Medical Policy:
Prolia® and Xgeva® (denosumab)

POLICY NUMBER	LAST REVIEW	ORIGIN DATE
MG.MM.PH.100	January 16, 2024	

Length of Authorization

Coverage is provided for 12 months and may be renewed.

Dosing Limits [Medical Benefit]

Max Units (per dose and over time):

Prolia	All indications: • 60 billable units every 6 months
Xgeva	*Giant Cell Tumor of Bone; Hypercalcemia of malignancy* – Loading Dose: • 120 billable units on days 1, 8, 15, and 29 – Maintenance: • 120 billable units every 4 weeks
	Bone metastases from solid tumors; Multiple Myeloma:

	• 120 billable units every 4 weeks

Guideline

I. INITIAL APPROVAL CRITERIA

1. **Prolia**

A. Patient must be supplementing with 1,000 mg of calcium and at least 400 IU of vitamin D daily; **AND**
B. Patient is at least 18 years of age; **AND**
C. Patient must not have hypocalcemia; **AND**
D. Patient must be at a high risk for fracture******; **AND**
E. Pregnancy ruled out prior to starting therapy in women of child-bearing potential; **AND**

Coverage is provided in the following conditions:

A. **Osteoporosis in Men and Women †**
   i. Women only: Patient must be post-menopausal; **AND**
   ii. Patient has a documented diagnosis of osteoporosis indicated by one or more of the following:
      a. Hip DXA (femoral neck or total hip) or lumbar spine T-score ≤-2.5 and/or forearm DXA 33% (one-third) radius; **OR**
      b. T-score ≤-1 or low bone mass and a history of fragility fracture to the hip or spine; **OR**
      c. T-score between -1 and -2.5 with a FRAX 10-year probability for major fracture ≥20% or hip fracture ≥3%; **AND**
   iii. Patient has one of the following:
      a. Documented treatment failure or ineffective response[±] to a minimum (12) month trial on previous therapy with bisphosphonates (oral or IV) such as alendronate, risedronate, ibandronate, or zoledronic acid; **OR**
      b. Patient has a documented contraindication***** or intolerance to **BOTH** oral bisphosphonates **AND** intravenous (IV) bisphosphonates such as alendronate, risedronate, ibandronate, or zoledronic acid

B. **Glucocorticoid-Induced Osteoporosis †**
   i. Patient will be initiating or is continuing systemic glucocorticoid therapy at a daily dosage equivalent to ≥ 7.5 mg of prednisone and is expected to remain on glucocorticoid therapy for at least 6 months; **AND**
      a. Documented treatment failure or ineffective response[±] to a minimum (12) month trial on previous therapy with bisphosphonates (oral or IV) such as alendronate, risedronate, ibandronate, or zoledronic acid; **OR**
      b. Patient has a documented contraindication***** or intolerance to **BOTH** oral bisphosphonates **AND** intravenous (IV) bisphosphonates such as alendronate, risedronate, ibandronate, or zoledronic acid

C. **Osteoporosis treatment and prevention in prostate cancer patients †**
   i. Documented Hip DXA (femoral neck or total hip) or lumbar spine T-score ≤-1 (or patient meets the diagnostic criteria for osteoporosis above); **AND**
   ii. Patient must be receiving androgen deprivation therapy for nonmetastatic prostate cancer

D. **Osteoporosis treatment and prevention in breast cancer patients †**
   i. Patient must be receiving adjuvant aromatase inhibitor therapy for breast cancer

±Ineffective response is defined as one or more of the following:
– Decrease in T-score in comparison with baseline T-score from DXA scan – Patient has a new fracture while on bisphosphonate therapy
**High risk for fractures include, but are not limited to, one or more of the following:
– History of an osteoporotic fracture as an adult – Parental history of hip fracture – Low BMI – Rheumatoid arthritis – Alcohol intake (3 or more drinks per day) – Current smoking – History of oral glucocorticoids ≥5 mg/d of prednisone (or equivalent) for >3 months (ever)
*Examples of contraindications to oral bisphosphonate therapy include the following:
– Documented inability to sit or stand upright for at least 30 minutes – Documented pre-existing gastrointestinal disorder such as inability to swallow, Barrett's esophagus, esophageal stricture, dysmotility, or achalasia – Surgical anastomoses are present in the GI tract after certain types of bariatric surgery (e.g., Roux-en-Y gastric bypass).
*Examples of contraindications to injectable bisphosphonate therapy include the following:
– Documented pre-existing hypocalcemia and disturbances of mineral metabolism – Documented pre-existing renal insufficiency defined as creatinine clearance < 35 mL/min

2. **Xgeva**

A. Administer calcium and vitamin D as necessary to treat or prevent hypocalcemia; **AND**

B. Patient must not have hypocalcemia; **AND**

Coverage is provided in the following conditions:

