PART B DRUG MEDICAL/PHARMACY	ASPIRE HEALTH	Effective Date August 15, 2024	
	XGEVA PRODUCTS (DENOSUMAB) **Wyost (denosumab-bbdz)**	**Policy#** Xgeva Products (denosumab) **Review Date** 05/28/2024	**Applicable to:** ☑ Medicare Advantage ☐ Commercial ☐ Elevance Health HMO ☐ Blue Shield Trio
	Approver's Name &Title QI & UM Drug Subcommittee		

Aspire Health Plan applies medical drug clinical criteria as a reference for medical policy information only. Federal and state laws or requirements, contract language, and Plan benefit may take precedence over the application of these clinical criteria. Please consult the applicable certificate or contract for benefit details. This policy is subject to revision at the discretion of the Plan and is therefore subject to change. Refer to the 'Disclaimer' section below for more information.

OVERVIEW

This policy addresses the coverage of Xgeva (denosumab) for its indication of bone metastases from solid tumors, giant cell tumor of bone, hypercalcemia of malignancy, and multiple myeloma:

- Prevention of skeletal-related events in patients with multiple myeloma and in patients 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

Denosumab, also available under the brand name **Prolia, with the following indications, are not addressed in this policy and available in the Prolia (denosumab) Clinical Policy.**

- Bone loss (treatment to increase bone mass), in men with non-metastatic prostate cancer at high risk for fracture receiving androgen deprivation therapy.
- Bone loss (treatment to increase bone mass), in women with breast cancer at high risk for fracture receiving adjuvant aromatase inhibitor (AI) therapy.
- Glucocorticoid-induced osteoporosis (treatment), in men and women at high risk of fracture who are either initiating or continuing systemic glucocorticoids in a daily dosage equivalent to 7.5 mg or greater of prednisone and expected to remain on glucocorticoids for at least 6 months.

APPLICABLE HCPCS

J0897: Injection, denosumab, 1 mg; 1 mg = 1 billable unit (60 billable units every 6 months)

C9399, J3490, J3590, J9999: Denosumab-bbdz (Wyost) (effective 03/05/24)

- Wyost (denosumab-bbdz): Biosimilar to Xgeva (FDA approved March 2024)

Available as: A single-use vial that contains 120 mg of denosumab per 1.7 mL (70 mg/mL)

Please note: Prolia (denosumab) and its respective indications are not addressed in this policy.

CLINICAL CRITERIA

I. INITIAL CRITERIA

Xgeva (denosumab) may be authorized when **ALL** of the following criteria are met with documentation:

A. Prescribed by, or in consultation with, a board-certified oncologist, hematologist, nephrologist, or physician specialist appropriate to member's condition. If prescribed in consultation, consultation notes must be submitted with initial request and reauthorization requests.

AND

B. Prescriber attestation or documentation of the following:

1. Denosumab will not be used in combination with other antiresorptive or anabolic agents (e.g., bisphosphonates, parathyroid hormone analogs, or romosozumab) or another RANKL-inhibitor (Prolia; Jubbonti); **and**

2. No pre-existing hypocalcemia (serum calcium or corrected calcium within normal limits per laboratory reference), or hypocalcemia has been corrected prior to initiation of treatment.

AND

C. Member has **ONE** of the following diagnoses:

1. Prevention of skeletal-related events in:

   a. Multiple Myeloma; **or**

   b. Bone Metastases from Solid Tumors (e.g., breast cancer, kidney cancer, lung cancer, prostate cancer, thyroid cancer).

2. Hypercalcemia of malignancy [i.e., albumin-corrected serum calcium level greater than 12.5 mg/dL (3.1 mmol/L)].

3. Giant cell tumor of bone that is unresectable or where surgical resection is likely to result in severe morbidity.

AND

D. Limitations / Exclusions

Denosumab is unproven and will not be authorized for the following indications:

1. Combination therapy of denosumab and intravenous bisphosphonates
2. Bone loss associated with hormone-ablation therapy (other than aromatase inhibitors) in breast/prostate cancer
3. Cancer pain
4. Central giant cell granuloma
5. Hyper-parathyroidism
6. Immobilization hypercalcemia
7. Osteogenesis Imperfecta
8. Osteopenia

Note: Requests for an 'Exception' may be authorized if AHP's Off-Label Use of Drugs and Biologic Agents Policy is met.

