Subject: Prolia (denosumab)	**Original Effective Date:** 10/31/2012
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DISCLAIMER

This Medical Policy is intended to facilitate the Utilization Management process. It expresses Molina's determination as to whether certain services or supplies are medically necessary, experimental, investigational, or cosmetic for purposes of determining appropriateness of payment. The conclusion that a particular service or supply is medically necessary does not constitute a representation or warranty that this service or supply is covered (i.e., will be paid for by Molina) for a particular member. The member's benefit plan determines coverage. Each benefit plan defines which services are covered, which are excluded, and which are subject to dollar caps or other limits. Members and their providers will need to consult the member's benefit plan to determine if there are any exclusion(s) or other benefit limitations applicable to this service or supply. If there is a discrepancy between this policy and a member's plan of benefits, the benefits plan will govern. In addition, coverage may be mandated by applicable legal requirements of a State, the Federal government or CMS for Medicare and Medicaid members. CMS's Coverage Database can be found on the CMS website. The coverage directive(s) and criteria from an existing National Coverage Determination (NCD) or Local Coverage Determination (LCD) will supersede the contents of this Molina Clinical Policy (MCP) document and provide the directive for all Medicare members.

SUMMARY OF EVIDENCE/POSITION

This policy addresses the coverage of **Prolia (denosumab)** for the treatment of **postmenopausal women or adult men with osteoporosis** AND **treatment of bone loss for adult women receiving adjuvant aromatase inhibitor therapy for breast cancer or adult men receiving androgen deprivation therapy for non-metastatic prostate cancer** when appropriate criteria are met.

***Denosumab is also marketed as Prolia and is addressed in **MCP-112: XGEVA (denosumab)**

This policy is intended to address coverage criteria that are appropriate for the majority of individuals/members with a particular disease, illness, or condition. Each member's unique clinical circumstances may warrant individual consideration, based on review of applicable medical records.

- **Denosumab** is a human monoclonal antibody. It acts by reducing the production of osteoclasts and therefore by reducing the turnover and destruction of bone. It does this by binding to the RANKL molecule and rendering it unable to bind to the RANK receptor.
  - Denosumab *(Prolia)* is FDA-approved for treatment of osteoporosis in postmenopausal women at high risk for fracture. Injected subcutaneously once every 6 months, denosumab has been shown to increase BMD and reduce the incidence of new vertebral and hip and other non-vertebral fractures in postmenopausal women (SR Cummings et al. Denosumab for prevention of fractures in postmenopausal women with osteoporosis. 2009). **It has been shown to increase BMD more than alendronate, but no studies directly comparing the efficacy of denosumab and bisphosphonates for prevention of fractures are available.**
  - **The optimal duration of treatment with denosumab is not known.** Data are available supporting its continued efficacy for 10 years (*HG Bone et al. 2017*)
  - **Denosumab's effects on BMD and bone turnover are reversible with discontinuation of the drug.** Discontinuation of the drug after 24 months of treatment resulted in increased bone turnover markers within 3 months and a decline in BMD to pretreatment values within 2 years (HG Bone et al. 2017). Vertebral fractures have been reported 8-16 months after stopping denosumab (AD Anastasilakis et al. 2017).

- Drug holidays are not recommended. If denosumab is stopped, administering another drug, typically a bisphosphonate, is recommended to prevent a rapid decline in BMD. Switching from denosumab to teriparatide has resulted in progressive or transient bone loss (BZ Leder et al. 2015).

- Denosumab is not considered initial therapy for most patients with osteoporosis. Initial therapy for most patients includes lifestyle measures and oral bisphosphonates (Rosen, HN 2017).

- Due to the lack of long-term safety data and the availability of other agents, denosumab is not recommended for osteoporosis prevention (Rosen, HN 2017).
  - Bisphosphonate treatment for prevention of bone loss, regardless of cause, is the standard of care due to the body of evidence supporting efficacy and track record of safety.
  - There are currently no head-to-head trials comparing the anti-fracture efficacy of denosumab with other available osteoporosis therapies (e.g., oral and intravenous bisphosphonates, teriparatide). The reduction in vertebral fracture noted with denosumab is similar to the reductions reported for subcutaneous teriparatide and intravenous zoledronic acid and greater than that reported for oral alendronate. However, these **data are based upon clinical trials in different patient populations, not head-to-head comparison trials**. There are few studies evaluating the benefits and risks of denosumab in men with osteoporosis that is unrelated to androgen deprivation therapy.

- According to new clinical guidelines from the American College of Physicians (ACP), women with osteoporosis should be treated with one of the three main bisphosphonates or the biologic denosumab for a duration of 5 years, during which time monitoring of bone-mineral density (BMD) is not necessary (ACP 2017). The ACP also advises physicians to prescribe **generics over brand-name drugs whenever possible** and to discuss medication adherence with their patients, especially for bisphosphonates.

- Serious risks associated with denosumab include hypocalcemia, osteonecrosis of the jaw (ONJ), atypical femur fractures, and serious infections.
  - Denosumab suppresses bone remodeling and therefore may contribute to adverse outcomes, such as ONJ. Refer to ‘Appendix 1’ for additional information.

CLASSIFICATION: Bone-Modifying Agent; Monoclonal Antibody; RANK Ligand Inhibitor

FDA INDICATIONS

Osteoporosis/Bone loss

- **Bone loss in men with prostate cancer:** Increase bone mass in men at high risk of fracture receiving androgen deprivation therapy for non-metastatic prostate cancer.

- **Bone loss in women with breast cancer:** Increase bone mass in women at high risk of fracture receiving adjuvant aromatase inhibitor therapy for breast cancer.

