Department:	Pharmacy Management	**Original Approval:**	12/24/2015
Policy #:	PM124	**Last Approval:**	06/14/2018
Title:	Zoledronic acid (Zometa®)		
Approved By:	UM Committee		

REQUIRED CLINICAL DOCUMENTATION FOR REVIEW

Documentation required to determine medical necessity for Zoledronic acid (Zometa): History and/or physical examination notes and relevant specialty consultation notes that address the problem and need for the service: -Diagnosis -Labs/diagnostics -Prescribed by or in consultation with a hematologist or oncologist as indicated -Dosing and duration requested -Age -Weight -Height -Renal function (eCrCl).

BACKGROUND

Zometa is indicated for the treatment of hypercalcemia of malignancy, defined as an albumin-corrected calcium (cCa) ≥ 12 mg/dL (3.0 mmol/L). Zometa is also indicated for the treatment of patients with multiple myeloma and patients with documented bone metastases from solid tumors, in conjunction with standard antineoplastic therapy. A limitation of use is that the efficacy and safety of Zometa in the treatment of hypercalcemia associated with hyperparathyroidism or with other nontumor-related conditions have not been established. Prostate cancer should have progressed after treatment with at least one hormonal therapy.[1] Another formulation of zoledronic acid injection is available, Reclast®, but is not included in this policy.[2] Zometa is supplied in a 5 mL single-use vial that contains 4 mg of the active agent, which is available generically. It is also available as bottles as a ready-to-use solution for infusion that contains overfill allowing for the administration of 100 mL of solution with the equivalent of 4 mg of zoledronic acid.[1]

DEFINITIONS

None.

INDICATIONS/CRITERIA

Medicaid Members	***Continue to criteria for approval below.***
Medicare Members	***Step-utilization of Part D drugs not required.***

Coverage of Zometa is recommended in those who meet the following criteria:

Food and Drug Administration (FDA)-Approved Indications

1. Hypercalcemia of Malignancy.

Criteria. *The patient must meet the following criteria (A and B):*

A) The patient has a current malignancy; AND

B) The patient's albumin-corrected calcium (cCa) is ≥ 11.5 mg/dL. If the cCa value is not given, an example of how to calculate cCa is provided in Appendix A (see page 10).

Zoledronic acid injection (Zometa) is indicated for the treatment of hypercalcemia of malignancy, defined as an albumin-corrected cCa of ≥ 12 mg/dL (3.0 mmol/L).[1] In the pivotal trials that led to the approval, hypercalcemia of malignancy was defined as a corrected serum calcium concentration of greater than or equal to 12.0 mg/dL. Normal total serum calcium concentration range is generally 8.5 to 10.5 mg/dL. In the professional opinion of specialist physicians reviewing the data, we have adopted these criteria.

Dosing in Hypercalcemia of Malignancy. *Dosing must meet the following:* The dose of Zometa in adults is 4 mg given as a single dose intravenous (IV) infusion.

Initial Approval/Extended Approval.

A) *Initial Approval.* Initial approval is for one dose.

B) *Extended Approval.* An additional dose may be given 7 days apart.

Duration of Therapy in Hypercalcemia of Malignancy. Up to two doses can be given to treat a standard course of hypercalcemia of malignancy with a minimum of 7 days elapsing before retreatment.

Labs/Diagnostics. Patients with hypercalcemia of malignancy must have an albumin-corrected calcium level as described previously.

2. Multiple Myeloma (Treatment).

Criteria. *The patient must meet the following criteria (A):*

A) The agent is prescribed by, or in consultation with, a hematologist or oncologist.

Zoledronic acid injection (Zometa)is indicated for the treatment of patients with multiple myeloma.[1] Osteolytic disease in a common complication of multiple myeloma, which results in skeletal related events (SREs) which is manifested as pathologic fractures, the need for radiation or surgery, and spinal cord compression.[1,3-5] Zoledronic acid injection (Zometa) has been shown to reduce the incidence of SREs and the time to the first and subsequent SRE.[1] In the professional opinion of specialist physicians reviewing the data, we have adopted these criteria.

Dosing in Multiple Myeloma. *Dosing must meet one of the following (A or B):*

A) 4 mg or less by intravenous infusion every 3 to 4 weeks; OR.[1]

B) 4 mg or less by intravenous infusion every 12 weeks.[16-17]

Recommended guidelines for dosing of Zoledronic acid injection (Zometa) are based on the prescribing information and in guidelines.[1,4-5] The recommended doses are based on estimated baseline creatinine

clearance (CrCl) and are listed below. These doses are guidelines only and the efficacy and safety of adjusted dosing based on this estimation of CrCl have not been assessed in a prospective study.

