09-J1000-25

Original Effective Date: 08/15/10

Reviewed: 09/10/25

Revised: 10/15/25

Subject: Denosumab Products (Prolia™; Xgeva™ and biosimilars)

THIS MEDICAL COVERAGE GUIDELINE IS NOT AN AUTHORIZATION, CERTIFICATION, EXPLANATION OF BENEFITS, OR A GUARANTEE OF PAYMENT, NOR DOES IT SUBSTITUTE FOR OR CONSTITUTE MEDICAL ADVICE. ALL MEDICAL DECISIONS ARE SOLELY THE RESPONSIBILITY OF THE PATIENT AND PHYSICIAN. BENEFITS ARE DETERMINED BY THE GROUP CONTRACT, MEMBER BENEFIT BOOKLET, AND/OR INDIVIDUAL SUBSCRIBER CERTIFICATE IN EFFECT AT THE TIME SERVICES WERE RENDERED. THIS MEDICAL COVERAGE GUIDELINE APPLIES TO ALL LINES OF BUSINESS UNLESS OTHERWISE NOTED IN THE PROGRAM EXCEPTIONS SECTION.

Position Statement	Dosage/ Administration	Billing/Coding	Reimbursement	Program Exceptions	Definitions
Related Guidelines	Other	References	Updates		

DESCRIPTION:

Denosumab (Prolia™, Xgeva™) is a fully human monoclonal antibody against receptor activator of nuclear factor κ-β ligand (RANKL) and inhibits its action on the surface receptors expressed on osteoclasts. This causes reduced osteoclast formation, function and survival, consequently decreasing bone resorption, increasing bone mass, and strengthening both cortical and trabecular bone. The role of excessive RANKL as a contributor to conditions characterized by bone loss or bone destruction has been well studied. A comprehensive clinical development program for denosumab resulted in a robust data set that supported global and regulatory approvals of the RANKL-targeted antibody denosumab in the bone loss and cancer inducted bone destruction settings.

About 10 million Americans (80% who are women) are estimated to have osteoporosis. In women over 50, one out of two will have an osteoporosis-related fracture in their remaining lifetime leading to significant healthcare costs. A T-score based on a dual energy x-ray (DXA) measurement is used to classify patients as being normal (-1 or more), having osteopenia (-1 to -2.5), or having osteoporosis (-2.5 or less). Denosumab was initially approved (as Prolia) by the FDA in June 2010 for the treatment of osteoporosis in postmenopausal women who are at high risk for fracture or have failed or did not tolerate other treatment. The initial approval was expanded to include the treatment of men at high risk for fractures, osteoporosis prophylaxis in women at high risk for bone fractures after receiving adjuvant aromatase inhibitor therapy for breast cancer, and osteoporosis prophylaxis in men at high risk for bone fractures after receiving androgen deprivation therapy for non-metastatic prostate cancer. Denosumab (as Xgeva) was approved in 2010 for the prevention of skeletal-related events (SRE) in individuals with bone metastases from solid tumors and in 2018 for prevention of SRE in patients with multiple myeloma. Denosumab (as Xgeva) is also approved for the treatment of hypercalcemia of malignancy

and treatment of giant cell tumor of bone that is unresectable or where surgical resection is likely to result in severe morbidity.

There are limited head-to-head studies comparing denosumab to other agents for osteoporosis prophylaxis in men (secondary to androgen deprivation therapy) or women (secondary to aromatase inhibitor therapy). However, data from a meta-analysis of four randomized, double-blind, controlled clinical trials including the Determining Efficacy: comparison of initiation denosumab versus alendronate (DECIDE) trial, showed no significant difference in fracture risk reduction between denosumab and alendronate (44 vs. 24 events, respectively; odds ratio 1.42, 95% CI 0.84 to 2.4, p=0.19), although denosumab was associated with greater increases in bone mineral density (BMD). All studies enrolled postmenopausal women aged 60.3 to 68.2 years who had low bone mass (all T-scores between -1.4 to 2.6). Omitting any single trial from analysis did not influence the fracture risk reduction outcomes and heterogeneity was not significant across the studies.

