CLINICAL GUIDELINES FOR MEDICAL NECESSITY

MEDICAL POLICY

Denosumab (Xgeva®/Prolia®) and Biosimilars: Denosumab-bbdz (Wyost®) Denosumab-bbdz (Jubbonti®) Denosumab-bmwo (Stoboclo®) Denosumab-bmwo (Osenvelt®) Denosumab-bnht (Bomyntra) Denosumab-bnht (Conexxence) Denosumab-dssb (Ospomyv™) Denosumab-dssb (Xbryk™)

Version: 1.0

EFFECTIVE DATE: 7/31/2025

NantHealth® | Eviti®

Please note the following:

For Medicare members/enrollees, to ensure consistency with the Medicare National Coverage Determinations (NCD) and Local Coverage Determinations (LCD), all applicable NCDs, LCDs, and Medicare Coverage Articles should be reviewed prior to applying the criteria set forth in this clinical policy. Please refer to the CMS website at http://www.cms.gov for additional information.

For Medicaid members/enrollees, circumstances when state Medicaid coverage provisions conflict with the coverage provisions within this clinical policy, state Medicaid coverage provisions take precedence. Please refer to the state Medicaid manual for any coverage provisions pertaining to this clinical policy.

Denosumab (Xgeva, Prolia) and Biosimilars (Bomyntra, Conexxence, Jubbonti, Osenvelt, Ospomyv, Stoboclo, Wyost, Xbryk)

Discussion

Denosumab binds to RANKL (Receptor Activator of Nuclear Factor Kappa-B Ligand), a transmembrane or soluble protein essential for osteoclasts' formation, function, and survival, the cells responsible for bone resorption. Denosumab prevents RANKL from activating its receptor, RANK, on the surface of osteoclasts and their precursors. Prevention of the RANKL-RANK interaction inhibits osteoclast formation, function, and survival, thereby decreasing bone resorption and increasing bone mass and strength in both cortical and trabecular bone.[1,2,3]

Densoumab (Xgeva and biosimilars) when used for multiple myeloma and bone metastasis from solid tumors, giant cell tumor of bone or hypercalcemia of malignancy can lead to fatigue/asthenia, hypophosphatemia, nausea, vomiting, constipation, diarrhea, anemia, back pain, thrombocytopenia, peripheral edema, hypocalcemia, upper respiratory tract infection, rash, headache, arthralgia, dyspnea and decreased appetite.[1]

Denosumab (Prolia and biosimilars) when used for bone loss due to hormone ablation for cancer, can lead to several common adverse reactions. The most frequently reported issues, occurring in 10% or more of patients and more often than with placebo, include joint pain (arthralgia) and back pain. Additionally, clinical trials have reported pain in the extremities (arms and legs) and musculoskeletal pain, which affects muscles, ligaments, tendons, and bones. These symptoms highlight the significant impact of hormone ablation therapy on patients' musculoskeletal health.[2]

Denosumab is approved by the Food and Drug Administration (FDA) for prevention of skeletal-related events in patients with multiple myeloma and in patients with bone metastases from solid tumors, giant cell tumor of bone, treatment of hypercalcemia of malignancy, to increase bone mass in men at high risk for fracture receiving androgen deprivation therapy for nonmetastatic prostate cancer, and to increase bone mass in women at high risk for fracture receiving adjuvant aromatase inhibitor therapy for breast cancer.[1,2]

The National Comprehensive Cancer Network (NCCN) endorses Denosumab for the following cancer types: bone cancer - giant cell tumor of bone, breast cancer, kidney, multiple myeloma, non-small cell lung cancer, prostate cancer, systemic mastocytosis, and thyroid cancer.[4,7,8,9,10,11,12,13]

Definitions

- **Food and Drug Administration (FDA)** - The FDA is responsible for protecting the public health by assuring the safety, efficacy, and security of human and veterinary drugs, biological products, medical devices, our nation's food supply, cosmetics, and products that emit radiation.[5]
- **National Comprehensive Cancer Network (NCCN)** - An alliance of more than 30 leading cancer centers devoted to patient care, research, and education. The NCCN guidelines are utilized for Radiation Therapy and Medical Oncology standards. NCCN

consensus clinical standards are periodically updated, and NantHealth, Inc. reviews these and updates its policies within a timely manner.[6]

- **Receptor Activator of Nuclear Factor Kappa-B Ligand (RANKL)** - An essential mediator of osteoclast formation, function, and survival, and plays a central role in cancer-induced bone destruction.[3]