Suggested Zometa Doses in Adults Based On Estimated Baseline CrC1.[1]

Estimated Baseline CrCl (mL/min)	Zometa Dose
> 60	4 mg
50 to 60	3.5 mg
40 to 49	3.3 mg
30 to 39	3 mg

CrCl – Creatinine clearance. If the CrCl is not given, an example of how to calculate an estimated CrCl is provided in Appendix B (see page 11).

During treatment, serum creatinine should be measured prior to each Zoledronic acid injection (Zometa) dose. According to the prescribing information treatment should be withheld for renal deterioration. In the clinical trials, 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 1.0 mg/dL.

These values are used as a guideline by the prescribing physician.

In clinical studies, Zoledronic acid injection (Zometa) treatment was resumed only when the creatinine returned to within 10% of the baseline value. Zoledronic acid injection (Zometa) should be restarted at the same doses as before the treatment interruption.

Initial Approval/Extended Approval.

A) *Initial Approval.* Initial approval is for up to 6 months.
B) *Extended Approval.* Extended approval is for up to 6-month intervals.

Duration of Therapy in Multiple Myeloma. Therapy is indefinite.

Labs/Diagnostics. Estimated calculated CrCl must be ≥ 30 mL/minute. If the CrCl is not given, an example of how to calculate the estimated CrCl is provided in Appendix B (see page 11).

3. Treatment of Bone Metastases From Solid Tumors (e.g., Breast Cancer, Prostate Cancer, Non-Small Cell Lung Cancer, Renal Cell Cancer, Small Cell Lung Cancer, Colorectal Cancer, Bladder Cancer, Gastrointestinal/Genitourinary Cancer, Head and Neck Cancer).

Criteria. *The patient must meet the following criteria (A, B, and C):*

A) The agent must be prescribed by, or in consultation with, a hematologist or oncologist; AND
B) The patient has bone metastases confirmed by radiographic or imaging studies; AND
C) Patients with prostate cancer have received at least one hormonal therapy (e.g., Lupron Depot® [leuprolide for depot suspension], Eligard® [leuprolide acetate for injectable suspension], Trelstar® [triptorelin pamoate for injectable suspension], or Zoladex® [goserelin implant]).

Zoledronic acid injection (Zometa) is indicated for patients with documented bone metastases from solid tumors.[1,3] It is recommended that patients with prostate cancer should have progressed after treatment with at least one hormonal therapy. In the studies, the bone metastases included many types of malignancies including breast cancer, prostate cancer, non-small cell lung cancer, renal cell cancer, small cell lung cancer, colorectal cancer, gladder cancer, gastrointestinal/genitourinary cancer, and head and neck cancer. Zoledronic acid injection (Zometa) has an impact on SREs. In the professional opinion of specialist physicians reviewing the data, we have adopted these criteria.

Dosing in Patients with Bone Metastases from Solid Tumors: *Dosing must meet one of the following (A or B):*

- **A)** 4 mg or less by intravenous infusion every 3 to 4 weeks[1]; OR
- **B)** 4 mg or less by intravenous infusion every 12 weeks.[3,16-18]

Recommended guidelines for dosing of Zoledronic acid injection (Zometa) are based on the prescribing information.[1] The recommended doses are based on estimated baseline CrCl and are listed below. These doses are guidelines only and the efficacy and safety of adjusted dosing based on this estimation of CrCl have not been assessed in a prospective study.

Suggested Zometa Doses in Adults Based On Estimated Baseline CrC1.[1]

Estimated Baseline CrCl (mL/min)	Zometa Dose
> 60	4 mg
50 to 60	3.5 mg
40 to 49	3.3 mg
30 to 39	3 mg

CrCl – Creatinine clearance. If the CrCl is not given, an example of how to calculate an estimated CrCl is provided in Appendix B (see page 11).

During treatment, serum creatinine should be measured prior to each Zometa dose. According to the prescribing information treatment should be withheld for renal deterioration. In the clinical trials, 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 1.0 mg/dL.

These values are used as a guideline by the prescribing physician.

In clinical studies, Zoledronic acid injection (Zometa) treatment was resumed only when the creatinine returned to within 10% of the baseline value. Zoledronic acid injection (Zometa) should be restarted at the same doses as before the treatment interruption.

Initial Approval/Extended Approval.

- **A)** *Initial Approval.* Initial approval is for up to 6 months.
- **B)** *Extended Approval.* Extended approval is for up to 6-month intervals.