- **Osteoporosis in postmenopausal women:** Treatment of postmenopausal women with osteoporosis at high risk of fracture, defined as a history of osteoporotic fracture, or multiple risk factors for fracture; or patients who have failed or are intolerant to other available osteoporosis therapies.

- **Osteoporosis in men:** Treatment to increase bone mass in men with osteoporosis at high risk for fracture, defined as a history of osteoporotic fracture, or multiple risk factors for fracture; or patients who have failed or are intolerant to other available osteoporosis therapy.

Available as: Single-use *prefilled syringe* and *single-use vial* containing 60 mg in a 1 mL solution

FDA Approved *XGEVA and Prolia are both marketed by Amgen, Inc. XGEVA is administered using a higher dose and with more frequent dosing than Prolia.*

- June 2010: Denosumab approved under the brand name Prolia for the treatment of postmenopausal women with osteoporosis at high risk for fracture
- November 2010: XGEVA brand was approved for the prevention of skeletal-related events in patients with bone metastases from solid tumors in November 2010
- September 2011: Prolia received FDA approval for osteoporosis prophylaxis in women at high risk for bone fractures after receiving adjuvant aromatase inhibitor therapy for breast cancer and in men at high risk for bone fractures after receiving androgen deprivation therapy for non-metastatic prostate cancer.
- September 2012: The FDA expanded the osteoporosis indication to include treatment of any man at high risk for fractures.

Black Box Warnings: *None at the time of this writing*

REMS: *Prolia has a REMS program that consists of a Medication Guide and a Dear Healthcare Professional Letter*

RECOMMENDATIONS/COVERAGE CRITERIA

Osteoporosis in Men and Postmenopausal Women

Initiation of therapy with may be authorized for members who meet **ALL** of the following criteria **[ALL]**

1. Prescriber specialty [ONE]

- ❑ Prescribed by, or in consultation with, a board-certified **rheumatologist or endocrinologist,** or osteoporosis specialist. Submit consultation notes if applicable.

  NOTE: Consultation notes must be submitted for initial request and for continuation of treatment requests at least ONCE annually.

2. Diagnosis/Indication [ALL]

- ❒ Diagnosis of men or postmenopausal women with osteoporosis and are at high risk for fracture
  - *Diagnosis of osteoporosis is based on the results of bone mineral density (BMD) testing or by the occurrence of a fragility fracture. Bone densitometry results are generally reported in terms of standard deviations (SD) from the mean value for young adults (T-score). [Ref: TML. Med Lett Drugs Ther.]*

- ❒ High risk for fracture defined by ONE (1) of the following criteria: **[ONE]**

  - ❍ History of osteoporotic hip or vertebral fracture

  - ❍ Low bone mineral density (BMD) evidenced by ONE (1) of the following T-scores [ONE]
    - Lumbar spine BMD T-score of -2.5 or below
    - Total hip BMD T-score of -2.5 or below
    - Femoral neck BMD T-score of -2.5 or below

  - ❍ Individual has TWO (2) or more of the following risk factors for osteoporotic fracture [TWO]
    - low body mass
    - smoking
    - rheumatoid arthritis
    - alcohol intake of 3 or more drinks/day
    - vitamin D deficiency
    - low calcium intake
    - hyperkyphosis
    - parental hip fracture
    - multiple falls
    - medication: anticoagulants, anticonvulsants, (glucocorticoid daily dosage equivalent to 5mg or greater of prednisone for at least 3 months)

  - ❍ Pre-treatment FRAX score of ≥ 20% for an occurrence of a major osteoporotic fracture
    OR
    Pre-treatment FRAX score ≥3% for hip fracture

Informational Note: The World Health Organization (WHO) defines osteoporosis in women as a T-score of -2.5 or below in the spine, femoral neck, or total hip. The computerized model, FRAX (www.shef.ac.uk/FRAX), was developed by the WHO to evaluate fracture risk of patients. FRAX estimates the 10-year probability of a hip fracture or other major osteoporotic fracture (forearm, shoulder or clinical vertebral fracture) based on clinical risk factors and BMD at the femoral neck.

3. Age/Gender/Other restrictions [ALL]

- ❒ 18 year or older
  - *Denosumab is not intended for use in premenopausal women or pediatric patients.*

- ❒ No evidence of hypocalcemia. Documentation of serum calcium.
  NOTE: Hypocalcemia must be corrected prior to initiation of denosumab therapy

4. Step/Conservative Therapy/Other condition Requirements [ALL]

- ❒ Documentation of ONE (1) of the following: **[ONE: A OR B]**

  A. Treatment failure* to at least **ONE (1) bisphosphonate** drug for a **12-month** trial [AT LEAST ONE]
  NOTE: *Documentation required in following criterion
  - ❍ alendronate (Fosamax, generic)
  - ❍ Binosto (alendronate effervescent)
  - ❍ Actonel (risendronate)
  - ❍ Atelvia (risedronate DR)
  - ❍ Boniva (ibandronate)

  B. BOTH **ORAL and IV bisphosphonates** are contraindicated or not tolerated*
  AND
  Treatment failure* to ONE (1) **non-**bisphosphonate drugs [ONE]

  ***NOTE: Documentation required and lists below may *not* be all inclusive.**

  - ❍ Oral Bisphosphonate
    - alendronate (Fosamax)
    - Boniva (ibandronate)
    - Actonel (risedronate)
    - Binosto (alendronate effervescent)
    - Atelvia (risedronate DR)
  - ❍ IV Bisphosphonate
    - Boniva (ibandronate IV)
    - Reclast (zoledronic acid IV)
    - Zometa (zoledronic acid IV)
    - pamidronate for IV
  - ❍ Non-bisphosphonate Drugs
    - Evista (raloxifene) [PREFERRED]
    - Forteo (teriparatide, recombinant, SQ)

