Pharmacy Medical Necessity Guidelines:
Prolia® and Xgeva® (denosumab)

Effective: February 14, 2017

<table>
<thead>
<tr>
<th>Prior Authorization Required</th>
<th>√</th>
<th>Type of Review – Care Management</th>
</tr>
</thead>
<tbody>
<tr>
<td>Not Covered</td>
<td></td>
<td>Type of Review – Clinical Review</td>
</tr>
</tbody>
</table>

Pharmacy (RX) or Medical (MED) Benefit

<table>
<thead>
<tr>
<th>MED /RX</th>
<th>Department to Review</th>
<th>PRECERT /MM /RXUM</th>
</tr>
</thead>
</table>

This Pharmacy Medical Necessity Guideline applies to the following:

**Tufts Health Plan Commercial Plans**
- Tufts Health Plan Commercial Plans – large group plans
- Tufts Health Plan Commercial Plans – small group and individual plans

**Tufts Health Public Plans**
- Tufts Health Direct – Health Connector
- Tufts Health Together – A MassHealth Plan
- Tufts Health RITogether – A RItte Care + Rhody Health Partners Plan

**Tufts Health Freedom Plan products**
- Tufts Health Freedom Plan – large group plans
- Tufts Health Freedom Plan – small group plans

**Fax Numbers:**
- All plans except Tufts Health Plan
  - Health Public Plans: PRECERT: 617.972.9409
  - Tufts Health Direct – Health Connector: MM: 888.415.9055
  - Tufts Health Together – A MassHealth Plan:
    - RxUM: 617.673.0988

**Note:** For Tufts Health Plan Medicare Preferred Members, please refer to the Tufts Health Plan Medicare Preferred Prior Authorization Criteria. Background, applicable product and disclaimer information can be found on the last page.

**OVERVIEW**

**FDA-APPROVED INDICATIONS**

**Prolia** (denosumab) is indicated
- For the treatment of postmenopausal women with osteoporosis at high risk for fracture, defined as a history of osteoporotic fracture, or multiple risk factors for fracture; or patients who have failed or are intolerant to other available osteoporosis therapy. In postmenopausal women with osteoporosis, Prolia reduces the incidence of vertebral, nonvertebral, and hip fractures.
- For treatment to increase bone mass in men with osteoporosis at high risk for fracture, defined as a history of osteoporotic fracture, or multiple risk factors for fracture; or patients who have failed or are intolerant to other available osteoporosis therapy.
- As a treatment to increase bone mass in men at high risk for fracture receiving androgen deprivation therapy for nonmetastatic prostate cancer. In these patients Prolia also reduced the incidence of vertebral fractures.
- As a treatment to increase bone mass in women at high risk for fracture receiving adjuvant aromatase inhibitor therapy for breast cancer.

**Xgeva** (denosumab) is indicated
- For the prevention of skeletal-related events in patients with bone metastases from solid tumors. Xgeva (denosumab) is not indicated for the prevention of skeletal-related events in patients with multiple myeloma.
- 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.
- For the treatment of hypercalcemia of malignancy refractory to bisphosphonate therapy.

Denosumab is a monoclonal antibody that binds to receptor activator of nuclear factor kappa-B ligand (RANKL), a transmembrane protein that is vital for osteoclast formation, function, and survival. Denosumab prevents the normal binding of RANKL to its receptor, RANK. This impairs normal osteoclast function of bone resorption, which causes increased bone mass and strength in the trabecular and cortical bone.
**COVERAGE GUIDELINES**

**For Xgeva (denosumab)**
The plan may authorize coverage of Xgeva (denosumab) when the following criteria are met:

1. The Member has bone metastases from solid tumors and is receiving Xgeva (denosumab) for prevention of skeletal-related events

   **OR**

2. The Member is being treated for unresectable giant cell tumor of bone (GCTB) or surgical resection of GCTB is likely to result in severe morbidity

   **OR**

3. The Member has a documented diagnosis of hypercalcemia of malignancy and has had an inadequate response to, or is unable to tolerate therapy with at least one bisphosphonate (e.g., pamidronate disodium, zoledronic acid)

**For Prolia (denosumab)**
The plan may authorize coverage of Prolia (denosumab) when the following criteria are met:

1. For the treatment of postmenopausal women with osteoporosis
   a) The Member is at high risk of fracture defined as:
      i) a history of osteoporotic fracture
      ii) multiple risk factors for fracture and a T score less than or equal to -2.0 as evidenced via bone density scan.

