Medicare Part B - Denosumab Prior Authorization Criteria

FDA APPROVED INDICATIONS AND DOSAGE[1-2]

Agent(s)	Indication(s)	Dosage
Prolia® (denosumab) Subcutaneous injection	• Treatment of postmenopausal women with osteoporosis at high risk for fracture, defined as a history of osteoporotic fracture, or multiple risk factors for fracture; or patients who have failed or are intolerant to other available osteoporosis therapy. • Treatment to increase bone mass in men with osteoporosis at high risk for fracture, defined as a history of osteoporotic fracture, or multiple risk factors for fracture; or patients who have failed or are intolerant to other available osteoporosis therapy. • Treatment of glucocorticoid-induced osteoporosis in men and women at high risk for fracture who are either initiating or continuing systemic glucocorticoids in a daily dosage equivalent to 7.5 mg or greater of prednisone and expected to remain on glucocorticoids for at least 6 months. • Treatment to increase bone mass in men at high risk for fracture receiving androgen deprivation therapy for nonmetastatic prostate cancer. • Treatment to increase bone mass in women at high risk for fracture receiving adjuvant aromatase inhibitor therapy for breast cancer.	The recommended dose is 60 mg via subcutaneous injection once every 6 months. Denosumab should be administered by a healthcare professional. All patients should receive calcium 1000 mg daily and at least 400 IU of vitamin D daily.
Xgeva® (denosumab) Subcutaneous injection	• Prevention of skeletal related events in patients with multiple myeloma and in patients with bone	**Skeletal related events in multiple myeloma:** 120 mg subcutaneously every 4 weeks

	metastases from solid tumors • Treatment of adults and skeletally mature adolescents with giant cell tumor of bone that is unresectable or resection likely to result in severe morbidity • Treatment of hypercalcemia of malignancy refractory to bisphosphonate therapy	**Giant cell tumor of bone:** 120 mg subcutaneously every 4 weeks with additional doses of 120 mg on Days 8 and 15 of the first month of therapy **Hypercalcemia of malignancy:** 120 mg subcutaneously every 4 weeks with additional doses of 120 mg on Days 8 and 15 of the first month of therapy

CLINICAL RATIONALE: PROLIA

Diagnosis of Osteoporosis

The National Osteoporosis Foundation states that the diagnosis of osteoporosis (OP) can be established by either measurement of bone mineral density (BMD) or by the occurrence of adulthood hip or vertebral fracture in the absence of major trauma (such as a motor vehicle accident or multiple story fall). For evaluation, BMD measurement should be taken by central dual-energy X-ray absorptiometry at the lumbar spine and femoral neck (hip). A BMD taken at the one-third (33%) radius site can be used for diagnosing osteoporosis when the hip and lumbar spine cannot be measured or are unusable or uninterpretable. In postmenopausal women and men age 50 and older, WHO diagnostic T-score criteria is applied to the BMD measurement. For those patients that are not postmenopausal women and not men age 50 and older, WHO BMD classification should not be applied, and the diagnosis of osteoporosis should not be made on densitometric criteria alone.[3]

WHO Definitions of bone density[3]

Normal	T-score ≥ -1.0
Low bone mass (osteopenia)	T-score between -1.0 and -2.5
Osteoporosis	T-score ≤ -2.5

The WHO absolute fracture risk model (Fracture Risk Algorithm, FRAX) was developed to calculate the 10-year probability of a hip fracture and the 10-year probability of a major osteoporotic fracture, taking into account femoral neck BMD and clinical risk factors.[3]

Treatment

According to the National Osteoporosis Foundation, postmenopausal women and men age 50 and older presenting with the following should be considered for treatment:

- A hip or vertebral fracture
- T-score of -2.5 or lower at the femoral neck, total hip, or lumbar spine (or at the 33% radius site if necessary)
- Low bone mass (T-score between -1 and -2.5) and a 10-year probability of a hip fracture ≥ 3% or a 10-year probability of a major osteoporosis-related fracture ≥ 20% based on the US-adapted WHO algorithm[3]

