Medical Drug Clinical Criteria

Subject:	Denosumab Agents		
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Overview

This document addresses the use of denosumab which are a subcutaneous, fully human monoclonal antibody that is specifically designed to target the human receptor activator of nuclear factor kappa-B ligand (RANKL). Denosumab is FDA approved for the treatment of individuals with osteoporosis, glucocorticoid-induced osteoporosis, treatment induced bone loss, bone metastases, multiple myeloma, giant cell tumor of the bone, hypercalcemia of malignancy and for all other indications as applicable. Agents addressed in this document include:

- Prolia, Jubbonti, Ospomyv, Stoboclo
- Xgeva, Wyost, Osenvelt, Xbryk

The American College of Endocrinology (AACE/ACE) (2020) osteoporosis treatment guidelines stratify initial treatment based on risk status. For those at high risk/no prior fractures, initial therapy options include bisphosphonates (alendronate, risedronate, or zoledronic acid) or denosumab. For those at very high risk/prior fractures, initial therapy options are denosumab, abaloparatide, teriparatide, romosozumab, or zoledronic acid. The Endocrine Society osteoporosis guideline update (2020) recommends initial therapy with bisphosphonates (alendronate, risedronate, zoledronic acid, or ibandronate) or alternatively denosumab for those at high risk.

Osteoporosis may be diagnosed by bone mineral density (BMD) testing indicating a T-score in the spine, femoral neck, total hip or distal 1/3 of the radius of less than or equal to -2.5 as compared to a young-adult reference population. It also may be clinically diagnosed based on a history of a fragility fracture (low trauma fracture).

Higher risk for fracture may be defined as:

1. History of osteoporotic fracture; or
2. Multiple risk factors for fractures, including but not limited to: Prior low-trauma fracture as an adult, advanced age, gender, ethnicity, low bone mineral density (T-score -1.0 to-2.5), low body weight (<57.6kg), family history of osteoporosis, use of glucocorticoids (daily dosage equivalent to 5 mg or greater prednisone for at least 3 months), current cigarette smoking, excessive alcohol consumption (3 or more drinks per day), secondary osteoporosis (such as rheumatoid arthritis), early menopause, height loss of kyphosis, fall risk and low calcium intake; or
3. Failure or intolerance to other osteoporosis therapies.

A failure of other osteoporosis therapies, otherwise known as refractory disease, may be defined as a decline in BMD while on therapy (≥5%) or a fragility fracture while on therapy.

AACE/ACE (2020) recommends obtaining a baseline axial (lumber spine and hip; 1/3 radius if indicated) dual-energy X-ray absorptiometry (DXA) and after treatment initiation, repeat DXA every 1 to 2 years until findings are stable. Depending on clinical circumstances, follow-up DXA every 1 to 2 years or less frequently can be continued thereafter. Successful response to osteoporosis therapy is considered when BMD is stable or increasing with no evidence of new fractures or vertebral fracture progression.

Biosimilar products: Biosimilar products must be highly similar to the reference product and there must be no clinically meaningful differences between the biological product and the reference product in terms of the safety, purity, and potency of the product. Biosimilars must utilize the same mechanism of action (MOA), route of administration, dosage form and strength as the reference product; and the indications proposed must have been previously approved for the reference product. The potential exists for a biosimilar product to be approved for one or more indications for which the reference product is licensed based on extrapolation of data intended to demonstrate biosimilarity in one indication. Sufficient scientific justification for extrapolating data is necessary for FDA approval. Factors and issues that should be considered for extrapolation include the MOA for each indication, the pharmacokinetics, bio-distribution, and immunogenicity of the product in different patient populations, and differences in expected toxicities in each indication and patient population.

Black box warnings on Prolia and its biosimilars address severe hypocalcemia in patients with advanced kidney disease. It is recommended that prior to treatment, these patients should be supervised by a healthcare provider with expertise in the diagnosis and management of chronic kidney disease with mineral bone disorder.

Clinical Criteria

When a drug is being reviewed for coverage under a member's medical benefit plan or is otherwise subject to clinical review (including prior authorization), the following criteria will be used to determine whether the drug meets any applicable medical necessity requirements for the intended/prescribed purpose.

