right hand, subsequent encounter for fracture with routine healing
M80.841G	Other osteoporosis with current pathological fracture, right hand, subsequent encounter for fracture with delayed healing
M80.841K	Other osteoporosis with current pathological fracture, right hand, subsequent encounter for fracture with nonunion
M80.841P	Other osteoporosis with current pathological fracture, right hand, subsequent encounter for fracture with malunion
M80.841S	Other osteoporosis with current pathological fracture, right hand, sequela
M80.842A	Other osteoporosis with current pathological fracture, left hand, initial encounter for fracture
M80.842D	Other osteoporosis with current pathological fracture, left hand, subsequent encounter for fracture with routine healing
M80.842G	Other osteoporosis with current pathological fracture, left hand, subsequent encounter for fracture with delayed healing
Prolia	
M80.842K	Other osteoporosis with current pathological fracture, left hand, subsequent encounter for fracture with nonunion

ICD-10 Diagnosis Code	Description
M80.842P	Other osteoporosis with current pathological fracture, left hand, subsequent encounter for fracture with malunion
M80.842S	Other osteoporosis with current pathological fracture, left hand, sequela
M80.849A	Other osteoporosis with current pathological fracture, unspecified hand, initial encounter for fracture
M80.849D	Other osteoporosis with current pathological fracture, unspecified hand, subsequent encounter for fracture with routine healing
M80.849G	Other osteoporosis with current pathological fracture, unspecified hand, subsequent encounter for fracture with delayed healing
M80.849K	Other osteoporosis with current pathological fracture, unspecified hand, subsequent encounter for fracture with nonunion
M80.849P	Other osteoporosis with current pathological fracture, unspecified hand, subsequent encounter for fracture with malunion
M80.849S	Other osteoporosis with current pathological fracture, unspecified hand, sequela
M80.851A	Other osteoporosis with current pathological fracture, right femur, initial encounter for fracture
M80.851D	Other osteoporosis with current pathological fracture, right femur, subsequent encounter for fracture with routine healing
M80.851G	Other osteoporosis with current pathological fracture, right femur, subsequent encounter for fracture with delayed healing
M80.851K	Other osteoporosis with current pathological fracture, right femur, subsequent encounter for fracture with nonunion
M80.851P	Other osteoporosis with current pathological fracture, right femur, subsequent encounter for fracture with malunion
M80.851S	Other osteoporosis with current pathological fracture, right femur, sequela
M80.852A	Other osteoporosis with current pathological fracture, left femur, initial encounter for fracture
M80.852D	Other osteoporosis with current pathological fracture, left femur, subsequent encounter for fracture with routine healing
M80.852G	Other osteoporosis with current pathological fracture, left femur, subsequent encounter for fracture with delayed healing
M80.852K	Other osteoporosis with current pathological fracture, left femur, subsequent encounter for fracture with nonunion
M80.852P	Other osteoporosis with current pathological fracture, left femur, subsequent encounter for fracture with malunion
M80.852S	Other osteoporosis with current pathological fracture, left femur, sequela
M80.859A	Other osteoporosis with current pathological fracture, unspecified femur, initial encounter for fracture
M80.859D	Other osteoporosis with current pathological fracture, unspecified femur, subsequent encounter for fracture with routine healing
M80.859G	Other osteoporosis with current pathological fracture, unspecified femur, subsequent encounter for fracture with delayed healing
M80.859K	Other osteoporosis with current pathological fracture, unspecified femur, subsequent encounter for fracture with nonunion
M80.859P	Other osteoporosis with current pathological fracture, unspecified femur, subsequent encounter for fracture with malunion
M80.859S	Other osteoporosis with current pathological fracture, unspecified femur, sequela
M80.861A	Other osteoporosis with current pathological fracture, right lower leg, initial encounter for fracture

