

Drug Policy:

Bone Modifying Agents (Aredia, Zometa, Xgeva/Prolia)

POLICY NUMBER UM ONC_1190	SUBJECT Bone Modifying Agents (Aredia, Zometa, Xgeva/Prolia)	DEPT/PROGRAM UM Dept	PAGE 1 of 4
DATES COMMITTEE REVIEWED 12/07/11, 06/01/13, 07/24/14, 12/04/14, 01/19/15, 07/26/16, 08/25/16, 06/12/17, 06/13/18, 07/10/19, 12/11/19, 04/08/20, 10/14/20, 01/13/21, 11/15/21, 12/08/21, 05/11/22, 08/10/22, 03/08/23	APPROVAL DATE March 8, 2023	EFFECTIVE DATE March 31, 2023	COMMITTEE APPROVAL DATES 12/07/11, 06/01/13, 07/24/14, 12/04/14, 01/19/15, 07/26/16, 08/25/16, 06/12/17, 06/13/18, 07/10/19, 12/11/19, 04/08/20, 10/14/20, 01/13/21, 11/15/21, 12/08/21, 05/11/22, 08/10/22, 03/08/23
PRIMARY BUSINESS OWNER: UM		COMMITTEE/BOARD APPROVAL Utilization Management Committee	
URAC STANDARDS HUM v8: UM 1-2; UM 2-1	NCQA STANDARDS UM 2		ADDITIONAL AREAS OF IMPACT
CMS REQUIREMENTS	STATE/FEDERAL REQUIREMENTS		APPLICABLE LINES OF BUSINESS Commercial, Exchange, Medicaid

I. PURPOSE

To define and describe the accepted indications for Bone Modifying Agents (Aredia, Zometa, Xgeva/Prolia) usage in the treatment of cancer, including FDA approved indications, and off-label indications.

New Century Health (NCH) is responsible for processing all medication requests from network ordering providers. Medications not authorized by NCH may be deemed as not approvable and therefore not reimbursable.

The use of this drug must be supported by one of the following: FDA approved product labeling, CMS-approved compendia, National Comprehensive Cancer Network (NCCN), American Society of Clinical Oncology (ASCO) clinical guidelines, or peer-reviewed literature that meets the requirements of the CMS Medicare Benefit Policy Manual Chapter 15.

II. INDICATIONS FOR USE/INCLUSION CRITERIA

- A. Continuation requests for a not-approvable medication shall be exempt from this NCH policy provided:**

1. The requested medication was used within the last year, **AND**
2. The member has not experienced disease progression and/or no intolerance to the requested medication, **AND**
3. Additional medication(s) are not being added to the continuation request.

B. Breast Cancer

1. The member has non-metastatic breast cancer and Zometa (zoledronic acid) is being used for the prevention or treatment of osteoporosis when the member is receiving adjuvant aromatase inhibitor therapy and/or ovarian suppression/ablation **OR**
2. Zometa (zoledronic acid) is being used as a part of the adjuvant therapy regimen in combination with adjuvant endocrine treatment for early breast cancer in a postmenopausal woman or a premenopausal woman on ovarian suppression/ablation. **NOTE:** Typical dosing in this setting is Zometa (zoledronic acid) 4 mg iv every 6 months.
3. **NOTE:** Per NCH Policy, Xgeva/Prolia (denosumab) are not approvable for members with breast cancer. Xgeva/Prolia (denosumab) would be Approvable for the above indications if the member has a documented intolerance/contraindications to Zometa (zoledronic acid) for example renal impairment and a CrCl of less than 30 mL/min. Please refer to NCH alternative agents/regimens recommended by NCH, including but not limited to regimens available at <http://pathways.newcenturyhealth.com>.

C. Giant Cell Tumor of Bone

1. The member is an adult or adolescent 12 years of age or older with giant cell tumor of the bone and Xgeva (denosumab) will be used as a single agent for unresectable localized disease **OR** for metastatic disease.

D. Hypercalcemia of Malignancy

1. Zometa (zoledronic acid) or Aredia (pamidronate) is being used in conjunction with hydration for hypercalcemia as defined as a corrected calcium of greater than or equal to 12 mg/dL (corrected for albumin level). The following formula is used to calculate the corrected calcium level:
 - a. $\text{Corrected Calcium (mg/dL)} = \text{Calcium} + 0.8 \times (4 - \text{patient Albumin})$.
2. **NOTE:** Per NCH Policy, Xgeva/Prolia (denosumab) are not approvable for Hypercalcemia of malignancy. Exception: Member with hypercalcemia of malignancy and the member has a documented intolerance/contraindications to bisphosphonates (e.g., pamidronate, zoledronic acid), for example renal impairment and a CrCl of less than 30 mL/min.

E. Multiple Myeloma

1. The member has multiple myeloma and Zometa (zoledronic acid) or Aredia (pamidronate) is being used with or without anti-myeloma therapy.
2. **NOTE:** Per NCH Policy, Xgeva/Prolia (denosumab) are not approvable for multiple myeloma. Xgeva/Prolia (denosumab) would be Approvable for members with Multiple Myeloma if the member has a documented intolerance/contraindications to bisphosphonates (e.g., pamidronate, zoledronic acid), for example renal impairment and a CrCl of less than 30 mL/min. Please refer to NCH alternative agents/regimens recommended by NCH, including but not limited to regimens available at <http://pathways.newcenturyhealth.com>.