The American Association of Clinical Endocrinologists (AACE)[5], the Endocrine Society[6], and the North American Menopause Society (NAMS)[7] all agree with these treatment thresholds for postmenopausal women. The Endocrine Society also agrees with these treatment thresholds for men with increased fracture risk.[7]

Postmenopausal women
The 2020 AACE Guidelines created a 'very high' risk category for post-menopausal women with osteoporosis. The following patients are considered to be a very high fracture risk:

- Patients with a recent fracture (within the past 12 months), fractures while on approved osteoporosis therapy multiple fractures, or fractures while on drugs causing skeletal harm (e.g., long-term glucocorticoids),
- Patients with a very low T-score (less than -3.0),
- Patients with a high risk for falls or history of injurious falls, and very high fracture probability by FRAX (e.g., major osteoporosis fracture >30%, hip fracture >4.5%) or other validated fracture risk algorithm.

Patients who have been diagnosed with osteoporosis but do not meet the above definition of very high fracture risk are to be considered to be at high risk.[4]

The AACE recommends alendronate, denosumab, risedronate, and zoledronate as appropriate initial therapy for most osteoporotic patients with high fracture risk. Abaloparatide, denosumab, romosozumab, teriparatide, and zoledronate should be considered for patients unable to use oral therapy and as initial therapy for patients at very high fracture risk.[4]

Men over the age of 50
The Endocrine Society recommends pharmacological therapy for men at high risk of fracture including, but not limited to:

- Men who have had a hip or vertebral fracture without major trauma
- Men who have not experienced a spine or hip fracture, but whose BMD of the spine, femoral neck, and/or total hip is 2.5 standard deviations below the mean of normal young white males
- In the US, men who have a T-score between -1.0 and -2.5 in the spine, femoral neck, or total hip plus a 10-year risk of hip fracture ≥ 3% using FRAX. For men outside the US, region-specific guidelines should be considered
- Men who are receiving long-term glucocorticoid therapy in pharmacological doses

Men at high risk of fracture can be treated with medication approved by regulatory agencies such as the U.S. FDA or the European Medicines Agency (EMA) (at the time of this writing, alendronate, risedronate, zoledronic acid, and teriparatide. Denosumab can also be used for men receiving ADT [androgen deprivation therapy] for prostate cancer). The selection of therapeutic agent should be individualized based on factors including fracture history, severity of osteoporosis (T-scores), the risk for hip fracture, patterns of BMD, comorbid conditions, cost, and other factors.[7]

The ACP recommends bisphosphonates to reduce the risk for vertebral fracture in men who have clinically recognized osteoporosis.[11]

Glucocorticoid-Induced Osteoporosis
Oral bisphosphonates are currently regarded as first line options on the grounds of their low cost. However, teriparatide has shown its effects on BMD and vertebral fracture risk in glucocorticoid-treated individuals with osteoporosis and should be considered as an alternative first line option in patients at high risk of vertebral fracture.[11] The American College of Rheumatology defines high risk of fracture as: adults aged ≥40 years, previous osteoporotic fracture, hip or spine BMD T-score ≤-2.5, or 10 year fracture risk of ≥20% (major osteoporotic fracture or ≥3% (hip fracture).[8]

Due to the lack of evidence on the effect on fracture risk, concomitant use of osteoporosis agents is not recommended. There are no head-to-head trials with a preplanned endpoint of reduced fractures comparing one drug with another for osteoporosis.[4]

Breast Cancer

The National Comprehensive Cancer Network (NCCN) Guidelines in Oncology-Breast Cancer state that:

