Medical Policy

Utilization Management and Clinical Medical Policy

Policy Name:	Policy Number:	Scope:	Origination Date:	Effective Date:
Zoledronic acid 4 mg	MP-RX-FP-130-24	☒ **MMM MA** ☒ **MMM MultiHealth**	6/28/2024	03/24/2026
			Last Review Date: 03/24/2026	**Frequently Revision:** Annual

Service Category

☐ Anesthesia
☐ Surgery
☐ Radiology Procedures
☐ Pathology and Laboratory Procedures
☐ Medicine Services and Procedures
☐ Evaluation and Management Services
☐ DME/Prosthetics or Supplies
☒ Part B Drugs

Service Description

This document addresses the use of *Zoledronic acid 4 mg injection,* a bisphosphonate agent approved by the Food and Drug Administration (FDA) for the treatment of hypercalcemia of malignancy, patients with multiple myeloma and patients with documented bone metastases from solid tumors, in conjunction with standard antineoplastic therapy. Prostate cancer should have progressed after treatment with at least one hormonal therapy.

Background Information

Zoledronic acid is a bisphosphonate and acts primarily on bone. It is an inhibitor of osteoclast-mediated bone resorption. Zoledronic acid inhibits osteoclastic activity and induces osteoclast apoptosis. Zoledronic acid also blocks the osteoclastic resorption of mineralized bone and cartilage through its binding to bone. Zoledronic acid inhibits the increased osteoclastic activity and skeletal calcium release induced by various stimulatory factors released by tumors.

Zoledronic acid is administered as an intravenous infusion and has a warning for Embryo-Fetal Toxicity.

Hypercalcemia of Malignancy

Zoledronic acid is indicated for the treatment of hypercalcemia of malignancy defined as an albumin-corrected calcium (cCa) of greater than or equal to 12 mg/dL [3.0 mmol/L] using the formula: cCa in mg/dL = Ca in mg/dL + 0.8 (4.0 g/dL - patient albumin [g/dL]).

Multiple Myeloma and Bone Metastases of Solid Tumors

Zoledronic acid is indicated for the treatment of patients with multiple myeloma and patients with documented bone metastases from solid tumors, in conjunction with standard antineoplastic therapy. Prostate cancer should have progressed after treatment with at least one hormonal therapy.

Approved Indications

A. Treatment of hypercalcemia of Malignancy.

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B. Patients with multiple myeloma and patients with documented bone metastases from solid tumors, in conjunction with standard antineoplastic therapy.
    a. Prostate cancer should have progressed after treatment with at least one hormonal therapy.

Other Uses

A. The safety and efficacy of Zoledronic acid has not been established for use in hyperparathyroidism or non-tumor-related hypercalcemia.
B. To prevent bone loss/osteoporosis in men with Prostate Cancer on Androgen Deprivation Therapy (ADT) with high fracture risk. (prophylaxis). (NCCN 2A)
C. To preserve bone density and reduce fracture risk in postmenopausal women with Breast Cancer . (NCCN 2A)
D. As adjuvant therapy in postmenopausal women with early-stage Breast Cancer. (NCCN 2A)
E. Bone disease with Langerhans Cell Histiocytosis. (NCCN 2A)

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Applicable Codes

The following list(s) of procedure and/or diagnosis codes is provided for reference purposes only and may not be all inclusive. Inclusion or exclusion of a procedure, diagnosis or device code(s) does not constitute or imply member coverage or provider reimbursement policy. Benefit coverage for health services is determined by the member specific benefit plan document and applicable laws that may require coverage for a specific service. The inclusion of a code does not imply any right to reimbursement or guarantee claim payment. Other Policies and Guidelines may apply.