Prolia (denosumab); Jubbonti (denosumab-bbdz); Ospomyv (denosumab-dssb); Stoboclo (denosumab-bmwo)

Initial requests for Prolia (denosumab), Jubbonti (denosumab-bbdz), Ospomyv (denosumab-dssb), or Stoboclo (denosumab-bmwo) may be approved when the following criteria are met:

I. Individual is a male or postmenopausal female with a diagnosis of osteoporosis (defined as a bone mineral density (BMD) T-score in the spine, femoral neck, total hip or distal 1/3 of the radius of less than or equal to -2.5 as compared to a young-adult reference population); **AND**
II. Individual has had at least one osteoporotic (minimal trauma) fracture; **OR**
III. Individual has two or more risk factors for osteoporotic fracture; **OR**
IV. Individual has failed, is intolerant to or has a medical contraindication to other available osteoporosis therapies (for example, bisphosphonates);

OR

V. Individual is a male or postmenopausal female with a diagnosis of osteoporosis based on history of at least one low trauma fracture (fragility fracture);

OR

VI. Individual has glucocorticoid-induced osteoporosis (defined as a bone mineral density (BMD) T-score in the spine, femoral neck, total hip or distal 1/3 of the radius of less than or equal to -2.5 as compared to a young-adult reference population OR a clinical diagnosis based on history of a low trauma fracture (fragility fracture)) and is initiating or continuing systemic glucocorticoids in a daily dosage equivalent to 7.5mg or greater of prednisone and expected to remain on glucocorticoids for a least 6 months;
AND
VII. Individual has had at least one osteoporotic (minimal trauma) fracture; **OR**
VIII. Individual has two or more risk factors for osteoporotic fracture; **OR**
IX. Individual has failed, is intolerant to or has a medical contraindication to other available osteoporosis therapies (for example, bisphosphonates);

OR

X. Individual is a postmenopausal (natural or induced) female receiving adjuvant aromatase inhibitor therapy for treatment of breast cancer;

OR

XI. Individual is a male receiving androgen deprivation therapy for non-metastatic prostate cancer; **AND**
XII. Individual has had at least one osteoporotic (minimal trauma) fracture; **OR**
XIII. Individual has one or more additional risk factors for osteoporotic fracture.

Continuation request for Prolia (denosumab), Jubbonti (denosumab-bbdz), Ospomyv (denosumab-dssb), or Stoboclo (denosumab-bmwo) may be approved if the following criterion is met:

I. There is clinically significant response to therapy (including but not limited to confirmation of no new fractures or reduction of fractures, or no worsening vertebral fractures, or no clinically significant adverse reaction); **AND**
II. If individual has been on therapy ≥ 24 months of treatment, a repeat BMD demonstrates a stable or increase in BMD.

Xgeva (denosumab); ; Osenvelt (denosumab-bmwo); Wyost (denosumab-bbdz); Xbryk (denosumab-dssb)

Requests for Xgeva (denosumab), , Osenvelt (denosumab-bmwo), Wyost (denosumab-bbdz), Xbryk (denosumab-dssb) may be approved when the following criteria are met:

I. Individual is 18 years of age or older; **AND**
II. Individual is using for the prevention of skeletal-related events with one of the following conditions:
A. Multiple myeloma; **OR**

B. Bone metastases from solid tumor other than prostate cancer; **OR**
C. Bone metastases from castration resistant/recurrent prostate cancer;

OR

III. Individual is 18 years of age or older; **AND**
IV. Individual is using for the treatment of hypercalcemia of malignancy (defined as an albumin-corrected serum calcium level greater than 12.5 mg/dL (3.1 mmol/L)) and is refractory to recent (within last 30 days) treatment with intravenous bisphosphonate therapy (such as pamidronate or zoledronic acid);

OR

V. Individual is using for the treatment of localized or metastatic giant cell tumor of the bone (GCTB) that is unresectable or where surgical resection is likely to result in severe morbidity; **AND**
   A. Individual is 18 years of age or older; **OR**
   B. Individual is a skeletally mature adolescent (defined by at least one mature long bone [for example; closed epiphyseal growth plate of the humerus]).