- ❒ Each treatment failure (required in criterion above) is defined and documented as ONE (1) of the following: [ANY]

  - ❍ Progression of bone loss as documented by bone density measurements (BMD) after *at least 12 months* of therapy
    NOTE: History of compliance as verified by member's medication fill history OR Prescriber documentation

  - ❍ Occurrence of an osteoporotic fracture after having been compliant on *at least 12 months* of therapy on an oral bisphosphonate
    NOTE: History of compliance as verified by member's medication fill history OR Prescriber documentation

  - ❍ **Intolerance** to IV bisphosphonate. Documentation of chart notes, applicable lab values and/or tests, adverse outcomes, or additional clinical notes from the member's medical records supporting clinical intolerance required.

  - ❍ **Contraindication** based on current medical literature and supporting documentation, *such as:* [ANY]
    NOTE: Gastroesophageal reflux disease (GERD) is NOT a labeled contraindication for oral bisphosphonate therapy
    - Hypersensitivity to bisphosphonates or any component of the formulations
    - Difficulty swallowing oral medications
    - Inability to remain in an upright position after oral bisphosphonate administration for the required length of time
    - History of esophagitis, gastritis, gastric ulcer, or peptic ulcer disease
    - Esophageal stricture, severe erosive esophagitis, achalasia, or other severe esophageal dysmotility condition
    - Severe malabsorption making the use of oral bisphosphonates ineffective
    - Renal insufficiency [creatinine clearance (CrCl) < 30 mL/min]

    Contraindication to IV bisphosphonates: [ANY]
    - Hypocalcemia
    - Renal insufficiency [creatinine clearance (CrCl) < 30 mL/min]
      - *Renal impairment: Patients with creatinine clearance less than 30 mL/min or receiving dialysis are at risk for hypocalcemia.*

- ❒ No combination use of prescription osteoporotic therapies (aside from the requested agent)
  NOTE: Do not administer Prolia and XGEVA to the same patient for different indications as this is duplicate therapy.
  NOTE: Combination therapy of denosumab and intravenous bisphosphonates is considered experimental and investigational because the effectiveness of this approach has not been established.

5. Contraindications/Exclusions to therapy [ANY]

Authorization will **not** be granted if **ANY** of the following conditions apply [ANY]

- ❒ Non-FDA approved indications
- ❒ Known hypersensitivity to denosumab or any ingredient in the formulation
  - *Anaphylactic reactions may occur. Discontinue permanently if a clinically significant reaction occurs.*
  - *Systemic hypersensitivity reactions (e.g., anaphylaxis, hypotension, dyspnea, throat tightness, facial and upper airway edema, lip swelling, rash, pruritus, and urticaria) have been reported in patients receiving denosumab.*
- ❒ Pre-existing hypocalcemia (must be corrected prior to initiating denosumab treatment)
  NOTE: Correct prior to initiating; treatment with denosumab may exacerbate hypocalcemia, especially in members with renal impairment. Members treated with denosumab should receive adequate calcium and vitamin D supplementation.
- ❒ Pregnancy [Category X (Prolia), Category D (XGEVA)]
  - *Prolia is classified as Pregnancy Category X and may cause fetal harm when administered to pregnant women based on findings in animals. XGEVA is classified as Pregnancy Category D, but also caused fetal harm when administered to pregnant women based on findings in animals.*

6. Labs/Reports/Documentation required [ALL]

All documentation for determination of medical necessity must be submitted for review. Prescriber to submit documentation as indicated in the criteria above, including but not limited to chart notes, applicable lab values and/or tests, adverse outcomes, treatment failures, or any other additional clinical information or clinical notes from the member's medical records supporting the diagnosis. Letters of support and/or explanation are often useful, but are not sufficient documentation unless ALL specific information required by this MCP are included.

NOTE: Additional documentation, rationale, and/or supporting evidence may be requested for review as deemed necessary or appropriate by Molina Medical/Pharmacy staff.

Cancer Treatment-Induced Bone Loss

Prolia (denosumab) is considered not medically necessary for the prevention of skeletal complications of bone metastases from solid tumor cancers, treatment of giant cell tumor of the bone, and hypercalcemia of malignancy.

Initiation of therapy with may be authorized for members who meet **ALL** of the following criteria **[ALL]**

1. Prescriber specialty [ONE]

- ❑ Prescribed by, or in consultation with, a board-certified oncologist or osteoporosis physician specialist. Submit consultation notes if applicable.

  NOTE: Consultation notes must be submitted for initial request and for continuation of treatment requests at least ONCE annually.

2. Diagnosis/Indication [ALL]

Documentation of diagnosis required and may include clinical notes from the member's medical records including any relevant labs and/or tests, supporting the diagnosis [ALL]

- ❒ Diagnosis of hormone receptor positive breast cancer OR non-metastatic prostate cancer

  NOTE: Diagnosis of skeletal complications of bone metastases from solid tumor cancers, treatment of giant cell tumor of the bone, and hypercalcemia of malignancy does **not** meet criterion and will not be authorized.

