Evolent Clinical Guideline 3074 for Bone Modifying Agents (Pamidronate, Zoledronic Acid, Denosumab Products)

Guideline Number: Evolent_CG_3074	**Applicable Codes**	
"Evolent" refers to Evolent Health LLC and Evolent Specialty Services, Inc. ***© 2011 - 2026 Evolent. All rights Reserved.***		
Original Date: December 2011	**Last Revised Date:** May 2026	**Implementation Date:** May 2026

TABLE OF CONTENTS

STATEMENT **2**
PURPOSE 2
INDICATIONS **2**
BREAST CANCER 2
GIANT CELL TUMOR OF BONE 2
HYPERCALCEMIA OF MALIGNANCY 3
MULTIPLE MYELOMA 3
PROSTATE CANCER 3
SOLID TUMORS WITH SKELETAL METASTASES 3
DOSE ADJUSTMENTS FOR ZOLEDRONIC ACID FOR USE IN MULTIPLE MYELOMA AND SOLID TUMORS WITH SKELETAL METASTASES 3
CONTRAINDICATIONS/WARNINGS **3**
EXCLUSION CRITERIA **4**
CODING AND STANDARDS **5**
CODES 5
APPLICABLE LINES OF BUSINESS 6
POLICY HISTORY **6**
LEGAL AND COMPLIANCE **7**
GUIDELINE APPROVAL 7
Committee 7
DISCLAIMER 7
REFERENCES **8**

STATEMENT

Purpose

To define and describe the accepted indications for Bone Modifying Agents [Pamidronate, Zoledronic Acid, Denosumab Products: Xgeva/Prolia (denosumab), Wyost/Jubbonti (denosumab-bbdz), Xbryk/Ospomyv (denosumab-dssb), Osenvelt/Stoboclo (denosumab-bmwo), Bomyntra/Conexxence (denosumab-bnht), Bilprevda/Bildyos (denosumab-nxxp), Aukelso/Bosaya (denosumab-kyqq), Xtrenbo/Enoby (denosumab-qbde), Jubereq/Osvyrti (denosumab-desu), Oziltus/Boncresa (denosumab-mobz), Ponlimsi (denosumab-adet)] usage in the treatment of cancer, including FDA approved indications, and off-label indications.

Evolent is responsible for processing all medication requests from network ordering providers. Medications not authorized by Evolent 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.

INDICATIONS

Continuation requests for a not-approvable medication shall be exempt from this Evolent policy provided

- The member has not experienced disease progression on the requested medication AND
- The requested medication was used within the last year without a lapse of more than 30 days of having an active authorization AND
- Additional medication(s) are not being added to the continuation request.

Breast Cancer

- The member has non-metastatic breast cancer and Bone Modifying Agents are being used for the prevention or treatment of osteoporosis when the member is receiving adjuvant aromatase inhibitor therapy and/or ovarian suppression/ablation OR
- Bone Modifying Agents are 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 zoledronic acid 4 mg iv every 6 months.

Giant Cell Tumor of Bone

- The member is an adult or adolescent 12 years of age or older with giant cell tumor of bone, and a Bone Modifying Agent will be used as a single agent for unresectable

localized disease OR for metastatic disease.

Hypercalcemia of Malignancy

- Bone Modifying Agents are 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:
  - Corrected Calcium (mg/dL) = Calcium + 0.8 x (4 – patient Albumin).

Multiple Myeloma

- The member has multiple myeloma and a Bone Modifying Agent is being used with or without anti-myeloma therapy.

Prostate Cancer

- The member has prostate cancer and a Bone Modifying Agent 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.