In individuals with advanced cancer, bone metastases can have significant clinical consequences such as bone pain, pathological fractures, or spinal cord compression that may result in physical and functional impairment, and increased mortality. Intravenous bisphosphonates, predominantly zoledronic acid (Zometa), are effective at reducing SREs. Several well-designed clinical studies have evaluated the efficacy of denosumab versus zoledronic acid in individuals with bone metastases secondary to solid tumors. In a phase 3 double-blind, double-dummy, non-inferiority trial, subjects with advanced breast cancer and bone metastases were equally randomized to denosumab 120 mg subcutaneously (SQ) or zoledronic acid 4 mg intravenously (IV) every four weeks and stratified according to history of previous SRE, treatment with chemotherapy prior to randomization, prior oral bisphosphonate therapy, and region. The primary outcome was the time to first SRE. Subjects treated with denosumab had an 18% reduction in the risk of first SRE when compared to subjected treated with zoledronic acid, demonstrating both the non-inferiority and superiority of denosumab therapy when compared to zoledronic acid ($p<0.001$ for non-inferiority, and $p=0.01$ for superiority). In a similarly designed study, denosumab was superior to zoledronic acid for delay of time to first SRE by 3.6 months in men with bone metastases from castrate-resistant prostate cancer. In a subset of patients with bone metastases from lung cancer, an improved median overall survival was demonstrated with denosumab as compared to zoledronic acid (9.5 versus 8 months; hazard ratio 0.78). Although denosumab was superior to zoledronic acid in the settings of breast cancer, prostate cancer and lung cancer, it was not superior when compared to zoledronic acid in subjects with other solid tumors. In an international, randomized, double-blind, double-dummy non-inferiority trial, adults with solid tumors other than breast and castrate-resistant prostate cancer with bone metastases were randomized to 120 mg denosumab SQ or 4 mg zoledronic acid IV. Denosumab demonstrated non-inferiority to zoledronic acid in the time to first SRE, but the difference was not statistically significantly different in the superiority analysis (20.6 months vs. 16.3 months, respectively; HR 0.84, 95% CI 0.71-0.98, $p<0.001$ for non-inferiority; $p=0.06$ for superiority). Denosumab has also demonstrated non-inferiority to zoledronic acid in delaying the time to first SRE in patients with lytic lesions due to multiple myeloma.

POSITION STATEMENT:

I. **Initiation of** denosumab (Prolia™, Xgeva™) **meets the definition of medical necessity** when the following are met:

1. When used for an indication in Table 1 and **ALL** of the indication-specific criteria are met
2. For Prolia or Conexxence requests only, the member has an inadequate response, contraindication, or intolerance to Jubbonti **AND** Stoboclo - documentation must be submitted
3. For Xgeva or Bomyntra requests only, the member has an inadequate response, contraindication, or intolerance to Wyost **AND** Osenvelt - documentation must be submitted

Table 1

Indications and Specific Criteria	
Indication	**Criteria**
Prolia and biosimilars (Conexxence, Jubbonti, Stoboclo) **(duration of approval: 1 year)**	
Postmenopausal Osteoporosis or Osteoporosis in biological males	**When ALL of the following are met:** a. Member meets **ONE** of the following: i. Member has a diagnosis of osteoporosis ii. Member has a BMD T-score between -1.0 and -2.5[a] and **ONE** of the following: i. FRAX[b] 10-year probability of major osteoporotic fracture ≥ 20% ii. FRAX[b] 10-year probability of hip fracture ≥ 3% iii. Fragility fracture b. Denosumab will not be used in combination with other antiresorptive or anabolic agents (e.g., bisphosphonates, parathyroid hormone analogs, or romosozumab) c. The dose does not exceed 60 mg SQ every 6 months d. **ONE** of the following: i. Member had an inadequate response or intolerance to bisphosphonate therapy (oral or IV) ii. Member is not a candidate for bisphosphonate therapy iii. Member has a history of a fragility or osteoporotic fracture iv. Member is at high risk of falls or has a history of falls v. Member has a BMD T-score of -3.0 or lower[a]

	vi. FRAX[b] 10-year probability of major osteoporotic fracture ≥ 30% vii. FRAX[b] 10-year probability of hip fracture ≥ 4.5%
Non-metastatic Prostate Cancer-Increase bone mass	**When ALL of the following are met:** 1. Member is diagnosed with non-metastatic prostate cancer 2. Member is receiving androgen deprivation therapy (e.g., surgical castration, medical castration, gonadotropin-releasing hormone agonist) 3. Member meets **ONE** of the following: a. Pre-treatment BMD T-score of -1 or lower[a] b. Member has a history of a fragility fracture 4. Denosumab will not be used in combination with other antiresorptive or anabolic agents (e.g., bisphosphonates, parathyroid hormone analogs, or romosozumab) 5. The dose does not exceed 60 mg SQ every 6 months
Breast Cancer-Increase bone mass	**When ALL of the following are met:** 1. Member is receiving concomitant aromatase inhibitor therapy (e.g., anastrozole [Arimidex], letrozole [Femara], exemestane [Aromasin]) as adjuvant therapy 2. Denosumab will not be used in combination with other antiresorptive or anabolic agents (e.g., bisphosphonates, parathyroid hormone analogs, or romosozumab) 3. Dose does not exceed 60 mg SQ every 6 months 4. **EITHER** of the following: a. Member had an inadequate response or intolerance to bisphosphonate therapy (oral or IV) b. Member is not a candidate for bisphosphonate therapy

