

Zometa (zoledronic acid) injection, for intravenous use

Policy Number: MC/PC 059
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[Instructions for Use](#)

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Related Policies

- N/A

Coverage Rationale

Hypercalcemia of malignancy

For initial coverage of Zometa (zoledronic acid) injection for hypercalcemia of malignancy, the following will be required:

- Diagnosis of hypercalcemia of malignancy **and**
- Trial and failure, contraindication, or intolerance to one oral bisphosphonate (e.g., alendronate)

For reauthorization coverage of Zometa (zoledronic acid) injection for hypercalcemia of malignancy, the following will be required:

- Patient demonstrates positive clinical response to therapy

Multiple myeloma and bone metastasis from solid tumors

For initial coverage of Zometa (zoledronic acid) injection for skeletal prevention in multiple myeloma and bone metastasis from solid tumors (BMST), the following will be required:

- One of the following:
 - Both of the following:
 - Diagnosis of multiple myeloma **and**
 - Trial and failure, contraindication or intolerance to one oral bisphosphonate (e.g. alendronate)**or**
 - Both of the following:
 - Diagnosis of solid tumors (e.g., breast cancer, kidney cancer, lung cancer, prostate cancer, thyroid cancer) **and**
 - Patient has one or more metastatic bone lesions

Applicable Codes

The following list(s) of procedure and/or diagnosis codes is provided for reference purposes only and may not be all inclusive. Listing of a code in this policy does not imply that the service described by the code is a covered or non-covered health service. 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 Code	Description
J3489	Injection, zoledronic acid, 1 mg

ICD-10 Code	Description
C40.00	Malignant neoplasm of scapula and long bones of unspecified upper limb
C40.01	Malignant neoplasm of scapula and long bones of right upper limb
C40.02	Malignant neoplasm of scapula and long bones of left upper limb
C40.10	Malignant neoplasm of short bones of unspecified upper limb
C40.11	Malignant neoplasm of short bones of right upper limb
C40.12	Malignant neoplasm of short bones of left upper limb
C40.20	Malignant neoplasm of long bones of unspecified lower limb
C40.21	Malignant neoplasm of long bones of right lower limb
C40.22	Malignant neoplasm of long bones of left lower limb
C40.30	Malignant neoplasm of short bones of unspecified lower limb
C40.31	Malignant neoplasm of short bones of right lower limb
C40.32	Malignant neoplasm of short bones of left lower limb
C40.80	Malignant neoplasm of overlapping sites of bone and articular cartilage of unspecified limb
C40.81	Malignant neoplasm of overlapping sites of bone and articular cartilage of right limb
C40.82	Malignant neoplasm of overlapping sites of bone and articular cartilage of left limb
C40.90	Malignant neoplasm of unspecified bones and articular cartilage of unspecified limb
C40.91	Malignant neoplasm of unspecified bones and articular cartilage of right limb
C40.92	Malignant neoplasm of unspecified bones and articular cartilage of left limb
C41.9	Malignant neoplasm of bone and articular cartilage, unspecified
C50.011	Malignant neoplasm of nipple and areola, right female breast
C50.012	Malignant neoplasm of nipple and areola, left female breast
C50.019	Malignant neoplasm of nipple and areola, unspecified female breast
C50.111	Malignant neoplasm of central portion of right female breast
C50.112	Malignant neoplasm of central portion of left female breast
C50.119	Malignant neoplasm of central portion of unspecified female breast
C50.211	Malignant neoplasm of upper-inner quadrant of right female breast
C50.212	Malignant neoplasm of upper-inner quadrant of left female breast
C50.219	Malignant neoplasm of upper-inner quadrant of unspecified female breast
C50.311	Malignant neoplasm of lower-inner quadrant of right female breast
C50.312	Malignant neoplasm of lower-inner quadrant of left female breast
C50.319	Malignant neoplasm of lower-inner quadrant of unspecified female breast