ICD-10 Diagnosis Code	Description
Prolia	
M80.861D	Other osteoporosis with current pathological fracture, right lower leg, subsequent encounter for fracture with routine healing
M80.861G	Other osteoporosis with current pathological fracture, right lower leg, subsequent encounter for fracture with delayed healing
M80.861K	Other osteoporosis with current pathological fracture, right lower leg, subsequent encounter for fracture with nonunion
M80.861P	Other osteoporosis with current pathological fracture, right lower leg, subsequent encounter for fracture with malunion
M80.861S	Other osteoporosis with current pathological fracture, right lower leg, sequela
M80.862A	Other osteoporosis with current pathological fracture, left lower leg, initial encounter for fracture
M80.862D	Other osteoporosis with current pathological fracture, left lower leg, subsequent encounter for fracture with routine healing
M80.862G	Other osteoporosis with current pathological fracture, left lower leg, subsequent encounter for fracture with delayed healing
M80.862K	Other osteoporosis with current pathological fracture, left lower leg, subsequent encounter for fracture with nonunion
M80.862P	Other osteoporosis with current pathological fracture, left lower leg, subsequent encounter for fracture with malunion
M80.862S	Other osteoporosis with current pathological fracture, left lower leg, sequela
M80.869A	Other osteoporosis with current pathological fracture, unspecified lower leg, initial encounter for fracture
M80.869D	Other osteoporosis with current pathological fracture, unspecified lower leg, subsequent encounter for fracture with routine healing
M80.869G	Other osteoporosis with current pathological fracture, unspecified lower leg, subsequent encounter for fracture with delayed healing
M80.869K	Other osteoporosis with current pathological fracture, unspecified lower leg, subsequent encounter for fracture with nonunion
M80.869P	Other osteoporosis with current pathological fracture, unspecified lower leg, subsequent encounter for fracture with malunion
M80.869S	Other osteoporosis with current pathological fracture, unspecified lower leg, sequela
M80.871A	Other osteoporosis with current pathological fracture, right ankle and foot, initial encounter for fracture
M80.871D	Other osteoporosis with current pathological fracture, right ankle and foot, subsequent encounter for fracture with routine healing
M80.871G	Other osteoporosis with current pathological fracture, right ankle and foot, subsequent encounter for fracture with delayed healing
M80.871K	Other osteoporosis with current pathological fracture, right ankle and foot, subsequent encounter for fracture with nonunion
M80.871P	Other osteoporosis with current pathological fracture, right ankle and foot, subsequent encounter for fracture with malunion
M80.871S	Other osteoporosis with current pathological fracture, right ankle and foot, sequela
M80.872A	Other osteoporosis with current pathological fracture, left ankle and foot, initial encounter for fracture
M80.872D	Other osteoporosis with current pathological fracture, left ankle and foot, subsequent encounter for fracture with routine healing
M80.872G	Other osteoporosis with current pathological fracture, left ankle and foot, subsequent encounter for fracture with delayed healing