  Informational Note:
  - *Treatment is indicated as first-line in patients who have been diagnosed with non-metastatic prostate cancer and who are undergoing treatment with androgen deprivation therapy (bilateral orchiectomy or GnRH-agonist therapy).*
  - *Treatment is indicated as first-line in patients who have been diagnosed with hormone receptor positive breast cancer and who are undergoing treatment with an aromatase inhibitor (such as anastrazole/Arimidex, exemastane/Aromasin, and letrozole/Femara).*

3. Age/Gender/Other restrictions [ALL]

- ❒ 18 years of age or older
  - *The safety and effectiveness of Prolia in pediatric patients has not been established*

- ❒ No evidence of hypocalcemia as confirmed by documentation of serum calcium. Documentation required.
  NOTE: Pre-existing hypocalcemia must be corrected prior to initiating therapy with Prolia and patients must adequately supplement with calcium and vitamin D

4. Step/Conservative Therapy/Other condition Requirements
Documentation of ALL of the following criteria required; may include clinical notes from the member's medical records including any relevant labs and/or tests, supporting the diagnosis [ALL]

- ❒ Prescribed to increase bone mass in the following members at high risk for fracture **[ONE]**

  - ❍ **Breast cancer**: female patients receiving or who have received adjuvant aromatase-inhibitor therapy for breast cancer [ONE]
    - o Arimidex (anastrozole)
    - o Aromasin (exemestane)
    - o Femara (letrozole)

  - ❍ **Non-metastatic prostate cancer**: male patients receiving or who have received androgen deprivation therapy for non-metastatic prostate cancer [ONE]
    - o Lupron (leuprolide)
    - o Casodex (bicalutamide)
    - o Nilandron (nilutamide)

- ❒ High-risk for fracture defined by ONE (1) or more of the following criteria: **[ONE]**

  - ❍ History of osteoporotic fracture

  - ❍ Low bone mineral density (BMD) evidenced by ONE (1) of the following T-scores [ONE]
    - o Lumbar spine BMD T-score less than minus 1.0
    - o Total hip BMD T-score less than minus 1.0
    - o Femoral neck BMD T-score less than minus 1.0

    Informational Note: T-score is the number of standard deviations the individual's bone density is above or below number normally expected in a healthy young adult of the same sex. A T-score between −1 and −2.5 indicates low bone mass, although not low enough to be diagnosed as osteoporosis. A T-score of −2.5 or lower indicates osteoporosis.

  - ❍ Individual has TWO (2) or more of the following risk factors for osteoporotic fracture [TWO]
    - o low body mass
    - o smoking
    - o rheumatoid arthritis
    - o alcohol intake of 3 or more drinks/day
    - o vitamin D deficiency
    - o low calcium intake
    - o hyperkyphosis
    - o parental hip fracture
    - o multiple falls
    - o medication: anticoagulants, anticonvulsants, (glucocorticoid daily dosage equivalent to 5mg or greater of prednisone for at least 3 months)

  - ❍ The probability is ≥20% for an occurrence of a major osteoporotic fracture or ≥3% for hip fracture, based on the US-adapted WHO algorithm Fracture Risk Assessment Tool (FRAX® tool)[F]

5. Contraindications/Exclusions to therapy [ANY]

Authorization will **not** be granted if ANY of the following conditions apply

- ❒ Non-FDA approved indications
- ❒ Known hypersensitivity to denosumab or any ingredient in the formulation
  - *Anaphylactic reactions may occur. Discontinue permanently if a clinically significant reaction occurs.*
- ❒ Pre-existing hypocalcemia (must be corrected prior to initiating denosumab treatment)
  NOTE: Correct prior to initiating; treatment with denosumab may exacerbate hypocalcemia, especially in members with renal impairment. Members treated with denosumab should receive adequate calcium and vitamin D supplementation.
- ❒ Pregnancy [Category X (Prolia), Category D (XGEVA)]
  - *Prolia is classified as Pregnancy Category X and may cause fetal harm when administered to pregnant women based on findings in animals. XGEVA is classified as Pregnancy Category D, but also caused fetal harm when administered to pregnant women based on findings in animals.*

Exclusions

- ❒ Combination therapy with teriparatide or any another osteoporosis therapy

6. Labs/Reports/Documentation required [ALL]

All documentation for determination of medical necessity must be submitted for review. Prescriber to submit documentation as indicated in the criteria above, including but not limited to chart notes, applicable lab values and/or tests, adverse outcomes, treatment failures, or any other additional clinical information or clinical notes from the member's medical records supporting the diagnosis. Letters of support and/or explanation are often useful, but are not sufficient documentation unless ALL specific information required by this MCP are included.

NOTE: Additional documentation, rationale, and/or supporting evidence may be requested for review as deemed necessary or appropriate by Molina Medical/Pharmacy staff.

CONTINUATION OF THERAPY

Prolia (denosumab) may be authorized for continuation of therapy if meet **ALL** of the following criteria are met: **[ALL]**

1. Initial Coverage Criteria

- ❑ Member currently meets ALL initial coverage criteria
- ❑ Consultation notes must be submitted for initial request and for continuation of treatment requests at least ONCE **annually**
  - *Patients who are evaluated for osteoporosis should be re-evaluated on a yearly basis to assess their adherence to the recommended prevention and therapeutic measures and to seek new signs or symptoms suggesting osteoporotic complications. These patients should have serial BMD measurements performed on the same DEXA machine.*

2. Compliance

- ❑ Adherence to therapy at least 85% of the time as verified by Prescriber and member's medication fill history (review Rx history for compliance), including:
  - ❍ Adherent to the prescribed medication regimen
  - ❍ Tolerance to therapy
  - ❍ No severe adverse reactions or drug toxicity

NOTE: Therapy may be discontinued due to poor adherence upon recommendation of the Molina Medical Director when adherence < 85% has been demonstrated in at least two months during the course of therapy

