REQUIRED CLINICAL DOCUMENTATION FOR REVIEW

Documentation required to determine medical necessity for Denosumab (Xgeva): History and/or physical examination notes and relevant specialty consultation notes that address the problem and need for the service: -Documentation that medication is being prescribed by or in consultation with a specialist -Medication list (current and past) -Diagnosis -Age -Radiographic or imaging studies -Dosing and duration requested -Initial/Extended approval -Labs/Diagnostics.

BACKGROUND

Xgeva, a receptor activator of nuclear factor kappa-B ligand (RANKL) inhibitor, is indicated for the prevention of skeletal-related events in patients with multiple myeloma and in patients with bone metastases from solid tumors. Xgeva is also indicated for 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. Xgeva is also indicated for the treatment of hypercalcemia of malignancy refractory to bisphosphonate therapy. Another injectable formulation of denosumab is available, Prolia®, but it is not included in this policy. The prescribing information for Xgeva notes that patients receiving Xgeva should not take Prolia. Xgeva is available as a single-use vial that contains 120 mg of denosumab per 1.7 mL (70 mg/mL).

DEFINITIONS

None.

INDICATIONS/Criteria

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<th>MediCAID Members</th>
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Coverage of Xgeva is recommended in those who meet the following criteria:

FDA-Approved Indications
1. **Prevention of Skeletal-Related Events in Patients with Bone Metastases from Solid Tumors (e.g., Breast Cancer, Prostate Cancer, Non-Small-Cell Lung Cancer).**

**Criteria.** The patient must meet the following criteria (A, B, C AND D):
- **A)** The patient is aged ≥ 18 years; AND
- **B)** The agent is prescribed by, or in consultation with, a hematologist or an oncologist; AND
- **C)** The patient has bone metastases confirmed by radiographic or imaging studies; AND
- **D)** Patients with prostate cancer have received at least one hormonal therapy (e.g., Lupron Depot® [leuprolide for depot suspension], Eligard® [leuprolide acetate for injectable suspension], Trelstar® [triptorelin pamoate for injectable suspension], or Zoladex® [goserelin implant]).

Xgeva is indicated for the prevention of skeletal-related events in patients with bone metastases from solid tumors. In the trials components of the first skeletal-related event included radiation to bone, pathological fracture, surgery to bone, or spinal cord compression. Several studies have established the efficacy of Xgeva for this use in a variety of cancers (e.g., breast cancer prostate cancer). In the trial involving patients with prostate cancer, patients were required to have documented failure of at least one hormonal therapy.

**Dosing in Adults with Bone Metastases from Solid Tumors.** Dosing must meet the following: The dose of Xgeva is 120 mg administered as a subcutaneous (SC) injection every 4 weeks in the upper arm, upper thigh, or abdomen.

**Initial Approval/Extended Approval.**
- **A)** Initial Approval. Initial approval is for up to 6 months.
- **B)** Extended Approval. Extended approval is for up to 6-month intervals.

**Duration of Therapy in Adults with Bone Metastases from Solid Tumors.** Therapy is indefinite.

**Labs/Diagnostics.** Radiographic or imaging studies (e.g., magnetic resonance imaging [MRI], plain film radiography, computerized tomography [CT] scan, skeletal scintigraphy, positron emission tomography [PET]) must confirm bone metastasis.

2. **Prevention of Skeletal-Related Events in Patients with Multiple Myeloma.**

**Criteria.** The patient must meet the following criteria (A and B):
- **A)** The patient is aged ≥ 18 years; AND
- **B)** The agent is prescribed by, or in consultation with, a hematologist or an oncologist.

Clinical practice guidelines from the American Society of Clinical Oncology regarding the role of bone-modifying agents in multiple myeloma also recommend use of Xgeva. The National Comprehensive Cancer Network (NCCN) guidelines for multiple myeloma (version 4. 2018) state that all patients receiving primary myeloma therapy should be given bisphosphonates (category 1) or Xgeva (category 2A).
Dosing in Adults for the Prevention of Skeletal-Related Events in Patients with Multiple Myeloma. Dosing must meet the following: The dose of Xgeva is 120 mg administered as a subcutaneous (SC) injection once every 4 weeks in the upper arm, upper thigh, or abdomen.

Initial Approval/Extended Approval.
A) Initial Approval. Initial approval is for up to 6 months.
B) Extended Approval. Extended approval is for up to 6-month intervals.

Duration of Therapy in Adults for the Prevention of Skeletal-Related Events in Patients with Multiple Myeloma. Therapy is indefinite.

Labs/Diagnostics. None required.

3. Giant Cell Tumor of Bone.

Criteria. Approve.

Xgeva is indicated for the treatment of adults and skeletally mature adolescents with giant cell tumor of bone that is unresectable or where surgical resection is likely to lead to severe morbidity. Several trials have assessed Xgeva for this use and noted tumor response for some patients. The National Comprehensive Cancer Network (NCCN) clinical practice guidelines regarding Bone Cancer (version 1.2018) discuss giant cell tumor of bone. Xgeva is recommended in several scenarios, including patients with metastatic disease at presentation that is unresectable, as well as patients with localized disease that is resectable with unacceptable morbidity and/or unresectable axial lesions.

Dosing in Giant Cell Tumor of Bone. Dosing must meet the following: The dose of Xgeva is 120 mg SC monthly (every 28 days) with loading doses on Day 8 and Day 15 of Month 1.