Glucocorticoid-induced osteoporosis	**When ALL of the following are met:** 1. History of prednisone or its equivalent at a dose of 2.5 mg/day or greater for 3 months or more 2. Member meets **ONE** of the following: a. Member has a diagnosis of osteoporosis b. Member has a BMD T-score between -1.0 and -2.5[a] and **ONE** of the following: i. FRAX[b] 10-year probability of major osteoporotic fracture ≥ 20% ii. FRAX[b] 10-year probability of hip fracture ≥ 3% iii. Fragility fracture 3. Denosumab will not be used in combination with other antiresorptive or anabolic agents (e.g., bisphosphonates, parathyroid hormone analogs, or romosozumab) 4. The dose does not exceed 60 mg SQ every 6 months 5. **ONE** of the following: a. Member had an inadequate response or intolerance to bisphosphonate therapy (oral or IV) b. Member is not a candidate for bisphosphonate therapy c. Member has a history of a fragility fracture d. Member is at high risk of falls or has a history of falls e. Member has a BMD T-score of -2.5 or lower[a] f. FRAX[b] 10-year probability of major osteoporotic fracture ≥ 20% g. FRAX[b] 10-year probability of hip fracture ≥ 3% h. High dose glucocorticoid use with prednisone equivalent of greater than or equal to 30 mg/day for 30 days or

	cumulative doses of greater than or equal to 5 grams per year
Systemic Mastocytosis	**When ALL of the following are met:** 1. Member is diagnosed with systemic mastocytosis 2. Denosumab will not be used in combination with other antiresorptive or anabolic agents (e.g., bisphosphonates, parathyroid hormone analogs, or romosozumab) 3. Dose does not exceed 60 mg SQ every 6 months 4. Member is not a candidate for, or had an inadequate response or intolerance to zoledronic acid (Reclast®)
Xgeva and biosimilars (Bomyntra, Osenvelt, Wyost) **(duration of approval: 180 days)**	
Bone metastases secondary to breast cancer	**When ALL of the following are met:** 1. Member is diagnosed with breast cancer 2. Member has bone metastases 3. Denosumab will be used in conjunction with standard antineoplastic therapy (i.e., chemotherapy or endocrine therapy) 4. Denosumab will not be used in combination with other antiresorptive or anabolic agents (e.g., bisphosphonates, parathyroid hormone analogs, or romosozumab) 5. Dose does not exceed 120 mg SQ every 4 weeks
Bone metastases secondary to lung cancer	**When ALL of the following are met:** 1. Member is diagnosed with lung cancer 2. Member has bone metastases 3. Denosumab will not be used in combination with other antiresorptive or anabolic agents (e.g., bisphosphonates, parathyroid hormone analogs, or romosozumab) 4. Dose does not exceed 120 mg SQ every 4 weeks
Bone metastases secondary to castrate-recurrent prostate cancer	**When ALL of the following are met:** 1. Member is diagnosed with castrate-recurrent prostate cancer

	2. Member has bone metastases 3. Denosumab will not be used in combination with other antiresorptive or anabolic agents (e.g., bisphosphonates, parathyroid hormone analogs, or romosozumab) 4. Dose does not exceed 120 mg SQ every 4 weeks
Bone metastases secondary to solid tumor (other than breast cancer, castrate-recurrent prostate cancer, or lung cancer)	**When ALL of the following are met:** 1. Member has a solid tumor cancer diagnosis (e.g., thyroid cancer, kidney cancer) 2. Member has an inadequate response, intolerance, contraindication, or is not a candidate for zoledronic acid (Zometa®) 3. Member has bone metastases 4. Denosumab will not be used in combination with other antiresorptive or anabolic agents (e.g., bisphosphonates, parathyroid hormone analogs, or romosozumab) 5. Dose does not exceed 120 mg SQ every 4 weeks
Giant Cell Tumor of the Bone	**When BOTH of the following are met:** 1. Denosumab will not be used in combination with other antiresorptive or anabolic agents (e.g., bisphosphonates, parathyroid hormone analogs, or romosozumab) 2. Dose does not exceed 120 mg every 4 weeks (Note: an additional dose of 120 mg on days 8 and 15 will be permitted for the first cycle only)
Hypercalcemia of Malignancy	**When ALL of the following are met:** 1. Member has a cancer diagnosis with tumor related hypercalcemia (albumin corrected calcium± of 12 mg/dL or greater) 2. Member has an inadequate response, intolerance, contraindication, or is not a candidate for intravenous bisphosphate therapy (e.g., zoledronic acid) 3. Denosumab will not be used in combination with other antiresorptive or anabolic agents (e.g., bisphosphonates, parathyroid hormone analogs, or romosozumab)