II. REAUTHORIZATION / CONTINUATION OF THERAPY CRITERIA

Xgeva (denosumab) may be authorized for continuation of therapy when initial criteria have been met **AND** there is documentation of beneficial response from previous course(s) of treatment:

A. Evidence of clinical improvement applicable to member's diagnosis:

1. Multiple Myeloma OR Bone metastases from solid tumors: Additional documentation or peer-to-peer with Aspire Medical Director or Pharmacy Clinician will be required if more than one fracture in the last 6 months or if treatment exceeds 2 years.

2. Giant Cell Tumor of the Bone: Tumor response with disease stabilization or decrease in size or spread of tumor.

3. Hypercalcemia of Malignancy: Decrease in albumin corrected serum calcium levels from baseline.

AND

B. Absence of unacceptable toxicity from the drug (e.g., severe symptomatic hypocalcemia, osteonecrosis of the jaw, atypical femoral fractures, dermatological adverse reactions, severe infection, severe hypersensitivity/anaphylaxis, musculoskeletal pain, etc.).

AND

C. Administer calcium and vitamin D as necessary to treat or prevent hypocalcemia.

STEPTHERAPY

Step therapy criteria do not apply for members who are currently being treated with the requested medications. Step therapy is only applied for members that are new to therapy (have not received the requested drug in the last 365 days.

A. PREFERRED DRUGS: Zoledronic acid (1st preferred) and Ibandronate (2nd preferred) – NO STEP THERAPY REQUIRED

Step therapy requirements are NOT applicable to the following FDA-approved indications:
1) Giant Cell Tumor of the Bone, or 2) Skeletal-related events in patients with bone metastases from metastatic breast cancer or metastatic castration-resistant prostate cancer.

B. Xgeva (denosumab) may be authorized when the initial clinical criteria are met with documentation of **ONE** of the following:

1. History of use of injectable bisphosphonate resulting in minimal clinical response to therapy (defined as a decrease in BMD or a fracture while on therapy), **OR**

2. *Contraindication, intolerance, or adverse event(s) to injectable bisphosphonate
   **Contraindications to zoledronic acid therapy: Hypersensitivity to zoledronic acid or any component of the formulation; hypocalcemia (Reclast only); pre-existing renal insufficiency (creatinine clearance < 35 mL/min).*
   **Contraindications to ibandronate: Hypocalcemia; known hypersensitivity to ibandronate or any component of the formulation.*

OR

3. Member has previously received Xgeva (denosumab) within the past 365 days and therefore not subject to step therapy requirements.

DOSAGE AND AUTHORIZATION TIMEFRAMES

1. Recommended Dose: Dosing is in accordance with the FDA-approved labeling. Administer calcium and vitamin D as necessary to treat or prevent hypocalcemia.

    a. **Multiple Myeloma:** Dose does not exceed 120 mg subcutaneously every 4 weeks by a health care provider.

    b. **Bone Metastasis from Solid Tumors:** 120 mg subcutaneously by a health care provider every 4 weeks.

    c. **Giant Cell Tumor of Bone:** 120 mg subcutaneously by a health care provider every 4 weeks with additional 120 mg doses on Days 8 and 15 of the first month of therapy.

    d. **Hypercalcemia of Malignancy:** 120 mg administered every 4 weeks with additional 120 mg doses on Days 8 and 15 of the first month of therapy.

2. Maximum Quantity (Xgeva 120 mg / 1.7 mL single-dose vial)

    - Loading dose: Total of 3 vials for the initial 28 days
    - Maintenance dose: 1 vial per 28 days (120 mg every 4 weeks)

3. Authorization Period (initial authorization and re-authorization): 12 months

DRUG INFORMATION

PHARMACOLOGIC CATEGORY: RANK Ligand (RANKL) Inhibitors

ROUTE OF ADMINISTRATION: Subcutaneous (should not be administered intravenously, intramuscularly, or intradermally.