F. Prostate Cancer

1. The member has prostate cancer and Zometa (zoledronic acid) is being used for the prevention or treatment of osteoporosis during androgen deprivation therapy for members who are 70 years of age or higher or are at high risk for fractures.

2. NOTE: Per NCH Policy, Xgeva/Prolia (denosumab) are not approvable for members with prostate cancer. Xgeva/Prolia (denosumab) would be approvable for members with prostate cancer if the member has a documented intolerance/contraindications to Zometa (zoledronic acid), for example renal impairment and a CrCl of less than 30 mL/min. Please refer to NCH alternative agents/regimens recommended by NCH, including but not limited to regimens available at <http://pathways.newcenturyhealth.com>.

G. Solid Tumors with Skeletal Metastases

1. Zometa (zoledronic acid) or Aredia (pamidronate) is being used for a member with a solid tumor and skeletal metastases documented on any imaging study.

DOSE ADJUSTMENTS FOR ZOLEDRONIC ACID FOR USE IN MYELOMA & SOLID TUMORS WITH SKELETAL METASTASES:

Creatinine Clearance in ml/min	Dose of Zoledronic Acid
>60	4 mg
50-60	3.5 mg
40-49	3.3 mg
30-39	3.0 mg
<30	Use is not recommended

2. NOTE: Per NCH Policy, Xgeva/Prolia (denosumab) are not approvable for members with solid tumors and skeletal metastases. Xgeva/Prolia (denosumab) would be Approvable for members with skeletal metastases if the member has a documented intolerance or contraindications to bisphosphonates (e.g., pamidronate, zoledronic acid), for example renal impairment and a CrCl of less than 30 mL/min. Please refer to NCH alternative agents/regimens recommended by NCH, including but not limited to regimens available at <http://pathways.newcenturyhealth.com>.

III. EXCLUSION CRITERIA

- A. Members with creatinine clearance less than 60 mL/min without Zometa dose adjustment, see table above.
- B. Dosing exceeds single dose limits for Zometa 4 mg, Aredia 90 mg, Xgeva 120 mg, and Prolia 60 mg.
- C. Investigational use of a Bone Modifying Agent with an off-label indication that is not sufficient in evidence or is not generally accepted by the medical community. Sufficient evidence that is not supported by CMS recognized compendia or acceptable peer reviewed literature is defined as any of the following:
 1. Whether the clinical characteristics of the patient and the cancer are adequately represented in the published evidence.
 2. Whether the administered chemotherapy/biologic therapy/immune therapy/targeted therapy/other oncologic therapy regimen is adequately represented in the published evidence.
 3. Whether the reported study outcomes represent clinically meaningful outcomes experienced by patients. Generally, the definitions of Clinically Meaningful outcomes are those recommended by ASCO, e.g., Hazard Ratio of less than 0.80 and the recommended survival benefit for OS and PFS should be at least 3 months.
 4. Whether the experimental design, considering 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).

5. 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.
6. That case reports are generally considered uncontrolled and anecdotal information and do not provide adequate supportive clinical evidence for determining accepted uses of drugs.
7. That abstracts (including meeting abstracts) without the full article from the approved peer-reviewed journals lack supporting clinical evidence for determining accepted uses of drugs.

IV. MEDICATION MANAGEMENT

- A. Please refer to the FDA label/package insert for details regarding these topics.

V. APPROVAL AUTHORITY

- A. Review – Utilization Management Department
- B. Final Approval – Utilization Management Committee

VI. ATTACHMENTS

- A. None

VII. REFERENCES

- A. Zoledronic acid Product Information 2021.
- B. Pamidronate Product Information 2021.
- C. Xgeva Product Information. Amgen Inc. Thousand Oaks, CA. 2020.
- D. Prolia Product Information. Amgen Inc, Thousand Oaks, CA. 2022.
- E. Clinical Pharmacology Elsevier Gold Standard 2023.
- F. Micromedex® Healthcare Series: Micromedex Drugdex Ann Arbor, Michigan 2022.
- G. National Comprehensive Cancer Network. Cancer Guidelines and Drugs and Biologics Compendium 2023.
- H. AHFS Drug Information. American Society of Health-Systems Pharmacists or Wolters Kluwer Lexi-Drugs. Bethesda, MD 2023.
- I. Ellis LM, et al. American Society of Clinical Oncology perspective: Raising the bar for clinical trials by defining clinically meaningful outcomes. J Clin Oncol. 2014 Apr 20;32(12):1277-80.
- J. Medicare Benefit Policy Manual Chapter 15 Covered Medical and Other Health Services: <https://www.cms.gov/Regulations-and-Guidance/Guidance/Manuals/Downloads/bp102c15.pdf>.
- K. NCQA UM 2023 Standards and Elements.