Denosumab

ACG: A-0644 (AC)
Link to Codes

MCG Health
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Clinical Indications

- Denosumab may be indicated for **1 or more** of the following(1)(2)(3):
  - Giant cell tumor of bone in adult or skeletally mature adolescent, as indicated by **ALL** of the following[A](19)(20)(21):
    - Documented need for denosumab, as indicated by **1 or more** of the following:
      - Recurrent disease
      - Unresectable disease, or located where planned surgery is likely to result in severe morbidity(29)(30)
    - Hypocalcemia absent or treated with calcium and vitamin D as necessary
    - Patient is not pregnant.(30)
  - Hypercalcemia of malignancy, as indicated by **ALL** of the following[B](6)(31)(32)(33):
    - 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[C](39)(40)(41)(42):
    - Postmenopausal female with osteoporosis and **ALL** of the following(38)(64)(67)(68):
      - Documented osteoporosis, as indicated by **1 or more** of the following(38)(64)(67)(68)(69)(70):
        - 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®)[D] 10-year probability for major osteoporotic fracture of 20% or greater
          - Fracture Risk Assessment Tool (FRAX®)[D] 10-year probability of hip fracture greater than country-specific threshold (eg, 3% or greater in the United States)[E]
        - 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
      - Need for therapy with denosumab, as indicated by **1 or more** of the following[F]:
        - 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(38)(64)(67)(69)(70)(73):
          - 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:
        - Age 18 years or older
        - Documented osteoporosis, as indicated by **1 or more** of the following(38)(64)(67)(68)(69)(70):
            - 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®)[D] 10-year probability for major osteoporotic fracture of 20% or greater
                - Fracture Risk Assessment Tool (FRAX®)[D] 10-year probability of hip fracture greater than country-specific threshold (eg, 3% or greater in the United States)[E]
            - 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
        - Need for therapy with denosumab, as indicated by **1 or more** of the following(74):
            - 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
                - Teriparatide
            - Risk factors for fracture, as indicated by **1 or more** of the following(38)(64)(67)(69)(70)(73):
                - 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(63)(75)(76):
        - 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(77)
            - History of osteoporotic fracture(78)
        - Duration of glucocorticoid therapy expected to be 6 months or greater
        - Glucocorticoid daily dose equivalent to 7.5 mg or greater of prednisone
        - Need for therapy with denosumab, 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
                - 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(38)(64)(67)(69)(70)(73):
                - 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[C](79)(80)(81)(82):N
- Patient receiving adjuvant therapy with aromatase inhibitor
- Clinical condition, as indicated by **1 or more** of the following(87):

- Bone mineral density T-score less than -2.0
- 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(88)
    - 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[C](80)(81)(89)(90):

- Age 50 years or older
- Bone mineral density T-score between -1.0 and -2.5
- Patient receiving androgen deprivation therapy(74)
- Risk factors for fracture, as indicated by **1 or more** of the following(38)(64)(67)(69)(70)(73):
    - 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[G](80)(81)(95)(96):

- 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(32)(101)(115)(116):
    - Breast cancer(100)(117)(118)
    - Prostate cancer(89)(92)(109)(110)(119)
    - Other solid tumors (eg, lung or renal cancer)(120)(121)(122)(123)
- Standard antineoplastic therapy continues.
- Patient is not pregnant.

Evidence Summary

Background

Denosumab is a fully human monoclonal antibody.(4)(5)(6) **(EG 2)** 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.(1)(2)(5)(7)(8) **(EG 2)**

Risk of fracture, including vertebral fractures, has been shown to increase when denosumab is discontinued, and initiation of alternative antiresorptive therapy should be considered.(1)(8)(9)(10)(11) **(EG 2)**

Denosumab is associated with osteonecrosis of the jaw. Risk factors include invasive dental procedures, immunosuppressive therapy, gingival disease, and poor oral hygiene.(1)(2)(12)(13) **(EG 2)**

Criteria

For giant cell tumor of bone, 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. **(RG A2)** Review articles indicate that denosumab may offer symptom and disease control for patients with giant cell tumor of bone who have no other treatment options.(22)(23)(24)(25) **(EG 2)** A multicenter open-label phase II study of 37 adult patients with recurrent or unresectable giant cell tumor of bone treated with monthly denosumab reported 86% tumor response (defined as elimination of at least 90% of giant cells on histology or no radiologic progression of the target lesion) at 25 weeks.(26) **(EG 2)** A multicenter open-label phase II study of 282 patients with giant cell tumors of the bone treated with denosumab found that 96% of 169 patients with surgically unresectable disease had no disease progression for a median duration of 13 months; 74% of 100 patients for whom surgery would have resulted in severe morbidity had no surgery; and 62% of 26 patients having surgery had a less morbid procedure than originally planned.(27) **(EG 2)** In long-term follow-up of 532 patients treated with denosumab for giant cell tumor of bone, including the 282 patients from the previously described multicenter phase II study, at median

follow-up of 58.1 months, 26% of patients had serious treatment-emergent adverse events, including 17 cases of osteonecrosis of the jaw (3% of total sample).(28) **(EG 2)**

