Medical Policy

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***Current Policy Effective Date: 5/1/12**
(See policy history boxes for previous effective dates)

Title: Denosumab (i.e., Xgeva) for the Prevention of Skeletal-Related Events (SREs) Secondary to Bone Metastasis from Solid Tumors

Description / Background

In June 2010, one dosage form of denosumab, a RANK Ligand inhibitor (a 1 mL single-use vial of which contains *60 mg* of denosumab [Prolia™]), was approved by the US Food and Drug Administration (FDA) for the treatment of osteoporosis in postmenopausal women who are at high risk of fracture. This policy is intended to discuss the use of denosumab for the prevention of skeletal-related events (SREs) in patients with bone metastases from solid tumors only.

On November 19, 2010, the U.S. Food and Drug Administration (FDA) approved Xgeva™ (denosumab-*120 mg* every four weeks as a subcutaneous injection) for patients who are at risk for developing skeletal related events (SREs) due to bone metastases from solid tumors, (e.g., prostate cancer, breast cancer). SREs include such conditions as pathological fractures, spinal cord compression, severe pain requiring radiotherapy or surgery and hypercalcemia. It was approved following a six month priority review by the FDA. Xgeva is not indicated for the prevention of SREs in patients with multiple myeloma.

Bone metastasis is a serious complication of advanced cancer and can lead to fractures and compression of the spinal cord. In order to treat these complications, major surgery and radiation may be necessary. The primary goal of treatment for bone metastases is to prevent the occurrence of debilitating and costly bone complications, which causes disability, pain and hospitalization. Seventy five percent of patients with advanced prostate, lung and breast cancer will experience bone metastasis.

RANK (receptor activator of nuclear factor κβ) Ligand, also known as osteoprotegerin ligand, is a protein expressed by osteoblasts and other cells which binds to RANK. RANK is classified as a tumor necrosis factor receptor that is expressed on osteoclasts and osteoclast progenitors. In healthy adult bone, the body regulates RANK Ligand activity to balance bone formation and bone resorption. Increased RANK Ligand signaling disrupts the natural balance of bone remodeling by

causing excessive osteoclast activity and enhancing the resorption of bone. The body then responds by trying to balance bone formation and bone resorption. This occurs when the body produces a substance called osteoprotegerin (OPG). This substance prevents the RANK Ligand from binding with its receptor RANK, thereby regulating osteoclast activity and bone resorption.

RANK Ligand can be overexpressed by osteoblasts which can drive excessive osteoclast activity. This is turn contributes to a cycle of bone destruction, which may further stimulate tumor growth. This vicious cycle can lead to devastating fractures and other skeletal-related events. The RANK Ligand pathway is believed to play a central role in cancer-induced bone destruction.

Xgeva (denosumab 120 mg every month) is a fully human monoclonal antibody that binds to RANK Ligand and prevents it from activating its receptor, RANK, on the surface of osteoclasts. It is administered by subcutaneous (SC) injection and is an alternative to treatment with intravenous Zometa® (zoledronic acid). According to one study, Xgeva appears to be comparable to zoledronic acid for reducing SREs in cancer patients with bone metastases and may be less toxic to the kidneys than Zometa. According to the same study, Xgeva may be superior to zoledronic acid for reducing SREs in patients with advanced breast cancer or prostate cancer. To date, the most serious side effects noted with denosumab are hypocalcemia and osteonecrosis of the jaw. These side effects are also associated with IV bisphosphonates such as Fosamax®, Boniva®, etc.

Xgeva is marketed as a therapy for the reduction and delay of SREs in cancer patients with bone metastases. The recommended dose of Xgeva is 120 mg administered as a subcutaneous injection every four weeks in the upper arm, upper thigh or abdomen. Calcium and vitamin D should be taken as necessary to treat or prevent hypocalcemia. (The same medication in a lower dose is currently marketed as Prolia™ which is given as a treatment of postmenopausal osteoporosis in women at high risk for fractures.)

The injections are generally given in the doctor's office because of the strict storage temperature requirement and the need to let the medication sit for one hour prior to injection. In addition, the medication must be reconstituted and care must be taken to avoid shaking the medication prior to administration. It is possible that this medication may be able to be given in the home setting by an experienced health care worker.

There are currently other drugs on the market which are given to prevent SREs in patients with metastatic bone cancer. An example of such a drug is zoledronic acid (Zometa®, Reclast®). The mechanism of action for zoledronic acid differs from denosumab, as do methods of administration and potential side effects. The treating physician should select the appropriate drug for each patient based on that patient's particular circumstances and needs.

