Medical Policy

Title: Denosumab (Prolia and Xgeva)

Prior Authorization Form:

For information concerning Prior Authorization Prescription Drugs:
http://www.bcbsks.com/CustomerService/PrescriptionDrugs/prior_authorization.htm

Link to Drug List (Formulary):
http://www.bcbsks.com/CustomerService/PrescriptionDrugs/drug_list.htm

Professional
Original Effective Date: April 30, 2012
Revision Date(s): August 14, 2012;
March 12, 2013
Current Effective Date: March 12, 2013

Institutional
Original Effective Date: April 30, 2012
Revision Date(s): September 13, 2012;
March 12, 2013
Current Effective Date: March 12, 2013

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The BCBSKS Medical Policies contained herein are for informational purposes and apply only to members who have health insurance through BCBSKS or who are covered by a self-insured group plan administered by BCBSKS. Medical Policy for FEP members is subject to FEP medical policy which may differ from BCBSKS Medical Policy.

The medical policies do not constitute medical advice or medical care. Treating health care providers are independent contractors and are neither employees nor agents of Blue Cross and Blue Shield of Kansas and are solely responsible for diagnosis, treatment and medical advice.

If your patient is covered under a different Blue Cross and Blue Shield plan, please refer to the Medical Policies of that plan.
DESCRIPTION
Denosumab is a fully human monoclonal antibody to the receptor activator of nuclear factor kappaB ligand (RANKL), an osteoclast differentiating factor. It inhibits osteoclast formation, decreases bone resorption, increases bone mineral density (BMD), and reduces the risk of fracture.

FDA Indications
Prolia
1. The treatment of postmenopausal women with osteoporosis at high risk for fracture.
2. Treatment to increase bone mass in women at high risk for fracture receiving adjuvant aromatase inhibitor therapy for breast cancer.
3. Treatment to increase bone mass in men at high risk for fracture receiving androgen deprivation therapy for nonmetastatic prostate cancer.
4. Treatment to increase bone mass in men with osteoporosis at high risk of fracture.

Xgeva
1. Prevention of skeletal-related events in patients with bone metastases from solid tumors.
2. Important limitation of use: Xgeva is not indicated for the prevention of skeletal-related events in patients with multiple myeloma.

Dosing
Prolia
1. Prolia should be administered by a healthcare professional.
2. Administer 60 mg every 6 months as a subcutaneous injection in the upper arm, upper thigh, or abdomen.

Xgeva
Administer 120 mg every 4 weeks as a subcutaneous injection in the upper arm, upper thigh, or abdomen.

POLICY
A. Prolia is considered medically necessary for the following indications:
   1. Treatment of osteoporosis (T-score below -2.5) in postmenopausal women who have failed or are unable to tolerate oral bisphosphonates [e.g. alendronate (Fosamax), risedronate (Actonel), ibandronate (Boniva)].
   2. Treatment of bone loss in women receiving aromatase inhibitor (AI) therapy for breast cancer and have failed or are unable to tolerate oral bisphosphonates [e.g. alendronate (Fosamax), risedronate (Actonel), ibandronate (Boniva)].
   3. Treatment of bone loss in men receiving androgen deprivation therapy (ADT) for nonmetastatic prostate cancer.
4. Treatment of osteoporosis (T-score below -2.5) in men who have failed or are unable to tolerate oral bisphosphonates [e.g. alendronate (Fosamax), risedronate (Actonel), ibandronate (Boniva)].

B. Xgeva is considered medically necessary for the prevention of skeletal-related events (e.g., fracture, spinal cord compression, bone pain requiring surgery / radiation therapy) in patients with bone metastases from solid tumors.