C. **Prevention of skeletal-related events in patients with multiple myeloma OR bone metastases from solid tumors †**

i. Patient is at least 18 years of age; **AND**

a. Patient must try and have an inadequate response, contraindication, or intolerance to at least a three (3) month trial of Zoledronic Acid; **OR**

b. Patient has metastatic breast cancer or metastatic castration-resistant prostate cancer, or metastatic lung cancer (both SCLC and NSCLC)

D. **Giant Cell Tumor of the Bone †**

i. Patient must be an adult or at least 12 years of age and skeletally mature; **AND**

ii. Disease is unresectable or surgical resection is likely to result in severe morbidity; **OR**

iii. Disease is localized, recurrent, or metastatic ‡; **AND**

a. Used as a single agent; **OR**

b. Used in combination with serial embolizationor radiation therapy

E. **Hypercalcemia of malignancy †**

i. Patient is at least 18 years of age; **AND**

ii. Patient must have a diagnosis of cancer (malignancy); **AND**

a. Patient must have a diagnosis of refractory hypercalcemia of malignancy defined as an albumin-corrected calcium of >12.5 mg/dL (3.1 mmol/L) despite treatment with a minimum seven (7) day trial on previous therapy with intravenous (IV) bisphosphonates such as ibandronate or zoledronic acid; **OR**

b. Patient has a documented contraindication or intolerance to intravenous (IV) bisphosphonates such as ibandronate or zoledronic acid

† FDA Approved Indication(s); ‡ Compendia recommended indication(s)

II. RENEWAL CRITERIA

Coverage can be renewed based on the following criteria:

A. Absence of unacceptable toxicity from the drug. Examples of unacceptable toxicity include the following: severe symptomatic hypocalcemia, osteonecrosis of the jaw, atypical femoral fractures, dermatological adverse reactions, severe infection, etc.; **AND**

1. Prolia

Disease response as indicated by one or more of the following:

i. Absence of fractures
ii. Increase in bone mineral density compared to pretreatment baseline; **AND**
iii. Osteoporosis in Men and Women ONLY:
    a. After 5 years of treatment, patient will have a repeat DXA performed; **AND**
        (1) Patients with low-to moderate risk disease will have therapy changed to an oral or IV bisphosphonate unless there is a contraindication or intolerance to both dosage forms

2. Xgeva

Disease response as indicated by the following:

i. Multiple Myeloma OR Bone metastases from solid tumors: absence/delay in skeletal-related events (e.g., pathologic fracture, radiation therapy to bone, surgery to bone, or spinal cord compression)
ii. Giant Cell Tumor of the Bone: tumor response with disease stabilization or decrease in size or spread of tumor
iii. Hypercalcemia of Malignancy: corrected serum calcium ≤ 11.5 mg/dL

Limitations/Exclusions

Prolia and Xgeva are not considered medically necessary for indications other than those listed above due to insufficient evidence of therapeutic value.

Applicable Procedure Codes

Code	Description
J0897	Injection, denosumab, 1 mg; 1 mg = 1 billable unit

Applicable NDCs

Code	Description

55513-0710-XX	Prolia 60 mg/1 mL single-use prefilled syringe
55513-0730-XX	Xgeva 120 mg/1.7 mL single-use vial

ICD-10 Diagnoses

Code	Description
C50.011- C50.929	Malignant neoplasms of breast
C61	Malignant neoplasm of prostate
M80.00XA- M80.08XS	Age-related osteoporosis with current pathological fracture
M80.80XA- M80.88XS	Other osteoporosis with current pathological fracture
M81.0	Age-related osteoporosis without current pathological fracture
M81.6	Localized osteoporosis [Lequesne]
M81.8	Other osteoporosis without current pathological fracture
M85.80	Other specified disorders of bone density and structure, unspecified site
M85.851	Other specified disorders of bone density and structure, right thigh
M85.852	Other specified disorders of bone density and structure, left thigh
M85.859	Other specified disorders of bone density and structure, unspecified thigh
M85.88	Other specified disorders of bone density and structure, other site
M85.89	Other specified disorders of bone density and structure, multiple sites
T38.0X5A	Adverse effect of glucocorticoids and synthetic analogues, initial encounter
T38.0X5S	Adverse effect of glucocorticoids and synthetic analogues, sequela

Dual coding requirement

- Osteoporosis treatment and prevention in breast cancer patients on aromatase inhibitors:
  - One code from the M80.00XA - M80.88XS, M81.X, or M85.X series plus one code from the C50.X
- Treatment of bone loss in men with prostate cancer receiving androgen deprivation therapy:
  - One code from the M80.00XA - M80.88XS, M81.X, or M85.X series plus C61