HCPCS	Description
J3489	Injection, zoledronic acid, 1 mg [when specified as zoledronic acid 4mg]

ICD-10	Description
C33	Malignant neoplasm of trachea
C34.00-C34.92	Malignant neoplasm of bronchus and lung
C50.011-C50.929	Malignant neoplasm of breast
C61	Malignant neoplasm of prostate
C64.1-C65.9	Malignant neoplasm of kidney and renal pelvis
C73	Malignant neoplasm of thyroid
C79.51	Secondary malignant neoplasm of bone
C80.1	Malignant (primary) neoplasm, unspecified
C90.00-C90.32	Multiple myeloma and malignant plasma cell neoplasms
C94.30-C94.32	Mast cell leukemia
C96.0	Multifocal and multisystemic (disseminated) Langerhans-cell histiocytosis
C96.20-C96.29	Malignant mast cell neoplasm
C96.5	Multifocal and unisystemic Langerhans-cell histiocytosis
C96.6	Unifocal Langerhans-cell histiocytosis
D05.10-D05.12	Intraductal carcinoma in situ of breast
D05.80-D05.82	Other specified type of carcinoma in situ of breast
D00.00-D09.9	In situ neoplasms
D47.02	Systemic mastocytosis
E83.52	Hypercalcemia
Z79.810	Long term (current) use of selective estrogen receptor modulators (SERMs)
Z79.811	Long term (current) use of aromatase inhibitors
Z85.00-Z85.9	Personal history of malignant neoplasm

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Medical Necessity Guidelines

When a drug is being reviewed for coverage under a member's medical benefit plan or is otherwise subject to clinical review (including prior authorization), the following criteria will be used to determine whether the drug meets any applicable medical necessity requirements for the intended/prescribed purpose.

Zoledronic acid 4 mg

A. Criteria For Initial Approval (*Provider must submit documentation [such as office chart notes, lab results, pathology reports, imaging studies, and any other pertinent clinical information] supporting the patient's diagnosis for the drug and confirming that the patient has met **all** approval criteria.)*

Requests for zoledronic acid 4 mg may be approved for any of the following indications:

I. Patients with documented bone metastases from solid tumors, in conjunction with standard antineoplastic therapy.
For Prostate cancer should have progressed after treatment with at least one hormonal therapy (Label);

OR

II. Treatment of hypercalcemia of malignancy (Label);

OR

III. Treatment of Multiple Myeloma (Label);

OR

IV. Prevention of bone loss associated with adjuvant hormone therapy (e.g., aromatase inhibitors) in women with breast cancer (NCCN 2A);

OR

V. Prevention of osteoporosis in men with prostate cancer receiving androgen deprivation therapy (ADT) and who are at high risk of fracture (NCCN 2A);

OR

VI. **Treatment of** bone disease associated with Langerhans Cell Histiocytosis (NCCN 2A).

B. Criteria For Continuation of Therapy

i. MMM considers continuation of zoledronic acid 4mg, therapy medically necessary in members requesting reauthorization for an indication listed in Section A above (Criteria for Initial Approval) if the following information is provided:

A. For hypercalcemia of malignancy, if serum calcium has not returned to or maintained normal levels following initial treatment; **AND**

1. A minimum of 7 days has elapsed since the last dose before retreatment is considered; **AND**

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B. Documentation of Serum Creatinine and Creatinine Clearance calculated based on actual body weight using Cockcroft-Gault formula; **AND**
C. Documentation of serum calcium levels, or documentation that patient is taking calcium and Vitamin D supplementation; **AND**
D. Documentation that, per FDA prescribing information, a routine oral exam has been performed, and the patient has been evaluated for thigh or groin pain (to rule out atypical femur fracture) and for severe bone, joint, or muscle pain.

C. Authorization Duration

i. Initial Approval Duration: Up to 12 months
ii. Reauthorization Approval Duration: Up to 12 months

D. Conditions Not Covered

Any other use is considered experimental, investigational, or unproven, including the following (this list may not be all inclusive):

i. Requests for zoledronic acid 4 mg may not be approved for any of the following conditions:

A. Use in patients with severe renal impairment, defined as creatinine clearance <30 mL/min, or with evidence of acute renal failure;

OR

B. Use in patients with bone metastases and moderate renal impairment (i.e., CrCl <60 mL/min) without appropriate dose adjustment;

