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*\* Please note: Alignment's policy is to make decisions on coverage based on the Centers for Medicare and Medicaid Services (CMS) regulations and guidance, benefit plan documents and contracts, and the member's medical history and condition. If CMS does not have a position addressing a service, Alignment makes coverage decisions based on Alignment's or the delegator's policy. Benefits may vary based on contract, and individual member benefits must be verified. Alignment determines medical necessity if the benefit exists and no contract exclusions are applicable. Although Alignment's policy is consistent with CMS's regulations and guidance, their payment methodology may differ from Medicare. Alignment reserves the right to reimburse the most cost effective durable medical equipment item that is appropriate to the member's medical needs and condition. The decision is based on the member's current medical condition.*

## AHC Denosumab

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**MCG Health**  
Ambulatory Care  
28th Edition

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## Clinical Indications

- Denosumab may be indicated for **1 or more** of the following:
  - ☐ Hypercalcemia of malignancy, as indicated by **ALL** of the following:
    - Age 18 years or older
    - Hypercalcemia due to current malignancy and refractory to bisphosphonate therapy
    - Serum calcium of 12.5 mg/dL (3.1 mmol/L) or greater, after correction for serum albumin
    - Patient is not pregnant.
  - ☐ Osteoporosis and need for treatment in patient at high risk for fracture, as indicated by **1 or more** of the following:
    - Postmenopausal female with osteoporosis and **ALL** of the following :
      - Documented osteoporosis, as indicated by **1 or more** of the following:
        - Femoral neck, spine, or total hip bone mineral density T-score between -1.0 to -2.5 and **1 or more** of the following:
          - Fracture Risk Assessment Tool (FRAX®) [A] 10-year probability for major osteoporotic fracture of 20% or greater
          - Fracture Risk Assessment Tool (FRAX®) [A] 10-year probability of hip fracture greater than country-specific threshold (eg, 3% or greater in the United States) [B]
        - Femoral neck, spine, or total hip bone mineral density T-score -2.5 or less
        - Hip or vertebral fragility (ie, low-trauma) fracture in patient 50 years or older
      - Patient at high risk for fracture, as indicated by **1 or more** of the following [C]:
        - Failure of, inability to tolerate, or contraindication to other available osteoporosis therapy, including **1 or more** of the following:
          - Abaloparatide
          - Calcitonin

- Intravenous bisphosphonate (eg, ibandronate, zoledronic acid)
  - Oral bisphosphonate (eg, alendronate, risedronate, ibandronate)
  - Raloxifene
  - Romosozumab
  - Teriparatide
- Risk factors for fracture, as indicated by **1 or more** of the following:
  - Alcohol intake of 3 or more drinks per day
  - BMI less than 20 BMI Calculator
  - Current cigarette use
  - Glucocorticoid use of 3 months' or greater duration
  - Parental hip fracture
  - Personal history of fragility or osteoporotic fracture
  - Rheumatoid arthritis (confirmed diagnosis)
- No hypocalcemia at time of administration
- Male with osteoporosis and **ALL** of the following:
  - Documented osteoporosis, as indicated by **1 or more** of the following:
    - Femoral neck, spine, or total hip bone mineral density T-score between -1.0 to -2.5 and **1 or more** of the following:
      - Fracture Risk Assessment Tool (FRAX®) [A] 10-year probability for major osteoporotic fracture of 20% or greater
      - Fracture Risk Assessment Tool (FRAX®) [A] 10-year probability of hip fracture greater than country-specific threshold (eg, 3% or greater in the United States) [B]
    - Femoral neck, spine, or total hip bone mineral density T-score -2.5 or less
    - Hip or vertebral fragility (ie, low-trauma) fracture in patient 50 years or older
  - Patient at high risk for fracture, as indicated by **1 or more** of the following:
    - Failure of, inability to tolerate, or contraindication to other available osteoporosis therapy, including **1 or more** of the following:
      - Calcitonin
      - Intravenous bisphosphonate (eg, ibandronate, zoledronic acid)
      - Oral bisphosphonate (eg, alendronate, risedronate, ibandronate)
      - Raloxifene
      - Teriparatide
    - Risk factors for fracture, as indicated by **1 or more** of the following:
      - Alcohol intake of 3 or more drinks per day
      - BMI less than 20 BMI Calculator
      - Current cigarette use
      - Glucocorticoid use of 3 months' or greater duration
      - Parental hip fracture
      - Personal history of fragility or osteoporotic fracture
      - Rheumatoid arthritis (confirmed diagnosis)
  - No hypocalcemia at time of administration
- Glucocorticoid-induced osteoporosis in male or female, as indicated by **ALL** of the following:
  - Age 18 years or older
  - Documented osteoporosis, as indicated by **1 or more** of the following:
    - Femoral neck, lumbar spine, or total hip bone mineral density T-score of less than -2.0
    - History of osteoporotic fracture
  - Duration of glucocorticoid therapy expected to be 6 months or greater
  - Glucocorticoid daily dose equivalent to 7.5 mg or greater of prednisone
  - Patient at high risk for fracture, as indicated by **1 or more** of the following:
    - Failure of, inability to tolerate, or contraindication to other available osteoporosis therapy, including **1 or more** of the following:
      - Abaloparatide (female only)
      - Calcitonin
      - Intravenous bisphosphonate (eg, ibandronate, zoledronic acid)
      - Oral bisphosphonate (eg, alendronate, risedronate, ibandronate)
      - Raloxifene

