BlueCross BlueShield of North Carolina

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Corporate Medical Policy

Denosumab (Prolia™, XGEVA™)

File Name:	denosumab_prolia_xgeva
Origination:	3/2011
Last CAP Review:	9/2019
Next CAP Review:	9/2020
Last Review:	4/2020

Description of Procedure or Service

Receptor activator of nuclear factor-κB ligand (RANKL), a protein expressed by osteoblastic stromal cells, binds to receptor activator of nuclear factor-κB (RANK) and is the primary mediator of osteoclast differentiation, activation, and survival. RANKL is responsible for osteoclast-mediated bone resorption in a broad range of conditions. Osteoprotegerin, a soluble RANKL decoy receptor that binds RANKL, is the key endogenous regulator of the RANKL–RANK pathway.

Denosumab (formerly known as AMG 162, Amgen) is a fully human monoclonal antibody (IgG2) that binds to RANKL with high affinity and specificity and blocks the interaction of RANKL with RANK, mimicking the endogenous effects of osteoprotegerin. In a phase 1 dose-escalation study, a single subcutaneous injection of denosumab resulted in a dose-dependent decrease in bone resorption, as measured by changes in serum and urinary N-telopeptide, markers of osteoclastic bone resorption.

Denosumab is marketed under the trade name XGEVA™ for the prevention of skeletal-related events in cancer patients with multiple myeloma or with bone metastases from solid tumors and for treatment of adults and skeletally mature adolescents with giant cell tumor of bone that is unresectable or where surgical resection is likely to result in severe morbidity. XGEVA™ is also indicated for the treatment of hypercalcemia of malignancy refractory to bisphosphonate therapy. XGEVA™ is supplied as an injection of 120 mg denosumab/1.7 mL (70 mg/mL) solution in a single-use vial for subcutaneous injection.

The same drug is marketed under the trade name Prolia™ for postmenopausal osteoporosis and as treatment to increase bone mass in patients with prostate and breast cancer who are on hormone ablation therapy. Prolia™ is supplied as a single-use prefilled syringe containing 60 mg denosumab in a 1 mL solution for subcutaneous injection.

Related Medical Policies:
Romosozumab-aqqg (Evenity™)

******Note: This Medical Policy is complex and technical. For questions concerning the technical language and/or specific clinical indications for its use, please consult your physician.***

Policy

BCBSNC will provide coverage for denosumab when it is determined to be medically necessary because the medical criteria and guidelines shown below are met.

Benefits Application

This medical policy relates only to the services or supplies described herein. Please refer to the Member's Benefit Booklet for availability of benefits. Member's benefits may vary according to benefit design; therefore member benefit language should be reviewed before applying the terms of this medical policy.

When denosumab is covered

Prolia™ may be considered medically necessary for these conditions:

- Treatment of postmenopausal women or men with osteoporosis at high risk for fracture (those who have had an osteoporotic fracture, or have multiple risk factors for fracture)
    - AND who have failed or are unable to tolerate at least one bisphosphonate
    - OR for whom bisphosphonate therapy is contraindicated (including inability to swallow or to remain in an upright position after oral bisphosphonate administration)
- Treatment to increase bone mass in individuals at high risk for fracture receiving aromatase inhibitors (anastrozole, letrozole, exemestane) for breast cancer
- Treatment to increase bone mass in individuals at high risk for fracture receiving androgen deprivation therapy for nonmetastatic prostate cancer
- Treatment of individuals with glucocorticoid-induced osteoporosis at high risk for fracture (those who have had an osteoporotic fracture, or have multiple risk factors for fracture)
    - AND who are initiating or continuing systemic glucocorticoids in a daily dosage equal to 7.5 mg or greater of prednisone and expected to remain on therapy for at least 6 months
    - AND who have failed or are unable to tolerate at least one bisphosphonate
    - OR for whom bisphosphonate therapy is contraindicated (including inability to swallow or to remain in an upright position after oral bisphosphonate administration)

XGEVA™ may be considered medically necessary for:

- Prevention of skeletal-related events in individuals with multiple myeloma or in individuals with bone metastases from solid tumors
- Treatment of adults and skeletally mature adolescents with giant cell tumor of bone that is unresectable or where surgical resection is likely to result in severe morbidity
- Treatment of hypercalcemia of malignancy refractory to bisphosphonate therapy

Use of Denosumab may be considered medically necessary for clinical indications not listed above when the drug is prescribed for the treatment of cancer either:

- In accordance with FDA label (when clinical benefit has been established, see Policy Guidelines); **OR**

- In accordance with specific strong endorsement or support by nationally recognized compendia, when such recommendation is based on strong/high levels of evidence, and/or uniform consensus of clinical appropriateness has been reached.

When denosumab is not covered

Denosumab (Prolia™ and XGEVA™) is considered investigational for the following indications (not an all inclusive list):

- Osteogenesis imperfecta
- Primary bone sarcomas (Ewing's sarcoma and osteosarcoma)
- Rheumatoid arthritis

Denosumab is considered investigational for cancer indications when criteria is not met regarding FDA labeling **OR** strong endorsement/support by nationally recognized compendia, as stated under "When Denosumab is covered."

Policy Guidelines

The same active ingredient (denosumab) is found in Prolia™ and XGEVA™. Patients should not receive both drugs.

Denosumab is contraindicated in patients with hypocalcemia. Hypocalcemia should be corrected prior to initiating denosumab therapy. Patients with creatinine clearance less than 30mL/min or receiving dialysis are at risk for hypocalcemia.

Denosumab is not recommended for use in pediatric patients.

Prolia™ may cause fetal harm when administered to a pregnant woman. Pregnancy testing should be performed prior to starting treatment in women of reproductive potential.

Drugs prescribed for treatment of cancer in accordance with FDA label may be considered medically necessary when clinical benefit has been established, and should not be determined to be investigational as defined in Corporate Medical Policy (CMP), "Investigational (Experimental) Services."

Please refer to CMP "Investigational (Experimental) Services" for a summary of evidence standards from nationally recognized compendia.

Billing/Coding/Physician Documentation Information

This policy may apply to the following codes. Inclusion of a code in this section does not guarantee that it will be reimbursed. For further information on reimbursement guidelines, please see Administrative Policies on the Blue Cross Blue Shield of North Carolina web site at www.bcbsnc.com. They are listed in the Category Search on the Medical Policy search page.

Applicable codes: *J0897, S0353, S0354*

ICD-10 Codes: C00.0-C49.9, C4A.0-C4A.9, C50.011-C79.9, C7A.00-C7A.8, C7B.00-C7B.8, C80.0-C86.6, C88.2-C96.Z, D00.00-D09.9, M81.0, M81.8, T50.905, Z51.11, Z51.12, Z79.811, Z87.311

For oncology use, the cancer diagnosis code must also be included when the following codes are used: M81.0, M81.8, T50.905, Z79.811, Z87.311

BCBSNC may request medical records for determination of medical necessity. When medical records are requested, letters of support and/or explanation are often useful, but are not sufficient documentation unless all specific information needed to make a medical necessity determination is included.

Scientific Background and Reference Sources

McClung MR, Lewiecki EM, Cohen SB, et al. (February 2006). Denosumab in Postmenopausal Women with Low Bone Mineral Density. *N Engl J Med* 2006; 354:821-831

Ellis GK, Bone HG, Chlebowski R, et al. (October 2008). Randomized Trial of Denosumab in Patients Receiving Adjuvant Aromatase Inhibitors for Nonmetastatic Breast Cancer. 26:4875-4882

U.S. Food and Drug Administration (FDA). FDA approves new injectable osteoporosis treatment for postmenopausal women. FDA News. Rockville, MD: FDA; June 1, 2010. Retrieved 3/23/11 from: http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm214150.htm.

Amgen, Inc. Prolia™ (denosumab) injection for subcutaneous use.Prescribing Information.Thousand Oaks, CA:Amgen; 2010. Retrieved 3/23/11 from: http://pi.amgen.com/united_states/prolia/prolia_pi.pdf.