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. **(RG A2)** In an open-label single-arm study of 33 patients with hypercalcemia of malignancy refractory to bisphosphonate therapy, corrected serum calcium was achieved in 64% of patients after 10 days. Median time to response was 9 days, and median response duration was 104 days.(34) **(EG 2)** A retrospective case series of 7 patients receiving denosumab for hypercalcemia of malignancy found effectiveness in reducing serum calcium, although hypocalcemia was an issue in some patients.(35) **(EG 2)** A single-arm proof-of-concept study of 15 patients with hypercalcemia of malignancy, either persisting or relapsing despite bisphosphonate therapy, found that 12 patients responded by day 10, with 10 patients exhibiting a complete response.(36) **(EG 2)**

For osteoporosis, evidence demonstrates at least moderate certainty of at least moderate net benefit. **(RG A1)** In postmenopausal women, denosumab is effective in significantly increasing bone mineral density at multiple trabecular and cortical sites.(43)(44)(45) **(EG 2)** Systematic reviews of randomized trials concluded that denosumab also decreased the risk of hip, vertebral, and nonvertebral fractures.(46)(47)(48) **(EG 1)** A systematic review and meta-analysis of 9 manufacturer-funded studies involving 4890 postmenopausal women found, at 12-month to 24-month follow-up, that safety and efficacy of denosumab in reducing fracture risk were comparable to those of bisphosphonates, although improvement in bone mineral density was significantly higher with denosumab.(49) **(EG 1)** A pooled analysis of 4 randomized controlled trials (2850 patients) comparing denosumab with a bisphosphonate (alendronate, risedronate, ibandronate, or zoledronic acid) in postmenopausal women age 55 years or older previously treated with an oral bisphosphonate found that, at 12-month follow-up, denosumab-treated patients had greater improvements in bone mineral density at the femoral neck, total hip, lumbar spine, and 1/3 radius.(50) **(EG 2)** An international randomized controlled trial with 7868 women with postmenopausal osteoporosis and at high risk for fracture assigned patients to denosumab or to placebo every 6 months for 36 months. After 36 months, new vertebral fractures occurred in 2.3% of the denosumab group and in 7.2% of the placebo group, a 68% relative risk reduction. Significant decreases in secondary endpoints of hip fractures (0.7% vs 1.2%) and nonvertebral fractures (6.5% vs 8%) were also noted. No significant increase in major adverse effects, including malignancy, cardiovascular disease, infection, delayed fracture healing, or hypocalcemia, was noted in this study population.(51)(52) **(EG 1)** An open-label extension of this trial with 4550 participants reported that bone mineral density continued to improve after 5 years of treatment in the long-term group, resulting in gains of 13.7% and 7% in the lumbar spine and hip, respectively. Bone mineral density also improved in the crossover group after 2 years of treatment, resulting in gains of 7.7% and 4% in the lumbar spine and hip, respectively.(53)(54) **(EG 2)** Another analysis of this study evaluating 2207 postmenopausal women treated with denosumab over a 7-year extension period found a significant reduction in fracture rate ratios of the upper limb, including at the wrist, forearm, and humerus.(55) **(EG 2)** Follow-up data remain consistent after 10 years of treatment with regard to both safety and efficacy, including continued increases in bone mineral density without plateau.(56)(57) **(EG 2)** A randomized trial of 100 women with postmenopausal osteoporosis compared treatment with denosumab, teriparatide, or combination therapy with both medications and found, at 12-month follow-up, that combination therapy was associated with improved bone mineral density at the lumbar spine, hip, and femoral neck.(58) **(EG 1)** A randomized trial of 76 women with postmenopausal osteoporosis compared treatment with denosumab combined with standard-dose (20 mcg) or high-dose (40 mcg) teriparatide and found, at 15-month follow-up, that high-dose teriparatide was associated with improved bone mineral density in the lumbar spine, hip, and femoral neck compared with standard-dose teriparatide.(59) **(EG 1)** For osteoporosis in men, a randomized placebo-controlled phase III study of 242 men reported that 1 year of denosumab therapy was well tolerated and resulted in a reduction in bone resorption and significant increases in bone mineral density at all assessed skeletal sites.(60)(61) **(EG 1)** For glucocorticoid-induced osteoporosis, a systematic review and network meta-analysis of 19 randomized controlled trials of treatments to prevent fractures in patients with glucocorticoid-induced osteoporosis or who are starting or continuing long-term glucocorticoid treatment, including 4 studies evaluating denosumab, found that denosumab was associated with a lower risk of vertebral fracture than placebo.(62) **(EG 1)** A phase III, double-blind, double-dummy, noninferiority trial randomized 795 adults with glucocorticoid-induced osteoporosis to treatment with denosumab every 6 months or daily risedronate for 24 months. In the 590 adults who completed 24-month follow-up, denosumab was associated with improved bone mineral density from baseline at the lumbar spine and total hip compared with risedronate. Limitations included absent outcomes data for fractures and a lack of information regarding treatment patterns or outcomes after completion of denosumab.(63) **(EG 1)** A specialty society guideline recommends initiating pharmacologic therapy for postmenopausal patients with low bone mass and a history of hip or spine fragility fracture or high risk for fracture. The guideline suggests that patients at very high fracture risk (eg, fracture within the past 12 months, high risk for falls, fractures while on osteoporosis pharmacotherapy) be treated with abaloparatide, denosumab, romosozumab, teriparatide, or zoledronate, but notes that there is limited evidence for defining who is at very high risk.(38) **(EG 2)** Another specialty society guideline and a review article recommend initial treatment with bisphosphonates for most postmenopausal women with osteoporosis at high fracture risk, with denosumab as an alternative initial treatment.(37)(64) **(EG 2)** Expert consensus guidelines recommend denosumab as a treatment option to reduce the risk for hip and vertebral fractures in women with osteoporosis.(65)(66) **(EG 2)**