   **OR**

   b) The Member has had an inadequate response to, or is unable to tolerate therapy with at least one of the traditional osteoporosis treatments [e.g., alendronate (Fosamax®), calcitonin (Miacalcin®), ibandronate (Boniva®), raloxifene (Evista®), risedronate (Actonel®), zoledronic acid (Reclast®)]

2. For treatment to increase bone mass in men with osteoporosis
   a) The Member is at high risk of fracture defined as:
      i) a history of osteoporotic fracture
      ii) multiple risk factors for fracture and a T score less than or equal to -2.0 as evidenced via bone density scan.

   **OR**

   b) The Member has had an inadequate response to, or is unable to tolerate therapy with at least one of the traditional osteoporosis treatments [e.g., alendronate (Fosamax®), calcitonin (Miacalcin®), ibandronate (Boniva®), risedronate (Actonel®), zoledronic acid (Reclast®)].

**For men with nonmetastatic prostate cancer**
1. The Member has a diagnosis of nonmetastatic prostate cancer

   AND

2. The Member is at high risk of fracture defined as:
   a) a history of osteoporotic fracture
   b) multiple risk factors for fracture and a T score at the lumbar spine, total hip, or femoral neck of less than -1.0 as evidenced via bone density scan.

   AND

3. The Member is receiving androgen deprivation therapy

**For women with breast cancer**
1. The Member has a diagnosis of breast cancer

   AND

2. The Member is at high risk of fracture defined as:
   a) a history of osteoporotic fracture
   b) multiple risk factors for fracture and a T score at the lumbar spine, total hip, or femoral neck of less than -1.0 as evidenced via bone density scan

   AND

3. The Member is receiving adjuvant aromatase inhibitor therapy

**Off-label Use Coverage for Other Cancer Diagnoses**
Coverage for other cancer diagnoses may be authorized provided effective treatment with such drug is recognized for treatment of such indication in one of the standard reference compendia, or in the medical literature, or by the Massachusetts commissioner of Insurance (commissioner) under the provisions of the "Sullivan Law": (M.G.L. c.175, s.47K ).

2 Pharmacy Medical Necessity Guidelines: Prolia® and Xgeva® (denosumab)
The plan may authorize coverage for use for other cancer diagnoses provided effective treatment with such drug is recognized as a "Medically Accepted Indication" according to the National Comprehensive Cancer Network (NCCN) Drugs and Biologics Compendium as indicated by a Category 1 or 2A for quality of evidence and level of consensus.

**Note:** The plan requires prescribers to submit clinical documentation supporting the drug's effectiveness in treating the intended malignancy, including the applicable NCCN guideline(s).

In cases where the requested off-label use for the diagnosis is not recognized by the NCCN Drugs and Biologics Compendium, the plan will follow the Centers for Medicare and Medicaid Services (CMS) guidance, unless otherwise directed by the commissioner, and accept clinical documentation referenced in one of the other "Standard Reference Compendia" noted below or supported by clinical research that appears in a regular edition of a "Peer-Reviewed Medical Literature" noted below.

"Standard Reference Compendia"
1. American Hospital Formulary Service – Drug Information (AHFS-DI)
2. Thomson Micromedex DrugDex
3. Clinical Pharmacology (Gold Standard)
4. Wolters Kluwer Lexi-Drugs

"Peer Reviewed Medical Literature"
- American Journal of Medicine
- Annals of Internal Medicine
- Annals of Oncology
- Annals of Surgical Oncology
- Biology of Blood and Marrow Transplantation
- Blood
- Bone Marrow Transplantation
- British Journal of Cancer
- British Journal of Hematology
- British Medical Journal
- Cancer
- Clinical Cancer Research
- Drugs
- European Journal of Cancer (formerly the European Journal of Cancer and Clinical Oncology)
- Gynecologic Oncology
- International Journal of Radiation, Oncology, Biology, and Physics
- The Journal of the American Medical Association
- Journal of Clinical Oncology
- Journal of the National Cancer Institute
- Journal of the National Comprehensive Cancer Network (NCCN)
- Journal of Urology
- Lancet
- Lancet Oncology
- Leukemia
- The New England Journal of Medicine
- Radiation Oncology