CPT / HCPCS Level II Codes *(Note: The inclusion of a code in this list is not a guarantee of coverage. Please refer to the medical policy statement to determine the status of a given procedure)*

Established codes:

96372 J0897

Other codes (investigational, not medically necessary, etc.):

N/A

Diagnoses / Medical Conditions

- Bone metastasis
- Cancer stage documented in medical record as metastatic and reviewed (ONC)

Medical Policy Statement

The safety and effectiveness of subcutaneous administration of Xgeva (denosumab 120 mg subcutaneously every month) for the prevention of skeletal related events secondary to bone metastasis from solid tumors have been established. It is a useful therapeutic option for patients meeting selection criteria.

Rationale

There is one published randomized, double-blind, phase III pivotal trial (NCT00321464) comparing denosumab with IV zoledronic acid in women with metastatic breast cancer for the reduction of SRE. Xgeva was statistically superior to zoledronic acid in delaying time to the first and subsequent skeletal related events. Osteonecrosis of the jaw incidence did not statistically differ between denosumab and zoledronic acid groups (2.0 percent and 1.4 percent, respectively). This trial was designed to primarily determine if denosumab was non-inferior to zoledronic acid. Secondary endpoints assessed denosumab superiority over zoledronic acid.

There are two small phase II trials comparing various doses of Xgeva with IV bisphosphonate that were published. Both of these phase II trials were designed to evaluate efficacy to reduce or delay SREs in cancer patients by measuring surrogate markers of bone reabsorption rather than the actual incidence of SREs. One trial (NCT00091832) reported similar outcomes for both treatments in breast cancer patients who had not been previously treated for metastases with IV bisphosphonate. The other trial (NCT00104650) reported statistically superior outcomes favoring denosumab in a mixed patient population with multiple myeloma or various metastatic cancers who were not responding adequately to ongoing IV bisphosphonate therapy. The incidence of adverse events did not statistically differ between denosumab and IV bisphosphonate groups in either study.

The receptor (RANKL) which denosumab binds to is part of the immune system and it also mediates bone remodeling. This has raised concerns that long-term treatment with denosumab may have adverse consequences for the immune system. Increased infection rates have not been observed in trials for metastatic disease, but current published trials have been too small and of too short a duration to prove or disprove such concerns. To date, the most serious side effects noted with denosumab are hypocalcemia and osteonecrosis of the jaw; a safety concern also associated with IV bisphosphonates.

The Food and Drug Administration (FDA) approved denosumab (Prolia-60 mg every six months) in June 2010 for the treatment of postmenopausal osteoporosis in women at high risk for a fracture. On November 19, 2010, the FDA approved denosumab (Xgeva-120 mg subcutaneously every month) for the reduction and delay of SREs in patients with bone metastases from solid tumors. The FDA approval does not include use in patients with multiple myeloma.

Xgeva is marketed for the reduction and delay of SREs in patients with bone metastases from solid tumors. It is marketed as Prolia™ for the osteoporosis indication. Xgeva is administered more frequently and at a higher dose than Prolia. Safety profiles differ between the oncology and osteoporosis approved indications.

Published and unpublished phase III evidence indicates that denosumab is comparable to zoledronic acid for reducing SREs in cancer patients with bone metastases. The evidence also suggested that denosumab was superior to zoledronic acid for reducing SREs in patients with advanced breast cancer and advanced prostate cancer. Two of three pivotal phase III trials comparing denosumab with zoledronic acid are unpublished to date. Publication of these additional head-to-head trials will help draw conclusions about relative safety and efficacy.

Inclusions, recommendations and exclusions

Inclusions:
There must be documentation that at least one IV bisphosphonate has been ineffective, not tolerated or contraindicated for the prevention of skeletal-related events in patients with metastasis from solid tumors.

Recommendations:
Because there is a risk of hypocalcemia and osteonecrosis of the jaw following treatment with Xgeva, the following recommendations are made:

Hypocalcemia
- Correct pre-existing hypocalcemia prior to Xgeva treatment.
- Monitor calcium levels and administer calcium, magnesium and vitamin D as necessary.
- Monitor calcium levels more frequently when Xgeva is administered with other drugs that can also lower calcium levels.
- Advise patients to contact a healthcare professional for symptoms of hypocalcemia (e.g., petechia, paresthesias [pins and needles sensation in and around the mouth and/or extremities], heightened tendon reflexes, irregular heartbeat, etc.)