For prevention of bone loss in women with breast cancer, evidence demonstrates at least moderate certainty of at least moderate net benefit. **(RG A1)** Expert guidelines and review articles recommend treatment with denosumab for women with breast cancer being treated with aromatase inhibitors.(79)(80)(83) **(EG 2)** 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.(84) **(EG 1)** Follow-up analysis of this study found, at a median follow-up of 73 months, that denosumab was associated with improved disease-free survival (defined as time to first evidence of metastatic disease, contralateral breast cancer, secondary carcinoma, or death from any cause) compared with placebo, with no difference in adverse events between the groups.(85) **(EG 2)** A mixed-treatment meta-analysis estimated that immediate use of denosumab, as compared with zoledronic

acid, for the treatment of early postmenopausal breast cancer treated with aromatase inhibitors provided significantly better protection (a 50% odds ratio reduction) against new fractures.(86) **(EG 1)**

For prevention of bone loss in men with prostate cancer, evidence demonstrates at least moderate certainty of at least moderate net benefit. **(RG A1)** 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.(91) **(EG 1)** 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.(89)(90)(92)(93) **(EG 2)**

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. **(RG A1)** 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.(95)(97) **(EG 1)** A systematic review concluded that the mechanism for reducing skeletal-related events rests primarily on denosumab delaying or preventing such painful bone-related events rather than on a direct analgesic effect.(98) **(EG 1)** In a meta-analysis of 3 phase III trials (with a total of 5543 patients with breast cancer, prostate cancer, or other solid tumors, and one or more bone metastases), denosumab was found to be significantly better than zoledronic acid in terms of risk of first or subsequent skeletal-related event, bone metastasis location and number, and visceral metastasis presence or absence across all subgroups of patients; however, this study did not address mortality or survival.(99) **(EG 1)** For breast cancer, systematic reviews concluded that denosumab reduces the risk of and delays the time to pathologic fractures, spinal cord compression, and need for surgery or radiation therapy to bone.(100)(101)(102) **(EG 1)** In addition, a randomized controlled trial of 2046 patients with advanced breast cancer and bone metastases found that denosumab was comparable to zoledronic acid for palliation of pain.(103) **(EG 1)** For skeletal lesions in multiple myeloma, review articles state that denosumab is usually well tolerated and effective in impairing malignant osteolysis, particularly in those myeloma patients with deteriorating renal function for whom bisphosphonates are contraindicated but denosumab is not.(104) **(EG 2)** A specialty society guideline states that denosumab provides an alternative to zoledronic acid for the prevention of skeletal-related events in patients with active symptomatic multiple myeloma requiring systemic therapy; this guideline notes that fewer adverse events related to renal toxicity have been seen with denosumab, and thus denosumab may be preferred over zoledronic acid in patients with renal impairment.(105) **(EG 2)** For prostate cancer, a systematic review and other review articles have confirmed the efficacy of denosumab in reducing the incidence of and delaying the time to skeletal-related events.(106)(107)(108) **(EG 1)** A multicenter, randomized, double-blind, placebo-controlled trial involving 1432 men reported a significant increase in bone metastasis-free survival by a median of 4.2 months; however, overall survival did not differ between groups.(109) **(EG 1)** Additionally, a double-blind randomized controlled trial assigned 1901 men with bone metastases from castration-resistant prostate cancer to either denosumab or zoledronic acid. After approximately 12 months, denosumab was found to be significantly more effective than zoledronic acid in terms of preventing skeletal-related events, delaying average time to a first event from 17 months with zoledronic acid to 21 months with denosumab.(110) **(EG 1)** Based on data from randomized trials of denosumab, a review article reported that the number needed to treat for denosumab to prevent skeletal-related events was 18 patients for breast cancer (over 34 months), 22 patients for prostate cancer (over 41 months), and 21 patients for other cancer sites (over 34 months).(111) **(EG 2)** 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.(89)(93)(112)(113)(114) **(EG 2)**