Duration of Therapy in Bone Metastases from Solid Tumors. Therapy is indefinite.

Labs/Diagnostics. Radiographic or imaging studies (e.g., magnetic resonance imaging [MRI], plain film radiography, computerized tomography [CT] scan, skeletal scintigraphy, positron emission tomography [PET]) must confirm bone metastasis. Estimated calculated CrCl must be ≥ 30 mL/minute. If the CrCl is not given, an example of how to calculate the estimated CrCl is provided in Appendix B (see page 11).

Other Uses with Supportive Evidence

4. Prevention of Bone Loss (To Increase Bone Mass) in Patients with Breast Cancer Receiving Aromatase Inhibitor Therapy.

Criteria. *The patient must meet the following criteria (A and B):*

A) The patient has breast cancer that is not metastatic to bone; AND

B) The patient is receiving an aromatase inhibitor therapy (e.g., anastrozole, letrozole, and exemestane).

Aromatase inhibitor therapy prevents peripheral production and suppress estrogen levels and can lead to accelerated bone loss beyond what would naturally occur in women.[3,8] This can place the patient at an risk for having a fracture. A review on the management of aromatase inhibitor-associated bone loss in postmenopausal women with breast cancer[9] states that Zoledronic acid injection (Zometa) (4 mg every 6 months) is the preferred agent for preventing and treatment aromatase inhibitor bone loss.[8] Zoledronic acid injection (Zometa) has been studied and shown benefits in postmenopausal women receiving adjuvant letrozole for breast cancer.[9-10]

Dosing in the Prevention of Bone Loss in Patients with Breast Cancer Receiving Aromatase Inhibitor Therapy. *Dosing must meet the following:* The dose is 4 mg or less by intravenous infusion every 6 months.

Initial Approval/Extended Approval.

A) *Initial Approval.* Initial approval is for up to 6 months.

B) *Extended Approval.* Extended approval is for up to 6-month intervals.

Duration of Therapy in the Prevention of Bone Loss in Patients with Breast Cancer Receiving Aromatase Inhibitor Therapy. Therapy is indefinite if the patient continues to receive aromatase inhibitor therapy.

Labs/Diagnostics. Estimated calculated CrCl must be ≥ 30 mL/minute. If the CrCl is not given, an example of how to calculate the estimated CrCl is provided in Appendix B (see page 11).

5. Prevention of Bone Loss (to Increase Bone Mass) in Patients with Prostate Cancer Who are Receiving Androgen Deprivation Therapy (ADT).

Criteria. *The patient must meet the following criteria (A and B):*

A) The patient has prostate cancer that is not metastatic to bone; AND

B) The patient is currently receiving androgen deprivation therapy (e.g., Lupron Depot® [leuprolide for depot suspension], Eligard® [leuprolide acetate for injectable suspension], Trelstar®

[triptorelin pamoate for injectable suspension], or Zoladex® [goserelin implant]), or the patient has undergone bilateral orchiectomy.

Androgen deprivation therapy (ADT) is associated with a variety of adverse events, including osteoporosis. The National Comprehensive Cancer Network (NCCN) clinical practice guidelines regarding prostate cancer (version 2.2017)[11] cite zoledronic acid as an option to increase bone density, a surrogate for fracture risk, during ADT for prostate cancer. Zoledronic acid injection (Zometa) has led to bone mineral density increases in patients with prostate cancer who are receiving androgen deprivation therapy.[12-13] A clinical practice guideline for osteoporosis in men from the Endocrine Society[13] recommends pharmacological treatment for osteoporosis for men with prostate cancer receiving ADT who have a high risk of fracture.

Dosing in the Prevention of Bone Loss in Patients with Prostate Cancer who are Receiving Androgen Deprivation Therapy. *Dosing must meet the following:* The dose is 4 mg or less by intravenous infusion every 3 to 6 months.

Initial Approval/Extended Approval.

A) *Initial Approval.* Initial approval is for up to 6 months.

B) *Extended Approval.* Extended approval is for up to 6-month intervals.

Duration of Therapy in the Prevention of Bone Loss in Patients with Prostate Cancer who are Receiving Androgen Deprivation Therapy. Therapy is indefinite if the patient continues to receive androgen deprivation therapy.

Labs/Diagnostics. Estimated calculated CrCl must be ≥ 30 mL/minute. If the CrCl is not given, an example of how to calculate the estimated CrCl is provided in Appendix B (see page 11).

6. Prevention of Bone Loss (to Increase Bone Mass) in Premenopausal Patients with Breast Cancer Who Have Developed Ovarian Failure.