Policy Guidelines
1. Given the absence of long-term safety data and availability of other agents, denosumab is not recommended for the prevention of osteoporosis.
2. For postmenopausal women with uncomplicated osteoporosis (T-score below -2.5), denosumab is not recommended as initial therapy. Oral bisphosphonates are preferred as initial therapy because of their efficacy, favorable cost, and the availability of long-term safety data.
3. In the absence of safety data, using denosumab for the treatment of osteoporosis in premenopausal women or children is not recommended.
4. Patients who have hypocalcemia should not receive denosumab until hypocalcemia is corrected.
5. Patients with chronic kidney disease (creatinine clearance <30 mL/min, including patients receiving dialysis) are at higher risk for hypocalcemia following denosumab administration than patients with normal renal function.
6. Because serious infections and skin reactions were reported more frequently in the denosumab than in the placebo group, patients should be advised to seek medical attention if they develop signs of an infection or skin reaction.
7. Additional recommendations include administration of calcium 1000 mg daily and at least 400 IU of vitamin D daily.
8. Men seem to respond to available therapies in the same way that women respond. Bisphosphonates are considered the treatment of choice for most men with osteoporosis requiring pharmacologic therapy. Denosumab is an alternative option for men who cannot tolerate oral or intravenous bisphosphonates.

Documentation

Prolia
- DEXA report and clinical records to include medication history

Xgeva
- Clinical records documenting bone metastases
RATIONALE

Postmenopausal Osteoporosis

The diagnosis of osteoporosis (OP) has been established by measurement of bone mineral density (BMD). BMD appears to be a predictor of fractures. BMD is expressed in absolute terms of grams of mineral per square centimeter scanned (g/cm²) and as a relationship to two norms: compared to the expected BMD for the patient’s age and sex (Z-score), or compared to “young normal” adults of the same sex (T-score). The difference between the patient’s score and the norm is expressed in standard deviations (SD) above or below the mean. Usually, 1 SD equals 10 to 15% of the BMD value in g/cm². The North American Menopause Society (NAMS), World Health Organization (WHO), International Society of Clinical Densitometry, and the National Osteoporosis Foundation (NOF) define OP in postmenopausal women or a man ≥50 years old as a BMD T-score ≤ -2.5 at the total hip, femoral hip, or lumbar spine (≥ 2 vertebral levels measured in the posterior-anterior projection not the lateral projection). In addition to diagnosis through densitometry, OP can be diagnosed clinically, regardless of the T-score. The presence of fragility fracture constitutes a clinical diagnosis of OP.

BMD-based definitions of bone density

<table>
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<tr>
<th>Normal</th>
<th>T-score ≥ -1.0</th>
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<tbody>
<tr>
<td>Low bone mass (osteopenia)</td>
<td>T-score between -1.0 and -2.5</td>
</tr>
<tr>
<td>Osteoporosis</td>
<td>T-score ≤ -2.5</td>
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A management strategy focused on lifestyle approaches may be all that is needed in postmenopausal women who are at low risk of OP fracture. All postmenopausal women, regardless of their BMD or clinical risk factors for OP, should be encouraged to eat a balanced diet, obtain adequate calcium and vitamin D, participate in appropriate exercise, avoid cigarette smoke and excessive alcohol consumption, and institute fall prevention measures.

The NAMS and NOF as well as the American Association of Clinical Endocrinologists (AACE) recommend adding OP drug therapy in the following populations:

- All postmenopausal women who have had an osteoporotic vertebral or hip fracture
- All postmenopausal women who have BMD values consistent with OP (i.e., T-scores -2.5) at the lumbar spine, femoral neck, or total hip region.
- All postmenopausal women who have T-scores from -1.0 to -2.5 at the femoral neck or spine and a 10-year probability of a hip fracture ≥ 3% or a 10-year probability of a major OP-related fracture ≥ 20%.

Patients with a fragility fracture of the spine or hip are at very high risk for another fracture regardless of whether the T-score is below -2.5 or just in the osteopenia range. Although bone densitometry is useful for assessing disease severity and monitoring therapy in patients with fractures, densitometry is not essential for the diagnosis of osteoporosis in this setting. (WHO Scientific Group on the Assessment of Osteoporosis at Primary Health Care Level, 2004)

The risk for a second fragility fracture decreases as time passes from the first fracture. The study by Johnell et al. found that for all fractures, more fractures occurred in the first year after
fracture than in subsequent years. The number of fractures decreased progressively thereafter with time.\textsuperscript{20} Schousboe et al. found that prior non-spine non-hip fracture confers a modest excess risk for incident hip fracture independent of BMD after 10 years; that excess risk, however, was only about one third the excess risk during the first 5 years of follow-up.\textsuperscript{21}