When the plan evaluates the evidence in published, peer-reviewed medical literature, consideration will be given to the following:
1. Whether the clinical characteristics of the beneficiary and the cancer are adequately represented in the published evidence.
2. Whether the administered chemotherapy regimen is adequately represented in the published evidence.
3. Whether the reported study outcomes represent clinically meaningful outcomes experienced by patients.
4. Whether the study is appropriate to address the clinical question.
   a. whether the experimental design, in light of the drugs and conditions under investigation, is appropriate to address the investigative question (for example, in some clinical studies, it may be unnecessary or not feasible to use randomization, double blind trials, placebos, or crossover);
   b. that non-randomized clinical trials with a significant number of subjects may be a basis for supportive clinical evidence for determining accepted uses of drugs; and,
   c. that case reports are generally considered uncontrolled and anecdotal information and do not provide adequate supportive clinical evidence for determining accepted uses of drugs.

**LIMITATIONS**
1. The plan will not authorize the use of Prolia (denosumab) or Xgeva (denosumab) for conditions other than those listed above without appropriate documentation.

**CODES**
The following HCPCS/CPT code(s) are:
<table>
<thead>
<tr>
<th>Code</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>J0897</td>
<td>Injection, denosumab, 1 mg</td>
</tr>
</tbody>
</table>

**REFERENCES**


APPROVAL HISTORY
November 9, 2010: Reviewed by Pharmacy & Therapeutics Committee.

Subsequent endorsement date(s) and changes made:
- January 11, 2011: Added Xgeva (denosumab) to Medical Necessity Guidelines. Added limitation for authorization of Prolia (denosumab) or Xgeva (denosumab) for conditions other than those listed above.
- November 15, 2011: Added pharmacy coverage guidelines for men with nonmetastatic prostate cancer and for women with breast cancer.
- January 1, 2012: Administrative update: Replaced HCPCS code C9272 with J0897
- May 8, 2012: For nonmetastatic prostate cancer and for breast cancer, changed the T score requirement from less than or equal to -2.0 to less than -1.0.
- November 6, 2012: Added pharmacy coverage guidelines for men with osteoporosis
- July 9, 2013: Added pharmacy coverage guidelines for treatment of adults and skeletally mature adolescents with giant cell tumor of bone. Added Off-label Use Coverage for Other Cancer Diagnoses criteria.
- July 8, 2014: No changes.
- January 13, 2015: Added medical necessity guidelines for approval of Xgeva (denosumab) for the diagnosis of hypercalcemia of malignancy.
- January 1, 2016: Administrative change to rebranded template.
- February 9, 2016: No changes.
- February 14, 2017: No changes.

BACKGROUND, PRODUCT AND DISCLAIMER INFORMATION
Pharmacy Medical Necessity Guidelines have been developed for determining coverage for plan benefits and are published to provide a better understanding of the basis upon which coverage decisions are made. They are used in conjunction with a Member's benefit document and in coordination with the Member's physician(s). The plan makes coverage decisions on a case-by-case basis considering the individual Member's health care needs. Pharmacy Medical Necessity Guidelines are developed for selected therapeutic classes or drugs found to be safe, but proven to be effective in a limited, defined population of patients or clinical circumstances. They include concise clinical coverage criteria based on current literature review, consultation with practicing physicians in the service area who are medical experts in the particular field, FDA and other government agency policies, and standards adopted by national accreditation organizations. The plan revises and updates Pharmacy Medical Necessity Guidelines annually, or more frequently if new evidence becomes available that suggests needed revisions.

This Pharmacy Medical Necessity Guideline does not apply to Uniformed Services Family Health Plan Members or to certain delegated service arrangements. Unless otherwise noted in the Member's benefit document or applicable Pharmacy Medical Necessity Guideline, Pharmacy Medical Necessity Guidelines do not apply to CareLinkSM Members. For self-insured plans, drug coverage may vary depending on the terms of the benefit document. If a discrepancy exists between a coverage guideline
and a self-insured Member’s benefit document, the provisions of the benefit document will govern. Applicable state or federal mandates will take precedence. For Tufts Health Plan Medicare Preferred, please refer to Tufts Health Plan Medicare Preferred Prior Authorization Criteria.

Treating providers are solely responsible for the medical advice and treatment of Members. The use of this policy is not a guarantee of payment or a final prediction of how specific claim(s) will be adjudicated. Claims payment is subject to Member eligibility and benefits on the date of service, coordination of benefits, referral/authorization and utilization management guidelines when applicable, and adherence to plan policies and procedures and claims editing logic.