- The use of a bisphosphonate generally the preferred intervention to improve bone mineral density
- Denosumab, zoledronic acid, or pamidronate (all with calcium and vitamin D supplementation) should be given in addition to chemotherapy or endocrine therapy if bone metastasis is present and expected survival ≥ 3 months. The optimal schedule for zoledronic acid is monthly for 12 doses, then quarterly. The optimal schedule and duration of denosumab or pamidronate is unknown (NCCN category 1).
- The use of estrogen, progesterone, or selective estrogen receptor modulators to treat osteoporosis or osteopenia in women with breast cancer is discouraged. The use of a bisphosphonate (oral/IV) or denosumab is acceptable to maintain or to improve bone mineral density and reduce risk of fractures in postmenopausal (natural or induced) patients receiving adjuvant aromatase inhibitor therapy.[9]

Prostate Cancer

The NCCN Guidelines in Oncology-Prostate Cancer state that:

- Screening and treatment for osteoporosis are advised according to guidelines for the general population from the NOF. Androgen depravation therapy (ADT) should be considered "secondary osteoporosis" using the FRAX algorithm. Zoledronic acid and alendronate increased bone mineral density, a surrogate for fracture risk, during ADT for prostate cancer. Treatment options to increase bone density include denosumab, zoledronic acid and alendronate.[10]

Safety

Prolia carries the following contraindications:

- Hypocalcemia
- Pregnancy
- Known hypersensitivity to Prolia

Hypocalcemia must be corrected before initiating Prolia therapy.[1]

For additional clinical information see the Prime Therapeutics Formulary Chapter 4.9A Calcium Regulators/Osteoporosis Agents.

CLINICAL RATIONALE: XGEVA

Giant cell tumor of bone[12]

Giant cell tumor of bone (GCTB) is a rare benign primary tumor of the bone predominant in young adults. In the United States, GCTB accounts for approximately 3 to 5 percent of all primary bone tumors and 15 to 20 percent of all benign bone tumors. GCTB usually occurs after skeletal maturity, with a peak incidence in patients between 20 and 39 years old.

Intralesional excision with or without an effective adjuvant is an adequate primary treatment for resectable tumors. Serial embolizations, denosumab, and interferon are included as primary treatment in the National Comprehensive Cancer Network (NCCN) guidelines as options for patients with lesions that are resectable with acceptable morbidity or unresectable axial lesions.[12]

Multiple myeloma[13]

The National Comprehensive Cancer Network (NCCN) Guidelines in Oncology for Multiple Myeloma recommend bisphosphonates or denosumab as preventative options for skeletal-related events for all patients receiving primary treatment. The preferred bisphosphonate in NCCN guidelines is zoledronic acid for these events. If the patient has renal insufficiency NCCN prefers denosumab over bisphosphonates.

Prostate cancer[14]

The National Comprehensive Cancer Network (NCCN) Guidelines in Oncology for (prostate cancer) prefer denosumab (category 1, preferred) to zoledronic acid to treat bone metastases related skeletal events, maintain or improve bone mineral density and reduce risk of fractures.

Solid tumor[15-18]
The National Comprehensive Cancer Network (NCCN) Guidelines in Oncology for several solid tumor types (i.e., thyroid, non-small cell lung cancer, kidney cancer, breast cancer, prostate cancer) recommend IV bisphosphonates or sub-cutaneous denosumab as therapeutics options to treat bone metastases related skeletal events, maintain or improve bone mineral density and reduce risk of fractures.