Osteonecrosis of the Jaw (ONJ)
Osteonecrosis of the jaw (localized death of bone tissue) is identified by the following symptoms:
- Jaw pain
- Osteomyelitis
- Bone erosion
- Tooth or periodontal infection
- Toothache
- Gingival ulceration or gingival erosion
- Persistent pain or slow healing of the mouth or jaw after dental surgery

Prevention and monitoring for ONJ includes:
- Oral examinations and appropriate preventive dentistry prior to the initiation of Xgeva and periodically during Xgeva therapy
- Instruction on appropriate oral hygiene
- If possible, invasive dental procedures should be avoided during treatment with Xgeva.

Exclusions

Treatment to prevent SREs in patients with multiple myeloma.

Related Policies

N/A

Government Regulations

National:

No NCD on this topic. This drug has been granted OPPS pass-through status effective October 1, 2010. Medicare article states: "Effective 11/18/2010, the FDA approved a second indication for denosumab (Xgeva™). Xgeva™ is approved for the treatment of patients with bone metastases from solid tumors.

The patient's medical record should contain documentation that fully supports the medical necessity for the administration of the denosumab (Xgeva™). Such documentation should include, but is not limited to:
1. Documentation of bone metastasis from a solid tumor and adequate calcium levels as well as the use of Vitamin D if indicated.

Effective for dates of service on or after 01/01/2011, HCPCS code C9272 should be used to report denosumab (Prolia™, Xgeva™) for claims submitted to the FI or Part A MAC.

Denosumab may not be billed using a chemotherapy administration code. The administration of the product should be billed using CPT code 96372, (Therapeutic, prophylactic, or diagnostic injection (specify substance or drug); subcutaneous or intramuscular)."

- No national or local coverage determination on this topic.
- Medicare article**,** ID Number A50361, effective 11/1/2010, revised 1/1/2011

"The patient's medical record should contain documentation that fully supports the medical necessity for the administration of the denosumab (Xgeva™). Such documentation should include, but is not limited to:
- Documentation of bone metastasis from a solid tumor
- Adequate calcium levels as well as the use of Vitamin D if indicated.

Denosumab (Xgeva™) is administered at a dose of 120mg every four weeks as a subcutaneous injection."

Local:

No LCD on this topic.

Michigan Department of Community Health:

No Medicaid policy on this topic; drug is payable, preauth required.

(The above Medicare information is current as of the review date for this policy. However, the coverage issues and policies maintained by the Centers for Medicare & Medicaid Services [CMS, formerly HCFA] are updated and/or revised periodically. Therefore, the most current CMS information may not be contained in this document. For the most current information, the reader should contact an official Medicare source.)

References

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The articles reviewed in this research include those obtained in an Internet based literature search for relevant medical references through 12/22/12, the date the research was completed.

Joint BCBSM/BCN Medical Policy History

Policy Effective Date	BCBSM Signature Date	BCN Signature Date	Comments
5/1/11	3/17/11	3/3/11	Joint policy established
5/1/12	2/21/12	2/21/12	Routine maintenance. Policy retired as a medical policy. Please refer to pharmacy policies for updates.

Next Review Date: No further review scheduled on this topic as a medical policy. Refer to pharmacy policies for updates.

BLUE CARE NETWORK BENEFIT COVERAGE
POLICY: DENOSUMAB (i.e., XGEVA) FOR THE PREVENTION OF SKELETAL-RELATED EVENTS (SREs) SECONDARY TO BONE METASTASIS FROM SOLID TUMORS

I. Coverage Determination:

Commercial HMO (includes Self-Funded groups unless otherwise specified)	Covered; criteria apply.
BCNA (Medicare Advantage)	Covered; criteria apply/
BCN65 (Medicare Complementary)	Coinsurance covered if primary Medicare covers the service.
BlueCaid	Covered; criteria apply.

II. Administrative Guidelines:

- The member's contract must be active at the time the service is rendered.
- The service must be authorized by the member's PCP except for Self-Referral Option (SRO) members seeking Tier 2 coverage.
- Services must be performed by a BCN-contracted provider, if available, except for Self-Referral Option (SRO) members seeking Tier 2 coverage.
- Payment is based on BCN payment rules, individual certificate benefits and certificate riders.
- Appropriate copayments will apply. Refer to certificate and applicable riders for detailed information.
- CPT - HCPCS codes are used for descriptive purposes only and are not a guarantee of coverage.