Initial Approval/Extended Approval.
A) Initial Approval. Initial approval is for up to 6 months.
B) Extended Approval. Extended approval is at 6-month intervals.

Duration of Therapy in Giant Cell Tumor of Bone. Therapy is indefinite.

Labs/Diagnostics. None required.

4. Hypercalcemia of Malignancy.

Criteria. The patient must meet the following criteria (A, B, AND C):
A) The patient has a current malignancy; AND
B) The patient has tried intravenous (IV) bisphosphonate therapy (e.g., zoledronic acid injection [Zometa], pamidronate injection [Aredia]) or has an estimated calculated creatinine clearance (CrCl) < 30 mL/min; AND (If the CrCl is not given, an example of how to calculate the estimated CrCl is provided in Appendix A [see page 5]).
C) The patient’s albumin-corrected calcium (cCa) is ≥ 11.5 mg/dL. (If the cCa value is not given, an example of how to calculate cCa is provided in Appendix B [see page 5]).

Xgeva is indicated for the treatment of hypercalcemia of malignancy refractory to bisphosphonate therapy. Normal total serum calcium concentration generally range from 8.5 to 10.5 mg/dL. Patients in the pivotal trial establishing the use of Xgeva for this indication involved adult patients with cancer and hypercalcemia that was refractory to IV bisphosphonates. In the pivotal trial that led to its approval, refractory hypercalcemia of malignancy was defined as an albumin-corrected calcium of > 12.5 mg/dL. Other data also involve a similar patient population. Other IV administered bisphosphonates indicated for the treatment of hypercalcemia of malignancy include Zometa® (zoledronic acid injection, generic), and Aredia® (pamidronate injection, generic). These medications have limited dosing information and are generally not recommended for use in patients with severe renal impairment (estimated calculated CrCl < 30 mL/min). In the professional opinion of specialist physicians reviewing the data, we have adopted this criterion.

**Dosing in Hypercalcemia of Malignancy.** *Dosing must meet the following:* The dose of Xgeva is 120 mg SC every 4 weeks with additional 120 mg doses on Days 8 and 15 of the first month of therapy.

**Initial Approval/Extended Approval.**
- A) **Initial Approval.** Initial approval is for up to 6 months.
- B) **Extended Approval.** Extended approval is at 6-month intervals.

**Duration of Therapy in Hypercalcemia of Malignancy.** Therapy is indefinite based on response.

**Labs/Diagnostics.** Patients with hypercalcemia of malignancy must have an albumin-corrected calcium level as previously described.

**Waste Management for All:**
Single-use vials are available that contain 120 mg of denosumab per 1.7 mL (70 mg/mL). Only one vial should be needed per dose.

**Conditions Not Recommended for Approval**
Xgeva has not been shown to be effective or there are limited or preliminary data, or potential safety concerns, that are not supportive of general approval for the following conditions. Rationale for non-coverage for these specific conditions are provided below.

1. **Concurrent Use of Xgeva with the Prolia Formulation of Denosumab.** The Warnings and Precautions section of the Xgeva prescribing information states that patients receiving Xgeva should not take Prolia.
2. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.
SPECIAL CONSIDERATIONS
Enter all special considerations here.

LIMITATIONS/EXCLUSIONS
Please refer to a product line’s certificate of coverage for benefit limitations and exclusions for these services:

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Citations & References

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**Revision History**

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<td>Revised</td>
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Appendix A: Cockcroft-Gault Equation for Estimating Creatinine Clearance

There are many different methods that can be used to calculate an estimated creatinine clearance (CrCl). The Cockcroft-Gault is one formula that provides an estimate of CrCl using serum creatinine. It is only for adults. This formula tends to overestimate CrCl in obese persons and to underestimate it in those who are lean. The Cockcroft-Gault equation for calculating CrCl is as follows:

\[
CrCl \text{ in adults (men)} = \frac{(140 \text{ minus age [in years]} \times \text{weight [in kg]})}{(72 \times \text{serum creatinine [in mg/dL]})}
\]

For women, multiple the above results by 0.85. The steps, for clarity, are as follows:

1) Subtract the patient’s age in years from 140.
2) Multiple by the patient’s weight in kg (if weight is in pounds, divide by 2.2 to get kg).
3) Multiple the patient’s serum creatinine (in mg/dL) by 72.
4) Divide the total from 2) by the total from 3).
5) If the patient is female, take the total from 4) and multiple by 0.85.

For example, a man who is 55 years of age, who weighs 160 pounds (72.7 kg), and with a serum creatinine 0.9 mg/dL, would have a calculated creatinine clearance of 95 mL/minute. For a woman with these same values, her CrCl would be 81 mL/minute.
Appendix B: Calculating albumin-corrected calcium (cCa)

If cCa value is not given, the following equation can be used to calculate cCa:
\[ \text{cCa in mg/dL} = \text{measured Ca (mg/dL)} + (0.8 \times [4.0 \text{ g/dL} - \text{patient albumin [g/dL]})]. \]

For example, a patient with a serum calcium level of 10.3 mg/dL, but an albumin level of 3.0 g/dL, appears to have a normal serum calcium level. However, when corrected for the low albumin, the real serum calcium value is 11.1 mg/dL, calculated as \((10.3 + 0.8 \times 1.0)\).