Hypercalcemia of malignancy
Hypercalcemia is relatively common in patients with cancer, occurring in approximately 20 to 30 percent of cases. There are three major mechanisms by which hypercalcemia of malignancy can occur: tumor secretion of parathyroid hormone-related protein, osteolytic metastases with local release of cytokines, and tumor production of 1,25-dihydroxyvitamin D (calcitriol).[19]

Mild hypercalcemia is defined as calcium between 10.5 and 11.9 mg/dL. Moderate hypercalcemia is defined as calcium between 12 and 13.9 mg/dL. Severe hypercalcemia is defined as calcium ≥ 14 mg/dL. Calcium in serum is bound to proteins, principally albumin. As a result, total serum calcium concentrations in patients with low or high serum albumin levels may not accurately reflect the physiologically important ionized (or free) calcium concentration. In patients with hypoalbuminemia or hyperalbuminemia, the measured serum calcium concentration should be corrected for the abnormality in albumin or for standard units.[20,21]

While evidence-based guidelines are lacking, in individuals with only mildly symptomatic disease immediate treatment can be deferred and the calcium may self correct. In patients with moderate hypercalcemia therapy should be based on symptoms and the clinician. Given the efficacy, tolerability, and cost effectiveness of the treatments involved, it may be reasonable to treat such individuals similar to those with more severe degrees of hypercalcemia. Patients with severe hypercalcemia should be promptly treated with current available regimens.[22]

Treatment of the underlying malignancy is always the primary goal of therapy. However, additional therapies, especially for moderate to severe hypercalcemia are essential when simultaneously treating the underlying malignancy. Bisphosphonates are first-line therapy and the mainstay for long-term therapy. Through direct mechanisms they induce osteoclast apoptosis, and indirectly by acting on the osteoblasts they can reduce osteoclastic bone resorption. Bisphosphonates affect proliferation and differentiation of osteoblasts and prevent their apoptosis, and they can also neutralize the RANKL-mediated stimulation of osteoclasts. After receiving the first dose of pamidronate or zoledronic acid patients can be retreated if serum calcium does not return to normal or remain normal. It is recommended that a minimum of 7 days elapse before retreatment, to allow for full response to the initial dose.[20-21]

Efficacy[2]
Xgeva (denosumab) is a human IgG2 monoclonal antibody that binds to human 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. 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. Denosumab prevents RANKL from activating its receptor, RANK, on the surface of osteoclasts, their precursors, and osteoclast-like giant cells.

Bone metastases from solid tumors

The safety and efficacy of Xgeva for the prevention of skeletal-related events in patients with bone metastases from solid tumors was demonstrated in three international, randomized, double-blind, active-controlled, non-inferiority trials (Study 20050136, Study 20050244, and Study 20050103) comparing Xgeva with zoledronic acid. In each trial, the main outcome measure was demonstration of noninferiority of time to first skeletal-related event (SRE) as compared to zoledronic acid. Supportive outcome measures were superiority of time to first SRE and superiority of time to first and subsequent SRE. An SRE was defined as any of the following: pathologic fracture, radiation therapy to bone, surgery to bone, or spinal cord compression. The results of these studies are summarized in the table below.

	Study 20050136 Metastatic Breast Cancer		**Study 20050244 Metastatic Solid Tumors or Multiple Myeloma**		**Study 20050103 Metastatic CRPC[a]**	
	Xgeva N=1026	**Zoledronic Acid N=1020**	**Xgeva N=866**	**Zoledronic Acid N=890**	**Xgeva N=950**	**Zoledronic Acid N=951**
First On-study SRE						
Number of Patients who had SREs (%)	315 (30.7)	372 (36.5)	278 (31.4)	323 (36.3)	341 (35.9)	386 (40.6)
Components of First SRE						
Radiation to Bone	82 (8.0)	119 (11.7)	119 (13.4)	144 (16.2)	177 (18.6)	203 (21.3)
Pathological Fracture	212 (20.7)	238 (23.3)	122 (13.8)	139 (15.6)	137 (14.4)	143 (15.0)
Surgery to Bone	12 (1.2)	8 (0.8)	13 (1.5)	19 (2.1)	1 (0.1)	4 (0.4)
Spinal Cord Compression	9 (0.9)	7 (0.7)	24 (2.7)	21(2.4)	26 (2.7)	36 (3.8)
Median Time to SRE (months)	NR[b]	26.4	20.5	16.3	20.7	17.1
Hazard Ratio (95% CI)	0.82 (0.71 ,0.95)		0.84 (0.71, 0.98)		0.82 (0.71, 0.95)	
Noninferiority p-value	< 0.001		< 0.001		< 0.001	
Superiority p-value[c]	0.010		0.060		0.008	
First and Subsequent SRE[d]						
Mean Number/Patient	0.46	0.60	0.44	0.49	0.52	0.61
Rate Ratio (95% CI)	0.77 (0.66, 0.89)		0.90 (0.77, 1.04)		0.82 (0.71, 0.94)	
Superiority p-value[c]	0.001		0.145		0.009	