	4. Dose does not exceed 120 mg every 4 weeks (Note: an additional dose of 120 mg on days 8 and 15 will be permitted for the first cycle only)
Multiple myeloma, prevention of skeletal-related events	**When ALL of the following are met:** 1. Member is diagnosed with active (symptomatic) multiple myeloma [i.e., NOT smoldering (asymptomatic) myeloma] 2. Denosumab will be used in combination with primary myeloma therapy 3. Member has an inadequate response, intolerance, contraindication, or is not a candidate for zoledronic acid (Zometa®) 4. Denosumab will not be used in combination with other antiresorptive or anabolic agents (e.g., bisphosphonates, parathyroid hormone analogs, or romosozumab) 5. Dose does not exceed 120 mg SQ every 4 weeks
BMD, bone mineral density; IV, intravenous [a] Measured at the femoral neck, total hip, lumbar spine, or 33% radius [b] FRAX® Fracture Risk Assessment Tool: https://www.sheffield.ac.uk/FRAX/index.aspx	

II. **Continuation** of denosumab **meets the definition of medical necessity** for the indications in Table 1 when **ALL** of the following are met

a. The member has been previously approved by Florida Blue or another health plan in the past 2 years, OR the member has previously met all indication-specific criteria for coverage

b. Denosumab will not be used in combination with other antiresorptive or anabolic agents (e.g., bisphosphonates, parathyroid hormone analogs, or romosozumab)

c. For Prolia or Conexxence requests only, the member has an inadequate response, contraindication, or intolerance to Jubbonti AND Stoboclo - documentation must be submitted

d. For Xgeva or Bomyntra requests only, the member has an inadequate response, contraindication, or intolerance to Wyost AND Osenvelt - documentation must be submitted

e. The dose does not exceed the following

1. Prolia and biosimilars (Conexxence, Jubbonti, Stoboclo): 60 mg every 6 months

2. Xgeva and biosimilars (Bomyntra, Osenvelt, Wyost): 120 mg every 4 weeks

Approval duration: 1 year

DOSAGE/ADMINISTRATION:

THIS INFORMATION IS PROVIDED FOR INFORMATIONAL PURPOSES ONLY AND SHOULD NOT BE USED AS A SOURCE FOR MAKING PRESCRIBING OR OTHER MEDICAL DETERMINATIONS. PROVIDERS SHOULD REFER TO THE MANUFACTURER'S FULL PRESCRIBING INFORMATION FOR DOSAGE GUIDELINES AND OTHER INFORMATION RELATED TO THIS MEDICATION BEFORE MAKING ANY CLINICAL DECISIONS REGARDING ITS USAGE.

Table 2

<table>
<tr><th colspan="2">FDA-approved indications and dosage</th></tr>
<tr><th colspan="2">Prolia and biosimilars (Conexxence, Jubbonti, Stoboclo)</th></tr>
<tr><th>Indication</th><th>Dose/Administration</th></tr>
<tr><td>Treatment of postmenopausal women with osteoporosis at high risk for fracture</td><td rowspan="5">• 60 mg SQ every 6 months
• Inject into upper arm, upper thigh, or abdomen (administered by a healthcare professional)
• Concomitant therapy with calcium 1000 mg and at least 400 IU vitamin daily is recommended
• Pregnancy must be ruled out prior to administration in all biological females of reproductive potential</td></tr>
<tr><td>Treatment to increase bone mass in men with osteoporosis at high risk for fracture</td></tr>
<tr><td>Treatment of glucocorticoid-incuded osteoporosis in men and women at high risk for fracture</td></tr>
<tr><td>Treatment to increase bone mass in men at high risk for fracture receiving androgen deprivation therapy for non-metastatic prostate cancer</td></tr>
<tr><td>Treatment to increase bone mass in women at high risk for fracture receiving adjuvant aromatase inhibitor therapy for breast cancer.</td></tr>
<tr><th colspan="2">Xgeva and biosimilars (Bomyntra, Osenvelt, Wyost)</th></tr>
<tr><th>Indication</th><th>Dose/Administration</th></tr>
<tr><td>Prevention of skeletal-related events in patients with multiple myeloma or bone metastases from solid tumors</td><td>• 120 mg SQ every 4 weeks
• Inject into upper arm, upper thigh, or abdomen
• Administer calcium and vitamin D as necessary to treat or prevent hypocalcemia</td></tr>
<tr><td>Giant cell tumor of bone</td><td>• 120 mg SQ every 4 weeks with additional 120 mg doses on days 8 and 15 of the first cycle.
• Inject into upper arm, upper thigh, or abdomen
• Concomitant therapy with calcium and vitamin D as necessary to treat or prevent hypocalcemia</td></tr>
<tr><td>Hypercalcemia of malignancy</td><td>• 120 mg SQ every 4 weeks with additional 120 mg doses on days 8 and 15 of the first cycle.
• Inject into upper arm, upper thigh, or abdomen</td></tr>
<tr><td colspan="2">SQ; subcutaneously</td></tr>
</table>

