BlueCross BlueShield of Louisiana

An independent licensee of the Blue Cross and Blue Shield Association.

denosumab (Xgeva)®

Policy # 00283
Original Effective Date: 01/19/2011
Current Effective Date: 08/20/2014

Applies to all products administered or underwritten by Blue Cross and Blue Shield of Louisiana and its subsidiary, HMO Louisiana, Inc.(collectively referred to as the "Company"), unless otherwise provided in the applicable contract. Medical technology is constantly evolving, and we reserve the right to review and update Medical Policy periodically.

Note: Denosumab (Prolia®)‡ is addressed separately in medical policy 00265.

When Services Are Eligible for Coverage
Coverage for eligible medical treatments or procedures, drugs, devices or biological products may be provided only if:

- *Benefits are available in the member's contract/certificate, and*
- *Medical necessity criteria and guidelines are met.*

Skeletal-Related Events Secondary to Bone Metastases from Solid Tumors
Based on review of available data, the Company may consider the use of denosumab (Xgeva®)‡ for the prevention of skeletal related events (SREs) in patients with bone metastases from solid tumors to be **eligible for coverage**.

Patient Selection Criteria:
Coverage eligibility will be considered for the use of denusomab (Xgeva) when the following criterion is met:

- Use in the prevention of skeletal related events (SREs) in patients with bone metastases from solid tumors.

Giant Cell Tumor of the Bone
Based on review of available data, the Company may consider the use of denosumab (Xgeva) for the treatment of giant cell tumor of the bone to be **eligible for coverage**.

Patient Selection Criteria:
Coverage eligibility will be considered for the use of denusomab (Xgeva) when the following criteria are met:

- Patient has diagnosis of giant cell tumor of the bone; and
- Patient is an adult OR skeletally mature adolescent; and
- Giant cell tumor of the bone is unresectable OR surgical resection is likely to result in severe morbidity

When Services Are Considered Investigational
Coverage is not available for investigational medical treatments or procedures, drugs, devices or biological products.

Based on review of available data, the Company considers the use of denosumab (Xgeva) when patient selection criteria are not met OR for any other use not mentioned above to be **investigational.***

Based on review of available data, the Company considers the use of denosumab (Xgeva) for the prevention of skeletal related events (SREs) in patients with multiple myeloma to be **investigational.***

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Background/Overview

Xgeva is a monoclonal antibody that works to inhibit RANKL (receptor activator of nuclear factor kappa-B ligand) or nuclear factor kB ligand. It is indicated for the prevention of skeletal related events (SREs) in patients with bone metastases from solid tumors. Xgeva is also indicated for the treatment of giant cell tumor of the bone that is unresectable or in an area where surgical resection is likely to result in severe morbidity. Xgeva is not indicated for the prevention of SREs in patients with multiple myeloma. In general, RANKL binds to the RANK receptor to increase differentiation and maturation of an osteoclastic precursor into a mature osteoclast. Osteoclasts work to increase bone resorption (in other words, increase the destruction of bone cells in order to release mineral contents within the bone cells). Under normal physiological situations, osteoclastic activity is important in bone development. When the activity is out of control, bone resorption can occur and make the bone more prone to fracture. Xgeva prevents RANKL from activating its receptor, RANK, on the surface of osteoclasts, their precursors, and osteoclast-like giant cells.

Other medications that have been approved for similar indications as Xgeva include Zometa and Aredia. Mechanisms are unclear and differ for each drug. Xgeva is administered subcutaneously every four weeks in a 120mg dose for the prevention of SREs secondary to bone metastases from solid tumors. In patients with giant cell tumor of the bone, Xgeva is dosed at 120mg every 4 weeks with additional 120mg doses on days 8 and 15 of the first month of therapy.

Skeletal related events are defined as pathologic fractures, surgical/radiotherapy interventions to bone lesions, spinal cord compression and hypercalcemia of malignancy. Skeletal related events result in negative quality of life and a worsening of prognosis. Biphosphonates are a standard of care for patients with bone metastasis.

Bone Metastases

Pathophysiology

Sites of bone metastasis are predominantly the axial skeleton, particularly the spine, pelvis, and ribs, where red marrow is most abundant. Bone metastases are classified as either osteolytic (destructive of normal bone) or osteoblastic (involving deposition of new bone) based upon the predominant radiologic appearance. In both types of lesions there is dysregulation of the normal bone remodeling process. Both breast cancer and prostate cancer bone metastases tend to be mixed osteoblastic and osteolytic, although osteolytic lesions generally predominate in breast cancer and osteoblastic lesions generally predominate in prostate cancer.

