Original Effective Date: 07/01/2012
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Last P&T Approval/Version: 07/27/2022
Next Review Due By: 07/2023
Policy Number: C8848-A

Prolia (denosumab)

PRODUCTS AFFECTED

Prolia (denosumab), Xgeva (denosumab)- See Xgeva Prior Authorization Criteria

COVERAGE POLICY

Coverage for services, procedures, medical devices, and drugs are dependent upon benefit eligibility as outlined in the member's specific benefit plan. This Coverage Guideline must be read in its entirety to determine coverage eligibility, if any.
This Coverage Guideline provides information related to coverage determinations only and does not imply that a service or treatment is clinically appropriate or inappropriate. The provider and the member are responsible for all decisions regarding the appropriateness of care. Providers should provide Molina Healthcare complete medical rationale when requesting any exceptions to these guidelines.

Documentation Requirements:
Molina Healthcare reserves the right to require that additional documentation be made available as part of its coverage determination; quality improvement; and fraud; waste and abuse prevention processes. Documentation required may include, but is not limited to, patient records, test results and credentials of the provider ordering or performing a drug or service. Molina Healthcare may deny reimbursement or take additional appropriate action if the documentation provided does not support the initial determination that the drugs or services were medically necessary, not investigational, or experimental, and otherwise within the scope of benefits afforded to the member, and/or the documentation demonstrates a pattern of billing or other practice that is inappropriate or excessive.

DIAGNOSIS:
Osteoporosis at high risk for fracture, treatment of glucocorticoid-induced osteoporosis, men at high risk for fracture and receiving androgen deprivation therapy (ADT) for non-metastatic prostate cancer, women at high risk for fracture receiving adjuvant aromatase inhibitor therapy for breast cancer

REQUIRED MEDICAL INFORMATION:
This clinical policy is consistent with standards of medical practice current at the time that this clinical policy was approved. If a drug within this policy receives an updated FDA label within the last 180 days, medical necessity for the member will be reviewed using the updated FDA label information along with state and federal requirements, benefit being administered and formulary preferencing. Coverage will be determined on a case-by case basis until the criteria can be updated through Molina Healthcare, Inc. clinical governance. Additional information may be required on a case-by-case basis to allow for adequate review.

A. POSTMENOPAUSAL OSTEOPOROSIS AND MEN WITH OSTEOPOROSIS AT HIGH RISK OF FRACTURE:
   1. Documented diagnosis of postmenopausal osteoporosis in women who are at a high risk

of fracture, OR osteoporosis in men
AND

2. (a) The member has had a T-score (current or at any time in the past) at or below -2.5 at the lumbar spine, femoral neck, total hip, and/or 33% (one-third) radius (wrist); OR
   (b) The member has had an osteoporotic fracture or a fragility fracture of the spine, hip, proximal humerus, pelvis, or distal forearm OR
   (c) The member has low bone mass (T-score [current or at any time in the past] between -1.0and -2.5 at the lumbar spine, femoral neck, total hip and/or 33% [one-third] radius [wrist]) and the prescriber determines the member is at high risk for fracture
   AND
3. Documentation of failure (12-month trial), contraindication, or intolerance to oral AND IV bisphosphonate therapy (Document drug, date, and duration of trial) NOTE: Treatment failure is defined by progression of bone loss as documented by bone density measurements (BMD) after at least 12 months of therapy OR Occurrence of an osteoporotic fracture after having been compliant on at least 12 months of therapy on an oral bisphosphonate
   AND
4. Prescriber attestation of the following: 1) Hypocalcemia was reviewed and corrected prior to initiation of treatment, AND 2) Member has been counseled to concurrently take calcium (1000 mg) and vitamin D (400-1200 international units) supplements in conjunction with Prolia (denosumab).

