Department:	Pharmacy Management	**Original Approval:**	12/24/2015
Policy #:	PM124	**Last Approval:**	01/07/2021
Title:	Zoledronic acid (Zometa®)		
Approved By:	UM Pharmacy Subcommittee		

Line(s) of Business

☒ WAH-IMC (HCA) ☐ BHSO ☒ Medicare Advantage (CMS)

☒ Medicare SNP (CMS) ☒ Cascade Select

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

Zoledronic acid injection (Zometa) is indicated for the treatment of hypercalcemia of malignancy, defined as an albumin-corrected calcium (cCa) ≥ 12 mg/dL (3.0 mmol/L). Zoledronic acid injection (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 Zoledronic acid injection (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]

Other Uses with Supportive Evidence

Data are available with zoledronic acid injection (Zometa) regarding off-label uses. One example is to prevent bone loss in patients with breast cancer receiving aromatase inhibitor therapy. Aromatase inhibitor therapy prevents peripheral production and suppress estrogen levels and can lead to accelerated bone loss beyond what would naturally occur in women.[3,4] 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[5] states that zoledronic acid injection (Zometa) [4 mg every 6 months] is the preferred agent for preventing and treatment aromatase inhibitor bone loss.4 Zoledronic acid injection (Zometa) has been studied and shown benefits in postmenopausal women receiving adjuvant letrozole for breast cancer.[5-6]

Zoledronic acid injection (Zometa) also has utilized to prevent bone loss in patients with prostate cancer who are receiving androgen deprivation therapy (ADT). ADT is associated with a variety of adverse events,

including osteoporosis. The National Comprehensive Cancer Network (NCCN) clinical practice guidelines regarding prostate cancer (version 4.2019 – August 19, 2019)[7] 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.[8,9] A clinical practice guideline for osteoporosis in men from the Endocrine Society[9] recommends pharmacological treatment for osteoporosis for men with prostate cancer receiving ADT who have a high risk of fracture.

Zoldedronic acid injection (Zometa) has utility in premenopausal patients with breast cancer who have developed ovarian failure. Chemotherapy-induced ovarian failure is an adverse effect associated with some adjuvant chemotherapy and can lead to rapid bone loss.[10-11] 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.

Policy Statement

Prior authorization is recommended for medical benefit coverage of zoledronic acid injection (Zometa). Approval is recommended for those who meet the Criteria and Dosing for the listed indication(s). Extended approvals are allowed if the patient continues to meet the Criteria and Dosing. Requests for doses outside of the established dosing documented in this policy will be considered on a case-by-case basis by an Express Scripts clinician (i.e., Medical Director or Pharmacist). All approvals are provided for the duration noted below. Because of the specialized skills required for evaluation and diagnosis of patients treated with zoledronic acid injection (Zometa) as well as the monitoring required for adverse events and long-term efficacy approval requires zoledronic acid injection (Zometa) to be prescribed by or in consultation with a physician who specializes in the condition being treated.

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. <u>Hypercalcemia of Malignancy.</u>

Criteria. Approve for 1 month if the patient meets the following criteria (A <u>and</u> 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).

Dosing. Approve 4 mg given as a single dose intravenous (IV) infusion for up to two doses with the second dose given separated by a minimum of 7 days from the first dose.

2. Multiple Myeloma (Treatment).

Criteria. Approve for 1 year if the agent is prescribed by or in consultation with a hematologist or oncologist.

Dosing in Multiple Myeloma.
Dosing: Approve up to 4 mg by intravenous infusion administered no more frequently than once every 3 weeks.

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. Approve for 1 year if *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; 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]).

Dosing. Approve up to 4 mg by intravenous infusion administered no more frequently than once every 3 weeks.

Other Uses with Supportive Evidence
4. Prevention of Bone Loss (To Increase Bone Mass) in Patients with Breast Cancer Receiving Aromatase Inhibitor Therapy. Approve for 1 year if the patient meets 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).

Dosing. Approve for 1 year up to 4 mg by intravenous infusion no more frequently than once every 6 months.

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

Criteria. Approve for 1 year if *the patient meets 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.

Dosing. Approve up to 4 mg by intravenous infusion no more frequently than once every 3 months.

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

Criteria. Approve for 1 year if *the patient meets 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.

Dosing. Approve up to 4 mg by intravenous infusion no more frequently than once every 3 months.

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. 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	https://medicare.chpw.org/chpw-washington-state-medicare-advantage-plans/all-medicare-plans-2020/

Washington Apple Health (Medicaid) Integrated Managed Care	https://www.chpw.org/for-members/benefits-and-coverage-imc/

Citations & References

References	• Zometa® injection for intravenous infusion [prescribing information]. East Hanover, NJ: Novartis; December 2018. • Reclast® injection [prescribing information]. East Hanover, NJ: Novartis; July 2017. • 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. • 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. • Brufsky AM, Harker WG, Beck JT, et al. Final 5-year results of Z-FAST trial: adjuvant zoledronic acid maintains bone mass in postmenopausal breast cancer patients receiving letrozole. *Cancer*. 2012;118(5):1192-1201. • Coleman R De Boer R, Eidtmann H, et al. Zoledronic acid (zoledronate) for postmenopausal women with early breast cancer receiving adjuvant letrozole (ZO-FAST study): final 60-month results. *Ann Oncol*. 2013;24:398-405. • The NCCN Prostate Cancer Clinical Practice Guidelines in Oncology (Version 4.2018 – August 15, 2018). © 2017 National Comprehensive Cancer Network, Inc. Available at: http://www.nccn.org. Accessed on February 22, 2019. • 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. • 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. • 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. • 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.	
CFR	42 CFR § 438.210	
WAC	284-43-2050	
RCW		
Contract Citation	☒ WAH - IMC	IMC section 17.3.2.1 General Description of Contracted Services - Pharmacy Benefit and Services - Apple Health Preferred Drug List and Plan Formularies
	☐ BHSO	

	☒ MA	
	☒ Cascade Select	
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
04/10/2019	Criteria completely updated and revised	Jennifer Farley, PharmD
05/09/2019	Approval	UM Pharmacy Subcommittee
02/24/2020	Annual review. No changes	Jennifer Farley, PharmD
02/27/2020	Approval	UM Pharmacy Subcommittee
12/30/2020	Annual review. No changes	Jennifer Farley, PharmD
01/07/2021	Approval	UM Pharmacy Subcommittee

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.