The bone destruction observed in osteolytic metastases is primarily mediated by osteoclasts and is not a direct effect of tumor cells. In breast cancer, a reciprocal interaction between breast cancer cells and the bone microenvironment results in a "vicious cycle" that increases both bone destruction and tumor burden. Tumor cells produce factors that directly or indirectly induce osteoclast formation. The resulting bone resorption caused by osteoclasts releases growth factors from the bone matrix that stimulate both tumor growth and further bone destruction.

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The pathogenesis of osteoblastic metastasis is less well understood than that of osteolytic lesions. Prostate specific antigen (PSA), released from prostate cancer cells, may lead to blockade of tumor-induced bone resorption and to release of osteoblastic growth factors in the bone microenvironment.

Clinical Presentation
Bone metastases can cause a wide range of symptoms that can impair the quality of life or shorten survival. Direct complications of bone involvement include severe pain, pathologic fractures, and epidural spinal cord compression. In addition to these local effects, osteolytic metastases can result in life-threatening hypercalcemia.

Metastatic bone pain is typically described as aching, with insidious onset and gradual increase in severity over weeks to months. However, there are exceptions, such as the sudden onset of back pain that accompanies the collapse of a cancer-containing vertebral body. Nerve root entrapment, a common complication associated with vertebral metastases, may cause a burning and/or radiating type of pain.

Diagnosis
Pain by itself is not a reliable indicator of the presence of bone metastases. Confusion with benign pathology is particularly a problem for elderly patients, in whom degenerative disease and osteoporosis are common. The differential diagnosis of new or increasing bone pain in a patient with malignancy includes:

- Worsening pain from nonmalignant conditions, such as arthritis, disc injury, osteoporosis, degenerative disease, and Paget's disease
- Musculoskeletal discomfort related to physical exertion
- Treatment-related complications, such as nerve root compression from vertebral body collapse

Structural information on skeletal damage from metastatic bone disease is best obtained by skeletal radiography supplemented by computerized tomography or magnetic resonance imaging (MRI). Isotope bone scanning is a sensitive but non-specific test to detect the presence of skeletal pathology. Preferential uptake of tracer occurs at sites of active bone formation and is influenced by osteoblastic activity and skeletal vascularity. The bone scan, therefore, reflects not only neoplastic but also traumatic and inflammatory processes. A false-negative scan will occur when there is pure lytic disease.
Serum and urinary levels of several biochemical markers of bone metabolism (e.g., C-telopeptide [CTx] and N-telopeptide [NTx], the C-terminal and N-terminal peptides, respectively, of mature type I collagen) are being investigated for their diagnostic and prognostic utility in patients with metastatic bone disease. Urinary NTx levels may have particular clinical relevance.

Giant Cell Tumor of the Bone
Giant cell tumor of the bone is a very rare disease and is typically located towards the end of a bone. The disease is characterized by the presence of multinucleated giant cells and imaging would provide classic features of malignant destruction (lytic destruction, cortical destruction, soft-tissue extension, and pathologic fracture).

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FDA or Other Governmental Regulatory Approval

U.S. Food and Drug Administration (FDA)
In November 2010, the FDA approved Xgeva for the prevention of SREs in patients with bone metastasis from solid tumors. In June 2013, Xgeva was approved for the treatment of giant cell tumor of the bone that is unresectable or in an area where surgical resection is likely to result in severe morbidity.

Rationale/Source

This medical policy was developed through consideration of peer-reviewed medical literature generally recognized by the relevant medical community, U.S. FDA approval status, nationally accepted standards of medical practice and accepted standards of medical practice in this community, Blue Cross and Blue Shield Association technology assessment program (TEC) and other non-affiliated technology evaluation centers, reference to federal regulations, other plan medical policies, and accredited national guidelines.

Skeletal Related Events Secondary to Bone Metastases from Solid Tumors
The safety and efficacy of Xgeva for the prevention of SREs in patients with bone metastases from solid tumors was demonstrated in three international, randomized (1:1), double-blind, active-controlled, noninferiority trials comparing Xgeva with zoledronic acid. In all three trials, patients were randomized to receive 120mg Xgeva subcutaneously every four weeks or 4mg zoledronic acid intravenously (IV) every four weeks (dose adjusted for reduced renal function). Patients with creatinine clearance less than 30mL/min were excluded. In each trial, the main outcome measure was demonstration of noninferiority of time to first SRE as compared to zoledronic acid. Supportive outcome measures were superiority of time to first SRE and superiority of time to first and subsequent SRE; testing for these outcome measures occurred if the main outcome measure was statistically significant. An SRE was defined as any of the following: pathologic fracture, radiation therapy to bone, surgery to bone, or spinal cord compression.