ICD-10 Diagnosis Code	Description
M80.872K	Other osteoporosis with current pathological fracture, left ankle and foot, subsequent encounter for fracture with nonunion
M80.872P	Other osteoporosis with current pathological fracture, left ankle and foot, subsequent encounter for fracture with malunion
Prolia	
M80.872S	Other osteoporosis with current pathological fracture, left ankle and foot, sequela
M80.879A	Other osteoporosis with current pathological fracture, unspecified ankle and foot, initial encounter for fracture
M80.879D	Other osteoporosis with current pathological fracture, unspecified ankle and foot, subsequent encounter for fracture with routine healing
M80.879G	Other osteoporosis with current pathological fracture, unspecified ankle and foot, subsequent encounter for fracture with delayed healing
M80.879K	Other osteoporosis with current pathological fracture, unspecified ankle and foot, subsequent encounter for fracture with nonunion
M80.879P	Other osteoporosis with current pathological fracture, unspecified ankle and foot, subsequent encounter for fracture with malunion
M80.879S	Other osteoporosis with current pathological fracture, unspecified ankle and foot, sequela
M80.88XA	Other osteoporosis with current pathological fracture, vertebra(e), initial encounter for fracture
M80.88XD	Other osteoporosis with current pathological fracture, vertebra(e), subsequent encounter for fracture with routine healing
M80.88XG	Other osteoporosis with current pathological fracture, vertebra(e), subsequent encounter for fracture with delayed healing
M80.88XK	Other osteoporosis with current pathological fracture, vertebra(e), subsequent encounter for fracture with nonunion
M80.88XP	Other osteoporosis with current pathological fracture, vertebra(e), subsequent encounter for fracture with malunion
M80.88XS	Other osteoporosis with current pathological fracture, vertebra(e), sequela
Xgeva	
C61	Malignant neoplasm of prostate
C79.00	Secondary malignant neoplasm of unspecified kidney and renal pelvis
C79.01	Secondary malignant neoplasm of right kidney and renal pelvis
C79.02	Secondary malignant neoplasm of left kidney and renal pelvis
C79.10	Secondary malignant neoplasm of unspecified urinary organs
C79.11	Secondary malignant neoplasm of bladder
C79.19	Secondary malignant neoplasm of other urinary organs
C79.2	Secondary malignant neoplasm of skin
C79.31	Secondary malignant neoplasm of brain
C79.32	Secondary malignant neoplasm of cerebral meninges
C79.40	Secondary malignant neoplasm of unspecified part of nervous system
C79.49	Secondary malignant neoplasm of other parts of nervous system
C79.51	Secondary malignant neoplasm of bone
C79.52	Secondary malignant neoplasm of bone marrow
C79.60	Secondary malignant neoplasm of unspecified ovary
C79.61	Secondary malignant neoplasm of right ovary
C79.62	Secondary malignant neoplasm of left ovary

ICD-10 Diagnosis Code	Description
C79.70	Secondary malignant neoplasm of unspecified adrenal gland
C79.71	Secondary malignant neoplasm of right adrenal gland
C79.72	Secondary malignant neoplasm of left adrenal gland
C79.81	Secondary malignant neoplasm of breast
C79.82	Secondary malignant neoplasm of genital organs
C79.89	Secondary malignant neoplasm of other specified sites
C79.9	Secondary malignant neoplasm of unspecified site
Xgeva	
C90.00	Multiple myeloma not having achieved remission
C90.02	Multiple myeloma in relapse
D47.02	Systemic mastocytosis
D48.0	Neoplasm of uncertain behavior of bone and articular cartilage
E83.52	Hypercalcemia

Maximum Dosage Requirements

Maximum Allowed Quantities by HCPCS Units

This section provides information about the maximum dosage per administration for denosumab administered by a medical professional.

Medication Name		Maximum Dosage per Administration	HCPCS Code	Maximum Allowed
Brand	Generic			
Prolia	Denosumab	60 mg	J0897	60 HCPCS units (1 mg per unit)
Xgeva	Denosumab	120 mg	J0897	120 HCPCS units (1 mg per unit)

Maximum Allowed Quantities by National Drug Code (NDC) Units

The allowed quantities in this section are calculated based upon both the maximum dosage information supplied within this policy as well as the process by which NDC claims are billed. This list may not be inclusive of all available NDC's for each drug product and is subject to change.

Medication Name		How Supplied	National Drug Code	Maximum Allowed
Brand	Generic			
Prolia	Denosumab	60 mg/1 ml vial	55513-0710-01	1 vial/1 ml
Xgeva	Denosumab	120 mg/1.7 ml vial	55513-0730-01	1 vial/1.7 ml

BACKGROUND

Current guidelines define osteoporosis as a bone mineral density (BMD) T-score of -2.5 or below, and osteopenia as a T-score between -1 and -2.5. Additionally, guidelines state that osteoporosis can also be diagnosed by the history of a low-trauma spine or hip fracture regardless of BMD, a history of a fragility fracture in osteopenic patients, or in osteopenic patients with an elevated fracture risk as defined by the FRAX[®] fracture assessment tool.¹ Available literature defines high risk for fracture as bone mineral density (BMD) T-scores of -3.5 or less, while it defines severe osteoporosis as T-scores of -2.5 or less with at least one fragility fracture.²⁻⁶ The FRAX tool is designed to assist clinicians in predicting the ten-year probability of fracture with or without the addition of femoral neck bone mineral density (BMD).⁷