Xgeva

Code	Description
C00-C14	Malignant neoplasms of lip, oral cavity and pharynx
C15-C26	Malignant neoplasms of digestive organs
C30-C39	Malignant neoplasms of respiratory and intrathoracic organs
C40-C41	Malignant neoplasms of bone and articular cartilage
C43-C44	Melanoma and other malignant neoplasms of skin
C45-C49	Malignant neoplasms of mesothelial and soft tissue
C50.011- C50.929	Malignant neoplasms of breast
C51-C58	Malignant neoplasms of female genital organs
C60-C63	Malignant neoplasms of male genital organs
C64-C68	Malignant neoplasms of urinary tract
C69-C72	Malignant neoplasms of eye, brain and other parts of central nervous system
C73-C75	Malignant neoplasms of thyroid and other endocrine glands
C7A.00- C7A.8	Malignant neuroendocrine tumors
C7B.00- C7B.8	Secondary neuroendocrine tumors
C76-C80	Malignant neoplasms of ill-defined, other secondary and unspecified sites

C81	Hodgkin lymphoma
C82	Follicular lymphoma
C83	Non-follicular lymphoma
C84	Mature T/NK-cell lymphomas
C85	Other specified and unspecified types of non-Hodgkin lymphoma
C86	Other specified types of T/NK-cell lymphoma
C88	Malignant immunoproliferative diseases and certain other B-cell lymphomas
C90.00	Multiple myeloma not having achieved remission
C90.02	Multiple myeloma, in relapse
C90.10	Plasma cell leukemia not having reached remission
C90.11	Plasma cell leukemia in remission
C90.12	Plasma cell leukemia in relapse
C90.20	Extramedullary plasmacytoma not having reached remission
C90.21	Extramedullary plasmacytoma in remission
C90.22	Extramedullary plasmacytoma in relapse
C90.30	Solitary plasmacytoma not having achieved remission
C90.31	Solitary plasmacytoma in remission
C90.32	Solitary plasmacytoma in relapse
C94.30	Mast cell leukemia not having achieved remission
C94.31	Mast cell leukemia, in remission
C94.32	Mast cell leukemia, in relapse
C96	Other and unspecified malignant neoplasms of lymphoid, hematopoietic and related tissue
C96.20	Malignant mast cell neoplasm, unspecified
C96.22	Mast cell sarcoma
C96.29	Other malignant mast cell neoplasm
D00-D09	In situ neoplasms
D10-D36	Benign neoplasms, except benign neuroendocrine tumors
D3A.00- D3A.8	Benign neuroendocrine tumors
D37-D44	Neoplasm of uncertain behavior of oral cavity and digestive organs - Neoplasm of uncertain behavior of endocrine glands
D48	Neoplasm of uncertain behavior of other and unspecified sites
D49.0- D49.9	Neoplasms of unspecified behavior
E83.52	Hypercalcemia
Z85	Personal history of malignant neoplasm
Z85.118	Personal history of other malignant neoplasm of bronchus and lung
Z85.528	Personal history of other malignant neoplasm of kidney

Revision History

Company(ies)	DATE	REVISION
EmblemHealth & ConnectiCare	1/16/2024	Annual Review: Initial Criteria: Xgeva: Added" Patient must not have hypocalcemia; AND" Giant Cell Tumor of the Bone Removed "interferon alpha" from the phrase "Used in combination with interferon alpha, serial embolization or radiation therapy " Renewal Criteria: Prolia: removed: "Documentation of improved or stable T-scores while on Prolia" Added: "Increase in bone mineral density compared to pretreatment baseline; AND Osteoporosis in Men and Women ONLY:

		After 5 years of treatment, patient will have a repeat DXA performed; AND Patients with low-to moderate risk disease will have therapy changed to an oral or IV bisphosphonate unless there is a contraindication or intolerance to both dosage forms
EmblemHealth & ConnectiCare	5/18/2023	Annual Review: Examples of contraindications to oral bisphosphonate therapy: Added: "Surgical anastomoses are present in the GI tract after certain types of bariatric surgery (e.g., Roux-en-Y gastric bypass)" Added "Examples of contraindications to injectable bisphosphonate therapy: -Documented pre-existing hypocalcemia and disturbances of mineral metabolism -Documented pre-existing renal insufficiency defined as creatinine clearance < 35 mL/min" Under Xgeva: Prevention of skeletal related events in patients with multiple myeloma or bone metastases: added "metastatic lung cancer (both SCLC and NSCLC)" Under Xgeva- Giant Cell Tumor of the bone. Decreased age from 13 to 12 years of age.; removed "i. For metastatic disease ‡; AND Used as a single agent; OR For localized disease ‡; AND Used as a single agent; OR In combination with interferon alpha or radiation therapy" added "o Disease is localized, recurrent, or metastatic ‡; AND Used as a single agent; OR Used in combination with interferon alpha, serial embolization, or radiation Therapy" Added codes: C90.11, C90.21, C90.30, C90.31, C90.32, C94.30, C94.31, C94.32, C96.20, C96.22, C96.29, Z85.118, Z85.528
EmblemHealth & ConnectiCare	09/27/2022	Transferred policy to new template
EmblemHealth & ConnectiCare	9/17/2020	Removed the following from renewal criteria: Patient continues to meet the criteria indicated above and Increase in bone mineral density compared to pretreatment baseline Added the following statement to renewal criteria for Prolia: Documentation of improved or stable T-scores while on Prolia

