Denosumab - Osteoporosis Medical Drug Criteria with Quantity Limit Program Summary

POLICY REVIEW CYCLE

Effective Date **Date of Origin**
3/1/2023

FDA APPROVED INDICATIONS AND DOSAGE

Agent(s)	FDA Indication(s)	Notes	Ref#
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.	Denosumab, under the name of Xgeva, is indicated for prevention of skeletal-related events in patients with bone metastases from solid tumors, 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 treatment of hypercalcemia of malignancy refractory to bisphosphonate therapy.(2)	1 ; 2

See package insert for FDA prescribing information: https://dailymed.nlm.nih.gov/dailymed/index.cfm

CLINICAL RATIONALE

Diagnosis of Osteoporosis	The National Osteoporosis Foundation (NOF) 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)

<table>
<tr><td></td><td>
WHO Definitions of bone density(3)
<table>
<tr><td>Normal</td><td>T-score ≥ -1.0</td></tr>
<tr><td>Low bone mass (osteopenia)</td><td>T-score between -1.0 and -2.5</td></tr>
<tr><td>Osteoporosis</td><td>T-score ≤ -2.5</td></tr>
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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)
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<tr><td>Treatment</td><td>
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 greater than or equal to 3% or a 10-year probability of a major osteoporosis-related fracture greater than or equal to 20% based on the US-adapted WHO algorithm(3)

The American Association of Clinical Endocrinologists (AACE)(4), the Endocrine Society(5), and the North American Menopause Society (NAMS)(6) 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)
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<tr><td>Postmenopausal women</td><td>
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)
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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 greater than or equal to 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 American College of Physicians (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 greater than or equal to 40 years, previous osteoporotic fracture, hip or spine BMD T-score less than or equal to -2.5, or 10 year fracture risk of greater than or equal to 20% (major osteoporotic fracture or greater than or equal to 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 is 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 greater than or equal to 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 endocrine 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.

REFERENCES

Number	Reference
1	Prolia prescribing information. Amgen Pharmaceuticals. March 2020.
2	Xgeva prescribing information. Amgen Pharmaceuticals. June 2020.
3	Cosman F, de Beur SJ, LeBoff MS, et. al. Clinician's Guide to Prevention and Treatment of Osteoporosis. National Osteoporosis Foundation, Osteoporosis Int 25:2359-2381, 2014. https://my.nof.org/bone-source/education/clinicians-guide-to-the-prevention-and-treatment-of-osteoporosis
4	Camacho PM, Petak SM, Binkley N, et al. American Association of Clinical Endocrinologists and American College of Endocrinology clinical practice guidelines for the diagnosis and treatment of postmenopausal osteoporosis – 2020 update. Available at https://www.aace.com/files/postmenopausal-guidelines.pdf.
5	~~Eastell R, Rosen CL, Black DM, et. al. Pharmacological Management of Osteoporosis in Postmenopausal Women: An Endocrine Society Clinical Practice Guideline. J ClinEndocrinol Metab 104: 1595-1622, 2019. https://academic.oup.com/jcem/article/104/5/1595/5418884~~ Reference no longer used.
6	~~North American Menopause Society. Management of osteoporosis in postmenopausal women: 2010 position statement of the North American Menopause Society. Menopause. 2010;17(1):25-54.~~ Reference no longer used.
7	Endocrine Society Guideline: Osteoporosis in Men: An Endocrine Society Clinical Practice Guideline 2012. https://academic.oup.com/jcem/article/97/6/1802/2536476
8	Buckley L, Guyatt G, Fink HA, et al. 2017 American College of Rheumatology guideline for the prevention and treatment of glucocorticoid-induced osteoporosis. Arthritis and Rheumatology Vol. 69, No. 8, August 2017, pp 1521–1537. Available at: https://www.rheumatology.org/Portals/0/Files/Guideline-for-the-Prevention-and-Treatment-of-GIOP.pdf
9	National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines in Oncology-Breast Cancer, version 4.2022. Available at: http://www.nccn.org/professionals/physician_gls/f_guidelines.asp
10	National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines in Oncology-Prostate Cancer, version 4.2022. Available at: http://www.nccn.org/professionals/physician_gls/f_guidelines.asp