Denosumab binds to RANKL, a transmembrane or soluble protein essential for the formation, function, and survival of osteoclasts, the cells responsible for bone resorption, thereby modulating calcium release from bone. Denosumab prevents RANKL from activating its receptor, RANK, on the surface of osteoclasts, their precursors, and osteoclast-like giant cells. Prevention of the RANKL/RANK interaction inhibits osteoclast formation, function, and survival, thereby decreasing bone resorption and increasing bone mass and strength in both cortical and trabecular bone. Increased osteoclast activity, stimulated by RANKL, is a mediator of bone pathology in solid tumors with osseous metastases.

Similarly, giant cell tumors of bone consist of stromal cells expressing RANKL and osteoclast-like giant cells expressing RANK receptor, and signaling through the RANK receptor contributes to osteolysis and tumor growth.^{13,14}

CLINICAL EVIDENCE

Prolia

Postmenopausal Patients with Osteoporosis

In a post-hoc analysis of the 7-year FREEDOM Extension trial, Kendler et al, analyzed whether women who experienced fracture while on denosumab was due to inadequate treatment response, or whether the risk of fracture remains low while continuing denosumab treatment. During the extension trial, all study participants were to receive denosumab. The authors of this analysis compared subsequent osteoporotic fracture rates between denosumab treated subjects during the initial FREEDOM or the extension and placebo-treated subjects in FREEDOM. During FREEDOM, 438 placebo- and 272 denosumab-treated subjects had an osteoporotic fracture. Exposure-adjusted subject incidence per 100 subject-years was lower for denosumab (6.7) vs placebo (10.1). Combining all subjects on denosumab from FREEDOM and the Extension for up to 10 years (combined denosumab), 794 (13.7%) had an osteoporotic fracture while on denosumab. One or more subsequent fractures occurred in 144 (18.1%) subjects, with an exposure-adjusted incidence of 5.8 per 100 subject-years, similar to FREEDOM denosumab (6.7 per 100 subject-years) and lower than FREEDOM placebo (10.1 per 100 subjectyears). Adjusting for prior fracture, the risk of having a subsequent on-study osteoporotic fracture was lower in the combined denosumab group vs placebo (hazard ratio [95% CI]: 0.59 [0.43–0.81]; P = 0.0012). The authors concluded that the post-hoc analysis demonstrates that denosumab decreases the risk of subsequent fracture and a fracture sustained while on denosumab, and not necessarily due to inadequate treatment response.²⁸

Brown JP et al compared the efficacy and safety of denosumab with alendronate in postmenopausal women with low bone mass in a phase 3, multicenter, double-blind study.¹¹ Participants included postmenopausal women with a T-score ≤ -2.0 at the lumbar spine or total hip and received subcutaneous denosumab injections (60 mg every 6 months [Q6M]) plus oral placebo weekly (n=594) or oral alendronate weekly (70 mg) plus subcutaneous placebo injections Q6M (n=595). Efficacy was measured by assessing changes in BMD at the total hip, femoral neck, trochanter, lumbar spine, and one-third radius at 6 and 12 months. Additionally bone turnover markers at months 1, 3, 6, 9, and 12 were assessed. Adverse events were monitored to evaluate safety. Denosumab significantly increased BMD at month 12 (3.5% versus 2.6%; $p < 0.0001$ for the total hip). Significantly greater increases in BMD were observed with denosumab at all measured skeletal sites over the twelve month treatment period. Denosumab showed significantly greater reduction of bone turnover markers compared to alendronate. Adverse events and laboratory values were similar for the two treatment groups. The authors conclude that denosumab showed a significantly larger gain in BMD and greater reduction in bone turnover markers compared with alendronate. Overall, the safety profile was similar for both treatment groups.