American Association of Clinical Endocrinologists (AACE) Medical Guidelines for Clinical Practice for the Diagnosis and Treatment of Postmenopausal Osteoporosis 2010\textsuperscript{3} state:

- Level 1 evidence for efficacy in reducing the risk of new vertebral fractures is available for all of the agents approved for the treatment of osteoporosis (alendronate, ibandronate, risedronate, zoledronic acid, calcitonin, denosumab, raloxifene, and teriparatide).
- Clinical trial data have demonstrated the effectiveness of alendronate, risedronate, zoledronic acid, denosumab, and teriparatide in reducing the risk of nonvertebral fractures. Only alendronate, risedronate, zoledronic acid, and denosumab have been shown to reduce the risk of hip fractures in prospective controlled osteoporosis trials.

The AACE recommends alendronate, risedronate, zoledronic acid, or denosumab as first line agents, ibandronate as a second line agent, raloxifene as a second or third line agent, and calcitonin as the last line agent. Teriparatide is best used in treating women with osteoporosis who are at high risk for fracture.

Regarding combination therapy, the AACE guidelines state: There are no studies showing that combination treatment with 2 or more osteoporosis drugs has a greater effect on fracture reduction than treatment with a single agent. Modest additive effects on BMD and bone turnover have been observed with combinations of 2 antiresorptive agents. The combined use of an antiresorptive drug and teriparatide or parathyroid hormone (PTH) may alter the BMD and bone turnover response, depending on which antiresorptive agent is used. Combination therapy substantially increases the cost and probably increases the potential for side effects. Until the effect of combination therapy on fracture risk is better understood, AACE does not recommend concomitant use of these agents for prevention or treatment of postmenopausal osteoporosis.\textsuperscript{3}

The FDA approval of denosumab for the treatment of postmenopausal osteoporosis (PMO) was based on a 3-year, randomized, double-blind, placebo-controlled trial.\textsuperscript{8} The Fracture Reduction Evaluation of Denosumab (FREEDOM) trial compared the fracture rates in 7,868 women with PMO who were randomized to receive denosumab or placebo every six months, for 36 months. Denosumab treatment significantly reduced the incidence of new radiographic vertebral fractures at 36 months vs. placebo (2.3% vs. 7.2%; absolute risk reduction [ARR] = 4.9%; number needed to treat [NNT] = 21; hazard ratio [HR]) = 0.32 [95% confidence interval {CI}: 0.26 to 0.41]; p<0.001). Risk of hip fractures was also significantly reduced (0.7% vs. 1.2%; unadjusted ARR = 0.5%; NNT = 200; HR: 0.60 [95% CI: 0.37 to 0.97]; p = 0.04).

Additional studies with denosumab:

- The DEFEND study (n = 332) compared the effect of denosumab and placebo on bone mineral density (BMD) in postmenopausal women with a T-score between -1 and -2.5 (osteopenia) over two years. Denosumab treatment significantly increased BMD at all measured skeletal sites compared with placebo (p<0.0001).\textsuperscript{5}
- The Determining Efficacy Comparison Initiating Denosumab versus Alendronate (DECIIDE) study compared the efficacy of denosumab and alendronate therapy (70 mg weekly) in 1,189 postmenopausal women with a T-score ≤-2. At 12 months, patients receiving denosumab had
greater BMD gains than those receiving alendronate, at all measured sites. The mean hip BMD increase (primary endpoint) was +3.5% vs. +2.6% (absolute difference = 1.0% [95% CI: 0.7 to 1.2], NNT = 100, p<0.0001).

The double-blind STAND study conducted in women previously treated with alendronate compared the effects of switching to denosumab on BMD, with continued alendronate therapy. Following a one month run-in period in which patients received alendronate once weekly, 504 postmenopausal women with T-scores of -2.0 to -4.0 at the lumbar spine or total hip were randomized to receive denosumab or continue therapy with alendronate (70 mg once weekly). In patients switching to denosumab, total hip BMD increased by 1.9% vs.1.05% in those continuing on alendronate after 12 months (absolute difference = 0.85% [95% CI 0.44% - 1.25%], NNT = 118, p<.0001); the lower limit of the CI excluded the prespecified noninferiority margin (-0.35%), thus showing the noninferiority of denosumab compared with alendronate.