NOTE: History of non-compliance or non-adherence as verified by member's medication fill history or prescription drug profile may result in continuation of therapy request not being authorized. [MOLINA MEDICAL/PHARMACY REVIEWER TO VERIFY

3. Labs/Reports/Documentation required [ALL APPLICABLE]

- ❒ Medical records must demonstrate a stable bone mineral density (BMD) or an increasing BMD after a minimum trial of one year of therapy **OR** demonstrate improvement by providing reference to the sequential progression or stability of the BMD
  - ❍ T-score test results may date back as far as five years
  - ❍ Depending on level of BMD progression retesting may be done from every one to five years
    - *There are several published guidelines for monitoring the response to osteoporosis therapy; all recommend follow-up BMD (DXA) testing. However, there is no consensus on the optimal frequency of monitoring and preferred site to monitor.*

4. Discontinuation of Treatment [ANY]

Discontinue treatment if ANY of the following conditions applies: [ANY]

- ❑ Intolerable adverse effects or drug toxicity
- ❑ Persistent and uncorrectable problems with adherence to treatment
- ❑ Poor response to treatment as evidenced by physical findings and/or clinical symptoms
- ❑ Contraindications/Exclusions to therapy
  - ❍ Non-FDA approved indications
  - ❍ Hypersensitivity: anaphylactic reactions may occur. Discontinue permanently if a clinically significant reaction occurs.
  - ❍ Pre-existing hypocalcemia (must be corrected prior to initiating denosumab treatment)
    NOTE: Correct prior to initiating; treatment with denosumab may exacerbate hypocalcemia, especially in members with renal impairment. Members treated with denosumab should receive adequate calcium and vitamin D supplementation.
  - ❍ Pregnancy [Category X (Prolia), Category D (XGEVA)]
    - *Prolia is classified as Pregnancy Category X and may cause fetal harm when administered to pregnant women based on findings in animals.*

ADMINISTRATION, QUANTITY LIMITATIONS, AND AUTHORIZATION PERIOD

Authorization may be subject to dosing limits in accordance with FDA-approved labeling, accepted compendia, and/or evidence-based practice guidelines.

1. **Recommended Dosing Regimen [ALL]**

- ❒ 60 mg every 6 months as a subcutaneous injection in the upper arm, upper thigh, or abdomen
- ❒ Concomitant therapy: 1,000 mg of calcium daily and at least 400 units of vitamin D daily
  - *The Institute of Medicine (IOM) recommends a total daily elemental calcium intake of 1000 mg for all women (including pregnant or lactating women) 19-50 years old and men 19-70 years old, and 1200 mg for women >50 years old and men >70 years old.*

2. Authorization Limit [AS APPLICABLE]

- ❑ Duration of treatment [AS APPLICABLE]
  - ❍ Initial authorization: 6 months
  - ❍ Subsequent authorizations: 12 months
- ❑ Quantity limit: One (1) injection every 6 months **OR** two (2) injections per year

3. Route of Administration [ALL]

- ❒ Prolia (denosumab) is considered a **provider-administered** subcutaneous injection administered by a health care professional. Site of administration should not be in a hospital outpatient setting when an alternative site of care (non-hospital outpatient setting such as physician's offices, infusion/injection centers, and home infusion/injection) is a treatment option
- ❒ If member meets all criteria and approval for therapy is granted, medication will be dispensed by a specialty pharmacy vendor at the discretion of Molina Healthcare.

COVERAGE EXCLUSIONS

All other uses of **Prolia (denosumab)** that are not an FDA-approved indication or not included in the 'Coverage Criteria' section of this policy are considered experimental/investigational or not a covered benefit of this policy. This subject to change based on research and medical literature, or at the discretion of Molina Healthcare.

*Pharmaceutical samples: The use of pharmaceutical samples (from the prescriber or manufacturer assistance program) will not be considered when evaluating the medical condition, prior prescription history, or as continuation of therapy.

**FDA-approved indication does not, in itself, dictate coverage. Molina Clinical Policy may not recommend coverage for all FDA-approved indications. Please review this Policy in its entirety for indications covered by Molina Healthcare.*

SUMMARY OF EVIDENCE/POSITION

Osteoporosis is a condition characterized by a loss of bone mass that occurs throughout the skeleton, which predisposes a patient to fractures. The Dual energy X-ray absorptiopmetry (DEXA) measures bone mineral density with results reported as a T-score. T-scores are reported according to standard deviations (SD) of World Health Criteria. The BMD diagnosis of normal, low bone mass, osteoporosis and severe or established osteoporosis is based on the WHO diagnostic classification:

- Normal: T-score within 1 SD of a young normal adult
- Osteopenia: T-score of -1 to 2.5 SD below that of a young normal adult
- Osteoporosis: T-score of -2.5 or less SD below that of a young normal adult
- Severe osteoporosis: T-score of -2.5 or less SD below normal with fragility fractures

Pharmacologic Agents/Conventional Therapy
Drugs to treat osteoporosis may be classified into two groups, 1) the anti-resorptive drugs, which slow down bone resorption, and 2) anabolic drugs, which stimulate bone formation. The anti-resorptive drugs include bisphosphonates, raloxifene, calcitonin and the new IgG2 monoclonal antibody, denusomab, which suppresses the RANKL pathway. Parathyroid hormone increases bone formation and is the only anabolic drug. All drugs require adequate serum levels of calcium and vitamin D for optimum effect.