Dose Adjustments

- **Renal Impairment:** dosage adjustments are not required for members with renal impairment. In clinical studies, subjects treated with denosumab with severe renal impairment (creatinine clearance less than 30 mL/min) or receiving dialysis were at greater risk of developing hypocalcemia. Clinical monitoring of calcium, phosphorus, and magnesium is highly recommended and adequate intake of calcium and vitamin D is important.
- **Hepatic Impairment:** clinical studies have not been conducted to evaluate the effect of hepatic impairment on the pharmacokinetics of denosumab.

Drug Availability

- **Prolia and biosimilars (Conexxence, Jubbonti, Stoboclo):** single-use prefilled syringe containing 60 mg in a 1 mL solution and single-use vial containing 60 mg in a 1 mL solution.
- **Xgeva and biosimilars (Bomyntra, Osenvelt, Wyost):** single-use vial containing 120 mg/1.7 mL (70 mg/mL)

PRECAUTIONS:

CONTRAINDICATIONS:

Prolia and Xgeva

- **Hypocalcemia:** 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.
- **Hypersensitivity:** do not administer to members with a history of systemic hypersensitivity to any component of the product.

Prolia

Pregnancy: Prolia is classified as Pregnancy Category X and may cause fetal harm when administered to pregnant women based on findings in animals. Of note, Xgeva is classified as Pregnancy Category D, but also caused fetal harm when administered to pregnant women based on findings in animals.

WARNINGS:

Prolia and Xgeva

Patients receiving Prolia should not receive Xgeva and vice-versa.

Hypersensitivity: anaphylactic reactions may occur. Discontinue permanently if a clinically significant reaction occurs.

Hypocalcemia: Must be corrected before initiating therapy and may worsen, especially in patients with renal impairment. Fatal cases of severe symptomatic hypocalcemia has occurred. Clinical monitoring of calcium is highly recommended. Encourage daily supplements of calcium and vitamin D.

Osteonecrosis of the jaw: has been reported by individuals treated with denosumab; monitor members for symptoms.

Atypical femoral fractures: have been reported by individuals treated with denosumab; evaluate members with thigh or groin pain to rule out a femoral fracture.

Multiple vertebral fractures: reports of multiple vertebral fractures have been reported following discontinuation. Evaluate risk of vertebral fractures and consider use of another antiresorptive if discontinued.

Prolia

Serious infections: may occur, including those leading to hospitalization. Members should be advised to seek prompt medical attention if they develop signs or symptoms of infection, including skin infections (e.g., cellulitis).

Dermatologic reactions: dermatitis, rashes, and eczema have been reported. Consider discontinuing therapy if severe symptoms develop.

Severe Bone, Joint Muscle Pain: Discontinue if severe symptoms develop.

Suppression of bone turnover: significant suppression has been demonstrated; monitor members for consequences of bone over-suppression.

Hypercalcemia in Pediatric Patients with Osteogenesis Imperfecta: Prolia is not approved for use in pediatric patients. Hypercalcemia has been reported in pediatric patients with osteogenesis imperfecta treated with denosumab products, and some cases required hospitalization.

Xgeva

Embryo-Fetal Toxicity: can cause fetal harm. Advise females of the potential risk to fetus and use highly effective contraception.

Hypercalcemia following discontinuation: Hypercalcemia has occurred following discontinuation in patients with Giant cell tumor of bone and in patients with growing skeletons.

BILLING/CODING INFORMATION:

The following codes may be used to describe:

HCPCS Coding:

J0897	Injection, denosumab, 1 mg
Q5136	Injection, denosumab-bbdz (jubbonti/wyost), biosimilar, 1 mg
Q5157	Injection, denosumab-bmwo (stoboclo/osenvelt), biosimilar, 1 mg
Q5158	Injection, denosumab-bnht (bomyntra/conexxence), biosimilar, 1 mg

ICD-10 Diagnosis Codes That Support Medical Necessity for Prolia™:

C50.011 – C50.929	Malignant neoplasm of breast
C61	Malignant neoplasm of prostate
C94.30 – C94.32	Mast cell leukemia