Trial 1 enrolled 2046 patients with advanced breast cancer and bone metastasis. Randomization was stratified by a history of prior SRE (yes or no), receipt of chemotherapy within six weeks prior to randomization (yes or no), prior oral bisphosphonate use (yes or no), and region (Japan or other countries). Forty percent of patients had a previous SRE, 40% received chemotherapy within six weeks prior to randomization, 5% received prior oral bisphosphonates, and 7% were enrolled from Japan. Median age was 57 years, 80% of patients were white, and 99% of patients were women. The median number of doses administered was 18 for denosumab and 17 for zoledronic acid.

Trial 2 enrolled 1776 adults with solid tumors other than breast and castrate-resistant prostate cancer (CRPC) with bone metastasis and multiple myeloma. Randomization was stratified by previous SRE (yes or no), systemic anticancer therapy at time of randomization (yes or no), and tumor type (non-small cell lung cancer, myeloma, or other). Eighty-seven percent were receiving systemic anticancer therapy at the time of randomization, 52% had a previous SRE, 64% of patients were men, 87% were White, and the median age was 60 years. A total of 40% of patients had non-small cell lung cancer, 10% had multiple myeloma, 9% had renal cell carcinoma, and 6% had small cell lung cancer. Other tumor types each comprised less than 5% of the enrolled population. The median number of doses administered was seven for both denosumab and zoledronic acid.

Trial 3 enrolled 1901 men with CRPC and bone metastasis. Randomization was stratified by previous SRE, PSA level (less than 10ng/mL or 10ng/mL or greater) and receipt of chemotherapy within six weeks prior to randomization (yes or no). Twenty-six percent of patients had a previous SRE, 15% of patients had PSA less than 10ng/mL, and 14% received chemotherapy within six weeks prior to randomization. Median age was 71 years and 86% of patients were white. The median number of doses administered was 13 for denosumab and 11 for zoledronic acid.

Xgeva delayed the time to first SRE following randomization as compared to zoledronic acid in patients with breast or CRPC with osseous metastases. In patients with bone metastasis due to other solid tumors or lytic lesions due to multiple myeloma, Xgeva was noninferior to zoledronic acid in delaying the time to first SRE following randomization. Overall survival and progression-free survival were similar between arms in all three trials. Mortality was higher with Xgeva in a subgroup analysis of patients with multiple myeloma (hazard ratio [95% CI] of 2.26 [1.13, 4.50]; n=180).

Giant Cell Tumor of the Bone
The safety and efficacy of Xgeva for the treatment of giant cell tumor of bone in adults or skeletally mature adolescents were demonstrated in two open-label trials (Trial 4 and 5) that enrolled patients with histologically confirmed measurable giant cell tumor of bone that was either recurrent, unresectable, or for which planned surgery was likely to result in severe morbidity. Patients received 120 mg Xgeva subcutaneously every 4 weeks with additional doses on Days 8 and 15 of the first cycle of therapy.

Trial 4 was a single arm, pharmacodynamic, and proof of concept trial conducted in 37 adult patients with unresectable or recurrent giant cell tumor of bone. Patients were required to have histologically confirmed giant cell tumor of bone and radiologic evidence of measurable disease from a computed tomography (CT) or MRI obtained within 28 days prior to study enrollment. Patients enrolled in Trial 4 underwent CT or MRI assessment of giant cell tumor of bone at baseline and quarterly during Xgeva treatment.

Trial 5 was a parallel-cohort, proof of concept, and safety trial conducted in 282 adult or skeletally mature adolescent patients with histologically confirmed giant cell tumor of bone and evidence of measurable active disease. Trial 5 enrolled 10 patients who were 13 – 17 years of age. Patients enrolled into one of three cohorts: Cohort 1 enrolled 170 patients with surgically unsalvageable disease (e.g., sacral or spinal sites of disease, or pulmonary metastases); Cohort 2 enrolled 101 patients with surgically salvageable disease where the investigator determined that the planned surgery was likely to result in severe morbidity (e.g., joint resection, limb amputation, or hemipelvectomy); Cohort 3 enrolled 11 patients who previously participated in Trial 4. Patients underwent imaging assessment of disease status at intervals determined by their treating physician.

An independent review committee evaluated objective response in 187 patients enrolled and treated in Trials 4 and 5 for whom baseline and at least one post-baseline radiographic assessment were available (27 of 37 patients enrolled in Trial 4 and 160 of 270 patients enrolled in Cohorts 1 and 2 of Trial 5). The primary efficacy outcome measure was objective response rate using modified Response Evaluation Criteria in Solid Tumors (RECIST 1.1).