U.S. Food and Drug Administration (FDA). FDA approves Xgeva to help prevent cancer-related bone injury. FDA News. Rockville, MD: FDA; November 19, 2010. Retrieved 3/23/11 from: http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm234346.htm

Amgen, Inc. Xgeva (denosumab). Prescribing Information. Thousand Oaks, CA: Amgen; 2010. Retrieved 3/23/11 from: http://www.amgen.com/medpro/products_xgeva.html.

North American Menopause Society (NAMS). Management of osteoporosis in postmenopausal women: 2010 position statement of The North American Menopause Society. *Menopause*, 2010: 17(1):25-54.

Amgen, Inc. Prolia™ (denosumab) injection for subcutaneous use. Prescribing Information. Thousand Oaks, CA:Amgen; Revised 9/2011. Retrieved 9/20/11 from: http://pi.amgen.com/united_states/prolia/prolia_pi.pdf

Medical Director review – October 2011

U.S. Food and Drug Administration (FDA). FDA granted approval for denosumab (Prolia, Amgen Inc.) as a treatment to increase bone mass in patients at high risk for fracture receiving androgen deprivation therapy (ADT) for nonmetastatic prostate cancer or adjuvant aromatase inhibitor (AI) therapy for breast cancer. Retrieved 7/11/12 from http://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDER/ucm272420.htm

Specialty Matched Consultant Advisory Panel – 9/2012.

National Institutes of Health (NIH). Clinical Trial # NCT00980174. Study to Compare the Efficacy and Safety of DenosumAb Versus Placebo in Males With Osteoporosis - The ADAMO Trial. Retrieved from http://clinicaltrials.gov/ct2/show/NCT00980174.

U.S. Food and Drug Administration (FDA). Supplement Approval Letter September 20, 2012. Approval of clinical indication for the treatment to increase bone mass in men with osteoporosis at high risk of fracture. Retrieved from http://www.accessdata.fda.gov/drugsatfda_docs/appletter/2012/125320Orig1s0051ltr.pdf

Medical Director review 9/2012

U.S. Food and Drug Administration (FDA). FDA approves Xgeva to treat giant cell tumor of the bone. Retrieved 6/17/13 from http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm356528.htm .

Amgen, Inc. Xgeva (denosumab). Prescribing Information. Thousand Oaks, CA: Amgen; 2010 - 2013. Retrieved 6/17/13 from: http://pi.amgen.com/united_states/xgeva/xgeva_pi.pdf .

Medical Director review 6/2013

Specialty Matched Consultant Advisory Panel – 9/2013

Amgen, Inc. Xgeva (denosumab). Prescribing Information. Thousand Oaks, CA: Amgen; 2010 - 2014. Retrieved 9/5/14 from: http://pi.amgen.com/united_states/xgeva/xgeva_pi.pdf .

Specialty Matched Consultant Advisory Panel – 9/2014

Amgen, Inc. Xgeva (denosumab). Prescribing Information. Thousand Oaks, CA: Amgen; 2010 - 2014. Retrieved 12/9/14 from: http://pi.amgen.com/united_states/xgeva/xgeva_pi.pdf .

Amgen, Inc. Prolia™ (denosumab) injection for subcutaneous use. Prescribing Information. Thousand Oaks, CA:Amgen; Revised 6/2014. Retrieved 12/12/14 from: http://pi.amgen.com/united_states/prolia/prolia_pi.pdf

Amgen, Inc. Xgeva (denosumab). Prescribing Information. Thousand Oaks, CA: Amgen; Revised 6/2015. Retrieved 8/21/15 from: http://pi.amgen.com/united_states/xgeva/xgeva_pi.pdf .

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Specialty Matched Consultant Advisory Panel – 9/2015

Medical Director review 6/2016

Medical Director review 9/2016

Senior Medical Director review 2/2017

Amgen, Inc. Xgeva (denosumab) injection for subcutaneous use. Prescribing Information. Thousand Oaks, CA:Amgen; Revised 1/2018. Available at: https://pi.amgen.com/~/media/amgen/repositorysites/pi-amgen-com/xgeva/xgeva_pi.pdf. Accessed May 2018.