B. FOR GLUCOCORTICOID-INDUCED OSTEOPOROSIS ONLY:

1. Documentation of history of prednisone or its equivalent at a dose of > 5 mg/day for > 3 months
   AND
2. (a) The member has had a T-score (current or at any time in the past) at or below -2.5 at the lumbar spine, femoral neck, total hip, and/or 33% (one-third) radius (wrist)
   OR
   (b) The member has had an osteoporotic fracture or a fragility fracture of the spine, hip, proximal humerus, pelvis, or distal forearm
   OR
   (c) Fracture Risk Assessment Tool (FRAX) (GC-adjusted) 10-year risk of major osteoporotic fracture score of 20% or greater OR FRAX (GC-adjusted) 10-year risk of hip fracture score of 3% or greater indicating member is at high risk for fracture
   AND
3. Must have tried and failed one oral generic and one intravenous generic bisphosphonate therapy unless contraindicated or intolerant
   AND
4. Prescriber attestation of the following: 1) Hypocalcemia was reviewed and corrected prior to initiation of treatment, AND 2) Member has been counseled to concurrently take calcium (1000 mg) and vitamin D (400-1200 international units) supplements in conjunction with Prolia (denosumab)

C. CANCER INDUCED BONE LOSS:

1. Diagnosis of hormone receptor positive breast cancer OR non-metastatic prostate cancer
   AND
2. Documentation member is currently or has received androgen deprivation therapy for nonmetastatic prostate cancer OR member is at high risk for bone fractures after receiving adjuvant aromatase inhibitor therapy for breast cancer
   AND
3. Must have tried and failed ONE of the following: zoledronic acid (Zometa), pamidronate, OR oral bisphosphonate
   AND
4. Prescriber attestation of the following: 1) Hypocalcemia was reviewed and corrected prior to initiation of treatment, AND 2) Member has been counseled to concurrently take calcium

(1000 mg) and vitamin D (400-1200 international units) supplements in conjunction with Prolia (denosumab)

CONTINUATION OF THERAPY:

A. FOR ALL INDICATIONS:

1. Adherence to therapy at least 85% of the time as verified by Prescriber and member's medication fill history
   AND
2. a) 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
   OR
   b) Member is currently or has received androgen deprivation therapy for nonmetastatic prostate cancer OR member is at high risk for bone fractures after receiving adjuvant aromatase inhibitor therapy for breast cancer

DURATION OF APPROVAL:

Initial authorization: 12 months. Continuation of therapy: 12 months

PRESCRIBER REQUIREMENTS:

None

AGE RESTRICTIONS:

18 years of age and older

QUANTITY:

One injection (60MG) every 6 months OR two (2) injections per year

Maximum Quantity Limits – 2 injections per year

PLACE OF ADMINISTRATION:

The recommendation is that injectable medications in this policy will be for pharmacy or medical benefit coverage and the SC injectable products administered in a place of service that is a non-hospital facility-based location as per the Molina Health Care Site of Care program.

Note: Site of Care Utilization Management Policy applies for Prolia (denosumab). For information on site of care, see
Specialty Medication Administration Site of Care Coverage Criteria (molinamarketplace.com)

DRUG INFORMATION

ROUTE OF ADMINISTRATION:

Subcutaneous

DRUG CLASS:

RANK Ligand (RANKL) Inhibitors

FDA-APPROVED USES:

Osteoporosis in postmenopausal females: For the treatment of postmenopausal women 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 therapies.
Osteoporosis in males: 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

Androgen deprivation-induced bone loss in males with prostate cancer: Treatment to increase bone mass in men at high risk for fracture receiving androgen deprivation therapy (ADT) for non- metastatic prostate cancer, Aromatase inhibitor- induced bone loss in females with breast cancer: Treatment to increase bone mass in women at high risk for fracture receiving adjuvant aromatase inhibitor therapy for breast Cancer Glucocorticoid-Induced Osteoporosis: Treatment of glucocorticoid-induced osteoporosis in men and women at high risk of fracture who are either initiating or continuing systemic glucocorticoids in a daily dosage equivalent to 7.5 mg or greater of prednisone and expected to remain on glucocorticoids for at least 6 months. High risk of fracture is defined as a history of osteoporotic fracture, multiple risk factors for fracture, or patients who have failed or are intolerant to other available osteoporosis therapy

COMPENDIAL APPROVED OFF-LABELED USES:
None

APPENDIX

APPENDIX:
Appendix A.

- Clinical reasons to avoid oral bisphosphonate therapy
- Esophageal abnormality that delays emptying such as stricture of achalasia
- Active upper gastrointestinal problem (e.g., dysphagia, gastritis, duodenitis, erosive esophagitis, ulcers)
- Inability to stand or sit upright for at least 30 to 60 minutes
- Renal insufficiency (creatinine clearance < 30 to 35 ml/min)

Appendix B.
WHO Fracture Risk Assessment Tool 10-year probability of major osteoporotic fracture; calculation tool available at: http://www.shef.ac.uk/FRAX/tool.jsp

BACKGROUND AND OTHER CONSIDERATIONS

BACKGROUND:
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 etal. 2017). Vertebral fractures have been reported 8-16 months after stopping denosumab (AD Anastasilakis etal. 2017).
Drug holidays are not recommended. If denosumab is stopped, administering another drug, typically 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 members with osteoporosis. Initial therapy for most members 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 member 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 members, 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.