ICD-10 Code	Description
C50.411	Malignant neoplasm of upper-outer quadrant of right fem
C50.412	Malignant neoplasm of upper-outer quadrant of left female breast
C50.419	Malignant neoplasm of upper-outer quadrant of unspecified female breast
C50.511	Malignant neoplasm of lower-outer quadrant of right female breast
C50.512	Malignant neoplasm of lower-outer quadrant of left female breast
C50.519	Malignant neoplasm of lower-outer quadrant of unspecified female breast
C50.611	Malignant neoplasm of axillary tail of right female breast
C50.612	Malignant neoplasm of axillary tail of left female breast
C50.619	Malignant neoplasm of axillary tail of unspecified female breast
C50.811	Malignant neoplasm of overlapping sites of right female breast
C50.812	Malignant neoplasm of overlapping sites of left female breast
C50.819	Malignant neoplasm of overlapping sites of unspecified female breast
C50.911	Malignant neoplasm of unspecified site of right female breast
C50.912	Malignant neoplasm of unspecified site of left female breast
C50.919	Malignant neoplasm of unspecified site of unspecified female breast
C61	Malignant neoplasm of prostate
C79.51	Secondary malignant neoplasm of bone
C90.00	Multiple myeloma not having achieved remission
C90.01	Multiple myeloma in remission
C90.02	Multiple myeloma in relapse
D05.00	Lobular carcinoma in situ of unspecified breast
D05.01	Lobular carcinoma in situ of right breast
D05.02	Lobular carcinoma in situ of left breast
D05.10	Intraductal carcinoma in situ of unspecified breast
D05.11	Intraductal carcinoma in situ of right breast
D05.12	Intraductal carcinoma in situ of left breast
D05.80	Other specified type of carcinoma in situ of unspecified breast
D05.81	Other specified type of carcinoma in situ of right breast
D05.82	Other specified type of carcinoma in situ of left breast
D05.90	Unspecified type of carcinoma in situ of unspecified breast
D05.91	Unspecified type of carcinoma in situ of right breast
D05.92	Unspecified type of carcinoma in situ of left breast
D48.0	Neoplasm of uncertain behavior of bone and articular cartilage
E83.52	Hypercalcemia
Z79.811	Long term (current) use of aromatase inhibitors
Z79.818	Long term (current) use of other agents affecting estrogen receptors and estrogen levels
Z79.899	Other long term (current) drug therapy
Z85.3	Personal history of malignant neoplasm of breast
Z85.46	Personal history of malignant neoplasm of prostate
Z86.000	Personal history of in-situ neoplasm of breast

Background

Hypercalcemia is relatively common in patients with cancer, occurring in approximately 20 to 30 percent of cases and is the most common cause of hypercalcemia in the inpatient setting (Bilezikian 1993). The most common cancers associated with hypercalcemia in the United States are breast, renal, lung, and squamous cell cancers and multiple myeloma. Malignancy is usually evident clinically by the time it causes hypercalcemia, and patients with hypercalcemia of malignancy often have a poor prognosis.

Zometa (zoledronic acid) is a bisphosphonate, which is an inhibitor of osteoclastic bone resorption. Zoledronic acid binds to the bone matrix, which decreases osteoclastic activity, prevents bone resorption and skeletal calcium release induced by various stimulatory factors released by tumors. The most common adverse events (greater than 25%) were nausea, fatigue, anemia, bone pain, constipation, fever, vomiting, and dyspnea (Zometa Prescribing Information 2011).

Clinical Evidence

Hypercalcemia of malignancy

Two identical multicenter, randomized, double-blind, double-dummy studies of zoledronic acid injection 4 mg given as a 5-minute intravenous infusion or pamidronate 90 mg given as a 2-hour intravenous infusion were conducted in 185 patients with hypercalcemia of malignancy (HCM) (Major et al 2021). The treatment groups in the clinical studies were generally well balanced with regards to age, sex, race, and tumor types. The most common tumor types were lung, breast, head and neck, and renal. In these studies, HCM was defined as a corrected serum calcium (CSC) concentration of greater than or equal to 12.0 mg/dL (3.00 mmol/L). The primary efficacy variable was the proportion of patients having a complete response, defined as the lowering of the CSC to less than or equal to 10.8 mg/dL (2.70 mmol/L) within 10 days after drug infusion. The results of the primary analysis revealed that the proportion of patients that had normalization of corrected serum calcium by Day 10 were 88% and 70% for zoledronic acid injection 4 mg and pamidronate 90 mg, respectively ($P = 0.002$). In these studies, no additional benefit was seen for zoledronic acid injection 8 mg over zoledronic acid injection 4 mg; however, the risk of renal toxicity of zoledronic acid injection 8 mg was significantly greater than that seen with zoledronic acid injection 4 mg (Major et al 2021).

Multiple myeloma and bone metastasis from solid tumors

The safety and effectiveness of Zometa was supported by three large international trials that included more than 3,000 subjects with multiple myeloma, breast cancer, prostate cancer, lung cancer and other solid tumors. The three trials consisted of a pamidronate-controlled trial in breast cancer and multiple myeloma (Rosen et al 2001), a placebo-controlled trial in prostate cancer (Saad et al 2002) and a placebo-controlled trial in other solid tumors (Rosen et al 2003). Each study evaluated skeletal-related events (SREs), defined as any of the following: pathologic fracture, radiation therapy to bone, surgery to bone, or spinal cord compression. The studies were amended twice because of renal toxicity and the zoledronic acid injection infusion duration was increased from 5 minutes to 15 minutes. Results demonstrated that Zometa decreased skeletal complications of subjects with multiple myeloma or metastases from solid tumors.