Denosumab is the first monoclonal antibody approved in the U.S. for the treatment of postmenopausal osteoporosis. The drug was approved by the FDA on June 1, 2010. It inhibits osteoclast-mediated bone resorption; thus, it is an antiresorptive agent like the bisphosphonates but has a different mechanism of action. Denosumab is a fully human monoclonal antibody which specifically targets the receptor activity of nuclear factor kappa B ligand (RANKL). RANKL is a protein which is essential for the formation, survival and function of osteoclasts, which are the cells responsible for bone resorption.

Denosumab is marketed as two brands, Prolia and XGEVA, which are indicated for different therapeutic uses and unique dosing schedules and indications for use. The manufacturer recommends that patients receiving Prolia should not receive XGEVA and vice versa.

- The most frequently observed adverse reactions (more than 5% and greater than placebo) reported with denosumab therapy include back pain, pain in extremity, hypercholesterolemia, musculoskeletal pain, and cystitis. Other common adverse reactions are various types of infections, anemia, vertigo, peripheral edema, and sciatica. The frequency of most adverse reactions did not differ between the denosumab and placebo treatment groups. Serious adverse reactions have included hypocalcemia, serious infections, dermatologic reactions, pancreatitis, and osteonecrosis of the jaw.

OSTEOPOROSIS

Treatment in Postmenopausal Women at High Risk for Fracture

Denosumab (Prolia) is used in the treatment of osteoporosis in postmenopausal women at high risk for fracture, defined as a history of osteoporotic fracture or multiple risk factors for fracture. Denosumab (Prolia) also is used in the treatment of osteoporosis in postmenopausal women who have failed or are intolerant of other osteoporosis therapies.

Fracture Reduction Evaluation of Denosumab in Osteoporosis Every 6 Months (FREEDOM) trial

FREEDOM is the largest pivotal trial conducted with denosumab. This trial a randomized, double-blind, placebo-controlled, multinational study (Cummings SR, et al. 2009) evaluating the efficacy of denosumab in preventing fractures in postmenopausal women with osteoporosis.

- 7,868 women aged 60-90 years with lumbar, spine, or total hip bone mineral density (BMD) T-score < -2.5 (but ≥ -4) were randomized to denosumab 60 mg vs. placebo subcutaneously every 6 months for 36 months
- All women received calcium ≥ 1 g/day and vitamin D ≥ 400 units/day orally
- 60 women from 1 center excluded due to unreliability of data
- 76% received all injections
- Cumulative incidence comparing denosumab vs. placebo
  - vertebral fracture in 2.3% vs. 7.2% ($p < 0.001$, NNT 21)
  - clinical vertebral fracture in 0.8% vs. 2.6% ($p < 0.001$, NNT 56)
  - non-vertebral fracture in 6.5% vs. 8% ($p = 0.01$, NNT 67)
  - hip fracture in 0.7% vs. 1.2% ($p = 0.04$, NNT 200)
- No significant differences in risk of cancer, infection, cardiovascular disease, delayed fracture healing, or hypocalcemia
- Denosumab associated with more eczema, flatulence, and serious adverse events of cellulitis (though no significant difference in overall cellulitis incidence)
- No cases of osteonecrosis of jaw
- Baseline BMD T-scores were between −2.5 and −4 measured at the lumbar spine or total hip.
- The primary outcome was the incidence of new morphometric (radiologically diagnosed) vertebral fractures at 3 years. The secondary outcomes were the incidence of hip and non-vertebral fractures.
- Exclusions
  - Women were excluded from the study if they had diseases that influence bone metabolism (e.g., rheumatoid arthritis, osteogenesis imperfecta, Paget's disease) or were receiving other drugs that affect bone metabolism.
  - Women with a history of more than 3 years of oral bisphosphonate therapy or any history of IV bisphosphonate therapy were excluded from the study; those who had received oral bisphosphonates for less than 3 years and had not received such therapy for at least 12 months could be included.
- The BMD increased at all anatomic sites. The treatment difference in BMD was increased by 8.8% at the lumbar spine, 6.4% at the total hip, and 5.2% at the femoral neck after 3 years. The BMD returned to baseline values within 12 months of discontinuation of therapy. Bone biopsies of the iliac crest were done in a subgroup of this study population (45 patients in the placebo group and 47 patients in the denosumab group). The median eroded surface was reduced by more than 80% and osteoclasts were absent from more than 50% of the biopsies in the denosumab group. Double labeling in trabecular bone was observed in 94% of the placebo group and 19% of the denosumab group.
- Results: Denosumab was more effective than placebo in reducing the rate of new morphometric vertebral fractures at 1, 2, and 3 years. Treatment with denosumab was associated with a 68% relative risk reduction in new vertebral fractures diagnosed using semi-quantitative radiographic assessments. At 3 years, 2.3% of women receiving denosumab had experienced a new vertebral fracture compared with 7.2% of women receiving placebo. In addition, at 3 years, treatment with denosumab was associated with a 20% relative risk reduction in new non-vertebral fractures and a 40% relative risk reduction in new hip fractures.

Treatment in Men at High Risk for Fracture

Denosumab (Prolia) is used in the treatment of osteoporosis in men at high risk for fracture, defined as a history of osteoporotic fracture or multiple risk factors for fracture. Denosumab (Prolia) also is used in the treatment of osteoporosis in men who have failed or are intolerant of other osteoporosis therapies.