Criteria. *The patient must meet the following criteria (A and B):*

A) The patient is a premenopausal patient with breast cancer that is not metastatic to bone; AND

B) The patient has received adjuvant chemotherapy and has developed ovarian failure.

Chemotherapy-induced ovarian failure is an adverse effect associated with some adjuvant chemotherapy and can lead to rapid bone loss.[14-15] Studies have demonstrated zoledronic acid injection (Zometa) to be efficacious in preserving bone mineral density in premenopausal women with breast cancer who developed ovarian failure due to adjuvant chemotherapy. In the professional opinion of specialist physicians reviewing the data, we have adopted these criteria.

Dosing in the Prevention of Bone Loss in Premenopausal Patients with Breast Cancer Who Have Developed Ovarian Failure. *Dosing must meet the following.* The dose is 4 mg or less by intravenous infusion every 3 months.

Initial Approval/Extended Approval.

A) *Initial Approval.* Initial approval is for up to 6 months.

B) *Extended Approval*. Extended approval is for up to 6-month interval if the patient continues to have ovarian failure.

Duration of Therapy in the Prevention of Bone Loss in Premenopausal Patients with Breast Cancer Who Have Developed Ovarian Failure. Therapy is indefinite as long as the patient continues to have ovarian failure.

Labs/Diagnostics. Estimated calculated CrCl must be ≥ 30 mL/minute. If the CrCl is not given, an example of how to calculate the estimated CrCl is provided in Appendix B (see page 11).

Waste Management for All:
Zometa is available in a 5 mL single-use vial that contains 4 mg of the active ingredient and as a single-use ready-to-use bottle that contains 100 mL of solution with the equivalent of 4 mg of Zometa. One 4-mg dose is sufficient for most situations.[1]

Conditions Not Recommended for Approval
zoledronic acid injection (Zometa) has not been shown to be effective or there are limited or preliminary data, or potential safety concerns, that are not supportive of general approval for the following conditions. Rationale for non-coverage for these specific conditions are provided below.

1. **Creatinine Clearance (CrCl) [Estimated/Calculated] is < 30 mL/min, Except for Patients with Hypercalcemia of Malignancy.** Renal toxicity is greater with zoledronic acid injection (Zometa) for patients with renal impairment. Limited pharmacokinetic information is available in patients with an estimated, calculated CrCl < 30 mL/min.

2. **Concurrent Use of Zometa with the Reclast Formulation of Zoledronic Acid.** The zoledronic acid injection (Zometa) prescribing information notes that patients being treated with zoledronic acid injection (Zometa) should not be treated with Reclast or other bisphosphonates.[1] Zometa and Reclast both the same active ingredient, zoledronic acid.[1-2]

3. Coverage is not recommended for circumstances *not* listed in the *Recommended Authorization Criteria*. Criteria will be updated as new published data are available.

SPECIAL CONSIDERATIONS
None.

LIMITATIONS/EXCLUSIONS
Please refer to a product line's certificate of coverage for benefit limitations and exclusions for these services:

PRODUCT LINE	LINK TO CERTIFICATE OF COVERAGE
MEDICARE ADVANTAGE	http://healthfirst.chpw.org/for-members/resource-library/handbooks-and-guides
WASHINGTON APPLE HEALTH	http://chpw.org/our-plans/apple-health/
INTEGRATED MANAGED CARE	http://chpw.org/our-plans/apple-health/

Citations & References

References

1. Zometa® injection for intravenous infusion [prescribing information]. East Hanover, NJ: Novartis; December 2016.
2. Reclast® injection [prescribing information]. East Hanover, NJ: Novartis; July 2017.
3. Van Poznak C, Somerfield MR, Barlow WE, et al. Role of bone-modifying agents in metastatic breast cancer: an American Society of Clinical Oncology-Cancer Care Ontario focused guideline update. *J Clin Oncol*. 2017;35(35):3978-3986.
4. Terpos E, Roodman GD, Dimopoulos MA. Optimal use of bisphosphonates in patients with multiple myeloma. *Blood*. 2013;121(17):3325-3328.
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6. Aapro M, Abrahamsson PA, Body JJ, et al. Guidance on the use of bisphosphonates in solid tumors: recommendations of an international expert panel. *Ann Oncol*. 2008;19:420-432.
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8. Hadji P, Aapro MS, Body JJ, et al. Management of aromatase inhibitor-associated bone loss in postmenopausal women with breast cancer: practical guidance for prevention and treatment. *Ann Oncol*. 2011;22:2546-2555.
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11. The NCCN Prostate Cancer Clinical Practice Guidelines in Oncology (Version 2.2017 – February 21, 2017). © 2017 National Comprehensive Cancer Network, Inc. Available at: http://www.nccn.org. Accessed on February 6, 2018.
12. Ryan CW, Huo D, Demers LM, et al. Zoledronic acid initiated during the first year of androgen deprivation therapy increases bone mineral density in patients with prostate cancer. *J Urol*. 2006;176(3):972-978.