Clinical Guidelines

Several National Comprehensive Cancer Network Clinical Practice Guidelines in Oncology (NCCN Guidelines) include zoledronic acid as a treatment for several conditions related to malignant disease:

- For invasive breast cancer, the NCCN recommends zoledronic acid (Category 1) to be used with calcium and vitamin D supplementation in addition to chemotherapy or endocrine therapy for bone metastasis in patients with expected survival ≥ 3 months with adequate renal function (NCCN 2025).
- For kidney cancer, the NCCN recommends bisphosphonates (Category 2A) to be used as a component of best supportive care for bony metastases (NCCN 2025).
- For multiple myeloma, the NCCN recommends bisphosphonates (category 1) or denosumab (Category 2A) for all patients receiving therapy for symptomatic MM regardless of documented bone disease (NCCN 2025).

- For non-small cell lung cancer, the NCCN recommends zoledronic acid supportive therapy in patients with bone metastases (NCCN 2025).
- For prostate cancer, the NCCN recommends denosumab (Category 1) ahead of zoledronic acid in the prevention of skeletal-related events (NCCN 2025).
- For thyroid carcinoma the NCCN recommends zoledronic acid (Category 2A) to be considered for bone metastases (NCCN 2025).

The 2023 Endocrine Society Clinical Practice Guidelines suggest denosumab over bisphosphonates for initial therapy of hypercalcemia of malignancy. The panel's recommendations are based on currently available evidence considering the most important outcomes in HCM to patients and key stakeholders but also underscore current knowledge gaps that can be used to establish future research agendas (Dickens et al 2023).

U.S. Food and Drug Administration (FDA)

This section is to be used for informational purposes only. FDA approval alone is not a basis for coverage.

[Zometa](#) is a bisphosphonate indicated 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.

Limitations of Use: The safety and efficacy of Zometa has not been established for use in hyperparathyroidism or non-tumor-related hypercalcemia.

References

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3. Major P, Lortholary A, Hon J, Abdi E, Mills G, Menssen HD, Yunus F, Bell R, Body J, Quebe-Fehling E, Seaman J. Zoledronic acid is superior to pamidronate in the treatment of hypercalcemia of malignancy: a pooled analysis of two randomized, controlled clinical trials. *Journal of clinical oncology*. 2001 Jan 15;19(2):558-67.
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12. Saad F, Gleason DM, Murray R, Tchekmedyian S, Venner P, Lacombe L, Chin JL, Vinholes JJ, Goas JA, Chen B. A randomized, placebo-controlled trial of zoledronic acid in patients with hormone-refractory metastatic prostate carcinoma. *Journal of the National Cancer Institute*. 2002 Oct 2;94(19):1458-68.
13. Zometa (zoledronic acid) concentrate for infusion [Package insert], Novartis Pharmaceuticals, East Hanover, New Jersey, February 2011.

Policy History/Revision Information

Date	Summary of Changes
12/13/2023	Approved by OptumRx P&T Committee
10/16/2024	Annual Review. References updated. No clinical content changed.
11/20/2025	Annual Review. References updated.

Instructions for Use

This Medical Benefit Drug Policy provides assistance in interpreting standard benefit plans. When deciding coverage, the member specific benefit plan document must be referenced as the terms of the member specific benefit plan may differ from the standard plan. In the event of a conflict, the member specific benefit plan document governs. Before using this policy, please check the member specific benefit plan document and any applicable federal or state mandates. The insurance reserves the right to modify its Policies and Guidelines as necessary. This Medical Benefit Drug Policy is provided for informational purposes. It does not constitute medical advice.

OptumRx may also use tools developed by third parties to assist us in administering health benefits. OptumRx Medical Benefit Drug Policies are intended to be used in connection with the independent professional medical judgment of a qualified health care provider and do not constitute the practice of medicine or medical advice.

Nondiscrimination & Language Access Policy



Discrimination is Against the Law. Aspirus Health Plan, Inc. complies with applicable Federal civil rights laws and does not discriminate on the basis of race, color, national origin, age, disability, or sex, (including sex characteristics, including intersex traits; pregnancy or related conditions; sexual orientation, gender identity and sex stereotypes), consistent with the scope of sex discrimination described at 45 CFR § 92.101(a)(2). Aspirus Health Plan, Inc. does not exclude people or treat them less favorably because of race, color, national origin, age, disability, or sex.

Aspirus Health Plan, Inc.:

Provides people with disabilities reasonable modifications and free appropriate auxiliary aids and services to communicate effectively with us, such as:

- Qualified sign language interpreters.
- Written information in other formats (large print, audio, accessible electronic formats, other formats).

Provides free language assistance services to people whose primary language is not English, which may include:

- Qualified interpreters.
- Information written in other languages.