- Romosozumab (female only)
  - Teriparatide
- Risk factors for fracture, as indicated by **1 or more** of the following:
  - Alcohol intake of 3 or more drinks per day
  - BMI less than 20 BMI Calculator
  - Current cigarette use
  - Glucocorticoid use of 3 months' or greater duration
  - Parental hip fracture
  - Personal history of fragility or osteoporotic fracture
  - Rheumatoid arthritis (confirmed diagnosis)
- No hypocalcemia at time of administration
- Patient is not pregnant.
- ☐ Prevention of bone loss in female with breast cancer, as indicated by **ALL** of the following:
  - Patient receiving adjuvant therapy with aromatase inhibitor
  - Risk factors for fracture, as indicated by **2 or more** of the following:
    - Age older than 65 years
    - Alcohol intake of 3 or more drinks per day
    - BMI less than 20 BMI Calculator
    - Bone mineral density T-score less than -1.5
    - Current cigarette use
    - Glucocorticosteroid use of 3 months' or greater duration
    - Parental hip fracture
    - Personal history of fragility fracture or osteoporotic fracture
    - Rheumatoid arthritis (confirmed diagnosis)
  - No hypocalcemia at time of administration
  - Patient is not pregnant.
- ☐ Prevention of bone loss in male with prostate cancer, as indicated by **ALL** of the following:
  - Age 50 years or older
  - Bone mineral density T-score between -1.0 and -2.5
  - Patient receiving androgen deprivation therapy
  - Risk factors for fracture, as indicated by **1 or more** of the following:
    - Alcohol intake of 3 or more drinks per day
    - BMI less than 20 BMI Calculator
    - Current cigarette use
    - Glucocorticoid use of 3 months' or greater duration
    - Parental hip fracture
    - Personal history of fragility or osteoporotic fracture
    - Rheumatoid arthritis (confirmed diagnosis)
  - No hypocalcemia at time of administration
- ☐ Prevention or treatment of skeletal-related events from cancer metastatic to bone, as indicated by **ALL** of the following
  - Age 18 years or older
  - Hypocalcemia absent or treated with calcium and vitamin D as necessary
  - Osteolytic bone lesions or bone metastases from solid tumors, including **1 or more** of the following:
    - Breast cancer
    - Prostate cancer
    - Other solid tumors (eg, lung or renal cancer)
  - Standard antineoplastic therapy continues.
  - Patient is not pregnant.
- Prevention of skeletal-related events in multiple myeloma, when **ALL** of the following are met:
  - Member is diagnosed with active (symptomatic) multiple myeloma [i.e., NOT smoldering (asymptomatic) myeloma]
  - Denosumab will be used in combination with primary myeloma therapy
  - Member has an inadequate response, contraindication, or intolerance to bisphosphonate therapy (oral or IV)

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## Evidence Summary

### Background

Denosumab is a fully human monoclonal antibody. It inhibits osteoclast formation, function, and survival, resulting in decreased bone resorption and consequent increased bone mass and strength in both trabecular and cortical bone.