Number	Reference
11	Qaseem A, Forciea MA, McLean RM, et. al. Treatment of Low Bone Density or Osteoporosis to Prevent Fractures in Men and Women: A Clinical Practice Guideline Update from the American College of Physicians. Ann Intern Med. 2017;166:818-839. https://annals.org/aim/fullarticle/2625385/treatment-low-bone-density-osteoporosis-prevent-fractures-men-women-clinical

POLICY AGENT SUMMARY – MEDICAL PRIOR AUTHORIZATION

HCPC Codes	Target Brand Agent Name(s)	Target Generic Agent Name(s)	Strength	Targeted MSC	Available MSC	Preferred Status	Effective Date
J0897	Prolia	Denosumab Inj Soln Prefilled Syringe 60 MG/ML	60 MG/ML	M ; N ; O ; Y	N		

POLICY AGENT SUMMARY QUANTITY LIMIT

Target Brand Agent Name(s)	Target Generic Agent Name(s)	Strength	QL Amount	Dose Form	Days Supply	Duration	Addtl QL Info	Allowed Exceptions	Targeted NDCs When Exclusions Exist	Effective Date
Prolia	Denosumab Inj Soln Prefilled Syringe 60 MG/ML	60 MG/ML	1.0	INJ	180	Days				

CLIENT SUMMARY – PRIOR AUTHORIZATION

Target Brand Agent Name(s)	Target Generic Agent Name(s)	Strength	Client Formulary
Prolia	Denosumab Inj Soln Prefilled Syringe 60 MG/ML	60 MG/ML	Commercial ; HIM ; ResultsRx

CLIENT SUMMARY – QUANTITY LIMITS

Target Brand Agent Name(s)	Target Generic Agent Name(s)	Strength	Client Formulary
Prolia	Denosumab Inj Soln Prefilled Syringe 60 MG/ML	60 MG/ML	Commercial ; HIM ; ResultsRx

PRIOR AUTHORIZATION CLINICAL CRITERIA FOR APPROVAL

Module	Clinical Criteria for Approval
	CRITERIA FOR APPROVAL **Target Agent(s)** will be approved when ALL of the following are met: 1. ONE of the following: A. The patient has a diagnosis of osteoporosis and ALL of the following: 1. ONE of the following: A. The patient's sex is male and the patient is over 50 years of age **OR** B. The patient is postmenopausal **OR** C. The prescriber has provided information that the requested agent is medically appropriate for the patient's sex **AND** 2. The patient's diagnosis was confirmed by ONE of the following: A. A fragility fracture in the hip or spine **OR** B. A T-score of -2.5 or lower **OR** C. A T-score of -1.0 to -2.5 and ONE of the following: 1. A fragility fracture of the proximal humerus, pelvis, or distal forearm **OR**

Module	Clinical Criteria for Approval
	2. A FRAX 10-year probability for major osteoporotic fracture of greater than or equal to 20% **OR** 3. A FRAX 10-year probability of hip fracture of greater than or equal to 3% **AND** 3. ONE of the following: A. The patient is at a very high fracture risk as defined by ONE of the following: 1. Patient had a recent fracture (within the past 12 months) **OR** 2. Patient had fractures while on approved osteoporosis therapy **OR** 3. Patient has had multiple fractures **OR** 4. Patient had fractures while on drugs causing skeletal harm (e.g., long-term glucocorticoids) **OR** 5. Patient has a very low T-score (less than -3.0) **OR** 6. Patient is at high risk for falls or has a history of injurious falls **OR** 7. Patient has a very high fracture probability by FRAX (e.g., major osteoporosis fracture greater than 30%, hip fracture greater than 4.5%) or by other validated fracture risk algorithm **OR** B. ONE of the following: 1. The patient has tried and had an inadequate response to a bisphosphonate (medical records required) **OR** 2. The patient has an intolerance or hypersensitivity to a bisphosphonate (medical records required) **OR** 3. The patient has an FDA labeled contraindication to ALL bisphosphonates (medical records required) **OR** B. The patient is requesting the agent for osteopenia (osteoporosis prophylaxis) **AND** ALL of the following: 1. ONE of the following: A. The patient's sex is male and the patient is over 50 years of age **OR** B. The patient is postmenopausal **OR** C. The patient is age 50 years of age or over and the prescriber has provided information that the requested agent is medically appropriate for the patient's sex **AND** 2. BOTH of the following: A. The patient has osteopenia, defined as a T-score between -1.0 to -2.5 **AND** B. ONE of the following: 1. A fragility fracture of the proximal humerus, pelvis, or distal forearm **OR** 2. 10-year probability of a hip fracture greater than or equal to 3% per FRAX **OR** 3. 10-year probability of a major osteoporosis-related fracture greater than or equal to 20% per FRAX **AND** 3. ONE of the following: A. The patient has tried and had an inadequate response to a bisphosphonate (medical records required) **OR** B. The patient has an intolerance or hypersensitivity to a bisphosphonate (medical records required) **OR** C. The patient has an FDA labeled contraindication to ALL bisphosphonates (medical records required) **OR** C. The patient has a diagnosis of breast cancer **AND** BOTH of the following: 1. The patient is currently receiving aromatase inhibitor therapy **AND** 2. ONE of the following: A. The patient has tried and had an inadequate response to a bisphosphonate (medical records required) **OR**