Policy

Denosumab (Xgeva) and Biosimilars

Coverage will be considered for FDA approved indications and for NCCN category 1, 2A, or 2B recommendations when the following criteria are met:

Bone Cancer - Giant Cell Tumor of Bone

1. Prescribed by or in consultation with an oncologist; AND

For **FDA** required criteria coverage:

2. 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;[1] OR

For **NCCN** required criteria coverage:

3. At least 18 years of age; AND
4. Single agent or combined with serial embolization, and/or radiation therapy for resectable disease with unacceptable morbidity and/or unresectable axial lesions for one of the following:
   a) Localized disease
   b) Metastases at presentation
   c) Disease recurrence; OR
5. Single agent for one of the following:
   a) Unresectable metastatic disease at presentation
   b) Unresectable metastatic recurrence
   c) Considered prior to surgery for resectable local recurrence.[4]

Bone Metastases

1. At least 18 years of age; AND
2. Prescribed by or in consultation with an oncologist; AND

For **FDA** required criteria coverage:

3. Prevention of skeletal-related events in patients with bone metastases from solid tumors;[1] OR

For NCCN required criteria coverage:

4. For bone metastases; each NCCN indication is noted under the appropriate disease.

Breast Cancer

1. At least 18 years of age; AND
2. Prescribed by or in consultation with an oncologist; AND

For **NCCN** required criteria coverage:

Invasive and Inflammatory Breast Cancer

3. Given with calcium and vitamin D supplementation in addition to systemic therapy or endocrine therapy for bone metastasis in patients with expected survival of ≥3 months and adequate renal function.[7]

Hypercalcemia of Malignancy

1. At least 18 years of age; AND
2. Prescribed by or in consultation with an oncologist; AND

For **FDA** required criteria coverage:

3. Treatment for hypercalcemia of malignancy refractory to bisphosphonate therapy.[1]

Kidney Cancer

1. At least 18 years of age; AND
2. Prescribed by or in consultation with an oncologist; AND

For **NCCN** required criteria coverage:

3. Component of best supportive care for bony metastases.[8]

Multiple Myeloma

1. At least 18 years of age; AND
2. Prescribed by or in consultation with an oncologist; AND

For **FDA** required criteria coverage:

3. For prevention of skeletal related events;[1] OR

For **NCCN** required criteria coverage:

4. In combination with primary myeloma therapy.[9]

Non-Small Cell Lung Cancer

1. At least 18 years of age; AND
2. Prescribed by or in consultation with an oncologist; AND

For **NCCN** required criteria coverage:

3. In those with bone metastases.[10]

Prostate Cancer

1. At least 18 years of age; AND
2. Prescribed by or in consultation with an oncologist; AND

For **NCCN** required criteria coverage:

3. For prevention of symptomatic skeletal-related events (SREs) in M1 castration-resistant prostate cancer (CRPC) if bone metastases are present.[11]

Systemic Mastocytosis

1. At least 18 years of age; AND
2. Prescribed by or in consultation with an oncologist; AND

For **NCCN** required criteria coverage:

3. Second-line therapy for osteopenia/osteoporosis in patients with bone pain not responding to bisphosphonates or for patients who are not candidates for bisphosphonates because of renal insufficiency.[12]

Thyroid Carcinoma

1. At least 18 years of age; AND
2. Prescribed by or in consultation with an oncologist; AND

For **NCCN** required criteria coverage:

Papillary/Follicular/Oncocytic/Medullary Carcinoma

For **NCCN** required criteria coverage:

3. For bone metastases; OR

Anaplastic Carcinoma

5. Palliative care for bone metastases.[13]

Denosumab (Prolia) and Biosimilars

Coverage will be considered for FDA approved indications and for NCCN category 1, 2A, or 2B recommendations when the following criteria are met:

Breast Cancer

1. At least 18 years of age; AND
2. Prescribed by or in consultation with an oncologist; AND

For **FDA** required criteria coverage:

3. To increase bone mass in women at high risk for fracture receiving adjuvant aromatase inhibitor therapy for breast cancer;[2] OR

For **NCCN** required criteria coverage:

Ductal Carcinoma in Situ (DCIS)/Inflammatory/Invasive

4. Postmenopausal (natural or induced) patients receiving adjuvant aromatase inhibition therapy along with calcium and vitamin D supplementation to maintain or improve bone mineral density and reduce the risk of fractures.[7]