Risk of fracture, including vertebral fractures, has been shown to increase when denosumab is discontinued, and initiation of alternative antiresorptive therapy should be considered.

Denosumab is associated with osteonecrosis of the jaw. Risk factors include invasive dental procedures, immunosuppressive therapy, gingival disease, and poor oral hygiene.(2)(3)

## Criteria

For hypercalcemia of malignancy, evidence demonstrates a net benefit, but of less than moderate certainty, and may consist of a consensus opinion of experts, case studies, and common standard care.

For osteoporosis, evidence demonstrates at least moderate certainty of at least moderate net benefit. In postmenopausal women, denosumab is effective in significantly increasing bone mineral density at multiple trabecular and cortical sites.

Prolia is prominently featured in guidelines for postmenopausal osteoporosis by the Endocrine Society (2019)(4) and the American Association of Clinical Endocrinologists and the American College of Endocrinology (2020)(5) . Prolia is one of several agents cited as an alternative for patients at high risk for fractures.

For prevention of bone loss in women with breast cancer, evidence demonstrates at least moderate certainty of at least moderate net benefit. Expert guidelines and review articles recommend treatment with denosumab for women with breast cancer being treated with aromatase inhibitors. In a randomized controlled trial of 3420 postmenopausal patients with early hormone receptor-positive breast cancer who were receiving treatment with aromatase inhibitors, denosumab doubled the time to first fracture as compared with placebo. (6)

For prevention of bone loss in men with prostate cancer, evidence demonstrates at least moderate certainty of at least moderate net benefit. A systematic review and meta-analysis of 27 clinical trials concluded that both bisphosphonates and denosumab improve bone mineral density in men with nonmetastatic prostate cancer who are receiving androgen deprivation therapy; a single randomized trial studied denosumab and found that its use was associated with reduced risk of vertebral fractures. Expert consensus guidelines recommend denosumab as a treatment option for men with prostate cancer treated with androgen deprivation therapy and a high probability of fracture.(7)

For prevention or treatment of skeletal-related events from cancer metastatic to bone, evidence demonstrates at least moderate certainty of at least moderate net benefit. Systematic reviews and meta-analyses have reported that denosumab was more effective than zoledronic acid in reducing the incidence of and delaying the time to skeletal-related events; however, no differences were found between the 2 drugs in terms of mortality or overall adverse events.(8)(9) Expert consensus guidelines support the use and role of denosumab in delaying or preventing skeletal-related events in patients with several types of solid tumors, including breast, prostate, lung, and kidney.(10)(11)

## Inconclusive or Non-Supportive Evidence

Denosumab (Prolia) is considered experimental, investigational or unproven for ANY other use including the following (this list may not be all inclusive):

1. **Concurrent Use with Other Medications for Osteoporosis.** Note: Examples include teriparatide subcutaneous injection (Forteo), Tymlos (abaloparatide subcutaneous injection), oral bisphosphonates (e.g., alendronate, risedronate, ibandronate), intravenous bisphosphonates (zoledronic acid intravenous infusion [Reclast], ibandronate intravenous infusion), calcitonin nasal spray (Miacalcin/Fortical), and Evenity (romosozumab-aqqg subcutaneous injection). Prolia is not indicated for use as combination therapy.
2. **Osteoporosis Prevention.** Prolia is not indicated for the prevention of osteoporosis.

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## Committee Approval

- 01/09/2024, 02/20/2025

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## Application

- This policy applies to the following states: Arizona, California, Nevada, North Carolina, and Texas.
- Please refer to the CMS website for the most current applicable National Coverage Determination (NCD)/ Local Coverage Determination (LCD)/Local Coverage Article (LCA)/CMS Online Manual System/Transmittals.