Request for denosumab agents (Prolia, Jubbonti, Osenvelt, Ospomyv, Stoboclo, Xgeva, Xbryk, Wyost) may not be approved when the above criteria are not met and for all other indications.

Quantity Limits

Denosumab Agents Quantity Limit

Drug	Limit
Prolia (denosumab) 60 mg/1 mL prefilled syringe	60 mg (1 prefilled syringe) every 6 months
Jubbonti (denosumab-bbdz) 60 mg/1 mL prefilled syringe	60 mg (1 prefilled syringe) every 6 months
Ospomyv (denosumab-dssb) 60 mg/1 mL prefilled syringe	60 mg (1 prefilled syringe) every 6 months
Stoboclo (denosumab-bmwo) 60 mg/mL prefilled syringe	60 mg (1 prefilled syringe) every 6 months
Xgeva (denosumab) 120 mg/1.7 mL vial*	1 vial per 28 days
Osenvelt (denosumab-bmwo) 120 mg/1.7 mL vial*	1 vial per 28 days
Xbryk (denosumab-dssb) 120 mg/1.7 mL vial*	1 vial per 28 days
Wyost (denosumab-bbdz) 120 mg/1.7 mL vial*	1 vial per 28 days
Override Criteria	
*Xgeva (denosumab), Osenvelt (denosumab-bmwo), Wyost (denosumab-bbdz), Xbryk (denosumab-dssb): Requests for increased quantities may be approved for one (1) month, only during the first month of therapy for two (2) additional 120 mg doses for the diagnosis of Giant Cell Tumor of Bone or Hypercalcemia of Malignancy	

Coding

The following codes for treatments and procedures applicable to this document are included below for informational purposes. Inclusion or exclusion of a procedure, diagnosis or device code(s) does not constitute or imply member coverage or provider reimbursement policy. Please refer to the member's contract benefits in effect at the time of service to determine coverage or non-coverage of these services as it applies to an individual member.

Prolia (denosumab), Jubbonti (denosumab-bbdz), Ospomyv (denosumab-dssb), Stoboclo (denosumab-bmwo)

HCPCS

J0897	Injection, denosumab, 1 mg [Prolia, Xgeva]
J3590	Unclassified biologics [when specified as Ospomyv (denosumab-dssb) or Stoboclo (denosumab-bmwo)]
Q5136	Injection, denosumab-bbdz (Jubbonti/Wyost), biosimilar, 1 mg

ICD-10 Diagnosis

C50.011-C50.929	Malignant neoplasm of breast
C61	Malignant neoplasm of prostate
M80.00XA- M80.88XS	Osteoporosis with current pathological fracture
M81.0-M81.8	Osteoporosis without current pathological fracture
M85.80-M85.9	Other specified disorders of bone density and structure [osteopenia]
N95.1	Menopausal and female climacteric states

Z08	Encounter for follow-up examination after completed treatment for malignant neoplasm
Z51.11-Z51.12	Encounter for antineoplastic chemotherapy and immunotherapy
Z78.0	Postmenopausal status NOS
Z79.51-Z79.52	Long term (current) use of steroids
Z79.811	Long term (current) use of aromatase inhibitors
Z79.899	Other long term (current) drug therapy [prophylactic drug therapy]
Z85.46	Personal history of malignant neoplasm of prostate
Z87.310	Personal history of (healed) osteoporosis fracture

Xgeva (denosumab), Wyost (denosumab-bbdz), Osenvelt (denosumab-bmwo), Xbryk (denosumab-dssb)

HCPCS

J0897	Injection, denosumab, 1 mg [Prolia, Xgeva]
J3590	Unclassified biologics [when specified as Osenvelt (denosumab-bmwo) or Xbryk (denosumab-dssb)]
Q5136	Injection, denosumab-bbdz (Jubbonti/Wyost), biosimilar, 1 mg