Solid Tumors with Skeletal Metastases

- Bone Modifying Agents are 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 Multiple Myeloma and 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

CONTRAINDICATIONS/WARNINGS

- Contraindications
  - Pamidronate

- Clinically significant hypersensitivity to pamidronate, other bisphosphonates, or any component of the formulation
    - Zoledronic Acid
        - Hypersensitivity to zoledronic acid or any component of the formulation
    - Denosumab Products
        - Hypocalcemia
        - Pregnancy
        - Hypersensitivity to denosumab products or any component of the formulations
- US Boxed Warning
    - Denosumab Products
        - Severe hypocalcemia in patients with advanced kidney disease
            - Patients with advanced chronic kidney disease (eGFR <30 mL/minute/1.73 m^2), including dialysis-dependent patients, are at greater risk of severe hypocalcemia following denosumab administration. Severe hypocalcemia resulting in hospitalization, life-threatening events and fatal cases have been reported.
            - The presence of chronic kidney disease-mineral bone disorder (CKD-MBD) markedly increases the risk of hypocalcemia in these patients.
            - Prior to initiating denosumab in patients with advanced chronic kidney disease, evaluate for the presence of CKD-MBD. Treatment with denosumab in these patients should be supervised by a health care provider with expertise in the diagnosis and management of CKD-MBD.

EXCLUSION CRITERIA

- Members with creatinine clearance less than 60 mL/min without zoledronic acid dose adjustment, see table above.
- Dosing exceeds single dose limits for Zoledronic Acid 4 mg, Pamidronate 90 mg, Xgeva/Wyost/Xbryk/Osenvelt/Bomyntra/Bilprevda/Aukelso/Xtrenbo/Jubereq/Oziltus 120 mg, and Prolia/Jubbonti/Ospomyv/Stoboclo/Conexxence/Bildyos/Bosaya/Enoby/Osvyrti/Boncresa /Ponlimsi 60 mg.
- 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:
    - Whether the clinical characteristics of the patient and the cancer are adequately represented in the published evidence.
    - Whether the administered chemotherapy/biologic therapy/immune therapy/targeted

therapy/other oncologic therapy regimen is adequately represented in the published evidence.

- 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.
- 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).
- 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.
- That case reports are generally considered uncontrolled and anecdotal information and do not provide adequate supportive clinical evidence for determining accepted uses of drugs.
- 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.

CODING AND STANDARDS

Codes

- J3489 - Injection, zoledronic acid, 1 mg
- J2430 - Injection, pamidronate disodium, per 30 mg
- J0897 - Injection, denosumab, 1 mg
- Q5136 - Injection, denosumab-bbdz (jubbonti/wyost), biosimilar, 1 mg
- Q5157 - Injection, denosumab-bmwo (stoboclo/osenvelt), biosimilar, 1 mg
- Q5158 - Injection, denosumab-bnht (bomyntra/conexxence), biosimilar, 1 mg
- Q5159 - Injection, denosumab-dssb (ospomyv/xbryk), biosimilar, 1 mg
- Q5161 - Injection, denosumab-kyqq (aukelso/bosaya), biosimilar, 1 mg
- Q5162 - Injection, denosumab-nxxp (bildyos/bilprevda), biosimilar, 1 mg
- J3590 - denosumab-qbde injection, denosumab-desu injection, denosumab-mobz injection, denosumab-adet injection

Applicable Lines of Business

☐	CHIP (Children's Health Insurance Program)
☒	Commercial
☒	Exchange/Marketplace
☒	Medicaid
☐	Medicare Advantage

POLICY HISTORY

Date	Summary
May 2026	• Added new biosimilar to policy • Updated HCPC codes • Updated references
April 2026	• Updated HCPC codes
February 2026	• Added new biosimilars to policy • Updated HCPC codes • Updated references
December 2025	• Added new biosimilars to policy • Updated HCPC codes • Updated references
November 2025	• Added new biosimilars to policy • Updated HCPC codes • Updated references
October 2025	• Added new biosimilars to policy • Updated contraindications/warnings • Updated HCPC codes • Updated references

Date	Summary
April 2025	• Converted to new Evolent guideline template • This guideline replaces UM ONC_1190 Bone Modifying Agents • Added new biosimilars to policy • Updated exclusion criteria • Updated references
September 2024	• Added new biosimilars “Wyost/Jubbonti (denosumab-bbdz)” to policy • Added new references
August 2024	• Replaced “Aredia” and “Zometa” with “pamidronate” and “zoledronic acid”, respectively, since only the generic formulations are currently available

LEGAL AND COMPLIANCE

Guideline Approval

Committee

Reviewed / Approved by Evolent Specialty Services Clinical Guideline Review Committee