Men with Low Bone Mineral Density

Langdahl BL et al evaluated denosumab therapy in men with low bone mineral density (BMD) in a multicenter, phase 3 study.⁹ The study consisted of 2 treatment periods including a 12-month double-blind, placebo-controlled phase and a 12-month open-label phase. Participants from the original denosumab (long-term) and placebo (crossover) groups received 60 mg of denosumab subcutaneous every 6 months. During the open-label phase, the following BMD increases occurred with long-term denosumab treatment (2.2% lumbar spine, 0.9% total hip, 1.3% femoral neck, 1.3% trochanter, and 0.2% 1/3 radius), resulting in cumulative 24-month gains from baseline of 8.0%, 3.4%, 3.4%, 4.6%, and 0.7%, respectively (all $P < .01$). The crossover group showed BMD gains similar to the long-term treatment group during the first 12 months of treatment. Similar adverse event rates were seen in both groups. The authors conclude that in the study population, denosumab treatment for a second year continued to increase BMD, maintained reductions in bone resorption, and was well tolerated. These results were similar to previous results in postmenopausal women with osteoporosis and in men with prostate cancer receiving androgen deprivation therapy.

Orwoll E. et al evaluated the safety and efficacy of denosumab compared with placebo in men with low BMD after 1 year of treatment in a placebo-controlled, phase 3 study.¹⁰ The primary endpoint was the percent change of BMD from baseline in lumbar spine (LS) at one year. After 12 months, denosumab resulted in BMD increases of 5.7% at the LS, 2.4% at the total hip, 2.1% at the femoral neck, 3.1% at the trochanter, and 0.6% at the one third radius (adjusted $P \leq 0.0144$ for BMD percent differences at all sites compared with placebo). The incidence of adverse events was similar

between groups. The authors conclude that 12 months of treatment with denosumab in men with low BMD was well tolerated and resulted in a reduction in bone resorption and significant increases in BMD at all skeletal sites assessed.

Patients at High Risk for Fracture Receiving Androgen Deprivation Therapy for Non-Metastatic Prostate Cancer

Smith ME et al investigated the effects of denosumab in a double-blind, multicenter study, on bone mineral density and fractures in patients with non-metastatic prostate cancer who are receiving androgen-deprivation therapy.⁸ Patients were randomly assigned to receive denosumab at a dose of 60 mg subcutaneously every 6 months or placebo (N=734 per group). The primary end point was percent change in bone mineral density at the lumbar spine at 24 months. Secondary end points included percent change in bone mineral densities at the femoral neck and total hip at 24 months and at all three sites at 36 months, as well as frequency of new vertebral fractures. At 24 months, patients receiving denosumab experienced an increase in bone mineral density of the lumbar spine by 5.6% as compared with a loss of 1.0% in the placebo group (P<0.001). Significant differences between the placebo and denosumab groups were seen at 1 month and continued through 36 months. Treatment was also associated with significant increases in bone mineral density at the total hip, femoral neck, and distal third of the radius. Patients who received denosumab had a decreased incidence of new vertebral fractures at 36 months (1.5%, vs. 3.9% with placebo) (relative risk, 0.38; 95% confidence interval, 0.19 to 0.78; P=0.006). Similar rates of adverse events were reported in the two groups. The authors conclude that denosumab is associated with increased bone mineral density at all sites and a reduction in the incidence of new vertebral fractures among patients receiving androgen-deprivation therapy for non-metastatic prostate cancer. (ClinicalTrials.gov number, NCT00089674)