Study to Compare the Efficacy and Safety of DenosumAb versus Placebo in Males with Osteoporosis

In a 1-year, randomized, double-blind, placebo-controlled study in men with osteoporosis, those receiving denosumab (Prolia) had greater increases in BMD than those receiving placebo (Orwoll E, et al. 2012). A total of 242 men 31-84 years of age (mean age 65 years) with baseline BMD t-scores between -2 and -3.5 (lumbar spine or femoral neck) or baseline lumbar spine BMD t-scores between -1 and -3.5 and a prior history of major osteoporotic fracture were randomized to receive either denosumab (60 mg) or placebo subcutaneously every 6 months. Men were excluded from the study if they had diseases that affect bone (e.g., rheumatoid arthritis, osteogenesis imperfecta, Paget's disease) or were receiving other drugs that affect bone. All patients were instructed to take at least 1 g of calcium and 800 units of vitamin D daily. The treatment difference in mean lumbar spine BMD from baseline to 1 year was 4.8% (5.7% increase in those receiving denosumab versus 0.9% increase in those receiving placebo). The treatment difference in mean BMD at the total hip or femoral neck from baseline to 1 year in those receiving denosumab versus placebo was 2 or 2.2%, respectively.[1] Consistent effects on BMD at the lumbar spine were reported regardless of age, race, baseline BMD, testosterone concentrations, and level of bone turnover.

BONE LOSS

Bone Loss Associated with Androgen Deprivation Therapy

Treatment in Men with Non-metastatic Prostate Cancer at High Risk for Fracture

Denosumab (Prolia) is used to increase bone mass in men at high risk for fracture receiving androgen deprivation therapy for non-metastatic prostate cancer. Denosumab also has reduced the incidence of vertebral fractures in these patients.

Denosumab in men receiving androgen-deprivation therapy for prostate cancer

In a 3-year, randomized, double-blind, placebo-controlled, phase 3 study in men receiving androgen deprivation therapy for non-metastatic prostate cancer, those receiving denosumab (Prolia) had greater increases in lumbar spine BMD from baseline to 2 years than those receiving placebo (Smith MR, et al. 2009). A total of 1468 men who were either 70 years of age or older or younger than 70 years of age with baseline BMD T-scores below -1 or history of prior osteoporotic fracture (mean age 75 years, mean baseline lumbar spine BMD T-score -0.4) were randomized to receive subcutaneous denosumab (60 mg) or placebo once every 6 months for a total of 6 doses. All patients were instructed to take at least 1 g of calcium and 400 units of vitamin D daily. The treatment difference in mean lumbar spine BMD from baseline to 2 years was 6.7% (5.6% increase in those receiving denosumab versus 1% decrease in those receiving placebo). At 3 years, the treatment difference in BMD from baseline in those receiving denosumab versus placebo was 7.9, 5.7, and 4.9% at the lumbar spine, total hip, and femoral neck, respectively. In addition, at 3 years, the cumulative incidence of new vertebral fractures was lower in men receiving denosumab (1.5%) than in those receiving placebo (3.9%).

Bone Loss Associated with Aromatase Inhibitor Therapy

Treatment in Women with Breast Cancer at High Risk for Fracture
Denosumab (Prolia) is used to increase bone mass in women at high risk for fracture receiving adjuvant aromatase inhibitor therapy for breast cancer.

Randomized trial of denosumab in patients receiving adjuvant aromatase inhibitors for non-metastatic breast cancer
In a 2-year, randomized, double-blind, placebo-controlled, phase 3 study in women receiving adjuvant aromatase inhibitor therapy for breast cancer who had low bone mass (BMD T-score -2.5 to -1), those receiving denosumab (Prolia) had greater increases in lumbar spine BMD from baseline to 1 year than those receiving placebo (Ellis GK, et al. 2008). A total of 252 women (median age 59 years, mean baseline lumbar spine BMD T-score -1.1) were randomized to receive subcutaneous denosumab (60 mg) or placebo once every 6 months for a total of 4 doses. All patients were instructed to take at least 1 g of calcium and 400 units of vitamin D daily. The treatment difference in BMD at the lumbar spine from baseline to 1 year was 5.5% (4.8% increase in those receiving denosumab versus 0.7% decrease in those receiving placebo). At 2 years, the treatment difference in BMD from baseline in those receiving denosumab versus placebo was 7.6, 4.7, and 3.6% at the lumbar spine, total hip, and femoral neck, respectively. A subsequent analysis revealed that the beneficial effects of denosumab were consistent across key clinical subgroups (i.e., duration of aromatase inhibitor therapy, type of aromatase inhibitor, prior tamoxifen use, age, time since menopause, baseline body mass index, baseline T-scores) (Ellis GK, et al. 2008).

DEFINITIONS

Adjuvant Treatment: Additional cancer treatment given after the primary treatment to lower the risk that the cancer will return. Adjuvant therapy may include chemotherapy, radiation therapy, hormone therapy, targeted therapy, or biologic therapy. Adjuvant therapy can be used after or in combination with another form of cancer therapy and is commonly used following removal of a cancerous tumor to further help in treatment.

Androgen deprivation: loss or absence of androgen.

Bone mineral density (BMD): useful in the diagnosis of osteoporosis. It is usually provided as the T score -- the number of standard deviations (SDs) the BMD falls below or above the mean value in a reference population (young, healthy adults). The World Health Organization (WHO) osteoporosis diagnostic classification assessment (1994) defines osteoporosis as a T score of 2.5 or more SDs below the mean (i.e., less than -2.5). Osteopenia is defined as a T score of -1.0 to -2.5; and a T score of -1.0 or higher is considered normal.

FRAX tool: The World Health Organization developed this risk assessment tool to assist clinicians in evaluating osteopenic patients. The algorithms take clinically proven risk factors to determine a 10 year probability of hip fracture and a 10 year probability for a major osteoporotic fracture. The US National Osteoporosis Foundation recommends treatment of osteopenic patients whose FRAX score for hip fracture is 3% or greater, or whose risk for other bone fracture is greater than 20%.