C96.20 – C96.29	Malignant mast cell neoplasm
D47.02	Systemic mastocytosis
M80.00XA – M80.00XS M80.011A – M80.011S M80.012A – M80.012S M80.019A – M80.019S M80.021A – M80.021S M80.022A – M80.022S M80.029A – M80.029S M80.031A – M80.031S M80.032A – M80.032S M80.039A – M80.039S M80.041A – M80.041S M80.042A – M80.042S M80.049A – M80.049S M80.051A – M80.051S M80.052A – M80.052S M80.059A – M80.059S M80.061A – M80.061S M80.062A – M80.062S M80.069A – M80.069S M80.071A – M80.071S M80.072A – M80.072S M80.079A – M80.079S M80.08XA – M80.08XS M80.0AXA – M80.0AXS M80.0B1A – M80.0B1S M80.0B2A – M80.0B2S M80.0B9A – M80.0B9S	Age-related osteoporosis with current pathological fracture
M80.80XA – M80.80XS M80.811A – M80.811S M80.812A – M80.812S M80.819A – M80.819S M80.821A – M80.821S M80.822A – M80.822S M80.829A – M80.829S M80.831A – M80.831S M80.832A – M80.832S M80.839A – M80.839S M80.841A – M80.841S M80.842A – M80.842S M80.849A – M80.849S M80.851A – M80.851S M80.852A – M80.852S	Other osteoporosis with current pathological fracture

M80.859A – M80.859S M80.861A – M80.861S M80.862A – M80.862S M80.869A – M80.869S M80.871A – M80.871S M80.872A – M80.872S M80.879A – M80.879S M80.88XA – M80.88XS M80.8AXA – M80.8AXS M80.8B1A – M80.8B1S M80.8B2A – M80.8B2S M80.8B9A – M80.8B9S	
M81.0	Age-related osteoporosis without current pathological fracture
M81.6	Localized osteoporosis (Lequesne)
M81.8	Other osteoporosis without current pathological fracture
M89.9	Disorder of bone, unspecified
M94.9	Disorder of cartilage, unspecified
N95.1	Menopausal and female climacteric states
T38.0X5A – T38.0X5S	Adverse effect of glucocorticoids and synthetic analogues
T38.6X5A – T38.6X5S	Adverse effect of antigonadotrophins, antiestrogens, antiandrogens, not elsewhere classified
T38.7X5A – T38.7X5S	Adverse effect of androgens and anabolic congeners
Z78.0	Asymptomatic menopausal state
Z79.811	Long term (current) use of aromatase inhibitors
Z79.818	Long term (current) use of other agents affecting estrogen receptors and estrogen levels

ICD-10 Diagnosis Codes That Support Medical Necessity for Xgeva™:

C33	Malignant neoplasm of trachea
C34.00 – C34.02	Malignant neoplasm of unspecified main bronchus
C34.10 – C34.12	Malignant neoplasm of upper lobe, unspecified bronchus or lung
C34.2	Malignant neoplasm of middle lobe, bronchus or lung
C34.30 – C34.32	Malignant neoplasm of lower lobe, unspecified bronchus or lung
C34.80 – C34.82	Malignant neoplasm of overlapping sites of unspecified bronchus and lung
C34.90 – C34.92	Malignant neoplasm of unspecified part of unspecified bronchus or lung
C40.00 – C40.92	Malignant neoplasm of bone and articular cartilage of limbs
C41.0 – C41.9	Malignant neoplasm of bone and articular cartilage of other and unspecified sites
C50.011 – C50.929	Malignant neoplasm of breast
C61	Malignant neoplasm of prostate
C64.1 – C64.9	Malignant neoplasm of unspecified kidney, except renal pelvis
C65.1 – C65.9	Malignant neoplasm of unspecified renal pelvis
C73	Malignant neoplasm of thyroid gland

C79.51 – C79.52	Secondary malignant neoplasm of bone and bone marrow
C90.00 – C90.32	Multiple myeloma
D48.0	Neoplasm of uncertain behavior of bone and articular cartilage
E83.52	Hypercalcemia

REIMBURSEMENT INFORMATION:

Refer to section entitled **POSITION STATEMENT**.

PROGRAM EXCEPTIONS:

Federal Employee Program (FEP): Follow FEP guidelines.

State Account Organization (SAO): Follow SAO guidelines.

Medicare Advantage Products: No National Coverage Determination (NCD) or Local Coverage Determination (LCD) was found at the time of the last guideline reviewed date.

If this Medical Coverage Guideline contains a step therapy requirement, in compliance with Florida law 627.42393, members or providers may request a step therapy protocol exemption to this requirement if based on medical necessity. The process for requesting a protocol exemption can be found at Coverage Protocol Exemption Request

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.

Metastatic cancer: when cancer spreads from the primary site (place where it started) to other places in the body.

Multiple myeloma: a disseminated type of plasma cell dyscrasia characterized by multiple bone marrow tumor foci

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.

Risk Factors for Osteoporosis: For osteoporotic fractures, includes low BMD, parental history of hip fracture, low body weight, previous fracture, smoking, excess alcohol intake, glucocorticoid use, secondary osteoporosis (e.g., rheumatoid arthritis) and history of falls. These readily accessible and commonplace factors are associated with the risk of hip fracture and, in most cases, with that of vertebral and other types of fracture as well.