Glucocorticoid-Induced Osteoporosis in Patients at High Risk for Fracture

Saag et al assessed the efficacy and safety of denosumab compared with risedronate in glucocorticoid-induced osteoporosis in a 24-month, double-blind, active-controlled, double-dummy, non-inferiority study.²⁴ The study enrolled patients aged 18 years or older who were receiving ≥ 7.5 mg prednisone daily or equivalent, for at least 3 months (glucocorticoid continuing) or less than 3 months (glucocorticoid initiating). Patients under 50 years of age were required to have a history of osteoporosis-related fracture. Patients 50 years and older needed a lumbar spine, total hip, or femoral neck bone mineral density T score of -2.0 or less, or -1.0 or less if they had a history of osteoporosis-related fracture. Study patients received either 60 mg subcutaneous denosumab every 6 months and oral placebo daily for, or 5 mg oral risedronate daily and subcutaneous placebo every 6 months for 24 months. The primary outcome was non-inferiority of denosumab to risedronate in terms of percentage change from baseline in lumbar spine bone mineral density at 12 months based on non-inferiority margins. In addition, superiority was also assessed. The safety analysis included all study patients who received one dose or more of their assigned investigational product. This study is registered with ClinicalTrials.gov (NCT01575873). Denosumab was both non-inferior and superior to risedronate at 12 months for effect on bone mineral density at the lumbar spine in both glucocorticoid-continuing (4.4% [95% CI 3.8-5.0] vs 2.3% [1.7-2.9]; p<0.0001) and glucocorticoid-initiating (3.8% [3.1-4.5] vs 0.8% [0.2-1.5]; p<0.0001) subpopulations. Incidence of adverse events and fractures was similar between treatment groups. The most common adverse events in both groups included back pain and arthralgia. Serious infection occurred in 15 (4%) patients in the risedronate group and 17 (4%) patients in the denosumab group. The authors conclude that denosumab could be a useful treatment option for patients taking glucocorticoids who are at risk for fractures.

Professional Societies:

Prolia

Several National Comprehensive Cancer Network Clinical Practice Guidelines in Oncology (NCCN Guidelines[®]) include denosumab as a treatment for several conditions related to malignant disease. The following NCCN Guidelines[®] state:¹⁷⁻²⁰

- **Breast cancer (V.3.2019): For invasive breast cancer, the NCCN recommends (Category 2A) denosumab to be considered in postmenopausal (natural or induced) patients receiving adjuvant endocrine therapy along with calcium and vitamin D supplementation to maintain or improve bone mineral density and reduce risk of fractures.**
- **Prostate cancer (V.4.2019): For prostate cancer, the NCCN recommends (Category 2A) denosumab for the prevention or treatment of osteoporosis during androgen deprivation therapy (ADT) for patients with high fracture risk.**

Xgeva

In a ad hoc analysis of the phase 3 clinical trial of 1,776 patients with metastases from solid tumors or multiple myeloma, where it was shown that denosumab was non-inferior to zoledronic acid (ZA) in delaying or preventing SREs, Henry et al reports outcomes in the subgroup of 1,597 patients with solid tumors, excluding multiple myeloma. In the ad hoc analysis, denosumab significantly delayed time to first on-study SRE compared to ZA (HR, 0.81; 95% CI, 0.68–0.96) and time to first-and-subsequent SREs (RR, 0.85; 95% CI, 0.72–1.00). Denosumab also significantly delayed time to development of moderate or severe pain (HR, 0.81; 95% CI, 0.66–1.00), pain worsening (HR, 0.83; 95% CI, 0.71–0.97), and worsening pain interference in patients with no/mild baseline pain (HR, 0.77; 95% CI, 0.61–0.96). Overall survival was similar in both groups. The median KM estimate was 10.7 months for denosumab-treated patients and 10.0 months for ZA-treated patients (HR, 0.92; 95% CI, 0.81–1.05; $p=0.215$). Similarly, there was no difference between groups in time to disease progression. The median KM estimate was 5.3 (4.9, 5.7) months for denosumab-treated and 5.4 (4.8, 5.7) months for ZA-treated patients (HR, 0.96; 95% CI, 0.85–1.08; $p=0.497$). The authors concluded that denosumab was more effective in delaying the incidence of SREs, however did not significantly effect the overall incidence or disease progression or overall survival.

