Denosumab:
Prolia®; Jubbonti®; Xgeva®; Wyost®
(Subcutaneous)

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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) [NDC Unit]:

- Prolia & Jubbonti: 60 mg/1 mL single-dose prefilled syringe: 1 syringe every 6 months
- Xgeva & Wyost: 120 mg/1.7 mL single-dose vial:
  - Load: 4 vials for one 29-day cycle
  - Maintenance: 1 vial monthly

B. Max Units (per dose and over time) [HCPCS Unit]:

Prolia	All indications: • 60 billable units every 6 months
Jubbonti	All indications: • 60 mg 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, & Systemic Mastocytosis:* • 120 billable units every 4 weeks

Wyost	*Giant Cell Tumor of Bone & Hypercalcemia of Malignancy* – Loading Dose: • 120 mg on days 1, 8, 15, and 29 – Maintenance: • 120 mg every 4 weeks *Bone metastases from solid tumors, Multiple Myeloma, & Systemic Mastocytosis:* • 120 mg every 4 weeks

III. Initial Approval Criteria

Prolia & Jubbonti

Coverage is provided in the following conditions:

- Patient is at least 18 years of age; **AND**

Universal Criteria [1,2,31,35]

- Patient must be supplementing with 1,000 mg of calcium and at least 400 IU of vitamin D daily; **AND**
- Patient must not have hypocalcemia; **AND**
- Patients with advanced kidney disease (i.e., eGFR < 30 mL/min/1.73 m^2 and including dialysis-dependent patients) will be monitored for the presence of chronic kidney disease-mineral and bone disorder (CKD-MBD) with intact parathyroid hormone (iPTH), serum calcium, 25(OH) vitamin D, and 1,25 $(OH)_2$ vitamin D prior to decisions regarding denosumab treatment; **AND**
- Pregnancy is ruled out prior to administration in biologic females of child-bearing potential; **AND**
- Will not be used in combination with other denosumab products, bisphosphonates, romosozumab, or parathyroid hormone analogs/related peptides; **AND**

Osteoporosis in Men and Women † [1,2,28,29,31,33,35]

- Biological female patient must be post-menopausal; **AND**
- Patient must be at a high risk for fracture**; **AND**
- Patient has a documented diagnosis of osteoporosis indicated by one or more of the following:
  - T-score by DXA of ≤-2.5 measured at the lumbar spine, femoral neck, total hip, or forearm at the 33% (one-third) radius site; **OR**
  - History of fragility fracture to the hip or spine, regardless of T-score; **OR**
  - T-score by DXA between -1.0 and -2.5 measured at the lumbar spine, femoral neck, total hip, or forearm at the 33% (one-third) radius site; **AND**
    - History of fracture of proximal humerus, pelvis, or distal forearm; **OR**

- FRAX 10-year probability for major fracture ≥ 20% or hip fracture ≥ 3%; **AND**

- Patient has one of the following:
  - 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 † ‡ [1,2,21,37]

- Patient will be initiating or is continuing systemic glucocorticoid therapy at a daily dosage equivalent to ≥ 2.5 mg of prednisone and is expected to remain on glucocorticoid therapy for at least 3 months; **AND**
- Patient must be at an increased risk for fracture **¥**; **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 † ‡ [1,2,5,22,38]

- Patient must be receiving androgen deprivation therapy; **AND**
- Patient must be at a high risk for fracture**

Osteoporosis treatment and prevention in breast cancer patients † ‡ [1,2,5,23,39]

- Patient must be receiving adjuvant aromatase inhibitor therapy for breast cancer

±Ineffective response is defined as one or more of the following: [31,33,35]
– 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:** [31,35]
– 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:** [32]
– Documented inability to sit or stand upright for at least 30 minutes – Documented pre-existing esophageal disorders such as achalasia, esophageal stricture, esophageal varices, or Barrett's esophagus

– Surgical anastomoses are present in the GI tract after certain types of bariatric surgery (e.g., Roux-en-Y gastric bypass) – Documented pre-existing hypocalcemia – Documented pre-existing renal insufficiency defined as creatinine clearance < 30-35 mL/min
***Examples of contraindications to injectable bisphosphonate therapy include the following: [32]**
– Documented pre-existing hypocalcemia – Documented pre-existing renal insufficiency defined as creatinine clearance < 30-35 mL/min
¥ Increased risk for glucocorticoid-induced osteoporosis fracture include, but are not limited to, one or more of the following: [1,2,37]
– Prior osteoporotic fracture – High-dose glucocorticoid use (i.e., prednisone [or equivalent] ≥30 mg/d >30 d or ≥5 g/year) – FRAX glucocorticoid adjusted◊ 10-year risk of major osteoporotic fracture ≥20% or hip >3% – T-score by DXA of ≤-2.5 measured at the lumbar spine, femoral neck, total hip, or forearm at the 33% (one-third) radius site ◊ Note: If glucocorticoid dose is >7.5 mg/day, multiply the FRAX 10-year risk of major osteoporotic fracture by 1.15 and the hip fracture risk by 1.2 (e.g., if hip fracture risk is 2.0% multiply by 1.2 = 2.4% risk)

Xgeva & Wyost

Coverage is provided in the following conditions:

Universal Criteria [3,4,34,35,38,39]

- Patient will receive calcium and vitamin D as necessary to treat or prevent hypocalcemia *(Note: excludes when use is for hypercalcemia of malignancy)*; **AND**
- Patient must not have hypocalcemia; **AND**
- Will not be used in combination with other denosumab products, bisphosphonates, romosozumab, or parathyroid hormone analogs/related peptides; **AND**

Prevention of skeletal-related events in patients with multiple myeloma OR bone metastases from solid tumors † [3-5,16-18,25,27,38,39]

