Prolia®/Xgeva® (denosumab)

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I. Length of Authorization

Coverage will be provided for 12 months and may be renewed.

II. Dosing Limits

A. Quantity Limit (max daily dose) [Pharmacy Benefit]:

- Prolia 60 mg/1 mL single-use prefilled syringe: 1 syringe every 6 months
- Xgeva 120 mg/1.7 mL single-use vial:
  - Load: 4 vials per 28 days x 1 dose
  - Maintenance: 1 vial monthly

B. Max Units (per dose and over time) [Medical Benefit]:

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

III. Initial Approval Criteria

Prolia

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

Coverage is provided in the following conditions:

Osteoporosis in Men and Women †

- Women only: Patient must be post-menopausal; **AND**
- Patient has a documented diagnosis of osteoporosis indicated by one or more of the following:
  - Hip DXA (femoral neck or total hip) or lumbar spine T-score ≤-2.5 and/or forearm DXA 33% (one-third) radius; **OR**
  - T-score ≤-1 or low bone mass and a history of fragility fracture to the hip or spine; **OR**
  - T-score between -1 and -2.5 with a FRAX 10-year probability for major fracture ≥20% or hip fracture ≥3%; **AND**
- 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**
- Patient has a documented contraindication* or intolerance to BOTH oral bisphosphonates AND intravenous (IV) bisphosphonates such as alendronate, risedronate, ibandronate, or zoledronic acid

Glucocorticoid-Induced Osteoporosis †

- 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
  - 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**
  - Patient has a documented contraindication* or intolerance to BOTH oral bisphosphonates AND intravenous (IV) bisphosphonates such as alendronate, risedronate, ibandronate, or zoledronic acid

Osteoporosis treatment and prevention in prostate cancer patients †

- Documented Hip DXA (femoral neck or total hip) or lumbar spine T-score ≤-1 (or patient meets the diagnostic criteria for osteoporosis above); **AND**
- Patient must be receiving androgen deprivation therapy for nonmetastatic prostate cancer

Osteoporosis treatment and prevention in breast cancer patients †

- 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

Xgeva

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

Coverage is provided in the following conditions:

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

- Patient is at least 18 years of age; **AND**
  - Patient must try and have an inadequate response, contraindication, or intolerance to at least a three (3) month trial of Zoledronic Acid; **OR**
  - Patient has metastatic breast cancer or metastatic castration-resistant prostate cancer

Giant Cell Tumor of the Bone †

- Patient must be an adult or at least 13 years of age and skeletally mature; **AND**
  - Disease is unresectable or surgical resection is likely to result in severe morbidity; **OR**
  - 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

Hypercalcemia of malignancy †

- Patient is at least 18 years of age; **AND**
- Patient must have a diagnosis of cancer (malignancy); **AND**
  - 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**
  - 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)

IV. Renewal Criteria

Coverage can be renewed based on the following criteria:

- Patient continues to meet the criteria indicated in section III; **AND**
- 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**

Prolia

- Disease response as indicated by one or more of the following:
  - Absence of fractures
  - Increase in bone mineral density compared to pretreatment baseline

Xgeva

- Disease response as indicated by the following:
  - 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)
  - Giant Cell Tumor of the Bone: tumor response with disease stabilization or decrease in size or spread of tumor
  - Hypercalcemia of Malignancy: corrected serum calcium ≤ 11.5 mg/dL

V. Dosage/Administration

Prolia

Indication	Dose
All indications	60 mg subcutaneously by a health care provider every 6 months

Xgeva

Indication	Dose
Bone metastases from solid tumors and Multiple Myeloma	120 mg subcutaneously by a health care provider every 4 weeks
Giant Cell Tumor of Bone	120 mg subcutaneously by a health care provider every 4 weeks with additional 120 mg doses on Days 8 and 15 of the first month of therapy.
Hypercalcemia of malignancy	120 mg subcutaneously by a health care provider every 4 weeks with additional 120 mg doses on Days 8 and 15 of the first month of therapy.

VI. Billing Code/Availability Information

Jcode:

- J0897 – Injection, denosumab, 1 mg; 1 mg = 1 billable unit

NDC:

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

VII. References

1. Prolia [package insert]. Thousand Oaks, CA; Amgen, Inc.; May 2018. Accessed May 2018.
2. Xgeva [package insert]. Thousand Oaks, CA; Amgen, Inc.; January 2018. Accessed May 2018.
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 tumour 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, randomised, 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.

Appendix 1 – Covered Diagnosis Codes

Prolia

ICD-10	ICD-10 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

ICD-10	ICD-10 Description
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

ICD-10	ICD-10 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
C90.12	Plasma cell leukemia in relapse
C90.20	Extramedullary plasmacytoma not having reached remission

ICD-10	ICD-10 Description
C90.22	Extramedullary plasmacytoma in relapse
C96	Other and unspecified malignant neoplasms of lymphoid, hematopoietic and related tissue
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

Appendix 2 – Centers for Medicare and Medicaid Services (CMS)

Medicare coverage for outpatient (Part B) drugs is outlined in the Medicare Benefit Policy Manual (Pub. 100-2), Chapter 15, §50 Drugs and Biologicals. In addition, National Coverage Determination (NCD) and Local Coverage Determinations (LCDs) may exist and compliance with these policies is required where applicable. They can be found at: http://www.cms.gov/medicare-coverage-database/search/advanced-search.aspx. Additional indications may be covered at the discretion of the health plan.

Medicare Part B Covered Diagnosis Codes (applicable to existing NCD/LCD):

Prolia and Xgeva

Jurisdiction(s): 6, K	**NCD/LCD Document (s):** A52399
https://www.cms.gov/medicare-coverage-database/search/article-date-search.aspx?DocID=A52399&bc=gAAAAAAAAAAAAA==	

Jurisdiction(s): N	**NCD/LCD Document (s):** L33270
https://www.cms.gov/medicare-coverage-database/search/lcd-date-search.aspx?DocID=L33270&bc=gAAAAAAAAAAAAA==	

Jurisdiction(s): 15	**NCD/LCD Document (s):** A52424
https://www.cms.gov/medicare-coverage-database/search/article-date-search.aspx?DocID=A52424&bc=gAAAAAAAAAAAAA==	

Medicare Part B Administrative Contractor (MAC) Jurisdictions		
Jurisdiction	**Applicable State/US Territory**	**Contractor**
E (1)	CA, HI, NV, AS, GU, CNMI	Noridian Healthcare Solutions, LLC

Medicare Part B Administrative Contractor (MAC) Jurisdictions		
Jurisdiction	**Applicable State/US Territory**	**Contractor**
F (2 & 3)	AK, WA, OR, ID, ND, SD, MT, WY, UT, AZ	Noridian Healthcare Solutions, LLC
5	KS, NE, IA, MO	Wisconsin Physicians Service Insurance Corp (WPS)
6	MN, WI, IL	National Government Services, Inc. (NGS)
H (4 & 7)	LA, AR, MS, TX, OK, CO, NM	Novitas Solutions, Inc.
8	MI, IN	Wisconsin Physicians Service Insurance Corp (WPS)
N (9)	FL, PR, VI	First Coast Service Options, Inc.
J (10)	TN, GA, AL	Palmetto GBA, LLC
M (11)	NC, SC, WV, VA (excluding below)	Palmetto GBA, LLC
L (12)	DE, MD, PA, NJ, DC (includes Arlington & Fairfax counties and the city of Alexandria in VA)	Novitas Solutions, Inc.
K (13 & 14)	NY, CT, MA, RI, VT, ME, NH	National Government Services, Inc. (NGS)
15	KY, OH	CGS Administrators, LLC