In a double-blind, double-dummy, phase III clinical trial, Henry et al compared denosumab with zoledronic acid (ZA) for delaying or preventing skeletal-related events (SRE) in patients with advanced cancer and bone metastases (excluding breast and prostate) or myeloma.²² Patients were randomly assigned to receive either monthly subcutaneous denosumab 120mg (n=886) or intravenous ZA 4mg (dose adjustment for renal impairment; n=890). The primary end point was time to first on-study SRE (pathologic fracture, radiation or surgery to bone, or spinal cord compression). The trial demonstrated that denosumab was noninferior to ZA in delaying time to first on-study SRE (hazard ratio, 0.84; 95% CI, 0.71 to 0.98; $P=0.0007$). Denosumab was not statistically superior to ZA in delaying time to first on-study SRE ($P=0.03$ unadjusted; $P=0.06$ adjusted for multiplicity) or time to first-and-subsequent (multiple) SRE (rate ratio, 0.90; 95% CI, 0.77 to 1.04; $P=0.14$). Overall survival and disease progression were similar between groups. Hypocalcemia occurred more frequently with denosumab. Osteonecrosis of the jaw occurred at similarly low rates in both groups. Acute-phase reactions after the first dose occurred more frequently with ZA, as did renal adverse events and elevations in serum creatinine. The authors concluded that denosumab was noninferior to ZA in preventing or delaying first on-study SRE in patients with advanced cancer metastatic to bone or myeloma.

Fizazi et al evaluated the comparison of denosumab with zoledronic acid (ZA) for the prevention of skeletal-related events in men with bone metastases from castration-resistant prostate cancer.²⁶ In a phase 3 clinical study, 1904 men with castration-resistant prostate cancer had no previous exposure to IV bisphosphonate were randomized 1:1 to either receive 120mg subcutaneous denosumab plus IV placebo (n=950), or 4mg IV ZA plus subcutaneous placebo (n=951) every 4 weeks. The primary endpoint was time to first on-study skeletal related event (pathological fracture, radiation therapy, surgery to bone, or spinal cord compression), and was assessed for non-inferiority. The same outcome was further assessed for superiority as a secondary endpoint. Efficacy analysis was by intention to treat. Median time to first on-study skeletal-related event was 20.7 months (95% CI 18.8–24.9) with denosumab compared with 17.1 months (15.0–19.4) with zoledronic acid (hazard ratio 0.82, 95% CI 0.71–0.95; $p=0.0002$ for non-inferiority; $p=0.008$ for superiority). While there was a three-month increase in the time to first skeletal-related events observed with denosumab in men with prostate cancer, there was no clinically meaningful difference in skeletal-related events for denosumab as compared with zoledronic acid: Overall confirmed events (ZA vs. denosumab) 41% vs. 36%; radiation to bone (21% vs. 19%); pathological fracture (15% vs. 14%); spinal cord compression (4% vs. 3%); surgery to bone (<1% vs. <1%). The authors concluded that denosumab was better than ZA for delaying the time to first SRE, however, was not significantly better at preventing the overall incidence of SREs versus zoledronic acid.

Several National Comprehensive Cancer Network Clinical Practice Guidelines in Oncology (NCCN Guidelines[®]) include denosumab as a treatment for several conditions related to malignant disease. The following NCCN Guidelines[®] state:¹⁵⁻²¹

- Bone **Cancer-cancer** (V.1.20192020): For giant cell tumor of the bone, the NCCN recommends (Category 2A) denosumab as a single agent or combined with interferon alfa or radiation therapy for localized disease. Denosumab is also recommended as a single agent for metastatic disease.
- Breast **Cancer-cancer** (V.1.3.20182019): For invasive breast cancer, the NCCN recommends (Category 1) denosumab to be used with calcium and vitamin D supplementation in addition to chemotherapy or endocrine therapy for bone metastasis in patients with expected survival ≥ 3 months with adequate renal function.
- Kidney **Cancer-cancer** (V.4.2.20182020): For kidney cancer, the NCCN recommends (Category 2A) denosumab to be used as a component of best supportive care for bony metastases.