Inconclusive or Non-Supportive Evidence

For rheumatoid arthritis, evidence is insufficient, conflicting, or poor and demonstrates an incomplete assessment of net benefit vs harm; additional research is recommended. **(RG B)** A systematic review and meta-analysis of 18 studies (2918 patients) comparing denosumab with bisphosphonates or placebo for the management of rheumatoid arthritis found, at 12-month follow-up, that denosumab was associated with increased bone mineral density scores of the hip and spine compared with bisphosphonates or placebo. However, the authors noted that the study was unable to demonstrate decreased fracture rates or disease activity in patients treated with denosumab, and further studies were recommended.(14) **(EG 1)** Randomized controlled studies demonstrated improvement in bone mineral density and cortical bone loss in the hand after 12 months of treatment with denosumab, but longer-term results, as well as other significant outcomes, require further study.(15)(16)(17) **(EG 1)** A review article indicates that further study is necessary to establish optimal treatment regimens and confirm longer-term safety of denosumab for this indication.(18) **(EG 2)**

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Footnotes

[A] For giant cell tumor of bone, denosumab is administered subcutaneously every 4 weeks, with additional doses on days 8 and 15 of the first month of treatment.(2) [A in Context Link 1]

[B] For hypercalcemia of malignancy, denosumab is administered subcutaneously every 4 weeks, with additional doses on days 8 and 15 of the first month of treatment. Denosumab may be associated with severe hypocalcemia, particularly in patients with renal dysfunction. Calcium levels should be monitored throughout denosumab therapy.(2) [B in Context Link 1]

[C] For osteoporosis, denosumab is administered as a single subcutaneous injection, by a health professional, every 6 months.(1) Patients with creatinine clearance of less than 30 mL/min/1.73m^2 (0.50 mL/sec/1.73m^2) or receiving hemodialysis are at greater risk of developing hypocalcemia with treatment.(1) Denosumab treatment is associated with suppression of bone turnover, and treatment cessation is associated with a rebound increase in bone turnover above pretreatment values, which may lead to increased fracture risk and loss of bone mineral density. Patients should be transitioned to an alternative antiresorptive therapy (eg, bisphosphonate) if denosumab is discontinued.(1)(37)(38) [C in Context Link 1, 2, 3]

[D] 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.(71) [D in Context Link 1, 2, 3, 4]

[E] The Fracture Risk Assessment Tool (FRAX®) country-specific threshold should be used in countries other than the United States.(71) [E in Context Link 1, 2]

[F] Bisphosphonates are first-line therapy for most women with postmenopausal osteoporosis with indications for treatment.(37) Two specialty society guidelines suggest that patients at very high risk of fracture be treated with alternate osteoporosis treatments.(37)(38) 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.(38) 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).(37)(72) [F in Context Link 1]

[G] For prevention of skeletal-related events in patients with skeletal osteolytic metastases from solid tumors, denosumab is administered as a subcutaneous injection every 4 weeks.(2)(94) The optimal duration of therapy is not known, but the median duration of exposure in several clinical trials was 12 months.(2) Denosumab may be associated with severe hypocalcemia, particularly in patients with renal dysfunction. Calcium levels should be monitored throughout denosumab therapy.(2) [G in Context Link 1]

Codes

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