Osteoporosis in Men
The efficacy and safety of denosumab in the treatment to increase bone mass in men with osteoporosis was demonstrated in a 1-year, randomized, double-blind, placebo-controlled trial. Enrolled men had a baseline BMD T-score between -2.0 and -3.5 at the lumbar spine or femoral neck. Men were randomized to receive subcutaneous injections of either placebo or denosumab 60 mg once every 6 months. All men received at least 1000 mg calcium and at least 800 IU vitamin D daily. Treatment with denosumab significantly increased BMD at 1 year (at lumbar spine, total hip, and femoral neck). Consistent effects on BMD were observed at the lumbar spine regardless of baseline age, race, BMD, testosterone concentrations and level of bone turnover.

Breast Cancer
The efficacy and safety of denosumab in the treatment of bone loss in women receiving adjuvant aromatase inhibitor (AI) therapy for breast cancer was assessed in a 2-year, randomized (1:1), double-blind, placebo controlled, multinational study. Women had baseline BMD T-scores between -1.0 to -2.5 at the lumbar spine, total hip, or femoral neck, and had not experienced fracture after age 25. Women were randomized to receive subcutaneous injections of either placebo (n = 125) or denosumab 60 mg (n = 127) once every 6 months for a total of 4 doses. All women received at least 1000 mg calcium and 400 IU vitamin D supplementation daily.

The primary efficacy variable was percent change in lumbar spine BMD from baseline to month 12. Lumbar spine BMD was higher at 12 months in denosumab-treated patients as compared to placebo-treated patients [-0.7% placebo, +4.8% denosumab; treatment difference 5.5% (95% CI: 4.8, 6.3); p < 0.0001]. With approximately 81% of patients followed for 2 years, treatment differences in BMD at 2 years were 7.6% (-1.4% placebo, +6.2% denosumab) at the lumbar spine, 4.7% (-1.0% placebo, +3.8% denosumab) at the total hip, and 3.6% (-0.8% placebo, +2.8% denosumab) at the femoral neck.

The National Comprehensive Cancer Network (NCCN) Guidelines in Oncology-Breast Cancer 2011 state that:

- Denosumab, zoledronic acid, or pamidronate (all with calcium and vitamin D supplementation) should be given in addition to chemotherapy or endocrine therapy if bone metastasis is present, expected survival ≥ 3 months, and renal function is adequate. The optimal schedule and duration of these three agents is unknown (category 1).
- Women on an aromatase inhibitor should have monitoring of bone health with a bone mineral density determination at baseline and periodically thereafter. The use of estrogen, progesterone, or selective estrogen receptor modulators to treat osteoporosis or osteopenia in women with breast cancer is discouraged. The use of a bisphosphonate is generally the preferred intervention to improve bone mineral density. Optimal duration of bisphosphonate therapy has not been established. Factors to consider for duration of anti-osteoporosis therapy include bone mineral density, response to therapy, and risk factors for continued bone loss or fracture. Women treated with a bisphosphonate should undergo a dental examination with preventive dentistry prior to the initiation of therapy, and should take supplemental calcium and vitamin D.

The American Society of Clinical Oncology (ASCO) Update on the Role of Bisphosphonates and Bone Health Issues in Women with Breast Cancer\(^1\),\(^2\) states that most women with newly diagnosed breast cancer are at risk of osteoporosis either because of their age or their breast cancer treatment. The update contains an algorithm for patient management. According to the algorithm, the following are considered factors for high risk: age >65 years; age 60-64 years and prior fracture, body weight <70 kg, family history; postmenopausal women of any age receiving aromatase inhibitor therapy; and premenopausal women with therapy associated premature menopause. Bisphosphonate or SERM therapy is recommended for women at high risk with a T score of -2.5 or lower.\(^1\)