RELATED GUIDELINES:

Abaloparatide (Tymlos™), 09-J2000-85
Bone Mineral Density Studies, 04-70000-21
Percutaneous Vertebroplasty, Kyphoplasty and Sacroplasty, 02-20000-18
Romosozumab-aqqg (Evenity), 09-J3000-03
Teriparatide (Forteo®, Teriparatide injection), 09-J0000-47

OTHER:

None applicable.

REFERENCES:

1. ACOG Practice Bulletin on Osteoporosis. American Family Physician. 2013; 88(4): 273 – 275.
2. Bomyntra (denosumab-bnht) [package insert]. Fresenius Kabi USA. Lake Zurich, IL. March 2025.
3. Buckley L, Guyatt G, Fink HA et al. 2017 American College of Rheumatology Guideline for the prevention and treatment of glucocorticoid-induced osteoporosis. Arthritis & Rheumatology. 2017: 69: 1521- 1537.
4. Camacho PM, Petak SM, Binkley N, et al. American Association of Clinical Endocrinologists and American College of Endocrinology Clinical Practice Guidelines for the Diagnosis and Treatment of Postmenopausal Osteoporosis. Endocr Pract. 2016; 22: Suppl 4;1-42.
5. Camacho PM, Petak SM, Binkley N, et al. American Association of Clinical Endocrinologists and American College of Endocrinology Clinical Practice Guidelines for the Diagnosis and Treatment of Postmenopausal Osteoporosis – 2020 Update. Endocr Pract. 2020; 26: Suppl 1;1-46.
6. Chawla S, Henshaw R, Seeger L, et al. Safety and efficacy of denosumab for adults and skeletally mature adolescents with giant cell tumor of bone: interim analysis of an open-label, parallel-group, phase 2 study. Lancet Oncol 2013:14:901-08.
7. Clinical Pharmacology [database online]. Tampa, FL: Gold Standard, Inc.;2025. URL www.clinicalpharmacilogy-ip.com Accessed 08/31/25.
8. Cohen SB, Dore RK, Lane NE, et al. Denosumab Treatment Effects on Structural Damage, Bone Mineral Density, and Bone Turnover in Rheumatoid Arthritis. Arthritis Rheum 2008;58:1299-1309.
9. Conexxence (denosumab-bnht) [package insert]. Fresenius Kabi USA. Lake Zurich, IL. March 2025.

10. Cosman F, de Beur SJ, LeBoff MS, et al. National Osteoporosis Foundation. Clinician's guide to prevention and treatment of osteoporosis. Osteoporos Int. 2014; 25 (10): 2359-81.
11. Cummins SR, San Martin J, McClung MR, et al. Denosumab for Prevention of Fractures in Postmenopausal Women with Osteoporosis. N Engl J Med 2009;361:756-65.
12. Denosumab. In: McEvoy GK, editor. AHFS drug information 2016[monograph on the Internet]. Bethesda (MD): American Society of Health-System Pharmacists; 2016 [cited 2016 Dec 16]. Available from: http://online.statref.com. Subscription required to view
13. Eastell R, Rosen CJ, Black DM et al. Pharmacological management of osteoporosis in postmenopausal women: an Endocrine Society clinical practice guideline. 2019; 104: 1595 – 1622.
14. Ellis GK, Bone HG, Chlebowski, et al. Randomized trial of denosumab in patients receiving adjuvant aromatase inhibitors for nonmetastatic breast cancer. J Clin Oncol 26:4875-82.
15. FRAX® Fracture Risk Assessment Tool. https://www.sheffield.ac.uk/FRAX/index.aspx
16. Humphrey MB, Russell L, Danila M et al. 2022 American College or Rheumatology for the prevention and treatment of Glucocorticoid-induced osteoporosis. Arthritis Rheumatol. 2023 75 (12): 2088-2102.
17. Jubbonti (denosumab-bbdz) [package insert]. Sandoz Inc. Princeton (NJ): October 2024.
18. Micromedex® Healthcare Series [Internet Database]. Greenwood Village, Colo: Thomson Healthcare. Updated periodically. Accessed 08/31/25.
19. National Comprehensive Cancer Network. Cancer Guidelines. Cancer Guidelines and Drugs and Biologics Compendium. Accessed 08/31/25.
20. North American Menopause Society (NAMS) Position Statement. Management of osteoporosis in postmenopausal women: 2010 position statement of the NAMS. Menopause. 2010; 17(1): 25-54.
21. NOF: fast facts on osteoporosis [Internet]. Washington DC: National Osteoporosis Foundation; c2010 [cited 2012 Dec 3]. Available from: http://www.NOF.org.
22. Stoboclo (denosumab-bmwo) [package insert]. Celtrion Inc. Jersy City (NJ). February 2025.
23. Prolia (denosumab) [package insert]. Amgen Inc. Thousand Oaks (CA): May 2025.
24. Scagliotti GV, Hirsh V, Siena S, et al. Overall survival improvement in patients with lung cancer and bone metastases treated with denosumab versus zoledronic acid; a subgroup analysis from a randomized phase 3 study. J Thorac Oncol 2012;7:1823-29.
25. Shoback D, Rosen CJ, Black DM et al. Pharmacological management of osteoporosis in postmenopausal women: an endocrine society guideline update. J Clin Endocrinol Metab. 2020; 105: 1-8.
26. Smith MR, Egerdie B, Toriz NH, et al. Denosumab in men receiving androgen-deprivation therapy for prostate cancer. N Engl J Med 2009;361:745-55.
27. Osenvelt (denosumab-bmwo) [package insert]. Celtrion Inc. Jersy City (NJ). February 2025.
28. Stopeck AT, Lipton A, Body JJ, et al. Denosumab compared with zoledronic acid for the treatment of bone metastases in patients with advance breast cancer: a randomized, double-blind study. J Clin Oncol 2010.
29. Watts NB, Adler RA, Bilezikan JP, Drake MT, et al. Osteoporosis in men: an endocrine society clinical practice guideline. J Clin Endocrinol Metab 2012;97(6):1802-22.
30. Watts NB, Bilezkian JP, Camacho PM et al. American Association of Clinical Endocrinologists medical guidelines for clinical practice for the diagnosis and treatment of postmenopausal osteoporosis. Endocrine Practice. 2010; 16 (Suppl 3): 1-37.
31. Wyost (denosumab-bbdz) [package insert]. Sandoz Inc. Princeton (NJ): March 2024.
32. Xgeva (denosumab) [package insert]: Amgen Inc. Thousand Oaks (CA): May 2025.