[a]CRPC = castrate-resistant prostate cancer
[b]NR = not reached
[c]Superiority testing performed only after denosumab demonstrated to be noninferior to zoledronic acid with trial
[d]All skeletal events postrandomization; new events defined by occurrence ≥ 21 days after preceding event
[e]Adjusted p-values are presented

Multiple myeloma
The efficacy of Xgeva for the prevention of skeletal-related events (SRE) in newly diagnosed multiple myeloma patients was evaluated in an international, randomized, double-blind, active-controlled, non-inferiority trial (Study 20090482) comparing Xgeva with zoledronic acid. The

main efficacy outcome measure was non-inferiority of time to first SRE. Additional efficacy outcome measures were superiority of time to first SRE, time to first and subsequent SRE, and overall survival. An SRE was defined as any of the following: pathologic fracture, radiation therapy to bone, surgery to bone, or spinal cord compression. The results of this study are summarized in the table below.

	Study 20090482 Multiple Myeloma	
	Xgeva N = 859	**Zoledronic Acid N = 859**
First On-study SRE		
Number of Patients who had SREs (%)	376 (43.8)	383 (44.6)
Components of First SRE		
Radiation to Bone	47 (5.5)	62 (7.2)
Pathological Fracture	342 (39.8)	338 (39.3)
Surgery to Bone	37 (4.3)	48 (5.6)
Spinal Cord Compression	6 (0.7)	4 (0.5)
Median time to SRE (months) (95% CI)	22.8 (14.7, NE[a])	24 (16.6, 33.3)
Hazard Ratio (95% CI)	0.98 (0.85, 1.14)	

[a]NE = not estimable

Giant cell tumor of bone
The safety and efficacy of Xgeva for the treatment of giant cell tumor of bone in adults or skeletally mature adolescents were demonstrated in two open-label trials (Study 20062004 and Study 20040215) that enrolled patients with histologically confirmed measurable giant cell tumor of bone that was either recurrent, unresectable, or for which planned surgery was likely to result in severe morbidity.

Study 20062004 was a single arm, pharmacodynamic, and proof concept trial conducted in 37 adult patients with unresectable or recurrent giant cell tumor of bone. Patients were required to have histologically confirmed giant cell tumor of bone and radiologic evidence of measurable disease from a computed tomography (CT) or magnetic imaging (MRI) obtained within 28 prior to study enrollment.

Study 20040215 was a parallel-cohort, proof of concept, and safety trial conducted in 282 adult or skeletally mature adolescent patients with histologically confirmed giant cell tumor of bone and evidence of measurable active disease. Patients enrolled into one of three cohorts: Cohort 1 enrolled 170 patients with surgically unsalvageable disease; Cohort 2 enrolled 101 patients with surgically salvageable disease where the investigator determined that the planned surgery was likely to result in severe morbidity; Cohort 3 enrolled 11 patients who previously participated in Study 20062004.

The primary endpoint in both Study 20062004 and Study 20040215 was objective response rate using modified Response Evaluation Criteria in Solid Tumors (RECIST 1.1). The RECIST 1.1 overall in both studies was 25% (95% CI; 19,32). All responses were partial responses.