Amgen, Inc. Prolia (denosumab) injection for subcutaneous use. Prescribing Information. Thousand Oaks, CA:Amgen; Revised 6/2018. Available at: https://pi.amgen.com/~/media/amgen/repositorysites/pi-amgen-com/prolia/prolia_pi.pdf. Accessed October 2018.

Specialty Matched Consultant Advisory Panel – 9/2018

Medical Director review 5/2019

Specialty Matched Consultant Advisory Panel – 9/2019

Amgen Inc. Prolia (denosumab) injection, for subcutaneous use. Highlights of prescribing information. March 2020. Available at: https://www.pi.amgen.com/~/media/amgen/repositorysites/pi-amgen-com/prolia/prolia_pi.ashx. Last accessed April 2020.

Medical Director review 4/2020

Policy Implementation/Update Information

7/1/2011 New policy developed. BCBSNC will provide coverage for denosumab when it is determined to be medically necessary because the medical criteria and guidelines outlined in the policy are met. Prolia™ may be considered medically necessary for treatment of postmenopausal women with osteoporosis at high risk for fracture. XGEVA™ may be considered medically necessary for prevention of skeletal-related events in patients with bone metastases from solid tumors. Notification given 7/1/2011 for effective date 9/29/2011. (adn)

10/1/2011 Added the following to Prolia in the When Denosumab Is Covered section: Prolia™ may be considered medically necessary for members who have failed or are unable to tolerate at least one oral bisphosphonate, or for whom oral bisphosphonate therapy is contraindicated, (including inability to swallow or to remain in an upright position after oral bisphosphonate administration), AND for: Treatment of postmenopausal women with osteoporosis at high risk for fracture (those who have had an osteoporotic fracture, or have multiple risk factors for fracture); OR Prevention of osteoporosis in persons receiving aromatase inhibitors (anastrozole, letrozole, exemestane); OR Treatment to increase bone mass in women at high risk for fracture receiving adjuvant aromatase inhibitor therapy for breast cancer; OR Treatment to increase bone mass in men at high risk for fracture receiving androgen deprivation therapy for nonmetastatic prostate cancer. The following statements were deleted from the When Denosumab Is Not Covered section: "Bone loss associated with hormone-ablation therapy in breast cancer or prostate cancer" and "Use of denosumab is not approved for use in pregnant women, nursing mothers or pediatric patients." The statement: "The same active ingredient (denosumab) is found in Prolia™ and XGEVA™. Patient should not receive both drugs" was added to Policy Guidelines. The statements "Denosumab is not recommended for use in pediatric patients" and "There are no adequate and well-controlled studies of Prolia™ in pregnant women and nursing mothers. Prolia™ should be used during pregnancy and lactation only if the importance of the drug to the mother justified the potential risk to the fetus/infant" were also added to the Policy Guidelines. Codes J3490 and J3590 were added to the Billing/Coding section. (adn)

10/11/11 Specialty Matched Consultant Advisory Panel review 9/28/11. Policy accepted as written. (adn)

10/25/11 *When Denosumab Is Covered* section revised to clarify requirement for oral biphosphonate. (adn)

1/1/12 Code C9272 deleted and replaced with J0897 in the Billing/Coding section. (adn)

10/30/12 References updated. Specialty Matched Consultant Advisory Panel review 9/21/12. Added the following clinical indication to the "When Covered" section: "Prolia™ may also be considered medically necessary as a treatment to increase bone mass in men with osteoporosis at high risk for fracture." (sk)

7/16/2013 Medical Director review. References updated. Added the following clinical indication to the "When Covered" section: "Xgeva may be considered medically necessary for treatment of adults and skeletally mature adolescents with giant cell tumor of bone that is unresectable or where surgical resection is likely to result in severe morbidity." (sk)

11/26/13 Specialty Matched Consultant Advisory Panel review 9/18/13. No change to Policy statement. (sk)

10/14/14 Reference updated. Specialty Matched Consultant Advisory Panel review 9/30/14. No change to Policy statement. (sk)