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## Policy Revision History

- 5/26/2022: Creation date
- 05/26/2023,10/9/2023 12/05/2023: Revision
- 11/12/2024: Annual review, Applicable states updated, Florida removed

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## References

1. Prolia (denosumab). Physician Prescribing Information [Internet] Amgen Inc. 2021 May Accessed at: <https://www.prolia.com/>. [created 2010; accessed 2021 Nov 17] [ Context Link 1 ]
2. Xgeva (denosumab) injection. Physician Prescribing Information [Internet] Amgen Inc. 2020 Jun Accessed at: <https://www.xgeva.com/>. [created 2010; accessed 2021 Nov 18] [ Context Link 1 ]
3. Eastell R, Rosen CJ, Black DM, et al. Pharmacological management of osteoporosis in postmenopausal women: an Endocrine Society clinical practice guideline. *J Clin Endocrinol Metab*. 2019;104(5):1595-1622. Available at: <https://www.endocrine.org/guidelines-and-clinical-practice/clinical-practiceguidelines/osteoporosis-in-postmenopausal-women>. [ Context Link 1 ]
4. 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-2020 update. *Endocrin Pract*. 2020;26(Suppl 1):1-46. [ Context Link 1 ]
5. The NCCN Breast Cancer Clinical Practice Guidelines in Oncology (Version 5.2021 – June 28, 2021). © 2021 National Comprehensive Cancer Network. Available at: <http://www.nccn.org>. [ Context Link 1 ]
6. The NCCN Prostate Cancer Clinical Practice Guidelines in Oncology (Version 2.2021 – February 17, 2021). © 2021 National Comprehensive Cancer Network. Available at: <http://www.nccn.org>. [ Context Link 1 ]
7. Peddi P, Lopez-Olivo MA, Pratt GF, Suarez-Almazor ME. Denosumab in patients with cancer and skeletal metastases: a systematic review and meta-analysis. *Cancer Treatment Reviews* 2013;39(1):97-104. DOI: 10.1016/j.ctrv.2012.07.002. [ Context Link 1 ]
8. Menshaw A, et al. Denosumab versus bisphosphonates in patients with advanced cancers-related bone metastasis: systematic review and meta-analysis of randomized controlled trials. *Supportive Care in Cancer* 2018;26(4):1029-1038. DOI: 10.1007/s00520-018-4060-1. [ Context Link 1 ]
9. Schaeffer E, et al. Prostate Cancer. NCCN Clinical Practice Guidelines in Oncology [Internet] National Comprehensive Cancer Network (NCCN). v. 1.2022; 2021 Sep Accessed at: <https://www.nccn.org/>. [accessed 2021 Oct 14] [ Context Link 1 ]
10. Gravalos C, et al. SEOM Clinical Guideline for bone metastases from solid tumours (2016). *Clinical and Translational Oncology* 2016;18(12):1243-53. DOI: 10.1007/s12094-016-1590-1. [ Context Link 1 ]

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## Footnotes

[A] The Fracture Risk Assessment Tool (FRAX®) was developed using demographic and clinical risk factors to predict a patient's nationality-adjusted 10-year risk for developing a hip fracture or major osteoporotic fracture. <https://frax.shef.ac.uk/FRAX/tool.aspx?country=9> [ A in Context Link 1, 2, 3, 4 ]

[B] The Fracture Risk Assessment Tool (FRAX®) country-specific threshold should be used in countries other than the United States. [ B in Context Link 1, 2 ]

[C] Bisphosphonates are first-line therapy for most women with postmenopausal osteoporosis with indications for treatment. Two specialty society guidelines suggest that patients at very high risk of fracture be treated with alternate osteoporosis treatments. One guideline recommends treatment with abaloparatide, denosumab, romosozumab, teriparatide, or zoledronate for patients with postmenopausal osteoporosis and very high fracture risk, as defined by recent fractures, fractures while on approved osteoporosis therapy, multiple fractures, fractures while on drugs causing skeletal harm (eg, long-term glucocorticoids), very low bone mineral density T-score (eg, less than -3.0), a high risk for falls or history of injurious falls, or a very high fracture probability by Fracture Risk Assessment Tool (FRAX®) or other validated fracture risk algorithm (eg, major osteoporosis fracture risk greater than 30% or hip fracture risk greater than 4.5%). The authors note limited evidence for defining patients at very high risk. A second guideline recommends initial treatment with bisphosphonates for most postmenopausal women at high risk of fractures, with denosumab as an alternative. The authors recommend teriparatide, abaloparatide, or romosozumab for those at very high risk of fractures (eg, history of multiple vertebral fractures). [ C in Context Link 1 ]

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## Codes

**HCPCS: J0897**