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The overall objective response rate (RECIST 1.1) was 25% (95% CI: 19, 32). All responses were partial responses. The estimated median time to response was 3 months. In the 47 patients with an objective response, the median duration of follow-up was 20 months (range: 2 to 44 months), and 51% (24/47) had a duration of response lasting at least 8 months. Three patients experienced disease progression following an objective response.

References

1. Blue Cross and Blue Shield Association. TEC Specialty Pharmacy Combined Capacity (SPCC) Report #8/15, Denosumab (Prolia™, Xgeva®), revised February 2013.
2. U. S. Food and Drug Administration. Labeling of the drug denosumab (Xgeva®). June 2014. http://www.fda.gov
3. Xgeva. [package insert]. Amgen: Thousand Oaks, California. 2013.
4. Beers M, Porter R, Jones T, Kaplan J, Berkwits M. The Merck Manual of Diagnosis and Therapy. Whitehouse Station, NJ: Merck Research Laboratories; 2006.

Coding

The five character codes included in the Blue Cross Blue Shield of Louisiana Medical Policy Coverage Guidelines are obtained from Current Procedural Terminology (CPT®)‡, copyright 2013 by the American Medical Association (AMA). CPT is developed by the AMA as a listing of descriptive terms and five character identifying codes and modifiers for reporting medical services and procedures performed by physician.

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CPT is a registered trademark of the American Medical Association.

Codes used to identify services associated with this policy may include (but may not be limited to) the following:

Code Type	Code
CPT	No codes
HCPCS	J0897
ICD-9 Diagnosis	All relative diagnoses
ICD-9 Procedure	No codes

Policy History

Original Effective Date: 01/19/2011
Current Effective Date: 08/20/2014
01/06/2011 Medical Policy Committee review
01/19/2011 Medical Policy Implementation Committee approval. New policy.

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03/01/2012	Medical Policy Committee review
03/21/2012	Medical Policy Implementation Committee approval. No change to coverage.
03/07/2013	Medical Policy Committee review
03/20/2013	Medical Policy Implementation Committee approval. Created a Patient Selection Criteria Section. Clarified the When Services are Considered Investigational section.
08/01/2013	Medical Policy Committee review
08/21/2013	Medical Policy Implementation Committee approval.
08/07/2014	Medical Policy Committee review
08/20/2014	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.

Next Scheduled Review Date: 08/2015

*****Investigational – A medical treatment, procedure, drug, device, or biological product is Investigational if the effectiveness has not been clearly tested and it has not been incorporated into standard medical practice. Any determination we make that a medical treatment, procedure, drug, device, or biological product is Investigational will be based on a consideration of the following:

A. whether the medical treatment, procedure, drug, device, or biological product can be lawfully marketed without approval of the U.S. Food and Drug Administration (FDA) and whether such approval has been granted at the time the medical treatment, procedure, drug, device, or biological product is sought to be furnished; or
B. whether the medical treatment, procedure, drug, device, or biological product requires further studies or clinical trials to determine its maximum tolerated dose, toxicity, safety, effectiveness, or effectiveness as compared with the standard means of treatment or diagnosis, must improve health outcomes, according to the consensus of opinion among experts as shown by reliable evidence, including:
    1. Consultation with the Blue Cross and Blue Shield Association technology assessment program (TEC) or other nonaffiliated technology evaluation center(s);
    2. credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community; or
    3. reference to federal regulations.

**Medically Necessary (or “Medical Necessity”) - Health care services, treatment, procedures, equipment, drugs, devices, items or supplies that a Provider, exercising prudent clinical judgment, would provide to a patient for the purpose of preventing, evaluating, diagnosing or treating an illness, injury, disease or its symptoms, and that are:

A. in accordance with nationally accepted standards of medical practice;
B. clinically appropriate, in terms of type, frequency, extent, level of care, site and duration, and considered effective for the patient's illness, injury or disease; and
C. not primarily for the personal comfort or convenience of the patient, physician or other health care provider, and not more costly than an alternative service or sequence of services at least as likely to produce equivalent therapeutic or diagnostic results as to the diagnosis or treatment of that patient's illness, injury or disease.

For these purposes, “nationally accepted standards of medical practice” means standards that are based on credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community, Physician Specialty Society recommendations and the views of Physicians practicing in relevant clinical areas and any other relevant factors.

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NOTICE: Medical Policies are scientific based opinions, provided solely for coverage and informational purposes. Medical Policies should not be construed to suggest that the Company recommends, advocates, requires, encourages, or discourages any particular treatment, procedure, or service, or any particular course of treatment, procedure, or service.