CONTRAINDICATIONS/EXCLUSIONS/DISCONTINUATION:

All other uses of Prolia (denosumab) are considered experimental/investigational and therefore, will follow Molina's Off-Label policy. Contraindications to Prolia (denosumab) include: Hypersensitivity (systemic) to denosumab or any component of the formulation; Pregnancy [Category X (Prolia); Pre-existing hypocalcemia (must be corrected prior to initiating denosumab treatment); Concomitant treatment with IV bisphosphonate or Xgeva
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.

OTHER SPECIAL CONSIDERATIONS:

Osteoporosis
Serial bone mineral density (BMD) should be evaluated at baseline and every 1 to 3 years (usually at approximately 2 years following initiation of therapy, then more or less frequently depending on patient-specific factors and stability of BMD) [Camacho PM, et al. AACE/ACE 2020; Cosman F, et al. National Osteoporosis Foundation 2014; Eastell R, et al. Endocrine Society 2019]

May consider monitoring biochemical markers of bone turnover (e.g., fasting serum C-terminal crosslinking telopeptide or urinary N-terminal telopeptide) at baseline, 3 months, and 6 months, to assess treatment response (Eastell R, et al. Endocrine Society 2019)

CODING/BILLING INFORMATION

Note: 1) This list of codes may not be all-inclusive. 2) Deleted codes and codes which are not effective at the time the service is rendered may not be eligible for reimbursement

HCPCS CODE	DESCRIPTION
J0897	Injection, denosumab, 1 mg

AVAILABLE DOSAGE FORMS:

REFERENCES

1. Prolia (denosumab) [prescribing information]. Thousand Oaks, CA: Amgen Inc; May 2022.
2. National Comprehensive Cancer Network. 2022. Prostate Cancer (Version 4.2022). [online] Available at < https://www.nccn.org/professionals/physician_gls/pdf/prostate.pdf> [Accessed 15 June 2022].National Comprehensive Cancer Network. 2022. Breast Cancer (Version 3.2022). [online]. Available at < https://www.nccn.org/professionals/physician_gls/pdf/breast.pdf. [Accessed 15 June 2022].
3. Cosman F, de Beur SJ, LeBoff MS, et al; National Osteoporosis Foundation. Clinician's guideto prevention and treatment of osteoporosis [published correction appears in Osteoporos Int. 2015;26(7):2045-2047]. Osteoporos Int. 2014;25(10):2359-2381. [PubMed 25182228]10.1007/s00198-014-2794-2
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6. Watts NB, Adler RA, Bilezikian JP, et al. Osteoporosis in men: an Endocrine Society clinical practice guideline. J Clin Endocr Metab. 2012;97(6):1802-1822.
7. FRAX® WHO fracture risk assessment tool. © World Health Organization Collaborating Centre for Metabolic Bone Diseases: University of Sheffield, UK. Available at: http://www.shef.ac.uk/FRAX
8. Camacho, P., Petak, S., Binkley, N., Diab, D., Eldeiry, L., Farooki, A., Harris, S., Hurley, D., Kelly, J., Lewiecki, E., Pessah-Pollack, R., McClung, M., Wimalawansa, S. and Watts, N., 2020. American Association of Clinical Endocrinologists/American College of Endocrinology Clinical Practice Guidelines for the Diagnosis and Treatment of Postmenopausal Osteoporosis—2020 Update. Endocrine Practice, 26, pp.1-46
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10. Watts NB, Adler RA, Bilezikian JP, et al; Endocrine Society. Osteoporosis in men: An Endocrine Society clinical practice guideline. J Clin Endocrinol Metab. 2012;97(6):1802- 1822. [PubMed 22675062]10.1210/jc.2011-3045

SUMMARY OF REVIEW/REVISIONS	DATE
REVISION- Notable revisions: Required Medical Information Continuation of Therapy Appendix Background Contraindications/Exclusions/Discontinuation Other Special Considerations References	P&T QUARTER/YEAR
Q2 2022 Established tracking in new format	Historical changes on file