- **Multiple Myeloma (V.2.2020): For multiple myeloma, the NCCN recommends (Category 2A) denosumab to be used in combination with primary myeloma therapy and the preferred agent in patients with renal insufficiency.**
- Non-Small Cell Lung Cancer (V.6.20182020): For non-small cell lung cancer, the NCCN recommends (Category 2A) denosumab to be considered for supportive therapy in patients with bone metastases.
- Prostate Cancer (V.4.20182019): For prostate cancer, the NCCN recommends (Category 1) denosumab for the prevention of skeletal-related events in men with castration-recurrent prostate cancer who have documented bone metastases and creatinine clearance greater than 30 ml/min.
- **Systemic mastocytosis (V.2.2019): For systemic mastocytosis, the NCCN recommends (Category 1) denosumab for second-line therapy for osteopenia/osteoporosis in patients with bone pain not responding to bisphosphonates or for patients who are not candidates for bisphosphonates because of renal insufficiency.**
- Thyroid Carcinoma (V.12.20182019): For thyroid carcinoma (anaplastic, follicular, Hürthle cell, medullary, papillary), the NCCN recommends (Category 2A) denosumab to be considered for bone metastases or palliative care for bone metastases (anaplastic).

U.S. FOOD AND DRUG ADMINISTRATION (FDA)

This section is to be used for informational purposes only. FDA approval alone is not a basis for coverage.

Prolia (denosumab) is a RANK ligand inhibitor indicated for the treatment of postmenopausal women with osteoporosis at high risk for fracture, to increase bone mass in men with osteoporosis at high risk for fracture, to increase bone mass in men at high risk for fracture receiving androgen deprivation therapy for nonmetastatic prostate cancer, to increase bone mass in women at high risk for fracture receiving adjuvant aromatase inhibitor therapy for breast cancer, and for the treatment of glucocorticoid-induced osteoporosis in men and women at high risk for fracture.¹³

Xgeva (denosumab) is a RANK ligand inhibitor indicated for the prevention of skeletal-related events in patients with multiple myeloma and in patients with bone metastases from solid tumors, the treatment of adults and skeletally mature adolescents with giant cell tumor of bone that is unresectable or where surgical resection is likely to result in severe morbidity, and for the treatment of hypercalcemia of malignancy refractory to bisphosphonate therapy.¹⁴

CENTERS FOR MEDICARE AND MEDICAID SERVICES (CMS)

Medicare does not have a National Coverage Determination (NCD) specifically for denosumab (XGEVA® and Prolia®). Local Coverage Determinations (LCDs) exist; see the LCDs for Bisphosphonates (Intravenous [IV]) and Monoclonal Antibodies in the Treatment of Osteoporosis and Their Other Indications and Drugs and Biologicals, Coverage of, for Label and Off-Label Uses.

In general, Medicare may cover outpatient (Part B) drugs that are furnished "incident to" a physician's service provided that the drugs are not usually self-administered by the patients who take them. Refer to the Medicare Benefit Policy Manual, Chapter 15, §50 - Drugs and Biologicals.

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POLICY HISTORY/REVISION INFORMATION

Date	Action/Description
<u>TBD</u>	<u>Annual review. Updated clinical evidence, CMS statement, and references. Approved by the National Pharmacy and Therapeutics Committee on 02/X/2020.</u>

INSTRUCTIONS FOR USE

This Medical Benefit Drug Policy provides assistance in interpreting UnitedHealthcare standard benefit plans. When deciding coverage, the federal, state or contractual requirements for benefit plan coverage must be referenced as the terms of the federal, state or contractual requirements for benefit plan coverage may differ from the standard benefit plan. In the event of a conflict, the federal, state or contractual requirements for benefit plan coverage govern. Before using this policy, please check the federal, state or contractual requirements for benefit plan coverage. UnitedHealthcare reserves the right to modify its Policies and Guidelines as necessary. This Medical Benefit Drug Policy is provided for informational purposes. It does not constitute medical advice.

UnitedHealthcare may also use tools developed by third parties, such as the MCG™ Care Guidelines, to assist us in administering health benefits. The UnitedHealthcare Medical Benefit Drug Policies are intended to be used in connection with the independent professional medical judgment of a qualified health care provider and do not constitute the practice of medicine or medical advice.