COMMITTEE APPROVAL:

This Medical Coverage Guideline (MCG) was approved by the Florida Blue Pharmacy Policy Committee on 09/10/25.

GUIDELINE UPDATE INFORMATION:

08/15/10	New Pharmacy Coverage Guideline.
11/15/10	Revision to guideline; consisting of modifying coverage criteria.
02/15/11	Revision to guideline; consisting of new brand name, new indication, update dosing, coding and references.
05/15/11	Review and revision to guideline; consisting of updating references.
08/17/11	Revision; ICD-10 codes updated.
11/15/11	Revision to guideline; consisting of adding two new FDA-approved indications to Position Statement.
01/01/12	Revision to guideline; consisting of modifying position statement and coding update.
05/15/12	Review and revision to guideline; consisting of updating position statement and coding.
09/15/12	Revision to guideline; consisting of updating position statement.
02/15/13	Review and revision to guideline; consisting of revising/reformatting position statement, dosage/administration section, precautions section; updated references; added definitions.
09/15/13	Revision to guideline; consisting of administrative action to remove requirement of high risk for fracture from position statement and add approval duration.
02/15/14	Review and revision to guideline; consisting of revising position statement to include new FDA-approved indication, updating dosage/administration, precautions, references, and coding.
02/15/15	Review and revision to guideline; consisting of revising position statement, updating dosage/administration, references.
10/01/15	Revision consisting of update to Program Exceptions section.
11/01/15	Revision: ICD-9 Codes deleted.
02/15/16	Review and revision to guideline; consisting of revising position statement, updating description, precautions, coding and references.
12/15/16	Review and revision to guideline; consisting of updating position statement and references.
02/15/17	Review and revision to guideline; consisting of updating position statement and references.
02/15/18	Review and revision to guideline; consisting of updating position statement, description, dosing, warnings, coding, and references.
04/15/18	Review and revision to guideline; consisting of updating position statement and references.
12/15/18	Revision to guideline; consisting of updating position statement.
04/15/19	Review and revision to guideline; consisting of updating position statement, coding and references.

04/15/20	Review and revision to guideline; consisting of updating position statement, warnings, and references.
10/01/20	Revision to ICD-10 coding.
02/15/21	Review and revision to guideline; consisting of updating the position statement and references.
07/15/21	Revision to guideline; consisting of updating the position statement and references.
02/15/22	Review and revision to guideline; consisting of updating references.
02/15/23	Review and revision to guideline; consisting of updating position statement, warnings, coding, and references.
10/01/23	ICD-10 additions.
02/15/24	Review and revision to guideline; consisting of updating glucocorticoid induced osteoporosis and updated references.
10/15/25	Review and revision to guideline; consisting of updating the position statement to include a step through preferred biosimilars.