Prostate Cancer

1. At least 18 years of age; AND
2. Prescribed by or in consultation with an oncologist; AND

For **FDA** required criteria coverage:

3. Increase bone mass in men at high risk for fracture receiving androgen deprivation therapy for nonmetastatic prostate cancer;[2] OR

For **NCCN** required criteria coverage:

4. Treatment related bone loss in those receiving androgen deprivation therapy (ADT) when the absolute fracture risk warrants drug therapy.[11]

Authorization Period and Renewal Criteria

1. Initial Authorization Period: 12 months
2. Renewal Criteria: No evidence of disease progression or unacceptable toxicity
3. Renewal Authorization Period: 12 months

Coding (CPT®, ICD-10, and HCPCS)

Procedure codes appearing in medical policy documents are only included as a general reference. This list may not be all-inclusive and is subject to updates. In addition, the codes listed are not a guarantee of payment. CPT codes are available through the AMA.

Code	Description
C34	Malignant neoplasm of bronchus and lung

C50	Malignant neoplasm of breast
C61	Malignant neoplasm of prostate
C64	Malignant neoplasm of kidney, except renal pelvis
C73	Malignant neoplasm of thyroid gland
C79.51	Secondary malignant neoplasm of bone
C90.0	Multiple myeloma
D05.1	Intraductal carcinoma in situ of unspecified breast
D48.0	Neoplasm of uncertain behavior of bone and articular cartilage
J0897	Injection, denosumab
J3590	Injection, denosumab-bmwo
J3590	Injection, denosumab-bnht
J3590	Injection, denosumab-dssb
Q5136	Injection, denosumab-bbdz

Revision and Review History

No.	Description	Date(s)
1	Original Effective Date:	7/31/2025
2	Policy Annual Review Dates:	
3	Department Owner:	Medical Affairs
4	NH Advisory Committee Approval Dates:	7/31/2025
5	Revision Changes:	

References

[1] Xgeva (Denosumab) [package insert]. https://www.accessdata.fda.gov/drugsatfda_docs/label/2025/125320s222lbl.pdf. Accessed May 28, 2025.

[2] Prolia (Denosumab) [package insert]. https://www.accessdata.fda.gov/drugsatfda_docs/label/2025/125320Orig1s221lbl.pdf. Accessed May 28, 2025.

[3] Narayanan P. Denosumab: A Comprehensive Review. *South Asian J Cancer.* 2013;2(4):272-277. https://pmc.ncbi.nlm.nih.gov/articles/PMC3889059/. Accessed May 09, 2025.

[4] National Comprehensive Cancer Network. NCCN Guidelines: Bone Cancer. https://www.nccn.org/professionals/physician_gls/pdf/bone.pdf. Accessed June 13, 2025.

[5] U.S. Food & Drug Administration. https://www.fda.gov/about-fda/what-we-do. Accessed April 23, 2025.

[6] National Comprehensive Cancer Network. https://www.nccn.org/home. Accessed April 23, 2025.

[7] National Comprehensive Cancer Network. NCCN Guidelines: Breast Cancer. https://www.nccn.org/professionals/physician_gls/pdf/breast.pdf. Accessed June 13, 2025.

[8] National Comprehensive Cancer Network. NCCN Guidelines: Kidney Cancer. https://www.nccn.org/professionals/physician_gls/pdf/kidney.pdf. Accessed June 13, 2025.

[9] National Comprehensive Cancer Network. NCCN Guidelines: Multiple Myeloma. https://www.nccn.org/professionals/physician_gls/pdf/myeloma.pdf. Accessed June 13, 2025.

[10] National Comprehensive Cancer Network. NCCN Guidelines: Non-Small Cell Lung Cancer. https://www.nccn.org/professionals/physician_gls/pdf/nscl.pdf. Accessed June 13, 2025.

[11] National Comprehensive Cancer Network. NCCN Guidelines: Prostate Cancer. https://www.nccn.org/professionals/physician_gls/pdf/prostate.pdf. Accessed June 13, 2025.

[12] National Comprehensive Cancer Network. NCCN Guidelines: Systemic Mastocytosis. https://www.nccn.org/professionals/physician_gls/pdf/mastocytosis.pdf. Accessed June 13, 2025.

[13] National Comprehensive Cancer Network. NCCN Guidelines: Thyroid Carcinoma. https://www.nccn.org/professionals/physician_gls/pdf/thyroid.pdf. Accessed June 13, 2025.