Medical Drug Clinical Criteria

Subject:	Denosumab for Osteoporosis		
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Overview

This document addresses the use of Prolia, which is a subcutaneous, fully human monoclonal antibody that is specifically designed to target the human receptor activator of nuclear factor kappa-B ligand (RANKL). Prolia is FDA approved for the treatment of individuals with osteoporosis, glucocorticoid-induced osteoporosis, and treatment induced bone loss. Agents addressed in this document include the reference product Prolia and associated biosimilar agents as noted below:

Prolia (denosumab)
Bildyos – denosumab-nxxp
Boncresa- denosumab-mobz
Bosaya – denosumab-kyqq
Conexxence – denosumab-bnht
Enoby – denosumab-qbde
Jubbonti – denosumab-bbdz
Ospomyv – denosumab-dssb
Osvyrti – denosumab-desu
Ponlimsi - denosumab-adet
Stoboclo – denosumab-bmwo

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.

Prolia and its biosimilars have a black box warning for severe hypocalcemia in individuals with advanced kidney disease. Severe hypocalcemia resulting in hospitalization, life-threatening events and fatal cases have been reported. Prior to starting Prolia therapy, evaluate for the presence of chronic kidney disease-mineral bone disorder (CKD-MBD). Treatment with Prolia in these patients should be supervised by a healthcare provider with expertise in the diagnosis and management of CKD-MBD.

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.

Denosumab Agents for Osteoporosis (Prolia, Bildyos, Boncresa, Bosaya, Conexxence, Enoby, Jubbonti, Ospomyv, Osvyrti, Ponlimsi, Stoboclo)

Initial requests for Prolia (denosumab), Bildyos (denosumab-nxxp), Boncresa (denosumab-mobz), Bosaya (denosumab-kyqq), Conexxence (denosumab-bnht), Enoby (denosumab-qbde), Jubbonti (denosumab-bbdz), Ospomyv (denosumab-dssb), Osvyrti (denosumab-desu), Ponlimsi (denosumab-adet), 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;

OR

XIV. Individual has a diagnosis of rheumatoid arthritis (DrugDex A, IIa); **AND**
XV. Individual is using to inhibit progression of bone erosion;

OR

XVI. Individual has systemic mastocytosis (NCCN 2A); **AND**
XVII. Individual is using for osteopenia/osteoporosis for bone pain not responding to bisphosphonates or who are not candidates for bisphosphonates.

Continuation request for Prolia (denosumab), Bildyos (denosumab-nxxp), Boncresa (denosumab-mobz), Bosaya (denosumab-kyqq), Conexxence (denosumab-bnht), Enoby (denosumab-qbde), Jubbonti (denosumab-bbdz), Ospomyv (denosumab-dssb), Osvyrti (denosumab-desu), Ponlimsi (denosumab-adet), 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.

Prolia (denosumab), Bildyos (denosumab-nxxp), Boncresa (denosumab-mobz), Bosaya (denosumab-kyqq), Conexxence (denosumab-bnht), Enoby (denosumab-qbde), Jubbonti (denosumab-bbdz), Ospomyv (denosumab-dssb), Ponlimsi (denosumab-adet), Osvyrti (denosumab-desu), and Stoboclo (denosumab-bmwo) may not be approved for the following:

I. In combination with another reference or biosimilar denosumab agent; **OR**
II. When the above criteria are not met and for all other indications.

Step Therapy

Note: When a denosumab is deemed approvable based on the clinical criteria above, the benefit plan may have additional criteria requiring the use of a preferred[1] agent or agents.

Denosumab Agents for Osteoporosis Step Therapy

A list of the preferred denosumab agents is available here.

Requests for a non-preferred denosumab agent for osteoporosis may be approved when the following criterion is met:

I. The individual has had a trial of one preferred agent and has an allergy or severe intolerance to an inactive ingredient in the preferred agent which interferes with the individual's ability to use the product; and the same allergy/severe intolerance is not expected with the non-preferred agent (NOTE: A non-preferred agent may not be approved based on convenience factors [such as the convenience of a certain dosage form or device, dosage concentration or regimen]).