FDA-APPROVED INDICATIONS:

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

COMPENDIAL APPROVED (OFF-LABEL) USES: NONE CONTRAINDICATIONS

- 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.
- 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.

OTHER CONSIDERATIONS:

Clinical Considerations: Correct hypocalcemia and vitamin D deficiency (e.g., to a 25-hydroxyvitamin D level ≥20 ng/mL [≥50 nmol/L]), when appropriate, before initiation, and ensure adequate calcium and vitamin D intake during therapy.

CLINICAL SUMMARY / APPENDIX

Xgeva (denosumab) is a RANK ligand inhibitor indicated for the prevention of skeletal-related events in patients with multiple myeloma and in patients with bone metastases from solid tumors, the 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, and for the treatment of hypercalcemia of malignancy refractory to bisphosphonate therapy (Amgen, 2020).

Xgeva received FDA approval for the prevention of skeletal-related events in patients with bone metastases from solid tumors from three noninferiority trials comparing treatment with zoledronic acid. Treatment with Xgeva delayed the time to first skeletal-related event following randomization as compared to zoledronic acid in patients with breast or castrate-resistant cancer 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 skeletal-related event following randomization. Overall survival and progression-free survival were similar between arms in all three trials.

FDA approval of Xgeva for the prevention of skeletal-related events in newly diagnosed multiple myeloma patients with treatment through disease progression was also shown in a noninferiority trial comparing treatment with zoledronic acid. Treatment with Xgeva was noninferior to zoledronic acid in delaying the time to first skeletal-related event following randomization. The results for overall survival were comparable between Xgeva and zoledronic acid treatment.

Xgeva gained indication for the treatment of giant cell tumor of bone in adults or skeletally mature adolescents from two open-label trials. The primary efficacy outcome measure was objective response rate using Response Evaluation Criteria in Solid Tumors (RECIST) v 1.1. The overall objective response rate (RECIST 1.1) was 25%.

FDA approval of Xgeva for the treatment of hypercalcemia of malignancy was also demonstrated in an open-label, single-arm trial of patients who are refractory to treatment with intravenous bisphosphonate therapy. Over sixty (63.6%) of patients responded to treatment defined as corrected serum calcium ≤11.5 mg/dL (2.9 mmol/L), within 10 days after drug administration.

Professional Society Guidelines

National Comprehensive Cancer Network Clinical Practice Guidelines in Oncology (NCCN Guidelines)
Several NCCN Clinical Practice Guidelines in Oncology include denosumab as a treatment for several conditions related to malignant disease. The following NCCN Guidelines state:

- For giant cell tumor of the bone, the NCCN recommends (Category 2A) denosumab as a single agent or combined with serial embolization (preferred), and/or radiation therapy for resectable disease with unacceptable morbidity and/or unresectable axial lesions for patients with localized disease, metastases at presentation, or recurrence, denosumab is also recommended as a single agent for unresectable metastatic disease, unresectable metastatic recurrence or considered prior to surgery for resectable local recurrence.
- For prostate cancer, the NCCN recommends (Category 2A) denosumab for prevention or treatment of osteoporosis during androgen deprivation therapy (ADT) for patients with high fracture risk, denosumab is also recommended (Category 1) as the preferred agent for the prevention of skeletal-related events in patients with castration-resistant prostate cancer who have documented bone metastases and creatinine clearance greater than 30 ml/min.
- For invasive or inflammatory breast cancer, the NCCN recommends (Category 1) denosumab to be used with calcium and vitamin D supplementation in addition to chemotherapy or endocrine therapy for bone metastasis in patients with expected survival ≥ 3 months with adequate renal function.
- For multiple myeloma, the NCCN recommends (Category 2A) denosumab to be used in combination with primary myeloma therapy and is the preferred agent in patients with renal insufficiency.
- For non-small cell lung cancer, the NCCN recommends (Category 2A) denosumab to be considered in patients with bone metastases.