Disclaimer

Evolent Clinical Guidelines do not constitute medical advice. Treating health care professionals are solely responsible for diagnosis, treatment, and medical advice. Evolent uses Clinical Guidelines in accordance with its contractual obligations to provide utilization management. Coverage for services varies for individual members according to the terms of their health care coverage or government program. Individual members’ health care coverage may not utilize some Evolent Clinical Guidelines. Evolent clinical guidelines contain guidance that requires prior authorization and service limitations. A list of procedure codes, services or drugs may not be all inclusive and does not imply that a service or drug is a covered or non-covered service or drug. Evolent reserves the right to review and update this Clinical Guideline in its sole discretion. Notice of any changes shall be provided as required by applicable provider agreements and laws or regulations. Members should contact their Plan customer service representative for specific coverage information.

REFERENCES

1. Zoledronic Acid prescribing information. Hospira, Inc. Lake Forest, IL 2021.
2. Pamidronate prescribing information. Hospira, Inc. Lake Forest, IL 2021.
3. Ponlimsi prescribing information. Teva Pharmaceuticals, Inc. Parsippany, NJ 2026.
4. Jubereq prescribing information. Accord BioPharma Inc. Raleigh, NC 2025.
5. Osvyrti prescribing information. Accord BioPharma Inc. Raleigh, NC 2025.
6. Aukelso prescribing information. Biocon Biologics Inc. Cambridge, MA 2025.
7. Bosaya prescribing information. Biocon Biologics Inc. Cambridge, MA 2025.
8. Xtrenbo prescribing information. Hikma Pharmaceuticals USA Inc. Cherry Hill, NJ 2025.
9. Enoby prescribing information. Hikma Pharmaceuticals USA Inc. Cherry Hill, NJ 2025.
10. Xbryk prescribing information. Samsung Bioepis Co., Ltd., Incheon, 21987, Republic of Korea 2025.
11. Ospomyv prescribing information. Samsung Bioepis Co., Ltd., Incheon, 21987, Republic of Korea 2025.
12. Osenvelt prescribing information. CELLTRION, Inc. Incheon, 22014 Republic of Korea 2025.
13. Stoboclo prescribing information. CELLTRION, Inc. Incheon, 22014 Republic of Korea 2025.
14. Bomyntra prescribing information. Fresenius Kabi USA, LLC Lake Zurich, IL 2025.
15. Conexxence prescribing information. Fresenius Kabi USA, LLC Lake Zurich, IL 2025.
16. Bilprevda prescribing information. Organon LLC. Jersey City, NJ 2025.
17. Bildyos prescribing information. Organon LLC. Jersey City, NJ 2025.
18. Xgeva prescribing information. Amgen Inc. Thousand Oaks, CA. 2020.
19. Prolia prescribing information. Amgen Inc. Thousand Oaks, CA. 2024.
20. Wyost prescribing information. Sandoz Inc. Princeton, NJ 2024.
21. Jubbonti prescribing information. Sandoz Inc. Princeton, NJ 2024.
22. Oziltus prescribing information. Amneal Pharmaceuticals LLC. Piscataway, NJ 2025.
23. Boncresa prescribing information. Amneal Pharmaceuticals LLC Piscataway, NJ 2025.
24. Clinical Pharmacology Elsevier Gold Standard 2026.
25. Micromedex® Healthcare Series: Micromedex Drugdex Ann Arbor, Michigan 2026.
26. National Comprehensive Cancer Network. Cancer Guidelines and Drugs and Biologics Compendium 2026.
27. AHFS Drug Information. American Society of Health-Systems Pharmacists or Wolters Kluwer Lexi-Drugs. Bethesda, MD 2026.
28. 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.
29. Medicare Benefit Policy Manual Chapter 15 Covered Medical and Other Health Services: https://www.cms.gov/Regulations-and-Guidance/Guidance/Manuals/Downloads/bp102c15.pdf.
30. Current and Resolved Drug Shortages and Discontinuations Reported to the FDA: http://www.accessdata.fda.gov/scripts/drugshortages/default.cfm.