

POLICY: Bone Modifiers – Zoledronic Acid IV (Zometa) [Zometa® {zoledronic acid injection}, – Novartis, generic]

APPROVAL DATE: 02/27/2019

OVERVIEW

Zoledronic acid injection (Zometa) is indicated for the treatment of hypercalcemia of malignancy, defined as an albumin-corrected calcium (cCa) \geq 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 cancer⁵ 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 4.2018 – August 15, 2018)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 Society⁹ recommends pharmacological treatment for osteoporosis for men with prostate cancer receiving ADT who have a high risk of fracture.

Zoledronic 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 a 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.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of zoledronic acid injection (Zometa) is recommended in those who meet the following criteria:

FDA-Approved Indications

1. Hypercalcemia of Malignancy. Approve for 1 month if the patient meets 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.

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

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). Approve for 1 year if the patient meets all of 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 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). Approve 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. 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.

REFERENCES

1. Zometa® injection for intravenous infusion [prescribing information]. East Hanover, NJ: Novartis; December 2018.
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. 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.
5. 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.
6. 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.
7. 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.
8. 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.
9. 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.
10. 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.
11. 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.

HISTORY

Type of Revision	Summary of Changes*	Approval Date
Annual revision	--	01/25/2017
Annual revision	Changed the name to add “Bone Modifiers” to the title of Zometa CC.	02/14/2018
Annual revision	<p>The name of the policy was changed from Bone Modifiers - Zometa to Bone Modifiers – Zoledronic Acid IV (Zometa) to reflect generic availability of the product. For all indications, except hypercalcemia of malignancy, the requirement that the creatinine clearance be ≥ 30 mL/min, which was cited in the labs/diagnostic section, was removed from the policy. Likewise, the criteria in the conditions not recommended for approval section that required the creatinine clearance to be < 30 mL/min was removed, which applies to all indications, except for hypercalcemia of malignancy. Also, the criteria listed in the conditions not recommended for approval section that stated that concurrent use of Zometa with the Reclast formulation of zoledronic acid injection is not recommended was removed. For the indication regarding hypercalcemia of malignancy, the duration of therapy was changed to 1 month. Previously, two doses, administered 7 days apart, were permitted for this use. Also, for hypercalcemia of malignancy, the reference to “adults” was removed from the dosing section. For the treatment of multiple myeloma, the approval duration was changed from 6 months to 1 year. The dosing for multiple myeloma was changed to approve up to 4 mg by intravenous infusion administered no more frequently than once every 3 weeks. Previously, the dosages were cited as 4 mg or less by intravenous infusion once every 3 to 4 weeks or once every 12 weeks. For the treatment of bone metastases from solid tumors, the approval duration was changed from 6 months to 1 year. For the criteria regarding treatment of bone metastases from solid tumors, the requirement that the patient have bone metastases which were “confirmed by radiographic or imaging studies” was removed from the criteria, as well as from the labs/diagnostic sections. The dosing for the treatment of bone metastases from solid tumors was changed to approve up to 4 mg by intravenous infusion administered no more frequently than once every 3 weeks. Previously, the dosages were cited as 4 mg or less by intravenous infusion once every 3 to 4 weeks or once every 12 weeks. For the prevention of bone loss in patients with breast cancer receiving aromatase inhibitor therapy, the approval duration was changed from 6 months to 1 year. The dosing for this use was changed from “The dose is 4 mg or less by intravenous infusion once every 6 months” to “approve up to 4 mg by intravenous infusion no more frequently than once every 6 months”. For the prevention of bone loss in patients with prostate cancer who are receiving androgen deprivation therapy, the approval duration was changed from 6 months to 1 year. The dosing for this use was changed from “The dose is 4 mg or less by intravenous infusion once every 3 to 6 months” to “approve up to 4 mg by intravenous infusion no more frequently than once every 3 months”. For the prevention of bone loss in premenopausal patients with breast cancer who have developed ovarian failure, the approval duration was changed from 6 months to 1 year. The dosing for this use was changed from “The dose is 4 mg or less by intravenous infusion once every 3 months” to “approve up to 4 mg by intravenous infusion no more frequently than once every 3 months”. For all indications the following sections were removed: initial approval/extended approval, duration of therapy, and labs/diagnostics. The Waste Management section of the policy was deleted, as well as Appendix A and B that detailed calculating albumin-corrected calcium (cCa) and creatinine clearance (CrCl).</p>	02/27/2019

TAC – Therapeutic Assessment Committee.