- 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, metastatic castration-resistant prostate cancer, or metastatic lung cancer (both SCLC and NSCLC)

Giant Cell Tumor of the Bone † Φ [3-5,7,25,26]

- Patient must be an adult or at least 12 years of age and skeletally mature; **AND**
  - Disease is unresectable or surgical resection is likely to result in severe morbidity; **OR**
  - Disease is localized, recurrent, or metastatic ‡; **AND**
    - Used as a single agent; **OR**
    - Used in combination with serial embolization and/or radiation therapy

Hypercalcemia of malignancy † Φ [3-5,11]

- 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

Systemic Mastocytosis ‡ [5,30]

- Patient has osteopenia or osteoporosis and coexisting bone pain; **AND**
  - Used as second line therapy if patient is not responding to bisphosphonate therapy; **OR**
  - Patient is not a candidate for bisphosphonate therapy due to renal insufficiency

*Examples of contraindications to injectable bisphosphonate therapy include the following: [32]
– Documented pre-existing hypocalcemia – Documented pre-existing renal insufficiency defined as creatinine clearance < 30-35 mL/min

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

IV. Renewal Criteria [1-4]

Coverage can be renewed based on the following criteria:

- Patient continues to meet universal and other indication-specific relevant criteria such as concomitant therapy requirements (not including prerequisite therapy), performance status, etc. identified in section III; **AND**
- Absence of unacceptable toxicity from the drug. Examples of unacceptable toxicity include: severe symptomatic hypocalcemia, osteonecrosis of the jaw, atypical femoral fractures, dermatological adverse reactions, severe infection, severe hypersensitivity/anaphylaxis, musculoskeletal pain, etc.; **AND**

Prolia & Jubbonti [1,2,5,28,29,33,37-39]

- Beneficial disease response as indicated by one or more of the following:
  - Absence of fractures
  - Increase in bone mineral density compared to pretreatment baseline; **AND**

Osteoporosis in Men and Women:

- 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

Glucocorticoid-Induced Osteoporosis:

- After 2 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

Xgeva & Wyost [3-5,26,38,39]

- Beneficial 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: stabilization of disease or decrease in size of tumor or spread of tumor
  - Hypercalcemia of Malignancy: corrected serum calcium ≤ 11.5 mg/dL (2.9 mmol/L)
  - Systemic Mastocytosis: improvement or resolution of bone pain as compared to pretreatment baseline

V. Dosage/Administration [1-4]

Prolia & Jubbonti

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

Xgeva & Wyost

Indication	Dose
Bone metastases from solid tumors, Multiple Myeloma, & Systemic Mastocytosis	120 mg administered subcutaneously by a health care provider every 4 weeks
Giant Cell Tumor of Bone & Hypercalcemia of Malignancy	120 mg administered 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

HCPCS Code(s):

Prolia & Xgeva

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

Jubbonti & Wyost

- J3590 – Unclassified biologics

NDC(s):

- Prolia 60 mg/1 mL single-dose prefilled syringe: 55513-0710-xx
- Jubbonti 60 mg/1 mL single-dose prefilled syringe: 61314-0240-xx
- Xgeva 120 mg/1.7 mL single-dose vial: 55513-0730-xx
- Wyost 120 mg/1.7 mL single-dose vial: 61314-0228-xx

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Appendix 1 – Covered Diagnosis Codes

Prolia & Jubbonti

ICD-10	ICD-10 Description
C50.011-C50.929	Malignant neoplasms of breast
C61	Malignant neoplasm of prostate
D05.10	Intraductal carcinoma in situ of unspecified breast
D05.11	Intraductal carcinoma in situ of right breast
D05.12	Intraductal carcinoma in situ of left breast

ICD-10	ICD-10 Description
D05.80	Other specified type of carcinoma in situ of unspecified breast
D05.81	Other specified type of carcinoma in situ of right breast
D05.82	Other specified type of carcinoma in situ of left breast
D05.90	Unspecified type of carcinoma in situ of unspecified breast
D05.91	Unspecified type of carcinoma in situ of right breast
D05.92	Unspecified type of carcinoma in situ of left breast
M80.00XA-M80.08XS	Age-related osteoporosis with current pathological fracture
M80.8B2A-M80.8B2S	Osteoporosis with current pathological fracture
M80.8B9A-M80.8B9S	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
Z79.810	Long term (current) use of selective estrogen receptor modulators (SERMs)
Z85.3	Personal history of malignant neoplasm of breast

Xgeva & Wyost

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

ICD-10	ICD-10 Description
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
C90.01	Multiple myeloma in 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
C96.20	Malignant mast cell neoplasm, unspecified

ICD-10	ICD-10 Description
C96.21	Aggressive systemic mastocytosis
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
D47.02	Systemic mastocytosis
D48.0	Neoplasm of uncertain behavior of bone and articular cartilage
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
Z85.3	Personal history of malignant neoplasm of breast
Z85.528	Personal history of other malignant neoplasm of kidney

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

The preceding information is intended for non-Medicare coverage determinations. 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 Determinations (NCDs) and/or Local Coverage Determinations (LCDs) may exist and compliance with these policies is required where applicable. Local Coverage Articles (LCAs) may also exist for claims payment purposes or to clarify benefit eligibility under Part B for drugs which may be self-administered. The following link may be used to search for NCD, LCD, or LCA documents: https://www.cms.gov/medicare-coverage-database/search.aspx. Additional indications, including any preceding information, may be applied at the discretion of the health plan.

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

Prolia and Xgeva

Medicare Part B Covered Diagnosis Codes		
Jurisdiction	**NCD/LCA/LCD Document (s)**	**Contractor**
6, K	A52399	National Government Services, Inc

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
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