12/30/14 Reference updated. Added the following clinical indication to the "When Covered" section: "Xgeva may be considered medically necessary for treatment of hypercalcemia of malignancy refractory to bisphosphonate therapy." Dosage forms and strengths information added to Description section. (sk)

10/30/15 References updated. Specialty Matched Consultant Advisory Panel review 9/30/15. (sk)

7/1/16 The wording in the "When denosumab is covered" section was revised. The statement regarding oral biphosphonate therapy was removed from the first paragraph and added to the first bulleted statement so that it now reads: "Treatment of postmenopausal women with osteoporosis at high risk for fracture (those who have had an osteoporotic fracture or have multiple risk factors for fracture) AND who have failed or are unable to tolerate at least one oral bisphosphonate OR for whom oral bisphosphonate therapy is contraindicated (including inability to swallow or to remain in an upright position after oral bisphosphonate administration)". (an)

9/30/16 Added ICD-10 diagnoses codes to "Billing/Coding" section. Medical Director review 9/2016. Notification given 9/30/16 for effective date 12/30/16. (lpr)

12/30/16 Added HCPCS codes S0353,S0354 and ICD10 codes M81.0, M81.8, T50.905, Z79.811, Z87.311 to Billing/Coding section. Deleted HCPCS codes J3490, J3590. Notification given 12/30/16 for effective date 4/1/2017. (lpr)

2/24/17 Added the following statement to "When Covered" section: "Use of Denosumab may be considered medically necessary for clinical indications not listed above when the drug is prescribed for the treatment of cancer either: In accordance with FDA label (when clinical benefit has been established, see Policy Guidelines); OR In accordance with specific strong endorsement or support by nationally recognized compendia, when such recommendation is based on strong/high levels of evidence, and/or uniform consensus of clinical appropriateness has been reached". Under "When Not Covered" section, added the statement "Denosumab is considered investigational for cancer indications when criteria is not met regarding FDA labeling **OR** strong endorsement/support by nationally recognized compendia, as stated under "When Denosumab is covered." Added the following statements under "Policy Guidelines" section: 1)Drugs prescribed for treatment of cancer in accordance with FDA label may be considered medically necessary when clinical benefit has been established, and should not be determined to be investigational as defined in Corporate Medical Policy, Investigational (Experimental) Services." 2) Please refer to CMP "Investigational (Experimental) Services" for a summary of evidence standards from nationally recognized compendia. Senior Medical Director review 2/2017. Remains on notice. Effective date 4/1/17. (lpr)

10/13/17 Specialty Matched Consultant Advisory Panel review 9/27/2017. No change to policy statement. (an)

5/11/18 Updated "When Covered" section regarding when Xgeva is considered medically necessary to add the statement "in individuals with multiple myeloma or" to the prevention of skeletal-related events indication to reference newly approved indication. Removed multiple myeloma as investigational from "When Not Covered" section. Reference added. (krc)

10/12/18 Added the following statement to "When Covered" section: "Treatment of individuals with glucocorticoid-induced osteoporosis at high risk for fracture (those who have had

an osteoporotic fracture or have multiple risk factors for fracture) AND who are initiating or continuing systemic glucocorticoids in a daily dosage equal to 7.5 mg or greater of prednisone and expected to remain on therapy for at least 6 months AND who have failed or are unable to tolerate at least one oral bisphosphonate OR for whom oral bisphosphonate therapy is contraindicated (including inability to swallow or to remain in an upright position after oral bisphosphonate administration)". Updated Policy Guidelines to include contraindication of Prolia use in pregnancy. References added. Specialty Matched Consultant Advisory Panel review 9/26/2018. (krc)

5/28/19 Revised wording in "When Covered" section for Prolia in the treatment of osteoporosis to state "bisphosphonate" instead of "oral bisphosphonate". Medical Director review 5/2019. (krc)

10/1/19 Added reference to the following related medical policy: "Romosozumab-aqqg (Evenity™)". Specialty Matched Consultant Advisory Panel review 9/18/2019. No change to policy intent. (krc)

4/28/20 Updated structure of policy statements in "When Covered" section for clarity and consistency with FDA label. No change to policy intent. Reference added. Medical Director review 4/2020. (krc)