ICD-10 Diagnosis

C00.0-C76.8	Malignant neoplasms
C79.51	Secondary malignant neoplasm of bone
C90.00-C90.32	Multiple myeloma and malignant plasma cell neoplasms
D48.0	Neoplasm of uncertain behavior of bone and articular cartilage [specified as GCTB]
E83.52	Hypercalcemia
Z08	Encounter for follow-up examination after completed treatment for malignant neoplasm
Z51.11-Z51.12	Encounter for antineoplastic chemotherapy and immunotherapy
Z79.899	Other long term (current) drug therapy [prophylactic drug therapy]
Z85.00-Z85.59	Personal history of malignant neoplasms
Z85.810-Z85.9	Personal history of malignant neoplasms

Document History

Revised: 03/10/2025
Document History:

- 03/10/2025 – Select Review: Add Ospomyv, Stoboclo, Osenvelt, and Xbryk clinical criteria and quantity limits, update step therapies. Coding Reviewed: Separated coding of Prolia and biosimilars (Jubbonti, Ospomyv, Stoboclo) from Xgeva and its biosimilars (Wyost, Osenvelt, Xbryk). Removed Jobbonti and Wyost from HCPCS NOC J3590 and removed effective date from Q5136. Prolia section: Added Ospomyv and Stoboclo to J3590. Removed ICD-10-CM C00.0-C60.9, C62.00-C76.8, C79.51, C90.00-C90.32, D48.0, E83.52, Z85.00-Z85.45, Z85.47-Z85.59, Z85.810-Z85.9. Added ICD-10-CM C50.011-C50.929. Xgeva section: Added Osenvelt and Xbryk to J3590. Removed ICD-10-CM M80.00XA-M80.88XS, M81.0-M81.8, M85.80-M85.9, N95.1, Z78.0, Z79.51-Z79.52, Z79.811, Z87.310. Consolidated malignant neoplasms into one code range of C00.0-C76.8. Consolidated Z85.00-Z85.45, Z85.46, Z85.47-Z85.59 into one code range of Z85.00-Z85.59.
- 08/16/2024 – Annual Review: Wording update, add Jubbonti and Wyost criteria and quantity limit. Coding Reviewed: Added HCPCS J3590 Unclassified biologics when specified as Jubbonti or Wyost. Effective 10/1/24 added HCPCS Q5136 [Jubbonti/Wyost].
- 08/18/2023 – Annual Review: Change document name, Wording changes. Coding Reviewed: No changes.
- 08/19/2022- Annual Review: No changes. Coding Reviewed: Added ICD-10-CM Z78.0.
- 09/13/2021- Annual Review: Reformat Prolia Quantity Limit. Coding reviewed: No changes.
- 08/20/2021- Annual Review: Add continuation Criteria, formatting changes. Coding reviewed: No changes.
- 02/21/2021 – Select Review: Wording and formatting updates. Coding Reviewed: No changes.
- 12/21/2020 – Add quantity limits for Prolia and Xgeva.
- 08/21/2020 – Annual Review: No Changes. Coding Reviewed: No changes.
- 12/09/2019 – Select Review: Clarify Xgeva use in prostate cancer; formatting changes for clarity. Coding reviewed: No changes.

- 08/16/2019 – Annual Review: Clarify Prolia PA definition of osteoporosis for consistency with other agents in the class. Wording and formatting changes for clarity.
- 11/08/2018 – Code review: no changes. Added X80.00XA-M80.88XS.
- 08/17/2018 – Annual Review: Initial review of CG-DRUG-73. Update Prolia PA to delete specific examples of fracture risk factors for consistency with other agents in the class review and as they are available in the overview section. Wording and formatting changes for clarity.

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    b. Breast Cancer. V4.2024. Revised March 11, 2024.
    c. Kidney Cancer. V4.2024. Revised May 30, 2024.
    d. Multiple Myeloma. V4.2024. Revised April 26, 2024.
    e. Non-Small Cell Lung Cancer. V5.2024. Revised April 23, 2024.
    f. Prostate Cancer. V4.2024. Revised May 17, 2024.
    g. Systemic Mastocytosis. V3.2024. Revised April 24, 2024.
    h. Thyroid Cancer. V2.2024. Revised March 12, 2024.

Federal and state laws or requirements, contract language, and Plan utilization management programs or polices may take precedence over the application of this clinical criteria.