13. Watts NB, Adler RA, Bilezikian JP, et al. Osteoporosis in men: an Endocrine Society clinical practice guideline. *J Clin Endocrinol Metab*. 2012;97:1802-1822.
14. Shapiro CL, Halabi S, Hars V, et al. Zoledronic acid preserves bone mineral density in premenopausal women who develop ovarian failure due to adjuvant chemotherapy: final results from CALGB trial 79809. *Eur J Cancer*. 2011;47:683-689.
15. Hershman DL, McMahon DJ, Crew KD, et al. Zoledronic acid prevents bone loss in premenopausal women undergoing adjuvant chemotherapy for early-stage breast cancer. *J Clin Oncol*. 2008;26:4739-4745.
16. Himelstein AL, Foster JC, Khatcheressian JL, et al. Effect of longer-interval vs. standard dosing of zoledronic acid on skeletal events in patients with bone metastases. A randomized clinical trial. *JAMA*. 2017;317(1):48-58.
17. Amadori D, Aglietta M, Alessi B, et al. Efficacy and safety of 12-weekly versus 4-weekly zoledronic acid for prolonged treatment of patients with bone metastases from breast cancer (ZOOM): a phase 3, open-label, randomized, non-inferiority trial. *Lancet Oncol*. 2013;14(7):663-670.
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19. Raje N, Vescio R, Montgomery CW, et al. Bone marker-directed dosing of zoledronic acid for the prevention of skeletal complications in patients with multiple myeloma: results of the Z-MARK study. *Clin Cancer Res*. 2016;22(6):1378-1384.

OTHER REFERENCES UTILIZED

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CFR		
WAC	WAC 284-43-2050	
RCW		
Contract Citation	☒ WAH	
	☒ IMC	
	☒ MA	
Other Requirements		
NCQA Elements		

Revision History

Revision Date	Revision Description	Revision Made By
12/23/2015	New	Kelly Force; Yusuf Rashid, RPh
12/24/2015	Approval	MMLT
01/11/2017	No revisions	Fran McGaugh

01/12/2017	Approval	MMLT
07/24/2017	Criteria completely updated and revised	Michael Sporck, Pharmacy Intern Sophia Yun, PharmD
07/25/2017	Approved	MMLT
03/09/2018	Reassigned from UM134 to PM124	Cindy Bush
04/27/2018	Transferred to new template	Cindy Bush
06/11/2018	Revised	Jennifer Farley, PharmD
06/14/2018	Approval	UM Committee

Appendix A: Calculating albumin-corrected calcium (cCa)

If cCa value is not given, the following equation can be used to calculate cCa:
cCa in mg/dL = measured Ca (mg/dL) + (0.8 X [4.0 g/dL – patient albumin [g/dL]).

For example, a patient with a serum calcium level of 10.3 mg/dL, but an albumin level of 3.0 g/dL, appears to have a normal serum calcium level. However, when corrected for the low albumin, the real serum calcium value is 11.1 mg/dL, calculated as (10.3 + 0.8 X 1.0).

Appendix B: Calculating creatinine clearance (CrCl)

There are many different methods that can be used to calculate an estimated CrCl. The Cockcroft-Gault is one formula that provides an estimate of CrCl using serum creatinine. It is only for adults. This formula tends to overestimate CrCl in obese persons and to underestimate it in those who are lean. The Cockcroft-Gault equation for calculating CrCl is as follows:

CrCl in adults **(men)** = $\frac{\text{(140 minus age [in years] X weight [in kg])}}{\text{(72 X serum creatinine [in mg/dL])}}$

For women, multiply the above results by 0.85. The steps, for clarity, are as follows:

1) Subtract the patient's age in years from 140.
2) Multiply by the patient's weight in kg (if weight is in pounds, divide by 2.2 to get kg).
3) Multiply the patient's serum creatinine (in mg/dL) by 72.
4) Divide the total from 2) by the total from 3).
5) If the patient is female, take the total from 4) and multiply by 0.85.

For example, a man who is 55 years of age, who weighs 160 pounds (72.7 kg), and with a serum creatinine 0.9 mg/dL, would have a calculated creatinine clearance of 95 mL/minute. For a woman with these same values, her CrCl would be 81 mL/minute.