Hypercalcemia of malignancy
The safety and efficacy of Xgeva was demonstrated in an open-label, single-arm trial (Study 20070315) that enrolled 33 patients with hypercalcemia of malignancy (with or without bone metastases) refractory to treatment with intravenous bisphosphonate therapy.

In this trial. refractory hypercalcemia of malignancy was defined as an albumin-corrected calcium of >12.5 mg/dL (3.1 mmol/L) despite treatment with intravenous bisphosphonate therapy in 7-30 days prior to initiation of Xgeva therapy. The primary outcome measure was the proportion of patients achieving a response, defined as corrected serum calcium ≤ 11.5 mg/dL. A complete

response was defined as corrected serum calcium ≤ 10.8 mg/dL. By day ten 63.6% had a response (95% CI). The median time to response was 9 days (95% CI), and the median duration of response was 104 days (95% CI). By day ten 36.4% of patients had a complete response (95% CI). The median time to complete response was 23 days (95% CI) and the median duration of complete response was 34 days (95% CI).

Safety
Hypocalcemia is contraindicated when using denosumab. The patient's calcium level should be corrected prior to use. This agent should not be used in pregnancy as it may cause fetal harm. Osteonecrosis of the jaw (ONJ) has been reported with the use of denosumab. A routine oral exam should be performed by the prescriber prior to therapy initiation and appropriate preventive dentistry should be considered prior to therapy in patients with risk factors for ONJ. Good oral hygiene should be maintained during therapy with denosumab.

Denosumab carries the following contraindications:
- Hypocalcemia
- Known hypersensitivity to denosumab

For additional clinical information see the Prime Therapeutics Formulary Chapter 4.9A Calcium Regulators/ Osteoporosis Agents.

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Document History
Original Prime Standard Part B criteria, approved by P&T UM Committee 06/2021
Mid-Year Review Prime Standard Part B criteria, with changes to criteria, approved by P&T UM Committee 12/2021

Medicare Part B Denosumab Prior Authorization Criteria

Coverage and policy application are contingent on National Coverage Determinations (NCD) and Local Coverage Determinations (LCD). An NCD or LCD that is applicable to the drug or product must be used in lieu of applicable medical necessity criteria. Also, please note that Prior Authorization criteria cannot be stricter than an NCD or LCD with specified step therapy requirements.

TARGET AGENT(S)	PREREQUISITE AGENT(S)
Target and prerequisite agent(s) determined by client	Target and prerequisite agent(s) determined by client
Prolia (denosumab)	bisphosphonates
Xgeva (denosumab)	zoledronic acid[a]

a – generic equivalent available

Brand (generic)	GPI	Multisource Code	HCPCS Code
Prolia (denosumab)			
60 mg/mL injection	30044530002020 3004453000E520	M, N, O, or Y	J0897
Xgeva (denosumab)			
120 mg/1.7 mL	30044530002030	M, N, O, or Y	J0897

CRITERIA FOR APPROVAL
Evaluation
Target Agent(s) will be approved when ALL of the following are met:

1. The requested agent is being used for ONE of the following:
    a. An FDA approved indication
    OR
    b. An indication in CMS approved compendia

    AND
2. ONE of the following:
    a. Information has been provided that indicates the patient has been treated with the requested agent in the past 365 days
    OR
    b. There is documentation that the patient has had an ineffective treatment response to the active ingredient(s) of ALL prerequisite agent(s)
    OR
    c. The patient has a documented intolerance, hypersensitivity, or FDA labeled contraindication to the active ingredient(s) of ALL prerequisite agent(s)
    OR
    d. The prescriber has submitted documentation indicating ALL prerequisite agent(s) are likely to be ineffective or are likely to cause an adverse reaction or other harm to the patient

    AND
3. The patient does NOT have any FDA labeled contraindications to the requested agent
    AND
4. The requested quantity (dose) is within FDA labeled dosing or supported in compendia for the requested indication

Length of Approval: up to 12 months