References

1. Prolia [package insert]. Thousand Oaks, CA; Amgen, Inc.; July 2019. Accessed December 2019.
2. Xgeva [package insert]. Thousand Oaks, CA; Amgen, Inc.; May 2019. Accessed December 2019.
3. Referenced with permission from the NCCN Drugs & Biologics Compendium (NCCN Compendium®) for Denosumab. National Comprehensive Cancer Network, 2018. The NCCN Compendium® is a derivative work of the NCCN Guidelines®. NATIONAL COMPREHENSIVE CANCER NETWORK®, NCCN®, and NCCN GUIDELINES® are trademarks owned by the National Comprehensive Cancer Network, Inc." To view the most recent and complete version of the Compendium, go online to NCCN.org. Accessed March 2018.
4. Branstetter DG, Nelson SD, Manivel JC, et al. Denosumab induces tumor reduction and bone formation in patients with giant-cell tumor of bone. Clin Cancer Res. 2012 Aug 15;18(16):4415-24.
5. Thomas D, Henshaw R, Skubitz K, et al. Denosumab in patients with giant-cell tumor of bone: an open-label, phase 2 study. Lancet Oncol. 2010 Mar;11(3):275-80.

6. WHO Scientific Group on the Prevention and Management of Osteoporosis. Prevention and management of osteoporosis: report of a WHO scientific group. (WHO technical report series; 921). Geneva, Switzerland: WHO; 2000.
7. Kanis JA on behalf of the World Health Organization Scientific Group (2007). Assessment of osteoporosis at the primary health care level. Technical Report. World Health Organization Collaborating Center for Metabolic Bone Diseases. University of Sheffield, UK; 2007.
8. National Osteoporosis Foundation. Clinician's Guide to Prevention and Treatment of Osteoporosis. Washington, DC: National Osteoporosis Foundation; 2014.
9. Hu MI, Glezerman IG, Leboulleux S, et al. Denosumab for treatment of hypercalcemia of malignancy. J Clin Endocrinol Metab. 2014 Sep;99(9):3144-52. doi: 10.1210/jc.2014-1001. Epub 2014 Jun 10.
10. 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 - 2016. Endocr Pract. 2016 Sep 2; 22(Suppl 4):1-42.
11. Gnant M, Pfeiler G, Dubsky PC, et al. Adjuvant denosumab in breast cancer (ABCSG-18): a multicentre, randomized, double-blind, placebo-controlled trial. Lancet. 2015 Aug 1;386(9992):433-43.
12. Qaseem A, Forciea MA, McLean RM, Denberg TD; Clinical Guidelines Committee of the American College of Physicians. 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 May 9. doi: 10.7326/M15-1361.
13. Jeremiah MP, Unwin BK, Greenawald MH, et al. Diagnosis and Management of Osteoporosis. Am Fam Physician. 2015 Aug 15;92(4):261-8.
14. Henry DH, Costa L, Goldwasser F, et al. Randomized, Double-Blind Study of Denosumab Versus Zoledronic Acid in the Treatment of Bone Metastases in Patients With Advanced Cancer (Excluding Breast and Prostate Cancer) or Multiple Myeloma. Journal of Clinical Oncology 2011 29:9, 1125-1132.
15. First Coast Service Options, Inc. Local Coverage Determination (LCD): Bisphosphonates (Intravenous [IV]) and Monoclonal Antibodies in the Treatment of Osteoporosis and Their Other Indications (L33270). Centers for Medicare & Medicaid Services, Inc. Updated on 02/02/2018 with effective date 02/08/2018. Accessed March 2018.
16. National Government Services, Inc. Local Coverage Article: Denosumab (Prolia ™, Xgeva ™) - Related to LCD L33394 (A52399). Centers for Medicare & Medicaid Services, Inc. Updated on 01/26/2018 with effective date 01/04/2018. Accessed March 2018.
17. CGS Administrators, LLC. Local Coverage Article: Denosumab (Prolia ™, Xgeva ™) - (A52424). Centers for Medicare & Medicaid Services, Inc. Updated on 03/16/2018 with effective date 02/01/2018. Accessed March 2018.