Module	Clinical Criteria for Approval
	B. The patient has an intolerance or hypersensitivity to a bisphosphonate (medical records required) **OR** C. The patient has an FDA labeled contraindication to ALL bisphosphonates (medical records required) **OR** D. The patient has a diagnosis of nonmetastatic prostate cancer **AND** BOTH of the following: 1. The patient is currently receiving androgen deprivation therapy (ADT) **AND** 2. ONE of the following: A. The patient has tried and had an inadequate response to a bisphosphonate (medical records required) **OR** B. The patient has an intolerance or hypersensitivity to a bisphosphonate (medical records required) **OR** C. The patient has an FDA labeled contraindication to ALL bisphosphonates (medical records required) **OR** E. The patient has a diagnosis of glucocorticoid-induced osteoporosis and ALL of the following: 1. The patient is either initiating or currently taking glucocorticoids in a daily dosage equivalent to 7.5 mg or higher of prednisone **AND** 2. The patient's expected current course of therapy of glucocorticoids is for a period of at least 6 months **AND** 3. The patient's diagnosis was confirmed by ONE of the following: A. A fragility fracture in the hip or spine **OR** B. A T-score of -2.5 or lower **OR** C. A T-score of -1.0 to -2.5 and ONE of the following: 1. A fragility fracture of a proximal humerus, pelvis, or distal forearm **OR** 2. A FRAX 10-year probability for major osteoporotic fracture of greater than or equal to 20% **OR** 3. A FRAX 10-year probability of hip fracture of greater than or equal to 3% **AND** 4. ONE of the following: A. The patient is at a very high fracture risk as defined by ONE of the following: 1. Patients had a recent fracture (within the past 12 months) **OR** 2. Patient had fractures while on approved osteoporosis therapy **OR** 3. Patient has had multiple fractures **OR** 4. Patient had fractures while on drugs causing skeletal harm (e.g., long-term glucocorticoids) **OR** 5. Patient has a very low T-score (less than -3.0) **OR** 6. Patient is at high risk for falls or has a history of injurious falls **OR** 7. Patient has a very high fracture probability by FRAX (e.g., major osteoporosis fracture greater than 30%, hip fracture greater than 4.5%) or by other validated fracture risk algorithm **OR** B. ONE of the following: 1. The patient has tried and had an inadequate response to a bisphosphonate (medical records required) **OR** 2. The patient has an intolerance or hypersensitivity to a bisphosphonate (medical records required) **OR** 3. The patient has an FDA labeled contraindication to ALL bisphosphonates (medical records required) **AND** 2. The patient will NOT be using the requested agent in combination with a bisphosphonate, another form of denosumab (e.g., Xgeva), romosozumab-aqqg, or parathyroid hormone analog (e.g., abaloparatide, teriparatide) **AND**

Module	Clinical Criteria for Approval
	3. The patient does NOT have any FDA labeled contraindications to the requested agent **AND** 4. ONE of the following: A. The requested quantity (dose) is less than or equal to the program quantity limit **OR** B. ALL of the following: 1. The requested quantity (dose) is greater than the program quantity limit **AND** 2. The requested quantity (dose) does NOT exceed the maximum FDA labeled dose for the requested indication **AND** 3. The requested quantity (dose) cannot be achieved with a lower quantity of a higher strength that does not exceed the program quantity limit **OR** C. ALL of the following: 1. The requested quantity (dose) is greater than the program quantity limit **AND** 2. The requested quantity (dose) is greater than the maximum FDA labeled dose for the requested indication **AND** 3. The prescriber has provided information in support of therapy with a higher dose for the requested indication **Length of approval:** 12 months