OR

C. Concurrent use with Reclast® (zoledronic acid 5 mg) or use in individuals receiving Reclast for other indications (e.g., osteoporosis, Paget's disease);

OR

D. When the above criteria are not met and for all other indications.

Limits or Restrictions

A. Therapeutic Alternatives

The list below includes preferred alternative therapies recommended in the approval criteria and may be subject to prior authorization.

i. N/A

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B. Quantity Limitations

Approvals may be subject to dosing limits in accordance with FDA-approved labeling, accepted compendia, and/or evidence-based practice guidelines. The chart below includes dosing recommendations as per the FDA-approved prescribing information.

Drug: zoledronic acid 4 mg inj 4 mg/5ml (single dose)	
Indication	**Recommended Dosing Schedule**
Hypercalcemia of malignancy	• 4 mg as a single-use intravenous infusion • 4 mg as retreatment after a minimum of 7 days
Multiple Myeloma and Bone Metastases of Solid Tumors	• 4 mg as a single-use intravenous infusion every 3-4 weeks for patients with creatinine clearance of greater than 60 mL/min. • Reduce the dose for patients with mild and moderate renal impairment: ○ CrCl 50 – 60 ml/min: 3.5 mg ○ CrCl 40 – 49 ml/min: 3.3 mg ○ CrCl 30 – 39 ml/min: 3 mg
Exceptions	
• Treatment in patients with severe renal impairment is not recommended. • Monitor serum creatinine before each dose. • Multiple Myeloma and Bone Metastases of Solid Tumors: Treatment should be withheld for renal deterioration. In the clinical studies, renal deterioration was defined as follows: ○ For patients with normal baseline creatinine, increase of 0.5 mg/dL. ○ For patients with abnormal baseline creatinine, increase of 1 mg/dL. • Patients should also be administered an oral calcium supplement of 500 mg and 400 international units of vitamin D daily.	

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Reference Information

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3. DrugPoints® System [electronic version]. Truven Health Analytics, Greenwood Village, CO. Updated periodically.
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7. U.S. Food and Drug Administration. (2022). *Zometa (zoledronic acid) prescribing information*. Retrieved January 28, 2026, from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2022/203231Orig1s019Lbl.pdf.
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9. Drugs.com — Generic Zometa Availability *Generic Zometa Availability & Release Information.* (n.d.). *Drugs.com*. Retrieved January 28, 2026, from https://www.drugs.com/availability/generic-zometa.html
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11. *NCCN Drugs & Biologics Compendium.* (n.d.). *National Comprehensive Cancer Network*. Retrieved January 28, 2026, from https://www.nccn.org/professionals/drug_compendium/content/

Federal and state laws or requirements, contract language, and Plan utilization management programs or polices may take precedence over the application of this clinical criteria.

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Policy History

Revision Type	Summary of Changes	P&T Approval Date	UM/CMPC Approval Date
Annual Review	Criteria initial approval updated. Criteria for continuation of therapy were revised to include safety documentation requirements consistent with the FDA Prescribing Information, such as evaluation for osteonecrosis of the jaw, atypical femur fractures, and severe bone, joint, or muscle pain. Indications were clarified and validated according to FDA-approved uses and NCCN Category 2A recommendations. Added Conditions Not Covered. And dosing exceptions in renal impairment. Coding was reviewed: ICD-10 codes removed: C81.00–C81.99, C82.00–C86.6, and C88.4. ICD-10 codes added: C33, C34.00–C34.92, C50.011–C50.929, C61, C64.1–C65.9, C73, C79.51, C80.1, C94.30–C94.32, C96.0, C96.20–C96.29, C96.5, C96.6, D05.10–D05.12, D05.80–D05.82, D47.02, Z79.810, and Z79.811. Updated references. Minor formatting and wording edits.	3/17/2026	3/24/2026
Annual Review	Validation of information to ensure is up to date. Word formatting editing and indentation alignment.	4/16/2025	5/6/2025
Policy Inception	New Medical Policy creation	4/18/2024	6/28/2024