If you need reasonable modifications, appropriate auxiliary aids and services, or language assistance services, contact the Nondiscrimination Grievance Coordinator at the address, phone number, fax number, or email address below.

If you believe that Aspirus Health Plan, Inc. has failed to provide these services or discriminated in another way on the basis of race, color, national origin, age, disability, or sex, you can file a *grievance* with:

Nondiscrimination Grievance Coordinator
Aspirus Health Plan, Inc.
PO Box 1890
Southampton, PA 18966-9998
Phone: 1-866-631-5404 (TTY: 711)
Fax: 763-847-4010
Email: customerservice@aspirushealthplan.com

You can file a *grievance* in person or by mail, fax, or email. If you need help filing a *grievance*, the Nondiscrimination Grievance Coordinator is available to help you.

You can also file a civil rights complaint with the U.S. Department of Health and Human Services, Office for Civil Rights, electronically through the Office for Civil Rights Complaint Portal, available at <https://ocrportal.hhs.gov/ocr/portal/lobby.jsf>, or by mail or phone at:

U.S. Department of Health and Human Services
200 Independence Avenue, SW
Room 509F, HHH Building
Washington, D.C. 20201
1.800.368.1019, 800.537.7697 (TDD)

Complaint forms are available at <http://www.hhs.gov/ocr/office/file/index.html>. This notice is available at Aspirus Health Plan, Inc.'s website: https://aspirushealthplan.com/webdocs/70021-AHP-NonDiscrim_Lang-Assist-Notice.pdf.

Language Assistance Services

Albanian: KUJDES: Nëse flitmi shqip, për ju ka në dispozicion shërbime të asistencës gjuhësore, pa pagesë. Telefononi në 1-800-332-6501 (TTY: 711).

Arabic: تنبيه: إذا كنت تتحدث اللغة العربية، فإن خدمات المساعدة اللغوية متاحة لك مجاناً. اتصل بن اعلى رقم الهاتف 1-800-332-6501 (رقم هاتف الصم والبك : 711)

French: ATTENTION: Si vous parlez français, des services d'aide linguistique vous sont proposés gratuitement. Appelez le 1-800-332-6501 (ATS: 711).

German: ACHTUNG: Wenn Sie Deutsch sprechen, stehen Ihnen kostenlos sprachliche Hilfsdienstleistungen zur Verfügung. Rufnummer: 1-800-332-6501 (TTY: 711).

Hindi: यान द : य द आप िहंदी बोलते ह तो आपके िलए मु त म भाषा सहायता सेवाएं उपल थ ह 1-800-332-6501 (TTY: 711) पर कॉल कर ।

Hmong: LUS CEEV: Yog tias koj hais lus Hmoob, cov kev pab txog lus, muaj kev pab dawb rau koj. Hu rau 1-800-332-6501 (TTY: 711).

Korean: 주의: 한국어를 사용하지는 경우, 언어 지원 서비스를 무료로 이용하실 수 있습니다. 1-800-332-6501 (TTY: 711) 번으로 전화해 주십시오.

Polish: UWAGA: Jeżeli mówisz po polsku, możesz skorzystać z bezpłatnej pomocy językowej. Zadzwoń pod numer 1-800-332-6501 (TTY: 711).

Russian: ВНИМАНИЕ: Если вы говорите на русском языке, то вам доступны бесплатные услуги перевода. Звоните 1-800-332-6501 (телетайп: 711).

Spanish: ATENCIÓN: si habla español, tiene a su disposición servicios gratuitos de asistencia lingüística. Llame al 1-800-332-6501 (TTY: 711).

Tagalog: PAUNAWA: Kung nagsasalita ka ng Tagalog, maaari kang gumamit ng mga serbisyo ng tulong sa wika nangwalang bayad. Tumawag sa 1-800-332-6501 (TTY: 711).

Traditional Chinese: 注意：如果您使用繁體中文，您可以免費獲得語言援助服務。請致電 1-800-332-6501 (TTY: 711)

Vietnamese: CHÚ Ý: Nếu bạn nói Tiếng Việt, có các dịch vụ hỗ trợ ngôn ngữ miễn phí dành cho bạn. Gọi số 1-800-332-6501 (TTY: 711).

Pennsylvania Dutch: Wann du Deitsch (Pennsylvania German / Dutch) schwetzsch, kamscht du mitaus Koschte ebbergricke, ass dihr helft mit die englisch Schprooch. Ruf selli Nummer uff: Call 1-800-332-6501 (TTY: 711).

Lao: ໂປດຊາບ: ຖ້າວ່າ ທ່ານເວົ້າພາສາ ລາວ, ການບໍລິການຊ່ວຍເຫຼືອດ້ານພາສາ ໂດຍບໍ່ເສັຽຄ່າ, ຈະມີມື້ອມໃຫ້ທ່ານ. ໂທສ 1-800-332-6501 (TTY: 711).