Osteopenia: reduced bone mass due to the decrease in the rate of osteoid synthesis to a level insufficient to compensate normal bone lysis. The World Health Organization (WHO) defines osteopenia as a T-score at the femoral neck of between –1.0 SD and –2.5 SD below the young female adult mean.

Osteoporosis: Osteoporosis is defined by the World Health Organization (WHO) as a bone mineral density (BMD) value for the hip, spine, or wrist of 2.5 standard deviations (SD) or more below the mean for healthy young white women, or a T-score of less than or equal to – 2.5. The disease is characterized by an increased risk of fractures, which can result in pain, diminished quality of life, decreased physical mobility and independence, inability to work, and increased burden on caregivers.

RANKL (Receptor Activator for Nuclear Factor κ B Ligand): also known as TNF-related activation-induced cytokine (TRANCE), osteoprotegerin ligand (OPGL), and ODF (osteoclast differentiation factor), is a molecule important in bone metabolism. This natural and necessary surface-bound molecule found on osteoblasts serves to activate osteoclasts, which are the cells involved in bone resorption. Overproduction of RANKL is implicated in a variety of degenerative bone diseases, such as rheumatoid arthritis and psoriatic arthritis.

T-score is the number of standard deviations the individual's bone density is above or below number normally expected in a healthy young adult of the same sex. A T-score between −1 and −2.5 indicates low bone mass, although not low enough to be diagnosed as osteoporosis. A T-score of −2.5 or lower indicates osteoporosis.

APPENDIX

APPENDIX 1: Osteonecrosis of the jaw (ONJ)

Osteonecrosis of the jaw (ONJ), also referred to as medication-related osteonecrosis of the jaw (MRONJ), has been reported in patients receiving denosumab. ONJ may manifest as jaw pain, osteomyelitis, osteitis, bone erosion, tooth/periodontal infection, toothache, gingival ulceration/erosion. Risk factors include invasive dental procedures (e.g., tooth extraction, dental implants, oral surgery), cancer diagnosis, immunosuppressive therapy, angiogenesis inhibitor therapy, chemotherapy, systemic corticosteroids, poor oral hygiene, use of a dental appliance, ill-fitting dentures, periodontal and/or other preexisting dental disease, diabetes and gingival infections, local infection with delayed healing, anemia, and/or coagulopathy. In studies of patients with cancer, a longer duration of denosumab exposure was associated with a higher incidence of ONJ, although a majority of patients had predisposing factors, including a history of poor oral hygiene, tooth extraction, or the use of a dental appliance. Patients should maintain good oral hygiene during treatment. A dental exam and appropriate preventive dentistry should be performed prior to therapy. The manufacturer's labeling recommends avoiding invasive dental procedures in patients with bone metastases receiving denosumab for prevention of skeletal-related events and to consider temporary discontinuation of therapy in these patients if invasive dental procedure is required. [Prolia (denosumab) [prescribing information]. Thousand Oaks, CA: Amgen Inc.; May 2017.]

According to a position paper by the American Association of Maxillofacial Surgeons (AAOMS), MRONJ has been associated with bisphosphonates and other antiresorptive agents (denosumab), and antiangiogenic agents (e.g., bevacizumab, sunitinib) used for the treatment of osteoporosis or malignancy; risk is significantly higher in cancer patients receiving antiresorptive therapy compared to patients receiving osteoporosis treatment (regardless of medication used or dosing schedule). MRONJ risk is increased with intravenous antiresorptive therapy compared to the minimal risk associated with oral bisphosphonate use, although risk appears to increase with oral bisphosphonates when duration of therapy exceeds 4 years. The AAOMS suggests that if medically permissible, initiation of denosumab for cancer therapy should be delayed until optimal dental health is attained (if extractions are required, antiresorptive therapy should delayed until the extraction site has mucosalized or until after adequate osseous healing). Once denosumab is initiated for oncologic disease, procedures that involve direct osseous injury and placement of dental implants should be avoided. Patients developing ONJ during therapy should receive care by an oral surgeon. [Ruggiero SL, Dodson TB, Fantasia J, et al; American Association of Oral and Maxillofacial Surgeons. American Association of Oral and Maxillofacial Surgeons position paper on medication-related osteonecrosis of the jaw—2014 update. J Oral Maxillofac Surg. 2014;72(10):1938-1956.[PubMed 25234529]10.1016/j.joms.2014.04.031]

According to the manufacturer, discontinuation of denosumab should be considered (based on risk/benefit evaluation) in patients who develop ONJ.

CODING INFORMATION: THE CODES LISTED IN THIS POLICY ARE FOR REFERENCE PURPOSES ONLY. LISTING OF A SERVICE OR DEVICE CODE IN THIS POLICY DOES NOT IMPLY THAT THE SERVICE DESCRIBED BY THIS CODE IS A COVERED OR NON-COVERED. COVERAGE IS DETERMINED BY THE BENEFIT DOCUMENT. THIS LIST OF CODES MAY NOT BE ALL INCLUSIVE.

CPT	Description
NA	

HCPCS	Description
J0897	Injection, denosumab, 1 mg

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Policy History	MCPC
Policy Developed	10/31/12
Revision	4/5/16
Revision: This policy was reviewed and updated for MCPC review on 3/8/2018. The revision included a comprehensive review and update of all content in the policy, including the clinical evidence, coverage criteria, practice guidelines, appendices and reference sections. There were no major revisions to criteria with the exception of informational notes and wordsmithing for clarity. *AMR Peer Review Network. 2/22/2018. Practicing Physician. Board certified in Internal Medicine, Rheumatology*	3/8/18