**Prostate Cancer**

The efficacy and safety of denosumab in the treatment of bone loss in men with nonmetastatic prostate cancer receiving androgen deprivation therapy (ADT) were demonstrated in a 3-year, randomized (1:1), double-blind, placebo-controlled, multinational study. Men less than 70 years of age had either a BMD T-score at the lumbar spine, total hip or femoral neck between -1.0 and -4.0, or a history of an osteoporotic fracture. Men were randomized to receive subcutaneous injections of either placebo (n = 734) or denosumab 60 mg (n = 734) once every 6 months for a total of 6 doses. All men received at least 1000 mg calcium and 400 IU vitamin D supplementation daily.\(^1\)\(^,\)\(^14\)

The primary efficacy variable was percent change in lumbar spine BMD from baseline to month 24. An additional key secondary efficacy variable was the incidence of new vertebral fracture through month 36. Lumbar spine BMD was higher at 2 years in denosumab-treated patients as compared to placebo-treated patients [-1.0% placebo, +5.6% denosumab; treatment difference 6.7% (95% CI: 6.2, 7.1); p < 0.0001]. With approximately 62% of patients followed for 3 years, treatment differences in BMD at 3 years were 7.9% (-1.2% placebo, +6.8% denosumab) at the lumbar spine, 5.7% (-2.6% placebo, +3.2% denosumab) at the total hip, and 4.9% (-1.8% placebo, +3.0% denosumab) at the femoral neck. Consistent effects on BMD were observed at the lumbar spine in relevant subgroups defined by baseline age, BMD, and baseline history of vertebral fracture. Denosumab significantly reduced the incidence of new vertebral fractures at 3 years (p = 0.0125).\(^1\)\(^,\)\(^14\)

The NCCN Guidelines in Oncology-Prostate Cancer 2011\(^10\) state:

- In men with castration-recurrent prostate cancer who have bone metastases, denosumab and zoledronic acid have been shown to prevent disease-related skeletal complications, which include fracture, spinal cord compression, or the need for surgery or radiation therapy to bone (NCCN category 1).
Screening and treatment for osteoporosis are advised according to guidelines for the general population from the National Osteoporosis Foundation. The NOF guidelines include recommendations for supplemental calcium (1200 mg daily) and vitamin D3 (800-1000 IU daily) for all men over age 50 years and additional treatment for men when the 10 year probability of hip fracture is >3% or the 10 year probability of a major osteoporosis-related fracture is >20%. Fracture risk can be assessed using the recently released algorithm called FRAX by the World Health Organization. ADT should be considered “secondary osteoporosis” using the FRAX algorithm. Zoledronic acid and alendronate increased bone mineral density, a surrogate for fracture risk, during ADT for prostate cancer. Treatment with either zoledronic acid or alendronate is recommended when the absolute fracture risk warrants drug therapy.

**CODING**

The following codes for treatment and procedures applicable to this policy are included below for informational purposes. Inclusion or exclusion of a procedure, diagnosis or device code(s) does not constitute or imply member coverage or provider reimbursement. Please refer to the member’s contract benefits in effect at the time of service to determine coverage or non-coverage of these services as it applies to an individual member.

**CPT/HCPCS**

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**DIAGNOSES**

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<td>V13.51</td>
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**REVISIONS**

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<tr>
<td>08-14-2012</td>
<td>Policy added to the bcbsks.com web site.</td>
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| 03-12-2013 | In Description section:  
  ▪ Added the Prolia FDA Indication, “4. Treatment to increase bone mass in men with osteoporosis at high risk of fracture.”  
  In Policy section:  
  ▪ Added in A. Prolia the medically necessary indication of:  "4. Treatment of osteoporosis (T-score below -2.5) in men who have failed or are unable to tolerate oral bisphosphonates [e.g. alendronate (Fosamax), risedronate (Actonel), ibandronate (Boniva)]."  
  ▪ In the Policy Guidelines removed from item 3, "... in men who are not receiving androgen deprivation therapy or..." to read, "In the absence of safety data, using denosumab for the treatment of osteoporosis in premenopausal women or children is not recommended." |
The document contains the following information:

- Added guideline "8. Men seem to respond to available therapies in the same way that women respond. Bisphosphonates are considered the treatment of choice for most men with osteoporosis requiring pharmacologic therapy. Denosumab is an alternative option for men who cannot tolerate oral or intravenous bisphosphonates."

Rationale section updated

References updated

REFERENCES