[1]Preferred, as used herein, refers to agents that were deemed to be clinically comparable to other agents in the same class or disease category but are preferred based upon clinical evidence and cost effectiveness.

Quantity Limits

Denosumab Agents for Osteoporosis Quantity Limit

Drug	Limit
Prolia (denosumab) 60 mg/1 mL prefilled syringe	60 mg (1 prefilled syringe) every 6 months
Bildyos (denosumab-nxxp) 60 mg/mL prefilled syringe or vial	60 mg (1 prefilled syringe or 1 vial) every 6 months
Boncresa (denosumab-mobz) 60 mg/mL prefilled syringe	60 mg (1 prefilled syringe) every 6 months
Bosaya (denosumab-kyqq) 60 mg/mL prefilled syringe	60 mg (1 prefilled syringe) every 6 months
Conexxence (denosumab-bnht) 60 mg/mL prefilled syringe	60 mg (1 prefilled syringe) every 6 months
Enoby (denosumab-qbde) 60 mg/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
Osvyrti (denosumab-desu) 60 mg/1 mL prefilled syringe	60 mg (1 prefilled syringe) every 6 months
Ponlimsi (denosumab-adet) 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

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.

HCPCS

J0897	Injection, denosumab, 1 mg [Prolia]
Q5136	Injection, denosumab-bbdz (Jubbonti), biosimilar, 1 mg
Q5157	Injection, denosumab-bmwo (Stoboclo), biosimilar, 1 mg
Q5158	Injection, denosumab-bnht (Conexxence), biosimilar, 1 mg
Q5159	Injection, denosumab-dssb (Ospomyv), biosimilar, 1 mg
Q5161	Injection, denosumab-kyqq (Bosaya), biosimilar, 1 mg
Q5162	Injection, denosumab-nxxp (Bildyos), biosimilar, 1 mg
Q5166	Injection, denosumab-desu (Osvyrti), biosimilar, 1 mg
Q5167	Injection, denosumab-qbde (Enoby), biosimilar, 1 mg
Q5171	Injection, denosumab-mobz (Boncresa), biosimilar, 1 mg
Q5173	Injection, denosumab-adet (Ponlimsi), biosimilar, 1 mg

ICD-10 Diagnosis

C50.011-C50.929	Malignant neoplasm of breast
C61	Malignant neoplasm of prostate

C94.30-C94.32	Mast cell leukemia
C96.20-C96.29	Malignant mast cell neoplasm
D47.02	Systemic mastocytosis
M05.00-M05.A	Rheumatoid arthritis with rheumatoid factor
M06.00-M06.9	Other rheumatoid arthritis
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

Document History

Revised: 08/14/2026
Document History:

- 10/27/2026 – Step therapy table updates.
- 08/14/2026 – Annual Review: Moved Xgeva and biosimilars clinical criteria, step therapy, quantity limits and coding into a separate document; Added new off-label DrugDex A, IIa indication for the inhibition of bone erosion in rheumatoid arthritis; added NCCN 2A indication for systemic mastocytosis related osteopenia/osteoporosis with bone pain; updated limitation of combination therapy to simplify denosumab agent listing. Coding Reviewed: Removed HCPCS NOC C9399 and J3590 for Ponlimsi effective 9/30/26 and added Q5173 effective 10/1/26. Added ICD-10-CM C94.30-C94.32, C96.20-C96.29, D47.02, M05.00-M05.A, M06.00-M06.9.
- 09/01/2026 – Step therapy table updates.
- 05/15/2026 – Select Review: Add Ponlimsi (Prolia biosimilar) to respective clinical criteria, step therapy, and quantity limits. Step therapy table updates. Coding Reviewed: Added Ponlimsi to HCPCS NOC C9399 and J3590 under Prolia and biosimilars. Removed Oziltus, Xtrenbo, and Jubereq from HCPCS NOC C9399, J3590 under Xgeva and biosimilars effective 6/30/26 and added Q5165, Q5166, Q5167 under Xgeva and biosimilars effective 7/1/26. Removed Osvyrti, Enoby, and Boncresa from HCPCS NOC C9399, J3590 under Prolia and biosimilars effective 6/30/26 and added Q5166, Q5167, and Q5171 under Prolia and biosimilars effective 7/1/26.
- 05/01/2026 – Step therapy table updates.
- 02/20/2026 – Select Review: Add Boncresa (Prolia biosimilar) and Oziltus (Xgeva biosimilar) to respective clinical criteria; Add Boncresa and Oziltus quantity limits. Step therapy table updates. Coding Reviewed: Removed Bildyos, Bilprevda, Aukelso and Bosaya from HCPCS NOC C9399 and J3590 effective 3/31/26. Added HCPCS Q5161 and Q5162 effective 4/1/26. Added Boncresa to HCPCS NOC C9399 and J3590 under Prolia and biosimilars, added Oziltus to HCPCS NOC C9399 and J3590 under Xgeva and biosimilars.
- 12/08/2025 – Select Review: Add Osvyrti (Prolia biosimilar) and Jubereq (Xgeva biosimilar) to respective clinical criteria; Added Osvyrti and Jubereq quantity limits. Step therapy table updates. Coding Reviewed: Added Osvyrti to HCPCS NOC C9399 and J3590 under Prolia and biosimilars. Added Jubereq to HCPCS NOC C9399 and J3590 under Xgeva and biosimilars.
- 11/14/2025 – Annual Review (metabolic bone disease): Add Prolia biosimilars to clinical criteria and step therapy – Bildyos, Bosaya, Enoby; Add Xgeva biosimilars to clinical criteria and step therapy – Aukelso, Bokprevda, Xtrenbo. Coding Reviewed: Added HCPCS NOC C9399 and J3590 for Bildyos, Bosaya and Enoby under Prolia and biosimilars and for Bilprevda, Aukelso and Xtrenbo under Xgeva and biosimilars.

- 09/24/2025 – Coding Update: Removed HCPCS NOC C9399 and J3590 for Stoboclo, Osenvelt, Bomyntra, Conexxence, Ospomyv, Xbryk effective 9/30/25 and added Q5157, Q5158, Q5159 effective 10/1/25.
- 8/15/2025 – Annual Review: Add may not be used in combination criteria. Add step therapies to align with standard biosimilar step therapy criteria and add step therapy tables. Wording and formatting changes. Coding Reviewed: Added HCPCS NOC C9399 for Osenvelt, Xbryk, Bomyntra, Ospomyv, Stoboclo, Conexxence.
- 05/16/2025 – Select Review: add Conexxence and Bomyntra biosimilars clinical criteria and quantity limits, update step. Coding Reviewed: Added Conexxence to HCPCS NOC J3590 under Prolia grouping. Added Bomyntra to HCPCS NOC J3590 under Xgeva grouping.
- 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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    a. Breast Cancer. V4.2026. Revised June 12, 2026.
    b. Prostate Cancer. V5.2026. Revised January 23, 2026.
    c. Systemic Mastocytosis. V2.2026. Revised April 9, 2026.

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CC-0027 Denosumab Agents for Osteoporosis

Commercial Medical Benefit

Effective Date	Preferred Agents	Non-Preferred Agents
08/01/2026	Prolia	Bildyos Boncresa Bosaya Conexxence Enoby Jubbonti Ospomyv Osvyrti Ponlimsi Stoboclo
11/01/2026	Prolia Bildyos Enoby	Boncresa Bosaya Conexxence Jubbonti Ospomyv Osvyrti Ponlimsi Stoboclo

Medicaid Medical Benefit

Effective Date	Preferred Agents	Non-Preferred Agents
N/A	N/A	N/A

Medicare Medical Benefit

Effective Date	Preferred Agents	Non-Preferred Agents
07/01/2026	Prolia	Bildyos Boncresa Bosaya Conexxence Enoby Jubbonti Ospomyv Osvyrti Stoboclo
11/01/2026	Prolia	Bildyos Boncresa Bosaya Conexxence Enoby Jubbonti Ospomyv Osvyrti Ponlimsi Stoboclo