- For ductal carcinoma, invasive breast cancer or inflammatory breast cancer, the NCCN recommends (Category 2A) denosumab to be considered in postmenopausal (natural or induced) patients receiving adjuvant aromatase inhibition therapy along with calcium and vitamin D supplementation to maintain or improve bone mineral density and reduce risk of fractures.
- For kidney cancer, the NCCN recommends (Category 2A) denosumab to be used as a component of best supportive care for bony metastases.
- For systemic mastocytosis, the NCCN recommends (Category 2A) denosumab as second-line therapy for osteopenia/osteoporosis in patients with bone pain not responding to bisphosphonates or for patients who are not candidates for bisphosphonates because of renal insufficiency.
- For thyroid carcinoma (anaplastic, follicular, medullary, oncocytic, papillary), the NCCN recommends (Category 2A) denosumab to be considered for bone metastases or palliative care for bone metastases (anaplastic).

REFERENCES

Government Agency

Centers for Medicare and Medicaid Services (CMS). Medicare coverage database: No NCD identified for denosumab (Prolia & Xgeva); no applicable LCD identified for MAC (search terms: denosumab; Prolia; Xgeva). Available from CMS.

Prescribing Information

1. Prolia (denosumab) [prescribing information]. Thousand Oaks, CA: Amgen Inc; January 2023.
2. Xgeva (denosumab) [package insert]. Thousand Oaks, CA: Amgen Inc.; June 2020.

Peer-reviewed Literature, Guidelines, Consensus

Referenced with permission from the NCCN Drugs & Biologics Compendium (NCCN Compendium®) for Denosumab. National Comprehensive Cancer Network, 2023. The NCCN Compendium® is a derivative work of the NCCN Guidelines®. NATIONAL COMPREHENSIVE CANCER NETWORK®, NCCN®, and NCCN GUIDELINES® are trademarks owned by the National Comprehensive Cancer Network, Inc. To view the most recent and complete version of the Compendium, go online to NCCN.org. Accessed April 2024.

IMPORTANT REMINDER

This Medicare Part B Step Therapy Medical Necessity Guideline is provided for informational purposes only and neither constitutes nor replaces professional medical advice. Physicians, hospitals, and other providers are expected to administer or use drugs/biologicals in the most effective and clinically appropriate manner. Treating physicians and other health care providers is solely responsible for all medical care decisions. In accordance with the member's Evidence of Coverage (EOC), every benefit plan has its own coverage provisions, limitations, and exclusions. In the event of a conflict between this policy and the member's EOC, the member's EOC provisions will take precedence.

Aspire Health Plan (AHP) adheres to Medicare guidelines, including National Coverage Determination (NCD), Local Coverage Determinations (LCDs), Local Coverage Articles (LCAs), and other relevant Medicare manuals established by CMS. Compliance with these guidelines is required when applicable. Refer to the CMS website at http://www.cms.hhs.gov. For the most up-to-date Medicare policies and coverage, please search the Medicare Coverage Database. All LCDS are the same for each state within a Jurisdiction. Medicare Part B Administrative Contractor (MAC) for CA [Jurisdiction E (1)]: Active LCDs - JE Part B – Noridian (noridianmedicare.com). In the event of a discrepancy between this policy and the Medicare NCD or LCD, the Medicare NCD/LCD will govern.

This policy is utilized by AHP to determine coverage in the absence of applicable CMS Medicare guidelines. Please refer to the links provided in the References section below to access the Medicare source materials that were used for developing this resource document. This document does not serve as a substitute for the official Medicare source materials that provide detailed information on Medicare coverage requirements. In the event of a conflict between this document and Medicare source materials, the Medicare source materials will take precedence.

The inclusion of a code in this policy does not imply that the health service it describes is covered or not covered. Benefit coverage for health services is determined by the member-specific plan document and applicable laws that may mandate coverage for a particular service. Inclusion of a code does not imply or guarantee reimbursement or payment of a claim. Other Policies and Standards may also apply. Providers are expected to retain or have access to the necessary documentation when requested in order to support coverage.

POLICY HISTORY

Version	Approval Date	Summary of Changes
1	05/28/2024	New Policy